Factors underlying +/- 3, 4-Methylenedioxymethamphetamine self administration.

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Abstract

Rationale: +/- 3, 4-Methylenedioxymethamphetamine (MDMA; Ecstasy) consumption has increased globally over the past two decades. Human studies have demonstrated that in a small proportion of users MDMA consumption may become problematic. Limited preclinical studies have evaluated the abuse potential of MDMA.
Objectives: The present study sought to determine if MDMA self-administration has similar addictive properties as other abused substances. Initial experiments sought to determine if MDMA could function as a reinforcer. Subsequent experiments assessed whether dopamine played a role in MDMA self-administration, whether MDMA self-administration was maintained by the presentation of a conditioned stimulus, and if extinguished MDMA self-administration could be reinstated.
Methods: Animals were surgically implanted with indwelling intravenous catheters that allowed delivery of MDMA solution upon depression of an active lever. MDMA self-administration was examined in drug naïve and cocaine-trained animals. Further assessment of the reliability of self-administration was assessed using a yoked procedure, dose effect curves were obtained, vehicle substitution occurred, and progressive ratio procedures were used. The underlying role of dopamine in mediating MDMA self-administration was determined using the D1-like antagonist, SCH23390, and D2-like antagonist, eticlopride. Manipulation of the light and/or drug stimulus was used to provide initial assessment of the conditioning properties of MDMA. The ability of 10 mg/kg MDMA to reinstate responding previously maintained by MDMA was also determined.
Results: MDMA was reliably self-administered in drug naïve and cocaine trained animals. Responding was selective to contingent MDMA administration, reduced with vehicle substitution, sensitive to dose manipulation, and increasing demand. A rightward shift in the dose effect curve was demonstrated after administration of SCH23390. Removal of both the light and drug stimuli produced a rapid reduction in responding. Removal of either the light or drug stimulus produced a gradual reduction over 15 days. Administration of MDMA reinstated responding previously maintained by MDMA.
Conclusion: The demonstration of reliable MDMA self-administration provided a baseline for assessing MDMA abuse potential. MDMA self-administration was mediated by dopaminergic mechanisms which may be similar to those demonstrated for other abused substances. MDMA self-administration also produced conditioning - a feature of compulsive drug use. Responding previously maintained by MDMA was later reinstated by MDMA, demonstrating that MDMA use may result in relapse. MDMA has similar behavioural properties as other commonly abused substances.

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Chapter 1 - Introduction

3,4-methylenedioxmethamphetamine (MDMA; ecstasy) is an amphetamine derivative that produces subjective effects with both stimulant and hallucinogenic properties (Battaglia et al 1988, Hegadoren et al 1999, Merck 1989, Oberlender & Nichols 1988, Paulus & Geyer 1992). MDMA has been categorised as an entactogen (Nichols 1986), a substance with both psycho-stimulant and hallucinogenic producing effects, with empathetic eliciting properties (Cami et al 2000, Downing 1986, Greer & Tolbert 1986, Grob et al 1990, Grob et al 1996, Liechti & Vollenweider 2000, Verheyden et al 2003).

The street names of MDMA allude to the acute positive subjective effects reported in both clinical and retrospective studies including; feelings of euphoria, increased energy, sexual and sensual arousal, elevated positive moods, reduction in negative thoughts, emotional openness, and positive depersonalisation (Cami et al 2000, Greer & Tolbert 1986, Hegadoren et al 1999, Liechti et al 2000, Liechti et al 2001, Parks & Kennedy 2004, Peroutka et al 1988, Parks & Kennedy 2004, Verheyden et al 2003, Vollenweider et al 1998). Many adverse side effects have also been reported after chronic MDMA use; including increased psychopathology, impaired neuropsychological functioning and aversive physiological effects (Curran & Travill 1997; Greer & Tolbert 1986; Liechti et al 2000b; Liechti & Vollenweider 2000; McCann et al 1996; Parrott 2001; Peroutka et al 1988; Schifano et al 1998; Verheyden et al 2003; Wareing et al 2004; 2005; Wareing et al 2000).

MDMA Epidemiology and patterns of use

MDMA consumption has been gradually increasing over the past decade (UNODC 2004). Use originated in "dance" subcultures (Bellis et al 2003, Parrott 2001, Parrott 2004), but has spread to mainstream populations (Bobes et al 2002, ter Bogt et al 2006, TF & Engels 2005, Wilkins et al 2003), as patterns of consumption and contexts of use have become more variable (Degenhardt et al 2005, Topp et al 2004, von Sydow et al 2002). Two major patterns of MDMA consumption are borne out in the epidemiological literature. A majority of MDMA users have consumed less than 10 pills (Scholey et al 2004, Solowij et al 1992, Topp et al 1999, von Sydow et al 2002), and consume only 1 (75-100mg) pill on each occasion (Schifano et al 1998, Scholey et al 2004, Solowij et al 1992, Topp et al 1999). Within this category, users reported consuming MDMA once to several times a month (Curran & Travill 1997, Peroutka et al 1988, Schifano et al 1998, Solowij et al 1992, Williams et al 1998), for a discrete period of time (von Sydow et al 2002).

In contrast, moderate - heavy MDMA use occurs in approximately a third of MDMA users. The frequency of MDMA consumption amongst this group of users varies considerably from once every few months (Solowij et al 1992), to more than once a week (Schifano et al 1998, von Sydow et al 2002) and binge patterns of consumption are typical (Parrott 2001, Parrott 2004, Parrott 2005, Scholey et al 2004). One study reported that a third of moderate-heavy MDMA users had consumed MDMA, continually for approximately 48 hours on a least one occasion in the past

6months (Topp et al 1999), while another reported that 50% of the sample had consumed more than 5 pills on at least one occasion (Winstock et al 2001). Binge patterns of MDMA consumption have been associated with increased frequency of regular MDMA use (Parrott 2005, Scholey et al 2004). Those who consume MDMA in binges tend to also be poly drug users (Scholey et al 2004, Topp et al 1999).

A significant proportion of moderate- heavy MDMA users met general DSM-IV criteria for dependence or abuse (Jansen 1999, Kurtz et al 2005, Topp et al 1999; Schuster et al 1998, von Sydow et al 2002). Increases in the amphetamine-like subjective properties of MDMA are hypothesised to underlie the transition from use to dependence (Jansen 1999), as is tolerance to the positive subjective effects (Levy et al 2005, O'Regan & Clow 2004, Parrott 2005, Solowij et al 1992). Moderate-heavy users reported the development of tolerance, the presence of withdrawal symptoms, and the use of alternative drugs as mood modulators, (Forsyth 1996; Fox et al 2002; Liechti 2003; McCann et al 1996; Parrott 2003; Parrott 2005; Peroutka et al 1988; Schifano et al 1998; Scholey et al 2004; Shulgin 1986; Solowij et al 1992; Topp et al 1999; Verheyden et al 2003; Verkes et al 2001; von Sydow et al 2002; Winstock 1991).

A number of studies have attempted to document the consequences of MDMA exposure. Unfortunately, human studies are confounded in a number of ways. Patterns of consumption have relied on retrospective, self-report methods, which required accurate recollection and awareness of types, and amounts of drugs taken. This is unlikely, given the

functional effects of polydrug use, and binge consumption of MDMA . Additionally MDMA tablets often contain other substances, such as MDEA, MDA, ketamine, amphetamine, and caffeine (Parrott 2004), therefore, people rarely know what they are taking or how much. Because MDMA users exhibit high levels of poly-drug use it is difficult to unambiguously attribute effects to MDMA alone. The use of animal models has allowed researchers to explore specific constructs, symptoms and mechanisms associated with addiction by controlling for a number of extraneous variables (Ahmed & Koob 1998, Ator & Griffiths 2003, Griffiths et al 1978, Koob & Le Moal 1997, Kozikowski et al 2003, O'Brien & Gardner 2005).

Self-administration

An important development in addiction research was the introduction of the indwelling catheter (Weeks 1962). This provided a procedure that allowed animals to chronically intravenously self-administer drugs. During the past four decades self-administration has been measured in many species including rhesus monkey (Segal et al 1972), 1969), squirrel monkey (Gerber & Stretch 1975), dog (Risner & Jones 1975), baboon (Griffiths et al 1976), cat (Ford & Balster 1976), rat (Pickens & Harris, 1968) and mouse (Criswell et al 1988).

Virtually all drugs of abuse are self-administered by laboratory animals, and the pattern of self-administration is comparable to the pattern exhibited by humans (Gardner 2000, Goldberg et al 1969, Griffiths & Balster 1979, Griffiths et al 1978, Pickens & Harris 1968, Segal et al 1972, Spealman & Goldberg 1978). A focus of early research

was to demonstrate reliable self-administration and to identify drugs with abuse potential. The abuse liability of a substance is defined by the likelihood that a substance can maintain 'non-medical self-administration resulting in disruptive or undesirable consequences' (FDA, pg 3). Therefore demonstration of reliable self-administration has been deemed necessary in the preclinical evaluation of substances with abuse potential (Ator & Griffiths 2003, Kozikowski et al 2003).

To convincingly demonstrate reliable self-administration operant behaviour must be selective (Ahmed & Koob 1998, Fischman & Schuster 1978, Griffiths & Balster 1979, Griffiths et al 1978, Koob 1992, O'Brien & Gardner 2005, Spealman & Kelleher 1981, Thompson 1981). This can be established through various methods, including simple-choice procedures and yoked procedures. When simple- choice procedures are employed, depression on one lever (active) results in drug delivery, while depression on another (inactive) lever has no programmed consequence, or produces delivery of a vehicle solution. Significant preference for the active lever suggests that a drug is reinforcing (Brady & Griffiths 1976, Griffiths et al 1978, Griffiths et al 1981). Yoked self-administration procedures also determine whether a drug is reinforcing. Under these conditions one animal receives drug delivery contingent on performance of the appropriate operant (Pickens & Crowder 1967, Yokel & Pickens 1974). Yoked animals receive either vehicle or drug infusions dependant on the contingent animal's responses. An elevated level of responding by only the response contingent animal, demonstrates selective self-administration behaviour. Once self-administration has been

demonstrated, it is also convincing to show extinction when vehicle solution is substituted for the drug (Yokel & Pickens 1973).

In self-administration experiments, responding is often demonstrated in a dose-dependant fashion (Arnold & Roberts 1997, Bickel et al 1990, Griffiths et al 1978, Winger et al 1989, Yokel & Wise 1976). Low doses of a drug are often too small to reinforce responding. In contrast, a threshold dose of a drug will maintain high levels of operant responding. Thereafter responding is generally inversely related to the dose of drug (Griffiths et al 1976, Yokel & Wise 1976). Fixed ratio dose-dependant responding is depicted in the shape of an inverted U (see Figure 1), and this has been demonstrated for many different self-administered substances (Ator & Griffiths 1983; Downs & Woods 1975; Goldberg et al 1971; Griffiths et al 1976; Harrigan & Downs 1978; Martin et al 1996; Meisch & Stewart 1994; O'Brien & Gardner 2005; Risner & Jones 1980; Schenk & Partridge 1997; Wilson et al 1971; Winger et al 1989; Woolverton et al 1980; Yokel & Wise 1976; Yokel & Pickens, 1973). When doses higher than threshold are available the rate of drug intake is inversely related to the injection dose. It is possible that the reductions in responding may be due to the rate-decreasing effects of high doses of a drug. For example, high levels of responding may be due to increased stereotyped behaviour (Patel et al 1996), however, this is unlikely as higher doses of a substance increase rather than decrease stereotyped behaviour. Furthermore, stereotyped behaviour is unlikely to directly influence specific drug-taking behaviours (Wise et al 1977). It is also possible that reductions in responding seen at high doses are due to

the toxic effects of a substance. The rate –decreasing effects of high doses are unlikely to be due to toxicity, as animals will acquire self-administration more rapidly when higher doses of a substance are used (Schenk et al, 1993; Carroll & Lac, 1997). A more likely explanation for the inverse relationship between unit dose and responding, is that an animal is titrating blood-brain levels of a substance through compensatory responding (Hurd et al 1989, Pettit & Justice 1989, Pettit & Justice 1991, Ranaldi et al 1999, Wise et al 1995, Wise et al 1995). For example, within-session analysis of response rate and blood levels of d-amphetamine revealed that rats performed an operant response when blood levels fell below 0.2µg/ml (Yokel & Pickens 1974). Microdialysis studies have also confirmed that responding maintained by cocaine is associated with reductions in elevated dopamine levels (Wise et al, 1995b).

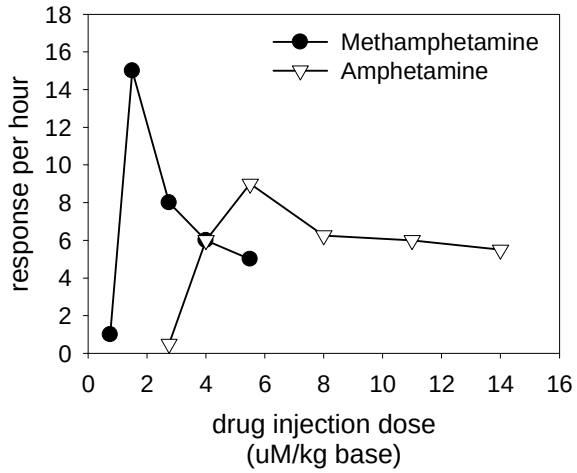


Figure 1: Dose effect curve
Adapted from Yokel & Pickens (1973).
Mean injections per hour for Methamphetamine and amphetamine.

Self-administration procedures can also be used to determine the incentive motivational properties of a substance (Griffiths et al, 1979; Arnold & Roberts, 1997; Richardson & Roberts, 1996). Increasing Fixed Ratio (FR) schedules of reinforcement produced an increased rate of responding demonstrating increased motivation and incentive to self-administer a substance, as a function of demand (Dworkin et al 1984, Goldberg & Henningfield 1988, Lemaire & Meisch 1984, Lemaire & Meisch 1985, Spealman & Goldberg 1978, Weeks & Collins 1978). The behavioural consequences of increased demand can also be demonstrated through use of the progressive ratio (PR) procedure (Arnold & Roberts 1997, Griffiths et al 1978, Li et al 1994, Li et al 2003, McGregor & Roberts 1995, Reid et al 1995, Shaham & Stewart 1994). In this procedure, the operant response requirement for delivery of a reinforcer increases in a step like fashion, until the requirement is so high that responding is no longer maintained – this point is referred to as the break point. Therefore, it is possible to determine the maximal level of behaviour or effort an animal will exert in order to receive a self-administered injection (Arnold & Roberts 1997, Foster et al 1989, Griffiths et al 1978, Patel et al 1996). Dose-response curves under progressive-ratio schedules demonstrate the reinforcing efficacy of a substance (Arnold & Roberts 1997, Foster et al 1989, Griffiths et al 1978, Patel et al 1996). Low doses of cocaine, GBR 12909, heroin, amphetamine and methamphetamine produced low breakpoints, as the unit dose increased the breakpoint increased (Foster et al 1989, Griffiths et al 1978, Roberts 1993, Roberts & Bennett 1993).

Despite the documentation of reliable self-administration of many commonly abused drugs (Ator & Griffiths 2003, Balster & Lukas 1985, Griffiths et al 1979, Griffiths et al 1981), self-administration of some substances widely abused by humans has not been easily demonstrated in animals. For example, reliable nicotine self-administration was difficult to demonstrate for many years (Hanson et al 1979, Lang et al 1977, Slifer & Balster 1983). However manipulation of experimental protocols such as reducing the dose, and allowing limited access produced robust self-administration (Corrigall 1999, Corrigall & Coen 1989, Corrigall & Coen 1991, Rose & Corrigall 1997). Subsequently, it was demonstrated that responding under some conditions was dose dependently reduced by some antagonistic pharmacological treatments and reduced following saline substitution (Corrigall & Coen 1989).

Initial attempts to demonstrate self-administration of Δ-9 THC were also inconclusive (Lew & Richardson 1981, Mansbach et al 1994, Takahashi & Singer 1979, Takahashi & Singer 1981). These findings led to varying explanations including (1) that Δ-9 THC was not a drug of abuse, (2) that the self-administration paradigm had reduced validity, (3) that the delayed effects of Δ-9 THC prevented operant conditioning and, (4) that Δ-9 THC was a depressant on operant behaviour (see (Tanda & Goldberg 2003)). Subsequent manipulation of experimental procedures including solution concentration, infusion speed and infusion duration resulted in reliable dose-dependant self-administration (Tanda & Goldberg 2003, Tanda et al 2000).

The demonstration of reliable and robust nicotine and Δ-9 THC self-administration despite initial claims that they were both weak reinforcers, indicates that a degree of caution in interpretation is required if a substance with known abuse potential in humans does not initially produce reliable self-administration. Furthermore, false negatives can be produced unless a variety of experimental procedures are employed.

MDMA self-administration

The establishment of reliable and replicable MDMA self-administration has largely evaded self-administration researchers and only a handful of studies have been published (Beardsley et al 1986b; Braida & Sala 2002; Cornish et al 2003; Fantegrossi 2007; Fantegrossi et al 2002; Fantegrossi et al 2004; Lamb & Griffiths 1987; Lile et al 2005; Ratzenboeck et al 2001; Reveron et al 2006; Trigo et al 2006; Wang & Woolverton 2007).

Substitution studies have demonstrated that MDMA can reinforceoperant behaviour (Beardsley et al 1986, Fantegrossi 2007, Fantegrossi et al 2002, Fantegrossi et al 2004, Lamb & Griffiths 1987, Lile et al 2005). Initial MDMA self-administration studies in cocaine-trained primates demonstrated that operant responding maintained by MDMA was higher than operant responding maintained by saline (Beardsley et al 1986, Lamb & Griffiths 1987). Lamb & Griffiths (1987) reported that MDMA self-administration produced lower levels of responding when compared to cocaine, and the data were characterised by high levels of variability amongst animals and between sessions. Fantegrossi et al (2002; 2004; 2007), Lile et al (2005) and Wang &

Woolverton (2007) have extended these findings. Animals were trained to self-administer cocaine on a daily basis and MDMA- racemic, S (+), and R (-) was substituted for cocaine (Fantegrossi et al 2002, Fantegrossi et al 2004, Lile et al 2005). Dose dependant self-administration of racemic MDMA and its stereoisomer's was demonstrated (Fantegrossi et al 2004). Lile and colleagues (2005) employed the same methodology with baseline behaviour maintained by cocaine, and a progressive ratio procedure was used to examine MDMA self-administration. MDMA maintained responding in a dose-dependant manner and a maximal mean breakpoint of 802 was obtained when PR schedules were employed. Breakpoints for all animals increased as the dose of MDMA (0.01-1.0mg/kg) increased (Lile et al 2005). Subsequently, Wang & Woolverton (2007) also demonstrated a dose dependant increase in breakpoint for MDMA self-administration (0.05-0.8 mg/kg/infusion), with comparable maximal rates of responding as those reported by Lile et al (2005).

Several studies have attempted to produce reliable MDMA self-administration in laboratory rats. Ratzenboeck and colleagues (2001) demonstrated MDMA (0.032-10mg/kg/infusion) self-administration in drug-naïve and cocaine –trained rodents. Low rates of operant responding were observed, however, leading to the suggestion that MDMA was a weak reinforcer (Cole & Sumnall 2003, Newton et al 2006, Ratzenboeck et al 2001). Alternatively, the acquisition methods used by Ratzenboeck et al (2001) may not have engendered optimal operant responding. Typically, in order for self-administration behaviours

to be established, repeated consistent discrete pairings of a drug-lever and drug delivery are required (Griffith et al, 1979). In the study conducted by Ratzenboeck et al (2001) animals received multiple discrete, MDMA, cocaine, and saline self-administration sessions per day. This may have intervened with the ability to acquire operant contingency due to inconsistent reinforcers. In addition, the comparatively long half-life of MDMA when compared to cocaine may have limited the possibility of distinguishing rates of responding for cocaine and MDMA.

Following the study conducted by Ratzenboeck et al (2001), four other studies have demonstrated MDMA self-administration in rats (Braida & Sala 2002, Cornish et al 2003, Newton et al 2006). Braida & Sala (2002) trained animals to receive intracerebroventricular (ICV) infusions of MDMA (0.01-2µg/infusion) according to an FR1 schedule during daily 1-h sessions. Animals acquired MDMA self-administration and self-administration was dose-dependant (Braida & Sala 2002). Cornish et al (2003) also reported dose dependant MDMA self-administration (0.1-1.0mg/kg/infusion; FR1, daily 2-H sessions). The acquisition of MDMA self-administration (1.0mg/kg/infusion) was also demonstrated by Reveron et al (2006), with responding increasing as the dose of MDMA made available was halved.

One other study has investigated MDMA self-administration in rats (De La Garza et al 2006). In one group, (N=5), animals were allowed access to MDMA (0.75mg/kg/infusion) according to an FR2 schedule of reinforcement for 24 daily 3-h sessions. In a second group (N=15), similar acquisition conditions were imposed, although the dose

of MDMA was reduced to 0.375mg/kg/infusion. Responding maintained by MDMA was comparable to responding maintained by saline in four out of five rats leading to the conclusion that MDMA was not as potent reinforcer as other commonly abused substances (De La Garza et al 2006). Low rates (2-7 responses) of responding were produced when animals were tested during the light phase of their circadian rhythms. When session times were extended to 12-h and animals were run in the dark phase of their circadian rhythm, responding maintained by MDMA increased to 8-12 infusions per session. Reduction of MDMA dose (0.1875mg/kg/infusion) during one session produced a reduction in responding. Responding failed to return to prior levels of responding when the initial dose was again available. Saline substitution reduced responding further but responding was not reinstated when MDMA was reintroduced. These authors also concluded that MDMA was a weak reinforcer. Unfortunately, only limited conditions were examined. It is equally possible that MDMA is a more effective reinforcer under different parameters. Additionally, responding was averaged across all days of acquisition and a mean response /day rate was presented. There is generally a protracted period of acquisition of self-administration with responding increasing gradually over days (Campbell & Carroll 2000, Deminiere et al 1989, Schenk & Partridge 2000). Therefore averaging data over this period might obscure reliable responding that might appear during later sessions. In addition, the use of small samples, single case examples, and the absence of statistical analysis renders this study inconclusive.

In order to further examine MDMA self-administration, a substitution paradigm will be used in this thesis to determine whether MDMA maintains responding in cocaine-trained rats. Acquisition of self-administration in drug naïve rats will also be examined. The selectivity of operant behaviours will also be assessed using a simple choice and a yoked self-administration procedure. Dose effect curves will be assessed and the effects of vehicle substitution will be measured. The effects of increasing demand will also be evaluated by manipulating schedules of reinforcement, and through the use of a P.R. schedule.

Pharmacology of drug abuse

A wealth of evidence has indicated that excitation of the mesolimbic dopaminergic tracts projecting from the ventral tegemental area (VTA) to the ventral striatum (nucleus accumbens; Nuc Accum), amgydala and frontal cortex is critical for the acute reinforcing effects of drugs of abuse (Carelli 2004; Carr et al 1988; Di Chiara 1999; Di Chiara et al 2004; Fibiger et al 1992; Koob & Hubner 1988; Koob & Weiss 1990; Pulvirenti & Koob 1990; Ranaldi et al 1999; Robinson & Berridge 1993; 2000; Sahakyan & Kelley 2002; Salamone & Correa 2002; Wise 1984; 1987; 1998; Wise & Bozarth 1982; 1985; Wise et al 1995b; Wolf 2002). PET scans have shown that reported positive subjective experiences are correlated with occupancy of the dopamine reuptake transporters (DAT) in experienced cocaine users (Volkow et al 1999, Volkow et al 1997), and long-term alterations in the D2-like receptor density in the striatum are found in chronic drug users (Volkow et al 2001, Volkow et al 2002, Volkow et al 1993).

Despite having varied pharmacological effects, self-administered substances all produce direct and/or indirect effects on dopaminergic systems. Administration of some psychostimulants resulted in direct increases in synaptic dopamine. For example, d-amphetamine binds directly to the DAT, causing a reversal of functioning and stimulating release (Pierce & Peroutka 1988), while cocaine blocks the DA transporters (Canfield et al 1990, Porrino et al 1989, Ritz et al 1987, Ritz et al 1988). In contrast, other drugs are indirect dopamine agonists, acting on neural substrates which interact with the mesolimbic dopamine system. For example, opiates produced stimulation of the dopamine system through activation of the mu- opioid receptor which inhibits GABBAergic neurons thereby disinhibiting DA neurons (Eidelberg & Erspamer 1975). Microdialysis studies have shown that administration of self-administered substances including cocaine, amphetamine, nicotine, opiates and PCP, preferentially stimulated dopamine transmission in the nucleus accumbens and VTA (Bassareo et al 1996, Di Chiara & Imperato 1988, Imperato et al 1992, Imperato et al 1996, Kuczenski et al 1997).

Several lines of evidence have implicated dopaminergic mechanisms in drug self-administration. Firstly, both direct and indirect dopamine agonists are readily self-administered (Howell & Byrd 1991, Nader & Mach 1996, Roberts et al 1999, Self & Stein 1992, Weed & Woolverton 1995, Woolverton et al 1984, Yokel & Wise 1978). Pre-treatment with dopaminergic agonists reduced subsequent drug self-administration, suggesting a leftward shift in the dose response curve and

an increased potency of the self-administered drug (Swerdlow et al 1991, Yokel & Wise 1978).

Secondly, selective neurotoxic lesions with 6-hydroxydopamine (6-OHDA) disrupted self-administration (Iannone et al 2006, Lyness et al 1979, Roberts & Koob 1982, Smith et al 1985). 6-OHDA lesions to the nucleus accumbens produced a 90% reduction in dopamine and attenuated cocaine maintained responding for at least 15 days (Roberts et al 1977). In addition, 6-OHDA lesions to the Nuc Accum abolished the acquisition and maintenance of amphetamine self-administration (Lyness et al 1979). 6-OHDA lesions of cell bodies in the VTA disrupted responding maintained by heroin, cocaine and morphine (Bozarth & Wise 1986, Roberts & Koob 1982). Lesions to the medial prefrontal cortex (MPFC) had no effect on the maintenance of d-amphetamine or cocaine self-administration under simple FR schedules (Leccese & Lyness 1987, Martin-Iverson et al 1986, McGregor et al 1996, Peltier & Schenk 1991), but 6-OHDA lesions to the MPFC increased breakpoints maintained by low doses of cocaine and apomorphine under PR schedules (Foster et al 1989, Lin et al 1994, McGregor et al 1996). These findings may indicate an increase in the sensitivity of the dopamine systems in the mPFC after repeated exposure to drugs of abuse. 6-OHDA lesions were selective and had no effect on responding maintained by food and water (Dworkin et al 1988, Smith et al 1985), suggesting a selective role for the mesocorticolimbic system projections in drug self-administration.

Thirdly, pharmacological manipulations of dopamine also modify drug self-administration. Pre-treatment with the D2 receptor antagonist,

chlorapromazine, increased responding maintained by cocaine, amphetamine, and methylphenidate in rhesus monkeys (Wilson & Schuster 1972). The increase in responding seen after antagonism is consistent with a rightward shift in the dose-response curve. Subsequently, self-administration of many substances including, opioids (Corrigall & Vaccarino 1988, Shippenberg & Elmer 1998), alcohol (Pfeffer & Samson 1985), nicotine (Corrigall & Coen 1991, Tanda et al 1999, Wilson et al 1992), THC (Tanda & Goldberg 2003, Tanda et al 1999), cocaine (Bergman et al 1990, Caine & Koob 1994, Corrigall & Coen 1991, Hubner & Moreton 1991, Koob et al 1987, Ranaldi & Wise 2001, Woolverton & Virus 1989), amphetamine (Phillips et al 1994), and diazepam (Pilotto et al 1984) were modified by pharmacological manipulations of dopamine.

Pharmacological antagonism of D1-like receptors produced a rightward shift in the dose effect curves for amphetamine, morphine, and cocaine self-administration (Anderson et al 2003; Bari & Pierce 2005; Barrett et al 2004; Caine & Koob 1994a; Corrigall & Coen 1991a; Di Ciano et al 1995; Hubner & Moreton 1991; Koob et al 1987; Maldonado et al 1993; Pich & Epping-Jordan 1998; Pierre & Vezina 1998; Quinlan et al 2004; Ranaldi & Wise 2001; Rodriguez De Fonseca et al 1995; Swerdlow et al 1991; Weed et al 1998; Yui et al 1997). Antagonism of the D2-like receptors produced similar effects. For example, pre-treatment with chlorpromazine, a D2-like receptor antagonist produced a dose dependant increase in cocaine self-administration (Wilson & Schuster 1972, Woods et al 1988). The production of a rightward shift in

the dose-effect after D2-like receptor antagonism has been demonstrated with amphetamine-, cocaine- and morphine- self-administration (Caine & Koob 1994, Corrigall & Coen 1991, David et al 2002, Haile & Kosten 2001, Hubner & Moreton 1991, Swerdlow et al 1991, Weed et al 1998, Yui et al 1997)). Pre-treatment with D1-like and D2-like receptor antagonists reduced the breakpoints for cocaine, amphetamine and opiate self- administration under a progressive ratio schedule (Bari & Pierce 2005, Hubner & Moreton 1991, Izzo et al 2001, Lin et al 1993, Ranaldi & Wise 2001, Ward et al 1996) consistent with a rightward shift in the dose effect curve, and a decrease in the potency of the self-administered substances. These data provided further evidence that dopamine receptor activation is required in order to maintain self-administration.

Fourthly, microdialysis studies have been used to measure synaptic overflow of neurotransmitters and major metabolites (Ranaldi et al 1999, Wise et al 1995, Wise et al 1995). Cocaine, heroin, and amphetamine self-administration dose-dependently increased extracellular levels of dopamine in the nucleus accumbens (Hemby et al 1997, Pettit & Justice 1989, Pettit & Justice 1991, Ranaldi et al 1999, Wise et al 1995, Wise et al 1995). Within session levels of dopamine were increased immediately after drug delivery, and gradually declined until a subsequent operant response was performed (Hurd et al 1989, Pettit & Justice 1989, Pettit & Justice 1991, Ranaldi et al 1999, Wise et al 1995, Wise et al 1995). Animals typically self-administered several infusions during the initial phases of self-administration (loading up phase) during which time rapid increases in extracellular dopamine were

reported (Ranaldi et al 1999, Wise et al 1995, Wise et al 1995). Following the initial loading up phase, phasic fluctuations in dopamine levels were associated with drug infusions, providing further evidence that operant responding was tied to a decrease in elevated dopamine levels (Ranaldi et al 1999, Wise et al 1995, Wise et al 1995).

While a clear dopaminergic role has been implicated in self-administration, the function of other neurotransmitter systems has also been investigated. Of relevance to the current thesis, serotonergic mechanisms have been implicated. Lecesse & Lyness (1984) reported reductions in amphetamine self-administration after pre-treatment with the serotonergic antagonists, cyproheptadine and methysergide, and Porrino et al (1989) reported that cinanserin, a 5-HT2 receptor antagonist, reduced amphetamine maintained responding. Cocaine self-administration, however, remained unchanged after pre-treatment with 5-HT3 antagonists GR38032F, and MDL 72222, 5-HT2A antagonists, ketanserin, and 5-HT1/2-antagonist, methysergide (Lacosta & Roberts 1993, Peltier & Schenk 1991). Further complicating interpretation, pre-treatment with the 5-HT reuptake inhibitors, fluoxetine and dexfenfluramine also reduced responding maintained by amphetamine and heroin (Higgins et al 1994, Leccese & Lyness 1984, Porrino et al 1989). It is likely that these effects may vary as a function of the interaction between antagonist dose used and levels of extracellular 5-HT, as some receptors require specific elevations of 5-HT prior to activation (Bankson & Cunningham 2002). Furthermore, interactions between the serotonin and dopamine system have been demonstrated. For example,

activation of the 5-HT2c receptor is known to inhibit Nuc Accum and dorsal striatum dopamine release (Alex et al, 2005; Navailles et al, 2006).

The role of dopamine in self-administration of many drugs of abuse is supported by a wealth of data, but the pharmacology of MDMA self-administration has not been established.

Pharmacology of MDMA

MDMA initially produces a rapid increase in extracellular 5-HT and DA (Colado et al 1993; Gudelsky & Nash 1996; Gudelsky et al 1994; Johnson et al 1986; Koch & Galloway 1997; McKenna & Peroutka 1990; O'Loinsigh et al 2001; Sabol & Seiden 1998; Schmidt et al 1987; Schmidt et al 1986; Stone et al 1987; White et al 1996; Yamamoto et al 1995). MDMA acts directly on the serotonin transporter, inhibiting 5-HT transport across plasma walls leading to a reduction in 5-HT reuptake and increases in extracellullar 5-HT (Cole & Sumnall 2003, Gudelsky & Nash 1996, Mechan et al 2002, Rudnick & Wall 1992, Schmidt et al 1987). MDMA also has direct affinities for the 5-HT receptors (Battaglia et al 1988, Koch & Galloway 1997, Schmidt & Taylor 1990). These mechanisms have been the focus of investigation for much research, and significant evidence indicates that activation of serotonin receptors are involved in the anxiogenic- (McGregor et al 2003, Morley et al 2005, Sumnall et al 2004) and hyperactive- (Callaway et al 1992, Callaway et al 1990, Fletcher et al 2002, Gold & Koob 1988, Gold et al 1988, Kehne et al 1996, McCreary et al 1999) effects of MDMA. For example, selective 5,7-DHT lesions and antagonism of the 5-HT1B, 5-HT2A, and 5-HT2B receptors attenuated MDMA –induced hyperactivity (Callaway et al

1990, Kehne et al 1996, McCreary et al 1999). Pre-treatment with 5-HT2C receptor agonists, however, also attenuated MDMA-induced hyperactivity (Fletcher et al 2002, Gold & Koob 1988), indicating differential roles of the 5-HT receptor subtypes in MDMA –induced behaviours.

MDMA also produces pronounced effects on dopamine neurochemistry via direct and indirect mechanisms. MDMA- induced inhibition of the dopamine transporter (DAT), increased DA synthesis, and inhibition of MAO,produced an increase extracellular dopamine levels (Crespi et al 1997, Nash & Brodkin 1991, Shankaran & Gudelsky 1998, White et al 1994, Yamamoto & Spanos 1988). MDMA administration produced a time- and dose- dependant increase in dopamine levels in the caudate nucleus and in the Nuc Accum , as measured by in vivo volumetry and HPLC methods (Yamamoto & Spanos 1988). MDMA increased dopamine levels in a dose dependant manner (0.32mg/kg-3.2mg/kg) preferentially in the Nuc Accum shell compared to the Nuc Accum core (Cadoni et al 2005 ,Di Chiara et al 1999). The enhancement of synaptic dopamine was of longer duration than the enhancement of synaptic 5-HT (Johnson et al 1986, Mayerhofer et al 2001, O'Shea et al 2005, Stone et al 1986, White et al 1994) and a delayed secondary increase in dopamine levels in the nucleus accumbens has also been reported (Koch & Galloway 1997, White et al 1994, Yamamoto et al 1995). Several studies have implicated DA mechanisms in the effects of MDMA. MDMA-induced excitation of striatal neurons was associated with increased hyperactivity, delayed after D1-like

receptor antagonism, and attenuated by D2-like receptor antagonism (Ball et al 2003). 6-OHDA lesions to the nucleus accumbens and systemic pre-treatment with D1-like and D2-like receptor antagonists attenuated the locomotor activity effects of MDMA (Gold et al 1989, Kehne et al 1996). Furthermore, the expression of MDMA-induced locomotor sensitisation was inhibited by pre-treatment with the D1-like antagonist, SCH23390 (Ramos et al 2004). These data suggest that the behavioural effects of MDMA are at least partially mediated by dopaminergic mechanisms.

Evidence for the modulation of DA release by MDMA-induced elevations in 5-HT has been reported. Pre-treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine partially attenuated MDMA-induced elevations of striatal dopamine (Koch & Galloway 1997). The reductions in dopamine after SSRI pre-treatment are likely to be due to competitive antagonism of the SERT, reducing MDMA-induced serotonin. Initial studies demonstrated that direct 5-HT2-receptor agonism with DOI, and 5-MeODMT, potentiated MDMA-induced DA release (Gudelsky et al 1994). Activation of different 5-HT2 receptors can have differential effects on dopamine release. Activation of 5-HT2A and 5-HT1B receptors increased dopamine release (Lucas & Spampinato 2000, Yan 2000), and antagonism of these receptors reduced MDMA-produced dopamine increases (Lucas & Spampinato 2000, Schmidt et al 1994). In contrast, antagonism of the 5-HT2C receptors in the VTA, resulted in reductions in VTA GABBA, which in turn disinhibited Nuc Accum DA release (Bankson & Yamamoto 2004). Both the 5-HT2A and 5-HT2C receptors have a relatively low affinity for

serotonin, therefore low doses of MDMA are unlikely to activate these receptors. These modulatory mechanisms may explain changes in the locomotor activating effects of MDMA after serotonergic pre-treatment. Further evidence for this hypothesis has been obtained from electrophysiology studies, as antagonism of the 5-HT2A receptor attenuated both MDMA-induced locomotor activity and striatal excitation; in contrast, antagonism of the 5-HT2C receptor had no effect on locomotor activity or striatal excitation (Ball & Rebec 2005).

The mechanisms underlying MDMA reinforcement in both humans and animals are poorly characterised and it is currently unclear whether dopamine is a critical neurotransmitter underlying the reinforcing effects of MDMA. Two studies have reported that the euphoria producing effects of MDMA may be due to dopaminergic mechanisms. In one, pre-treatment with the dopamine antagonist, haloperidol, reduced the subjective ratings of positive mood and 'mania' produced by MDMA (Liechti & Vollenweider 2000). In another, MDMA users reported preferences for MDMA or d-amphetamine when compared to the serotonergic agonist MCPP, as measured by a multiple cost-benefit choice preference procedure (Tancer & Johanson 2003). These data indicate that in humans, MDMA was more reinforcing than a direct serotonergic agonist, and at least as reinforcing as a dopamine agonist.

Animal studies attempting to characterise the pharmacology of MDMA reinforcement and reward have focused on serotonergic mechanisms. In one study pre-treatment with high doses of the 5-HT1A agonist, 8-OH-DPAT attenuated MDMA self-administration in rats (De

La Garza et al, 2006). In another study, the non-selective 5-HT2A/C receptor antagonist, Ketanserin and 5-HT2A receptor antagonist, MDL 100907, produced differential effects on responding maintained by racemic MDMA, S(+) MDMA and R(-) MDMA (Fantegrossi et al, 2006). Ketanserin produced a general reduction in responding for all three forms of MDMA. While MDL 100907 failed to significantly alter responding maintained by racemic MDMA. A rightward shift in the ascending limb of the S (+) MDMA dose effect curve, and attenuation of responding maintained by R (-) MDMA was found. These findings might be related to differential effects of the different isomers on DA neurotransmitters. S (+) - and R (-) - MDMA differentially activated DA and 5-HT systems, with the former producing greater DA effects and the later producing greater 5-HT effects (Baker et al 1995, Battaglia & Napier 1998). The changes in self-administration behaviour seen after 5-HT antagonism indicates that 5-HT mechanism are involved in MDMA self-administration. Given the wealth of data implicating dopamine in self-administration, the alterations in MDMA self-administration seen after 5-HT receptor antagonism may also be due to the serotonergic effects on DA release (Fantegrossi et al, 2006).

In order to evaluate the role of dopamine in MDMA self-administration, the second major experiment conducted for this thesis will determine the effects of the D1-like and D2-like receptor antagonists on MDMA self-administration. The D1-like receptor antagonist, SCH23390, and the D2-like receptor antagonist, eticlopride, will be used

in both self-administration and locomotion studies to determine if the effects of MDMA are sensitive to dopaminergic manipulations.

Transition from use to abuse and dependence

Pathological drug use has been defined as the development of compulsive drug taking, and an inability to cease drug consumption (Koob 2006, Robinson & Berridge 2000). There are specific features that characterise compulsive drug-taking and differentiate drug abuse and dependence from drug use. Compulsive drug-taking elicits subjective states not produced by controlled drug taking. Inexperienced drug users did not report a state of 'craving', whereas experienced cocaine users reported, and differentiated the state of 'craving' from the state of being 'high'(Childress et al 1988, Childress et al 1986, Ehrman et al 1990, Haney et al 1999, O'Brien et al 1992, O'Brien et al 1992, Robinson & Berridge 1993). Experienced drug users reported that exposure to drug associated cues, and threshold doses of a substance, elicited states of craving and motivation to consume a substance (Carter & Tiffany 1999; Childress et al 1988, Childress et al 1986, Childress et al 1986, Ehrman et al 1991, Panlilio et al 2005). Experienced drug users also reported a reduction in the subjective effects of higher doses of a substance (Ward et al, 1997). In addition, compulsive drug taking reduced the motivation towards, and salience of alternative goals or stimuli (Cuddy 2004, London et al 2000), thereby narrowing the behavioural repertoire exhibited in experienced drug users. These features of compulsive drug-taking have lead to speculation that alterations in the processing of drug-associated stimuli may increase the incentive-motivational properties of

stimuli associated with a substance, thereby causing ‘craving’ or ‘wanting’, leading to compulsive drug use (Leshner & Koob 1999, Robinson & Berridge 1993; 2000; 2001; 2003).

Evidence for alterations in the processing of drug stimuli has been derived from the widely reported persistence in cue reactivity to drug related stimuli in current and former drug abusers. For example, the presentation of exteroceptive drug associated stimuli produced increased motivation for drug consumption in humans (Carter & Tiffany 1999, Childress et al 1986, Ehrman et al 1992, Ehrman et al 1990, See 2002). Users of crack cocaine distinguished cues experimentally paired with cocaine consumption, based on their physiological and psychological response to these stimuli (Childress et al 1993, Foltin & Haney 2000). The ability of drug-associated stimuli to elicit a state of craving has been demonstrated in cocaine (Childress et al 1993, Ehrman et al 1991, Ehrman et al 1992, Harris et al 2004, Risinger et al 2005), heroin- (Childress et al 1986, Franken et al 2004), nicotine- (Hutchison et al 2004) and alcohol- (Drummond et al 1990) abstinent abusers. In populations of intravenous drug users, conditioning is so profound that the phenomenon of ‘needle freaking’ is reported, whereby drug users will maintain drug-taking behaviours in the absence of a drug, injecting a vehicle solution (Pert 1994, Pert et al 1990).

In laboratory animals, the ability for situational cues to elicit a response similar to a drug-induced response after repeated pairings with a given substance, has been noted since 1927, when apomorphine associated cues elicited a physiological response in the absence of

apomorphine (Pavlov, 1927; cited in(Pert et al 1990). The potential involvement of Pavlovian conditioning as an underlying mechanism in drug addiction was subsequently ignored until the 1960's, when conditioned locomotor responses were established after treatment with methamphetamine (Irwin & Armstrong, 1961). The development of conditioned responses has since been found following repeated administration of amphetamine (Gold et al 1988, Pickens & Crowder 1967, Tilson & Rech 1973), methamphetamine (Irwin & Armstrong, 1961), cocaine (Barr et al 1983, Hinson & Poulos 1981, Kalivas et al 1998, Post et al 1976) and morphine (Hinson & Siegel 1983, Kamat et al 1974). These conditioned response include locomotor activation, rotational behaviour, cataleptic effects, and avoidance behaviours (Blakenship et al, 2000; Cassas et al, 1988; Cervo & Samanin, 1996; Chinen & Frussa-Filo, 1999; Pert et al 1990). These findings suggest that alteration in the processing of drug associated stimuli occurred after repeated exposure to commonly abused substances.

Conditioned place preference (CPP) studies have also demonstrated that the repeated pairing of neutral stimuli with drug stimuli will produce a conditioned response when the neutral stimulus alone is presented. In CPP paradigms, an animal is typically pre-treated with a drug in a distinct environment, and subsequent preference, as measured by either increased time or locomotor activity, for the drug treated environment and an alternative environment is measured (Tzschentke et al 2002, Tzschentke et al 2006). CPP studies have demonstrated that repeated exposure to cocaine (Brown & Fibiger 1993, Calcagnetti et al 1995, de Wit & Stewart

1983, Hemby et al 1994, Kosten & Nestler 1994, Phillips & Fibiger 1990, Ziedonis & Kosten 1991), morphine (de Wit & Stewart 1983, Duarte et al 2003, Vezina & Stewart 1987, Vezina & Stewart 1987, Wang et al 2003), amphetamine (Campbell & Spear 1999, Pucilowski et al 1995, Schildein et al 1998, Swerdlow & Koob 1984, Tran-Nguyen et al 1998), ethanol (Itzhak & Martin 2000, Rochester & Kirchner 1999) and nicotine (Dewey et al 1999, Le Foll & Goldberg 2005, Le Foll et al 2005, Spina et al 2006), produced a preference for the drug associated environment. In addition, many DA agonists have also facilitated CPP, including apomorphine (Parker 1992), quinpirole (Hoffman et al 1988), bromocriptine (Hoffman et al 1988), 7-OH-DPAT (Kling-Petersen et al 1995), while DA receptor antagonists attenuated cocaine- (Calcagnetti et al 1995), amphetamine- (Bardo et al 1999), methamphetamine- (Suzuki & Misawa 1995), and morphine- (Suzuki & Misawa 1995) produced CPP, thus, conditioned reinforcing effects appear to dopaminergically mediated.

Several different lines of evidence from self-administration studies have indicated that stimuli associated with drug taking behaviours are important components in the maintenance of drug self-administration. Discriminative stimuli have been used in many self-administration studies to facilitate and maintain drug taking of commonly abused substances such as cocaine (Balster et al 1992, Balster & Schuster 1973, Goldberg & Gardner 1981, Weiss et al 2003), amphetamine (Davis & Smith 1976, Di Ciano et al 2001), and morphine (Davis & Smith 1976). For example, repeated selective presentation of stimuli prior to cocaine availability

subsequently maintained responding in the absence of cocaine (Panlilio et al 1996, Weiss et al 2001, Weiss et al 2003). Furthermore, presentation of drug-associated stimuli produced a rapid dopaminergic response immediately prior to responding in the absence of self-administered substances (Carelli & Ijames 2000, Phillips et al 2003). The discriminative ability of drug-associated stimuli to indicate the onset or availability of self-administration is hypothesised to result in drug- taking behaviours being controlled by these associated stimuli (Beninger et al 1989, Foltin & Haney 2000). More complex discriminative stimuli studies have further demonstrated that stimuli associated with drug reinforcement can maintain responding. For example, some studies use multiple stimuli, typically a light and tone, to indicate the availability of drug reinforcement (Panlilio et al 1996, Panlilio et al 2000). The additive summation of discrete discriminative stimuli has been demonstrated to reliably increase responding maintained by cocaine and heroin at a greater magnitude than drug stimuli alone, or single discriminative stimuli (Panlilio et al 1996, Panlilio et al 2000).

Stimuli previously associated with drug self-administration also reinstated extinguished self-administration (Crombag & Shaham 2002; De Vries et al 2001; Deroche-Gamonet et al 2003; Di Ciano et al 2003; Fuchs et al 2004; Grimm et al 2002; McFarland & Ettenberg 1997; See 2002; Tran-Nguyen et al 1998; Weiss et al 2001b). This cue induced reinstatement persisted after both short and long extinction periods (Arroyo et al 1998, Meil & See 1996). The ability for drug associated stimuli to produce responding after self-administration behaviour has

been extinguished further supports the hypothesis that drug associated stimuli acquired some properties of the reinforcing substance, and that presentation lead to drug seeking.

Second-order schedules have also been used to evaluate the influence of drug -associated stimuli on responding. Second-order schedules are defined as a behavioural sequence that is created by schedule, as a single unit, in turn reinforced by another schedule of reinforcement (Kelleher 1966). Animals respond for the presentation of conditioned reinforcer commonly on a fixed ratio or fixed interval schedule. The presentation of the conditioned stimuli then initiates a second schedule controlling delivery of the unconditioned stimulus (Goldberg & Gardner 1981, Goldberg et al 1975, Kelleher 1966). Goldberg (1973) published the first study to systematically look at drug self-administration under second-order schedules. Using squirrel monkeys, animals were maintained on a FR30 or FR10 schedule of cocaine, or d-amphetamine delivery, or food delivery. The implementation of a second schedule governing delivery of the conditioned stimulus, produced elevated levels of responding prior to first delivery of the unconditioned reinforcer, and throughout self-administration sessions (Goldberg 1973, Goldberg & Gardner 1981). Second-order schedules have been shown to maintain high rates of responding, due to the intermittent presentation of conditioned stimuli, indicating that after significant experience these conditioned stimuli may have become conditioned reinforcers capable of maintaining responding (Everitt & Robbins 2000, Kelleher 1966). Accordingly, the removal of the conditioned stimulus resulted in a reduction in responding (Arroyo et

al 1998, Everitt & Robbins 2000, Goldberg et al 1981, Kelleher 1966). The use of second-order schedules was further demonstrated with other types of drugs of abuse, including morphine (Goldberg & Tang 1977), heroin (Alderson et al 2000), THC (Beardsley et al 1986) and nicotine (Dougherty et al 1981). The development of second-order schedules not only provided further evidence that alterations in the processing of drug-associated stimuli occurred, but also that drug-associated stimuli acquired reinforcing properties (Everritt & Robins, 2000).

Several self-administration studies have evaluated the effects of drug-associated stimuli on the maintenance on drug self-administration. Nicotine self-administration was reported to be susceptible to manipulation of a discriminative stimulus and simultaneous conditioned stimulus, with reductions in responding noted when either stimulus was omitted (Caggiula et al 2002). The effects of conditioned stimuli on the maintenance of cocaine self-administration have been assessed in two studies. The removal of a contingent stimulus light reduced low dose cocaine self-administration (Schenk & Partridge 2001), yet in another study, removal of the stimulus light had no effect on responding maintained by higher cocaine doses (Deroche-Gamonet et al 2002). These discrepancies may be due to differences in cocaine acquisition doses and duration of stimuli presentation. Deroche- Gamonet et al (2003) used a 2” light presentation with the dose of 1.0mg/kg/infusion during acquisition, whereas Schenk & Partridge (2003) presented the light stimuli for 12” with the dose of 0.5mg/kg/infusion used during acquisition. The prolonged light exposure may have resulted in the drug-

associated stimuli having more salience. While Deroche- Gamonet (2002) reported no influence of the light stimulus on the maintenance of cocaine self-administration, a decreased acquisition latency was noted when cocaine was paired with the light stimulus, indicating that the presentation of a previously neutral stimulus may promote the acquisition of drug self-administration.

Conditioned behaviours produced by drugs of abuse are common to all abused drugs; however few studies have assessed the conditioning properties of MDMA. One study thus far has assessed the role of a MDMA – associated stimulus in the production of a conditioned locomotor response. Animals were pre-treated with MDMA or saline in a novel environment with a distinct olfactory stimulus for five consecutive days (Gold & Koob 1989). On the sixth day animals received injections of saline and locomotor activity was recorded. Pre-treatment with MDMA produced elevated levels of locomotion when compared to saline pre-treatment (Gold & Koob 1989). CPP after MDMA administration has been demonstrated after extended withdrawal periods (Bilsky et al 1991, Bilsky et al 1990, Horan et al 2000, Marona-Lewicka et al 1996, Meyer et al 2002).

No self-administration studies have assessed the role of continued presentation of a drug-associated stimulus on self-administration maintained by MDMA. However, all published studies purporting reliable MDMA self-administration have used a discriminative or co-incidental light stimulus indicating that the presentation of a conditioned stimulus may function in the acquisition and/or maintenance of MDMA

self-administration (Lamb& Griffiths et al, Fantegrossi et al 2004; Beardsley et al, Lile et al, 2005, Trigio et al 2006). It is hypothesised that like other psychostimulants, MDMA will elicit associative learning, with conditioned stimuli acquiring reinforcing properties. To determine whether the continued presentation of an MDMA-associated stimulus has an effect on responding maintained by MDMA, animals will be trained to self-administer MDMA, and the effect of manipulation of the light stimulus, drug stimulus and light and drug stimuli on responding will be determined.

Relapse

One final characteristic of drug dependence is the inability of drug users to remain abstinent (Chang & Haning 2006, Mendelson & Mello 1996, O'Brien et al 1992, Shalev et al 2002). Resumption of drug taking behaviours after a period of abstinence is referred to as relapse. Rates of relapse amongst samples of abstinent drug abusers are as high as 80%, and relapse can occur after prolonged periods of abstinence (Childress et al 1988, Hyman & Malenka 2001, Mendelson & Mello 1996). Relapse has lead to the suggestion that drug addiction results in chronic neuropathology and neuronal adaptation (Chang & Haning 2006, Childress et al 1988, Di Chiara 1998, Koob 2006, Robinson & Berridge 1993).

Research with abstinent drug abusers has identified three main precipitators of relapse. Exposure to drug , stress, and drug-associated stimuli, have all been suggested to elicit drug craving and subsequently the resumption of drug taking behaviours (Childress et al 1986b;

Ciccocioppo et al 2001; Drummond et al 2000; Fisher et al 1998; Haney et al 1997; Hertling et al 2001; Ingersoll et al 1995; Llorente del Pozo et al 1998; Mann et al 1984; Milkman et al 1983; Miller et al 1997; O'Brien et al 1998; O'Brien et al 1991; Shaham et al 2003; Spealman et al 1999; Stewart 2000; Washton 1988; Weiss et al 2001a; Weiss et al 2001b). Exposure to drug-associated paraphernalia and cues elicited strong subjective states of craving in cocaine and heroin abusers (Carter & Tiffany 1999, Childress et al 1993, See 2002). Exposure to 'stressful' images also increased craving, and physiological arousal in abstinent cocaine users (Sinha 2001), while exposure to low doses of a previously abused substance produced craving and increased drug taking behaviours in cocaine abusers (Risinger et al 2005). Drug abusers distinguish between these types of stimuli, however, it is hypothesised that all three produce a common introceptive state that leads to drug taking behaviours (Carter & Tiffany 1999, Robinson & Berridge 1993, Robinson & Berridge 2000, Robinson & Berridge 2001, Robinson & Berridge 2003, Sinha 2001). The development of a relapse model in animals, has allowed researchers to explore possible mechanisms underlying relapse.

Initially developed by Stretch (1971) on studies using non-human primates, and subsequently by de Wit & Stewart (1981) on studies using lab rats, the reinstatement paradigm has been extensively utilised to explore mechanisms associated with relapse of psychostimulant abuse, and to a lesser extent alcohol, nicotine and heroin abuse (Ciccocioppo et al 2001; Crombag & Shaham 2002; Epstein et al 2006; Erb et al 1996; Katz & Higgins 2003; Shaham et al 2000; Shaham & Hope 2005;

Shaham et al 1994; Shaham et al 2003; ShahamY et al 1991; Shalev et al 2002; Shalev et al 2000; Weiss et al 2001a). The reinstatement paradigm has typically been composed of three phases. In phase one, animals learn to reliably self-administer a given substance. In phase two, the drug is substituted for a vehicle solution until responding for the drug stimulus is attenuated. In phase three, animals are exposed to a stimulus and reinstatement of responding is measured. The commonality between stimuli associated with relapse in humans and reinstatement in animals has lent considerable support to the validity of the reinstatement paradigm (Katz & Higgins 2003; Bossert et al 2005, Ciccocioppo et al 2002, Di Ciano & Everitt 2002, Grimm et al 2002, Liu & Weiss 2002, See et al 2003, Shaham et al 2003, Shalev et al 2002), and to the hypothesis that common neuronal mechanisms may mediate responses to stimuli that produce reinstatement (Kalivas & McFarland 2003).

Robust drug primed reinstatement of extinguished self-administration of a number of drugs including cocaine; heroin, alcohol and nicotine has been reported (Shalev et al 2002). Drug-primed reinstatement increased in magnitude with the dose of drug (de Wit & Stewart 1981, Shalev et al 2002). Higher doses of a drug prime also produced elevated levels of responding maintained for a longer duration (de Wit & Stewart 1981). It may be argued that administration of a drug stimulus, particularly psychostimulants produces a general increase in motor activation resulting in increased responding. Analysis of active and inactive lever responses, however, has indicated that responding is selective to the lever

previously associated with drug self-administration (Shalev et al 2002, Stewart 2000).

Reinstatement produced by drug primes has been attributed to dopaminergic mechanisms. Priming injections of DA agonists, including amphetamine, 7-OH-DPAT, GBR 12909 and methylphenidate (Khroyan et al 2000, Schenk & Partridge 1999, Self et al 1996, Shaham et al 2003) reinstated previously extinguished responding. Activation of the D2-like receptor has been implicated in reinstatement. The D2-like selective agonists, quinpirole and bromocriptine, reinstated responding previously maintained by cocaine and heroin (De Vries et al 2002, Wise et al 1990). Furthermore, pre-treatment with the D2-like receptor antagonists, sulpride, haloperidol and raclopride attenuated reinstatement produced by drug primes (Anderson & Pierce 2005, Ettenberg et al 1996, Shaham & Stewart 1996). Pre-treatment with D1-like receptor antagonist, SCH23390 attenuated cocaine induced reinstatement (Ciccocioppo et al 2001, Norman et al 1999), but reports of the effects of D1-like receptor agonists have been mixed. The D1-like agonist, SKF 81297 reinstated responding previously maintained by cocaine (Koeltzow & Vezina 2005), but another D1-like agonist, SKF 82958 did not reinstate extinguished drug-taking behaviour (De Vries et al 1999, Self et al 1996). Furthermore, pre-treatment with D1-like agonist attenuated cocaine primed reinstatement (Khroyan et al 2000, Self et al 1996). Thus, activation of the D2-like receptors potentiated and induced drug-primed reinstatement, while activation of the D1-like receptor appeared to inhibit

reinstatement (Kalivas & McFarland 2003, Khroyan et al 2000, Self et al 1996, Shaham et al 2003).

Relapse after MDMA exposure?

The current status of knowledge regarding MDMA relapse or reinstatement is limited. One longitudinal human study has assessed long-term MDMA use and relapse (von Sydow et al 2002). A small proportion of people (0.6% of total sample N=3021), reported difficulty abstaining from MDMA consumption; dependence and relapse indicators in this sample were stable over time (von Sydow et al 2002), suggesting that MDMA may have a relapse potential in a small proportion of people. Unfortunately, clinical and retrospective studies have repeatedly omitted the systematic assessment of MDMA relapse and associated parameters.

Preclinical studies have also failed to evaluate the relapse potential of MDMA. No studies have yet evaluated MDMA primed reinstatement after extinction of MDMA self-administration. This paucity of knowledge is partially attributable to the limited number of laboratories studying MDMA self-administration. One study assessing the effects of MDMA administration on the reinstatement of prior amphetamine self-administration reported that MDMA reinstated responding previously maintained by amphetamine in animals that had been pre-treated with MDMA, but not in animals without prior MDMA experience (Morley et al 2004), suggesting that MDMA can induce reinstatement after prior MDMA exposure.

Determination of the relapse potential of MDMA is an important and novel contribution to the MDMA literature. Assessments of MDMA

primed reinstatement can be used to further clarify the abuse potential of MDMA and to further understand mechanisms governing MDMA use. A determination of whether responding previously maintained by MDMA, can be reinstated with DA agonists can provide information regarding the neural mechanisms underlying repeated MDMA use. Furthermore, the demonstration of DA primed reinstatement would lend support to the hypothesis of a common neurobiological mechanism underlying reinstatement, and relapse. A simple evaluation of whether MDMA can prime responding after extinction of self-administration behaviours will be assessed using a reinstatement paradigm.

Aims

In summary, the aim of this thesis is to determine if MDMA is a reinforcer of responding, and to explore some of the basic parameters of MDMA self-administration. Four fundamental features of self-administration will be assessed. Firstly, the reliability of MDMA self-administration will be determined using a variety of self-administration techniques. Secondly, the role of DA in the maintenance of MDMA self-administration will be evaluated. Thirdly, the development of conditioned responding after MDMA self-administration will be evaluated. Finally, the ability for MDMA administration to elicit reinstatement of responding previously maintained by MDMA will be assessed.

Chapter 2 - Method

Subjects

Subjects were male, Sprague Dawley rats bred in the vivarium at Victoria University of Wellington. Rats were housed in hanging polycarbonate cages in groups of 4-6 until they reached weights of 200-250gm (locomotion experiments) or 300-325 gm (self-administration experiments). Thereafter, they were separated and housed in isolation. The animal colony was temperature- (21 ° C) and humidity- (74%) controlled, and food and water were available ad libitum except during testing. The colony was maintained on a 12:12-h light/dark cycle with lights on at 0700. All procedures were in accord with OLAW regulations (USA) and were approved by the Animal Ethics Committee of Victoria University of Wellington.

Surgery for self-administration studies:

Rats in the self-administration experiments were implanted with an indwelling silastic catheter in the right jugular vein. Animals received atropine (1.0mg/kg; IP) 30 minutes prior to anesthesia. The rats were deeply anesthetized with ketamine (60.0 mg/kg, IP; Kelburn Vet Centre, Wellington, New Zealand) and sodium pentobarbital (20.0 mg/kg, IP; Kelburn Vet Centre, Wellington, New Zealand). The external jugular vein was isolated, the catheter was inserted and the distal end (22 ga stainless steel tubing) was passed subcutaneously to an exposed portion of the skull where it was fixed to embedded jeweler's screws with dental acrylic.

Each day, the catheters were infused with 0.1 ml of a sterile saline solution containing heparin (30.0 U/ml; Kelburn Vet Centre, Wellington, New Zealand), Penicillin G sodium (250,000 U/ml Kelburn Vet Centre, Wellington, New Zealand) and streptokinase (8000/ml Kelburn Vet Centre, Wellington) to prevent infection and the formation of clots. The rats were allowed five days post-surgery for recovery prior to behavioral testing.

Apparatus

Self-administration

Self-administration training and testing occurred in test chambers (Med Associates, ENV 001; Vermont, USA) enclosed in sound attenuating closets. The testing room containing the 32 test chambers was humidity- (74%) and temperature- (21 ° C) controlled. Each chamber was equipped with 2 levers and a stimulus light. Depression of one lever (the active lever) resulted in an infusion of drug. Depression of the other lever (the inactive lever) was without programmed consequence. Infusions were in a volume of 0.1 ml delivered over 12.0 sec via Razel pumps equipped with 1.0 rpm motors and 20.0 ml syringes. Coincident with each infusion was the illumination of a stimulus light located above the active lever.

LocomotionEight Open field chambers (Med Associates; Vermont, USA) equipped with banks of 16 photocells on each wall were used to measure horizontal locomotion. The open field boxes were

interfaced with a computer and data were obtained using Med Associates software. Each activity chamber was enclosed in a sound attenuating box (Med associates; Vermont USA). As the animal moved around the chamber, broken light beams were counted.

All testing was conducted during the light cycle between 1000 and 1600 hours. A red house light was illuminated during testing and white noise was also continually present to mask extraneous disturbances.

General Self-administration Procedures

Unless otherwise stated, each session began with an experimenter-administered infusion of MDMA or cocaine. Thereafter, infusions were delivered according to an FR-1 schedule of reinforcement by depression of the active lever. Depressions on the inactive lever were recorded but had no programmed consequence. Self-administration was considered acquired when during a session (1) at least 7 active lever responses were produced, and (2) the ratio of active: inactive lever responses was at least 2:1. When these criteria were met for at least three consecutive days with less than 20% variation in active lever responses across days, the drug dose was halved. Training continued until there was less than 20% variability in the number of responses produced across three consecutive testing days.

Drugs

For self-administration studies, racemic MDMA HCL (ESR Ltd, Porirua, New Zealand) and cocaine HCL (Merek Pharmaceuticals.

Palmerston North, New Zealand) were dissolved in sterile 3u /heparinzed saline (0.9%NaCl). For locomotor activity studies, racemic MDMA was dissolved in saline (0.9% NaCl). MDMA purity was examined by gas chromatography/mass spectrometry and NMR, and assessed at greater than 98%. Intravenous infusions were delivered in a volume of 0.1 ml and intraperitoneal injections were delivered in a volume of 1.0 ml/kg.

SCH 23390 (NIDA, USA), eticlopride (SIGMA; Australia), SKF 81297 (Tocris, Natick, Massachusetts) were dissolved in 0.9% saline. Subcutaneous (SC) or Intraperitoneal (IP) injections were in a volume of 1 ml/kg. All drug doses refer to the salt.

Chapter 3- Experiment 1

Acquisition and maintenance of MDMA self-administration

The aim of the first experiment was to determine if MDMA can function as a behavioural reinforcer . A substitution procedure was used, as other published studies have reported MDMA self-administration under this procedure (Beardsley et al 1986, Fantegrossi et al 2002, Fantegrossi 2002, Lamb & Griffiths 1987, Ratzenboeck et al 2001). Factors involved in the maintenance and acquisition of MDMA self-administration were will also determined.

Method

Procedures

Acquisition of MDMA self-administration in either drug naïve rats (n=11), or animals that had received cocaine self-administration training (0.5 mg/kg/infusion; 5-12 daily 2-h tests; N=5) was assessed. Drug naïve rats received 26 daily tests. MDMA (1.0 mg/kg/infusion) was available for self-administration during daily 2-h (n=5) or 6-h (n=6) sessions for 11 days. Most responses were recorded in the initial hour of testing and there was no difference in responding as a function of test duration. Therefore data obtained from the 11 initial self-administration days for both groups were combined. Animals that had received 6-h sessions were run for a further 8 daily 6-h sessions with the dose of 0.5mg/kg/infusion MDMA available. The test session was then reduced to 2-h duration and saline was substituted for MDMA during the next two

test days. This was followed by 5 days of 2-h tests during which the dose of 0.5mg/kg/infusion was again available. Rats (n=5) first trained with cocaine self-administration (0.5mg/kg/infusion; FR1; 8-12 days) received subsequent 6-h tests of MDMA self-administration (1.0mg/kg/infusion).

Eight rats received additional tests to further examine the dose dependant nature of responding maintained by MDMA. For these tests, different doses of MDMA (0.25-2.0mg/kg/infusion) were available during daily 2-h sessions. The starting dose for MDMA self-administration was 2.0mg/kg/infusion and the dose was reduced by half every two successive sessions. Data from the second day of each dose were used for analyses. A final additional test measured responding maintained by MDMA (1.0mg/kg/infusion) during a 24-h test (n=5). For these tests, the test chambers were equipped with a water bottle and food tray.

To further determine whether MDMA reliably reinforced operant responding, animals (n=12, 3/per triad) were yoked and operant response rates were assessed for rats that received contingent MDMA, non-contingent MDMA, or vehicle. In each triad, one animal responded contingently for MDMA (1.0mg/kg/infusion), the second animal received a non-contingent infusion of MDMA based on the behaviour of the contingent rat, while the third animal received non-contingent saline based on the behaviour of the contingent rat. All animals were run for 20 days in daily 2-h sessions. No prior training had occurred for any

animals, and all subjects were drug naïve prior to beginning the experiment. Due to technical difficulties one animal in the non-contingent MDMA group had to be removed from the study, therefore final group numbers were; contingent MDMA (n=4), non-contingent MDMA (n=3), non-contingent saline (n=4).

In order to establish whether MDMA self-administration was sensitive to schedule manipulation (see Table 1), a group of drug naïve animals (n=12) was trained to self-administer 1.0mg/kg/infusion MDMA during daily 6-hr sessions under an FR1 schedule. The dose was then reduced to 0.5 mg/kg/infusion. Once the number of responses showed less than 20% variability over three consecutive days, the schedule was then increased to FR2 and finally FR5. MDMA was then replaced with vehicle solution and the light stimulus was removed during the next two self-administration sessions. Thereafter, responding was reinforced with MDMA (0.5mg/kg/infusion) and the light stimulus, according to an FR-5 schedule of reinforcement.

MDMA dose (mg/kg/infusion)	1.0	0.5	0.5	0.5	saline	0.5
FR schedule	FR1	FR1	FR2	FR5	FR1	FR5

Table 1: Procedure for schedule manipulation

A final of group of animals (n=6) was trained to self-administer MDMA as above. Following training the schedule was then changed to a progressive ratio schedule. Under this schedule, the first response

produced an infusion of MDMA (0.5 mg/kg/infusion), thereafter the FR requirements increased by FR8 for each successive reinforcer. The session concluded after one hour had elapsed since the last ratio completion. The "break point" was defined as the last ratio completed. The total number of infusions was also recorded. The initial dose available was 0.5mg/kg/infusion MDMA, and then the dose was changed to 0.25mg/kg/infusion or 1.0mg/kg/infusion. Rats were tested with at least two doses of MDMA and two animals received three doses. Final group number for each dose were 0.5mg/kg/infusion (n=5), 0.25mg/kg/infusion (n=4), 1.0mg/kg/infusion (n=4)

Data Analysis:

Data from self-administration experiments were subjected to a two-way between measure ANOVA (days X pre-exposure condition). Dose dependant responding was analysed using a two- way repeated measure ANOVA (dose X lever). To compare contingent MDMA, non-contingent MDMA and saline response rates in yoked animals, a 2-way repeated measures ANOVA (Day x Group) was performed. Schedule dependent responding were analyzed using repeated measures ANOVA to compare the number of responses produced on the "Active" lever for each day. For the progressive ratio experiments, break points, as defined by the highest number of response recorded for a single infusion of MDMA were measured averaged over three days for each dose that a subject self-administered.

All post-hoc analyses were performed using paired-samples t-tests (within-subject design), tukey's (between subject designs) or simple

contrasts (repeated measures). Results were deemed significant at a level of $p<0.05$.

Results

Figure 1 shows responding maintained by MDMA for rats that were initially drug naïve. Responding on the inactive lever remained low throughout the 26 days of testing. During the first 6 days of testing when 1.0mg/kg/infusion MDMA was available, responding on both the inactive and active lever remained low. Between days 7-11, responding maintained by 1.0mg/kg/infusion MDMA increased and a preference for the active lever developed ($F (1, 11) =5.844$, $p<0.039$). When the dose of MDMA was reduced by half to 0.5mg/kg/infusion between days 12-19, responding on the active lever increased further over days, ($F (7, 30) =2.859$, $p<0.022$), and a preference for the active lever was demonstrated ($F (1, 5) = 9.375$, $p<0.038$). Saline substitution on days 20-21 produced a reduction in responding when compared to the two prior self-administration sessions ($F(3,12) = 4.449$, $p<0.025$), and responding was reinstated when MDMA was made available on days 22-26 ($F(3,12)= 5.162$, $p<0.016$).

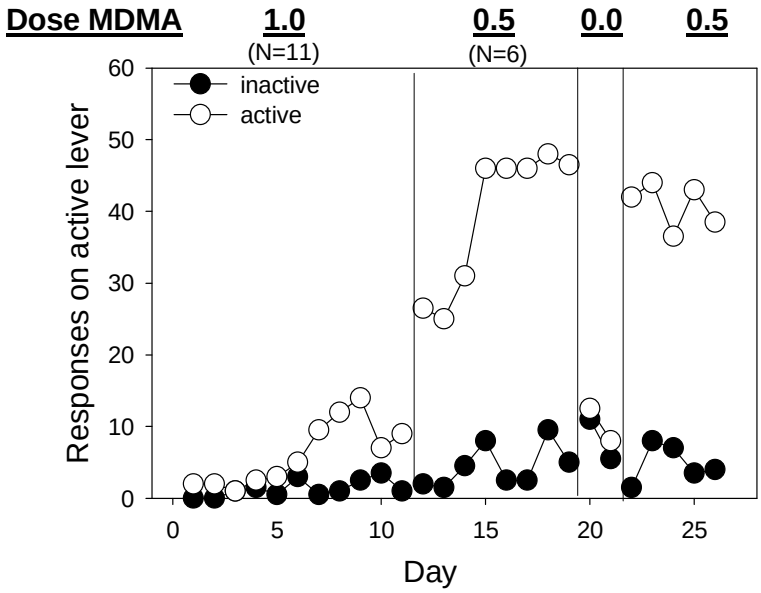


Figure 1. From Schenk et al (2003): Acquisition of MDMA self-administration by drug naïve rats. Mean response (+SEM) on the active and inactive levers are presented as a function of day of testing and dose of MDMA.

Figure 2 compares active and inactive lever responding maintained by MDMA (1.0mg/kg/infusion) during the initial six 6-h daily tests for animals that were drug-naive and animals that had prior cocaine self-administration experience. Active lever responding of cocaine-trained rats was significantly higher ($F(1,8)=5.137$, $p<0.05$) when compared to drug –naïve animals.

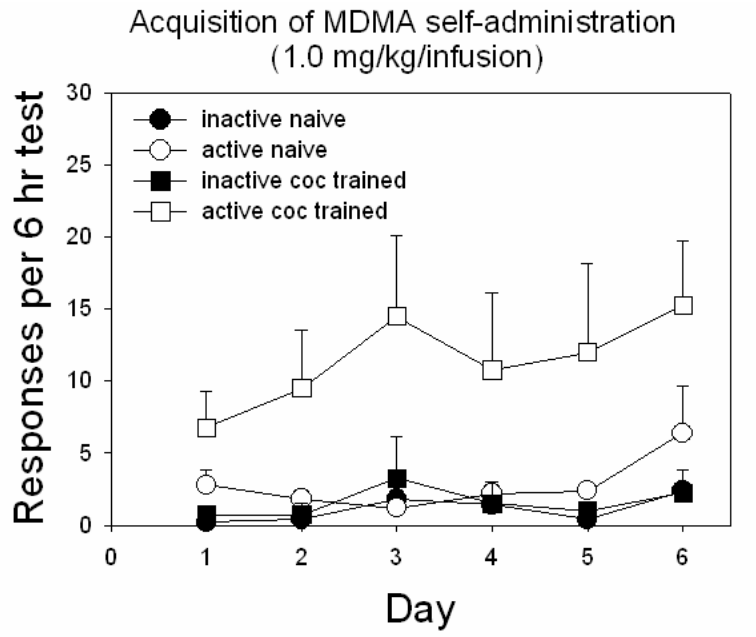
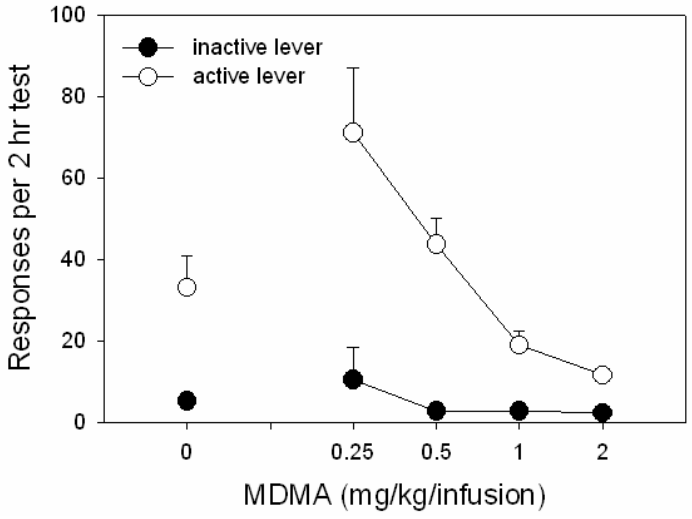


Figure 2. From Schenk et al (2003): Acquisition of MDMA self-administration for animals that had received either cocaine self-administration (n=4), or drug naïve animals (n=6). Mean responses (+SEM) on the active lever and inactive levers are presented as a function of day of testing.

Figure 3 shows responding as a function of MDMA dose. Decreasing the dose of MDMA produced an increase in responding ($F(4,12)= 9.767$, $p<0.01$). Post hoc simple contrasts revealed that responding maintained by 2.0mg/kg/infusion was significantly lower than that maintained by 1.0mg/kg/infusion ($p<0.049$), 0.5mg/kg/infusion ($p<0.029$) and 0.25mg/kg/infusion ($p<0.003$). No difference was found

between responding maintained by saline and 2.0mg/kg/infusion MDMA



(p=0.06).

Figure 3. From Schenk et al (2003): Responding maintained by different doses of MDMA (n=5). Symbols represent the mean number of responses (+SEM) during daily 2 hour sessions.

Figure 4 shows the pattern of responding during each 2-h daily self-administration for a representative rat. Higher doses of MDMA were self-administered primarily during the first 30min of each session. Self-administration of the lower dose of MDMA (0.25mg/kg/infusion) produced persistent responding throughout the session. The number of infusions maintained by saline was comparable to the number of infusions maintained by the higher doses of MDMA; however, responding maintained by 2.0mgkg/infusion MDMA was elevated in the first hour and then reduced in the second hour. Responding maintained by saline was sporadic throughout the session.

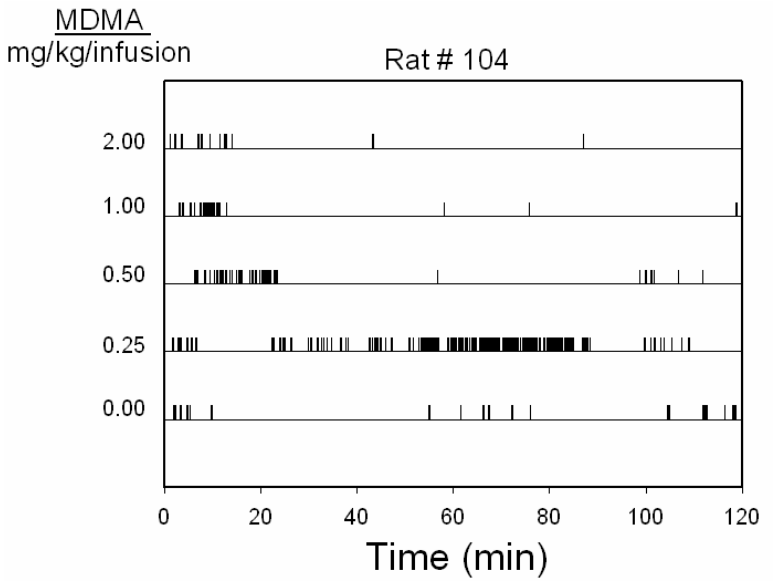


Figure 4. From Schenk et al (2003): Temporal pattern of responding during a 2-h session maintained by different doses of MDMA for a representative rat. Each vertical dash represents an infusion of MDMA

Figure 5 shows the average number of active lever responses produced during each hour of the 24-h session. One of the eight animals died after 11.5 hours. During the initial hour, responding was elevated (figure 5; insert) and during the subsequent hours responding was reduced and stable at 2-4 responses per hour. For one animal responding was increased in the 20th hour.

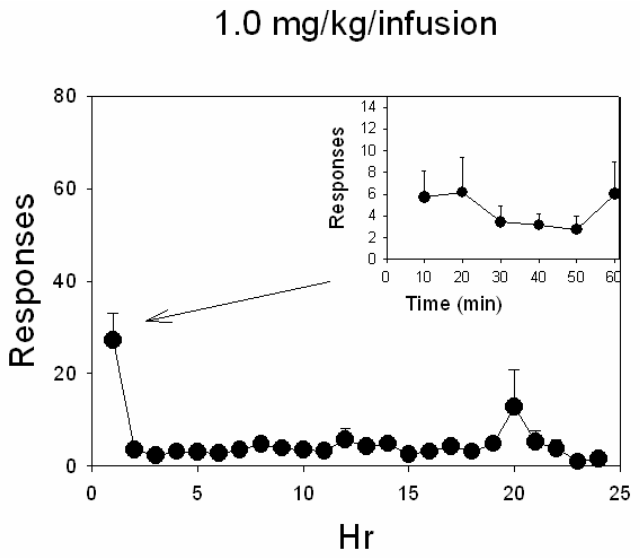


Figure 5. From Schenk et al (2003): temporal pattern of responding maintained by 1.0mg/kg/infusion during a 24-h self-administration session. The average number of responses (+SEM) during each hour of the test is shown. One animal died after approximately 11.5h of self-administration. The insert shows the average number of responses (+SEM) during each 10-min interval of the first hour of testing.

MDMA self-administration was acquired in animals receiving MDMA infusions and co-incidental light presentation, contingent on lever depression (figure 6). In comparison, animals receiving non-contingent MDMA or saline demonstrated low levels of responding on both the active and inactive lever. The average number of MDMA infusions (0.5mg/kg/infusion) received by contingent and non-contingent animals was 268.5 (SEM=49.97) during the 20 days of testing. Repeated measures analyses revealed a significant interaction between self-administration days and lever, and group ($F(38,152)=2.574$, $p<0.001$).

A significant difference between groups was found ($F(2,8)=8.985$, $p<0.009$), with post-hoc analyses revealing differences between contingent and non-contingent MDMA groups ($p<0.007$). In addition, an interaction between day and group was revealed ($F(38,152) = 2.057$, $p<0.001$). Post hoc simple contrasts revealed differences from contingent MDMA ($p<0.05$), for both non-contingent saline and non-contingent MDMA.

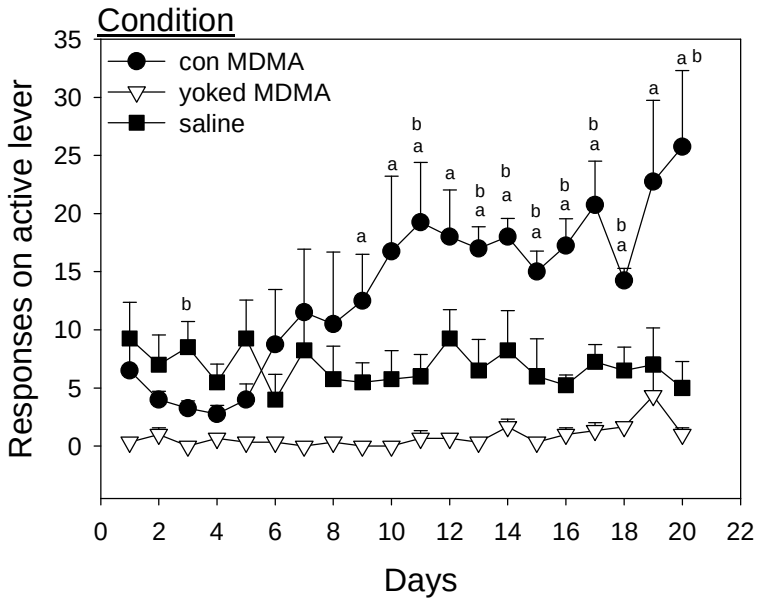


Figure 6. Responding on the active lever by animals receiving, 1) contingent MDMA infusions, 2) non-contingent MDMA infusions, and 3) non-contingent saline infusions.

Lower case letters a) Denotes significant differences in responding on the active lever between animals receiving non-contingent and contingent MDMA, b) Denotes significant differences in responding in animals receiving contingent MDMA and non-contingent saline.

Figure 7 shows that responding on the inactive and active levers varied as function of group ($F(2,8)=7.639$, $p<0.014$). Subsequent within-subject repeated measures analyses for each group revealed a preference for the active lever for animals receiving contingent MDMA ($F(1,3)=4.557$, $p<0.032$), whereas non-contingent MDMA and non-contingent saline failed to show a lever preference ($p=0.276$, $p=0.072$ respectively).

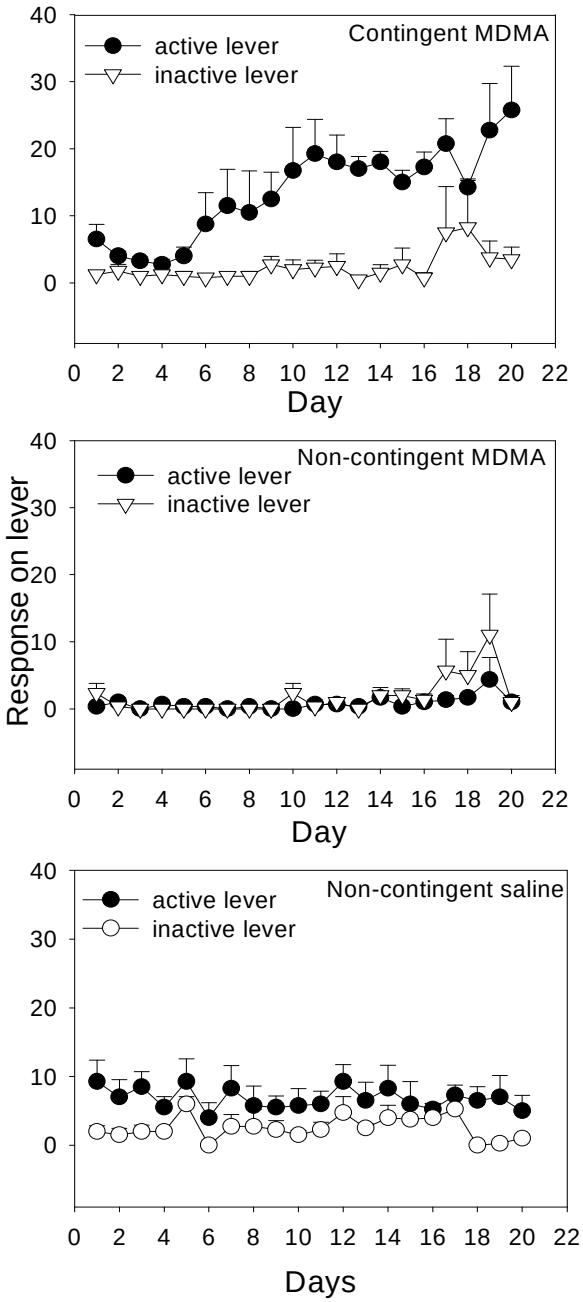


Figure 7. Symbols represent the mean active and inactive lever responses per day (+SEM) for each group; Contingent MDMA, non-contingent MDMA, non-contingent saline.

Figure 8 shows active lever responding on (1) the last day of testing under the various schedules of reinforcement (FR1, FR2, and FR5), (2) the two days when saline was substituted for MDMA and (3) the day when MDMA and the light stimulus were reintroduced as reinforcers of operant responding (FR5). Responding increased as FR value increased, decreased when MDMA and the light stimulus were removed and was reinstated to a comparable level when MDMA and the light stimulus were again available to reinforce operant responding ($F(5,55)=24.172$, $p<0.001$). Post hoc simple contrasts revealed no difference between baseline FR5 responding and re-initiation FR5 responding, or between saline days.

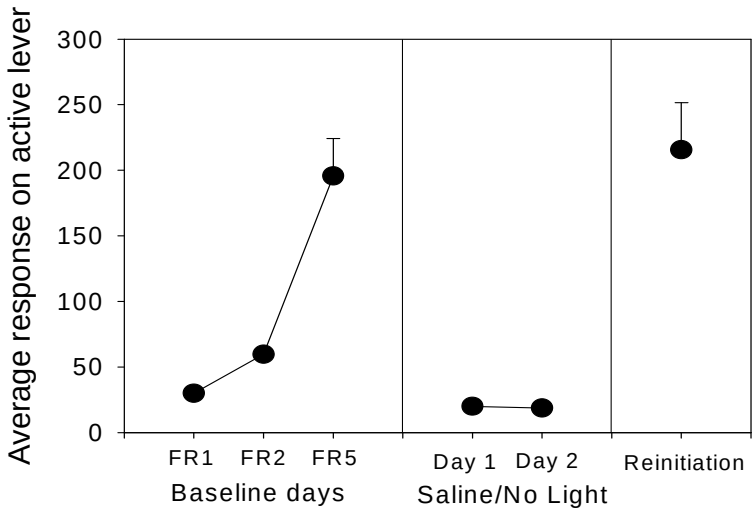


Figure 8. From Daniela et al (2006): Effects of increasing demand (FR1, FR2, FR5) and saline substitution on MDMA self-administration. Symbols represent the mean number of responses per 2 hr session (+ SEM).Figure 9 shows responding maintained on a progressive ratio schedule of reinforcement. Breakpoint, and the number of infusions self-administered increased as the dose of MDMA available was increased (breakpoint ($F(2,10)=7.0321$, $p<0.012$), number of infusions ($F(2,10) = 7.032$, $p<0.012$)). Responding as a function of dose approached significance ($p<0.053$). Post-hoc analysis revealed a significant difference between 0.25mg/kg/infusion MDMA and 1.0mg/kg/infusions for both breakpoint ($p<0.01$) and number of infusions received ($p<0.01$).

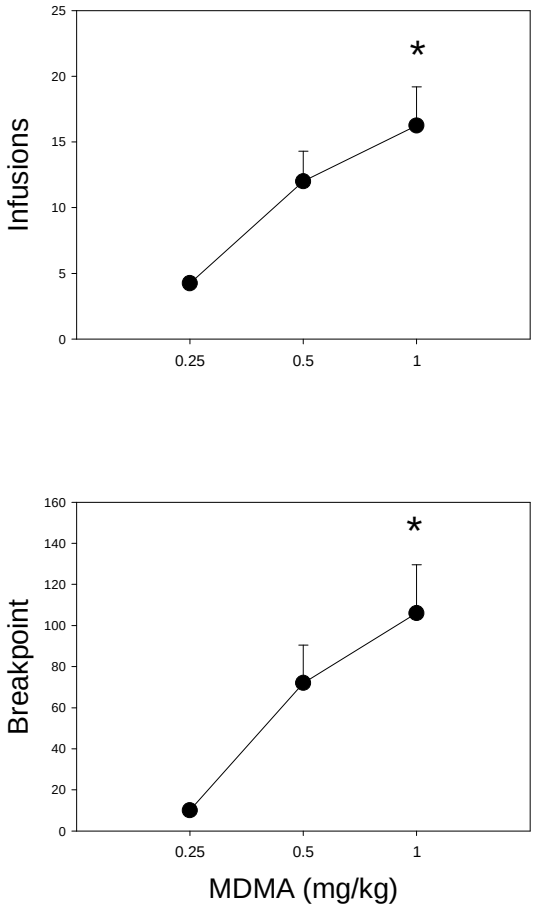


Figure 9. Number of infusions and breakpoints maintained under a progressive ratio schedule of reinforcement. Symbols represent the mean number (+/- SEM) of responses, breakpoint and infusion totals received, for each dose of MDMA. * denotes significant difference from 0.25mg/kg/infusion MDMA

Summary

MDMA was reliably self-administered. MDMA was self-administered by drug naïve and cocaine- trained animals, but those with prior cocaine self-administration experience acquired MDMA self-

administration with decreased latencies. A preference for the active lever was produced only when drug delivery was dependent on lever depressions. Rats that received non-contingent MDMA or vehicle injections failed to demonstrate a preference for the active lever. MDMA self-administration was dose dependent, when either FR or PR schedules were imposed. Responding for MDMA increased as the FR ratio was increased, decreased when MDMA was substituted for a vehicle solution, and then increased when MDMA was reintroduced. MDMA self-administration was demonstrated to be sensitive to demand, as measured by a progressive ratio schedule of reinforcement. Under the current parameters, MDMA reliably reinforced responding, and was self-administered by animals under a variety of conditions.

Chapter 4- Experiment 2

Role of Dopamine in MDMA self-administration

The aim of the second experiment was to determine if MDMA self-administration wass sensitive to dopaminergic manipulation. The activation of dopaminergic substrates is a common feature to all drugs of abuse (Carelli 2004; Carr et al 1988; Di Chiara 1999; Di Chiara et al 2004; Fibiger et al 1992; Koob & Hubner 1988; Koob & Weiss 1990; Pulvirenti & Koob 1990; Ranaldi et al 1999; Robinson & Berridge 1993; 2000; Sahakyan & Kelley 2002; Salamone & Correa 2002; Wise 1984; 1987; 1998; Wise & Bozarth 1982; 1985; Wise et al 1995b; Wolf 2002). In order to obtain effective dose and pre-treatment times to be used in subsequent self-administration experiments, preliminary tests on the effects of the D1-like antagonist SCH23390, and the D2-like antagonist eticlopride, on the locomotor activating effects of MDMA were conducted. Thereafter, these doses were used in self-administration experiments.

Method - locomotion studies

Procedure

Locomotion

Prior studies conducted in our lab have demonstrated that 20mg/kg MDMA produced maximal locomotor response (Brennan et al, 2006). Accordingly, the present study examined the effects of SCH

23390 and eticlopride on hyperactivity produced by 20.00 mg/kg MDMA.

Separate groups of rats (n=6) were injected with SCH 23390 (0.01-0.08 mg/kg; SC), eticlopride (0.125- 1.0 mg/kg; IP) or the saline vehicle and were immediately placed in the activity boxes. After a 15- (SCH 23390) or 30- (eticlopride) min pre-treatment period, they received an injection of MDMA (20mg/kg; IP) and activity counts were measured for an additional 60 min.

In order to determine whether SCH23390 or eticlopride altered basal levels of activity, the lowest doses of SCH23390 (0.02mg/kg) or eticlopride (0.05mg/kg) that produced an effect on MDMA- induced hyperactivity were administered to animals that received saline. Animals (n=8/per group) were placed into the activity chambers and received immediate injections of either saline or SCH23390 (0.02mg/kg; n=8) saline/eticlopride (0.05mg/kg; n=8) or saline/saline (n=8). Activity counts were recorded every 5 minutes for 60 minutes.

Data Analysis

Activity data were analyzed using repeated measures ANOVA (Antagonist dose X Time). Post hoc tukey tests were then performed to determine direction and variables of significance.

Results - locomotion studies

Figure 10 shows the effect of SCH 23390 on MDMA-produced hyperactivity as a function of dose and time. The insert shows the total counts during the 60 min period following the MDMA injection for

groups that received various doses of the antagonist. SCH 23390 produced a dose-dependant decrease in MDMA-produced hyperactivity ($F(4,16) = 4.274$, $p<0.05$). Post-hoc analyses revealed that decreases produced by doses equal to or greater than 0.02 mg/kg SCH23390 were significant ($p<0.05$). The interaction between dose and time was also significant ($F(44, 253) = 2.457$, $p<0.001$) and post-hoc analyses revealed that the decreases were produced primarily during the first 30 min following the injection of MDMA ($p<0.05$).

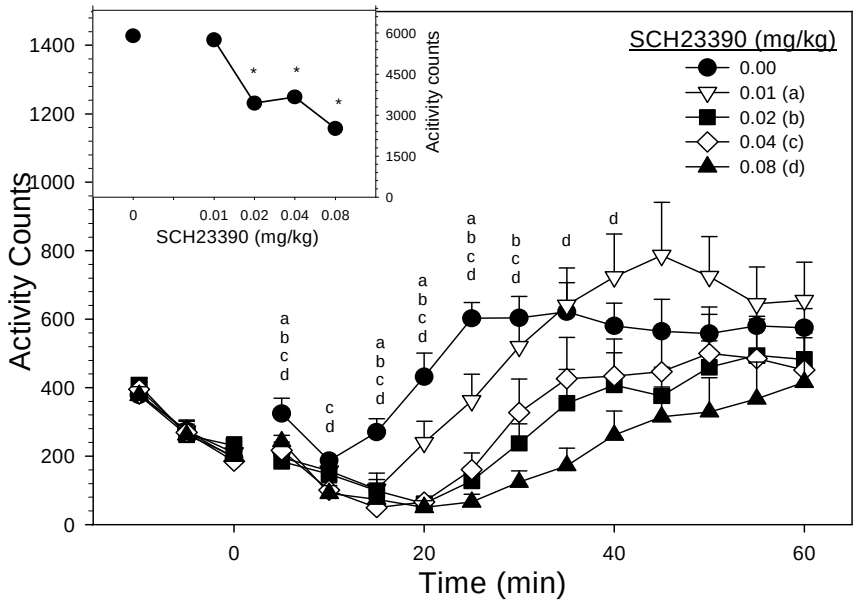


Figure 10. From Daniela et al (2004). Effect of SCH23390 (0.00mg/kg – 0.08mg/kg) on locomotor activity produced by MDMA (20mg/kg) administration. SCH23390 was injected at time -15min and MDMA was injected at time 0 min. Symbols represent the mean number of activity counts (+/- SEM) as a function of SCH23390 dose and time. Lower case

letters denote significant decrease ($p<0.05$) from 0.0mg/kg SCH23390. Insert: total activity counts produced by each group during the 60 min period following MDMA injection.

Figure 11 shows the effect of SCH 23390 (0.02 mg/kg) or the saline vehicle on baseline activity levels. For both groups, activity levels are initially high and decrease progressively throughout the session. Activity levels of the SCH 23390 group were comparable to activity levels of the control group and there was no significant decrease as a result of antagonist treatment ($F(1,14)=0.105$, NS).

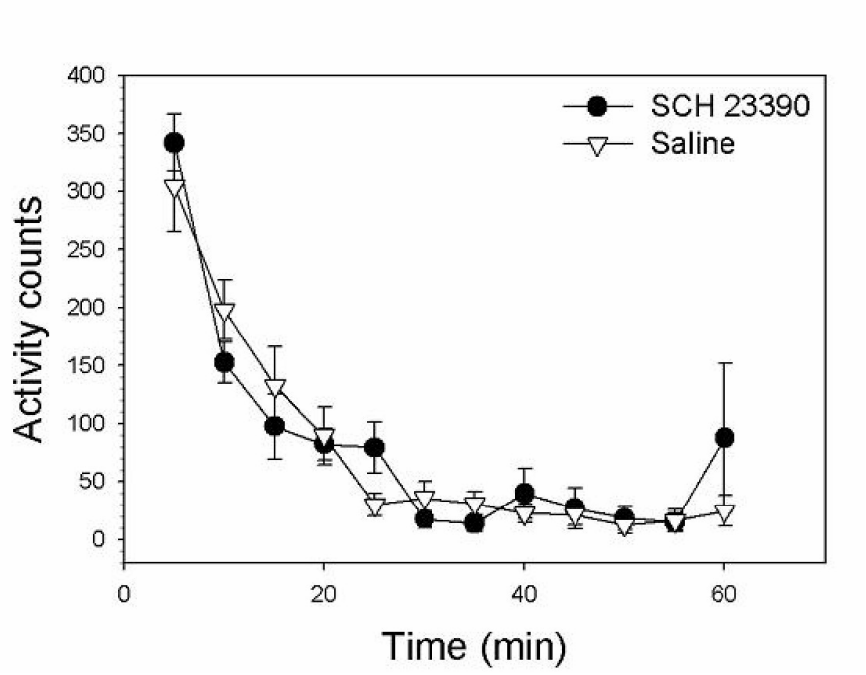


Figure 11. From Daniela et al (2004). Effects of SCH23390 (0.02mg/kg) on baseline locomotor activity. SCH23390 or the saline vehicle was

administered at time 0. Symbols represent the mean activity count (+ SEM).

Figure 12 shows the effect of eticlopride on MDMA-induced hyperactivity as a function of time. MDMA-induced locomotor activity was dose dependently reduced by eticlopride ($F(4, 16) = 5.345$, $p<0.01$). In addition, eticlopride dose dependently increased the latency to MDMA- induced hyperactivity ($F(11,264)= 18.686$, $p<0.001$). Significant decreases were produced by eticlopride doses greater than 0.025 mg/kg ($p<0.05$). The effects were apparent 20 min following the MDMA injection and persisted throughout the 60 min test.

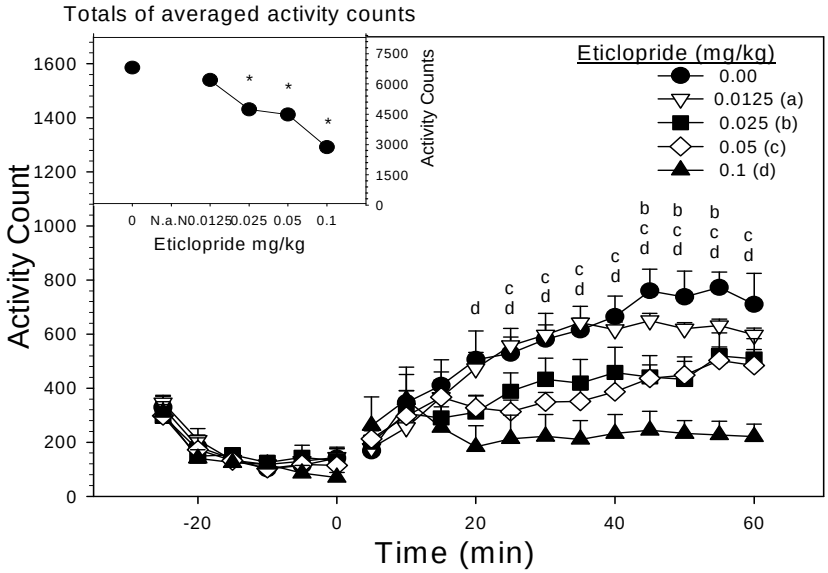


Figure 12. Effects of eticlopride (0.0mg/kg- 0.1mg/kg) on MDMA-induced (20mg/kg) locomotor activity. Eticlopride was injected at time -30 min and MDMA was injected at time 0 min. Symbols represent the

mean number of activity counts (+/-SEM) as a function of eticlopride dose and time. Lower case letters denote significant difference from 0.0mg/kg eticlopride. Insert: total activity counts produced by each group during the 60mins following MDMA injection.

Figure 13 shows the effect of eticlopride (0.05 mg/kg) or the saline vehicle on baseline activity levels. For both groups, activity levels are initially high and decrease progressively throughout the session. Activity levels of the eticlopride group were comparable to activity levels of the control group and there was no significant decrease as a result of antagonist treatment (F(1,14)=0.178, NS).

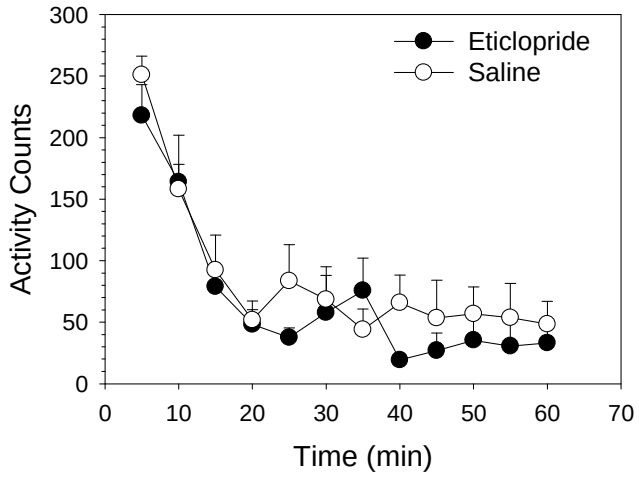


Figure 13. Figure 2 Effects of eticlopride (0.02mg/kg) on baseline locomotor activity. Eticlopride or the saline vehicle was administered at time 0. Symbols represent the mean activity count (+ SEM).

Method - self-administration

Procedure

Self-administration

Drug naive animals were trained to self-administer MDMA and responding was stabilized. Tests were conducted to assess the effect of SCH23390 (0.02 mg/kg, SC) or eticlopride (0.05mg/kg, IP) on responding maintained by a range of MDMA (0.25-2.0 mg/kg/infusion) doses. These doses were chosen based on the results of the hyperactivity tests since they produced minimal effects on baseline activity but attenuated MDMA-produced hyperactivity.

A recurring series of tests comprised of baseline and test days was used. At least two days of baseline testing were interspersed between tests of the antagonist effect. Antagonists were administered only when there were at least two prior and consecutive baseline tests during which the number of responses did not vary by more than 20%.

Initially, the dose of MDMA available for self-administration was 0.5 mg/kg/infusion. Once the effect of SCH 23390 or eticlopride on responding maintained by this dose of MDMA was measured, the MDMA dose was either increased or decreased for individual subjects and the effect of the antagonist on responding maintained by this new dose of MDMA was assessed. Data for all doses of MDMA were obtained for some of the rats (n=4) but for others tests of the effects of antagonists on responding maintained by a subset of the doses of MDMA were obtained (n=6). Final group numbers were; 0.25 mg/kg/infusion (n=7), 0.5mg/kg/infusion (n=8), 1.0mg/kg (n=7), 2.0mg/kg/infusions

(n=7). The effects of eticlopride (0.05mg/kg) on responding maintained by 0.25-2.0mg/kg/infusion MDMA were assessed in one group of animals (n=4).

Further tests were also conducted on separate groups of rats to assess the effects of various doses of SCH23390 (0.02-0.005mg/kg) on responding maintained by 0.5 (n =5), 1.0 (n=4) and 2.0mg/kg MDMA (n=4). Effects of eticlopride (0.05-0.125mg/kg) on responding maintained by 1.0mg/kg/infusion were also measured (n=6/group).

Data Analysis

The effects of SCH23390 on MDMA self-administration data were determined using an ANOVA (Dose). Eticlopride self-administration data were analysed using a repeated measures ANOVA (dose eticlopride X MDMA dose). Post-hoc t-tests were subsequently performed to determine change between baseline and antagonist treatment for each dose. Baseline data were obtained from the last self-administration day prior to antagonist pre-treatment.

Results - self-administration

Figure 14 shows the effect of SCH23390 (0.02 mg/kg) on responding maintained by a range of self-administered MDMA doses. MDMA-reinforced responding decreased as MDMA dose increased ($F(3, 25) = 12.959$, $p<0.005$). Responding maintained by 0.25mg/kg/infusion MDMA was elevated significantly when compared to

responding maintained by 2.0mg/kg/infusion ($p<0.05$) and 1.0mg/kg/infusion ($p<0.05$). Furthermore, responding maintained by 0.5mg/kg/infusion was also elevated when compared to 2.0mg/kg/infusion MDMA ($p<0.013$). SCH23390 (0.2mg/kg) produced a rightward shift in the MDMA dose-effect curve. ANOVA revealed a significant interaction between MDMA and SCH 23390 dose ($F(3, 25) = 8.234$, $p<0.001$). Paired-sample t-tests revealed that responding maintained by 0.25mg/kg/infusion MDMA was attenuated by SCH23390 ($t(6)= 4.494$, $p<0.004$) whereas responding maintained by 1.0 ($t(6)=2.509$, $p<0.049$) and 2.0 ($t(6)= 4.264$, $p<0.005$) mg/kg/infusion MDMA was increased by SCH23390.

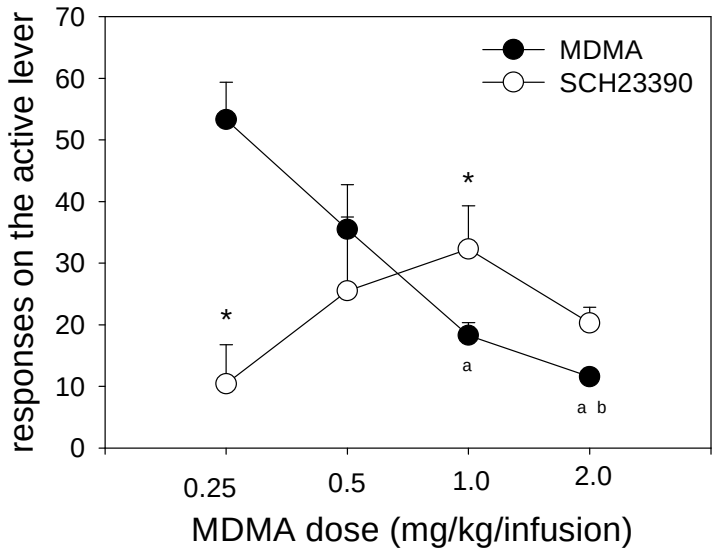


Figure 14. From Daniela et al, (2004). Dose dependant responding maintained by MDMA self-administration (0.25-2.0mg/kg/infusion; filled circles) and responding maintained by MDMA after SCH23390 (0.02mg/kg; empty circles) administration. Symbols represent the mean

number of responses (+/-SEM). * indicates significant difference (P<0.05) from baseline levels of responding.

Figure 15 shows the effects of SCH23390 (0.005mg/kg-0.02mg/kg) on responding maintained by 2.0mg/kg/infusion MDMA. Responding increased after pre-treatment with 0.01mg/kg SCH23390 ($F(1, 3) = 10.206$, $p<0.05$) and 0.02mg/kg SCH23390 ($F(1, 3) = 10.947$, $p<0.045$). The effects of 0.005-0.02mg/kg SCH23390 on responding maintained by 0.5 mg/kg/infusion and 1.0mg/kg/infusion MDMA failed to reveal any significant interaction ($p=0.375$, $p= 0.208$).

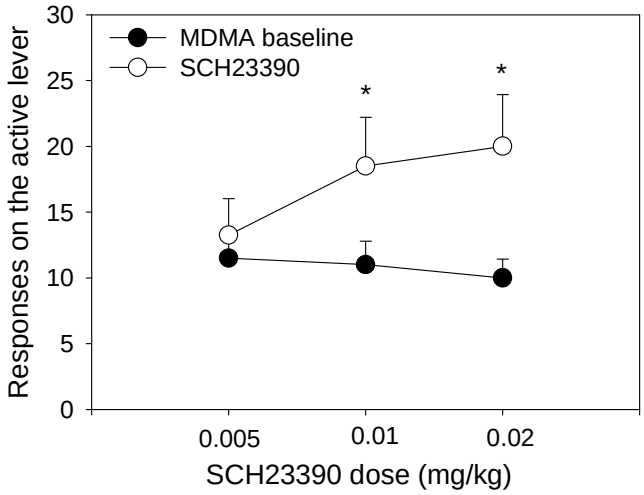


Figure 15. Effects of different doses of SCH23390 (0.005-0.02mg/kg) on responding maintained by 2.0mg/kg/infusion MDMA. Symbols represent the mean number of responses (+/- SEM). * indicates significant ($p<0.05$) increase from baseline responding.

Responding maintained by MDMA (0.25-2.0mg/kg/infusion) was also dose dependant ($F(3,9)=34.202$, $p<0.001$) in animals receiving eticlopride pre-treatment (Figure 16). Analyses, however, failed to reveal a significant interaction between MDMA dose and eticlopride treatment ($p=.817$). Responding was not altered by changes in eticlopride dose ($p = 0.093$).

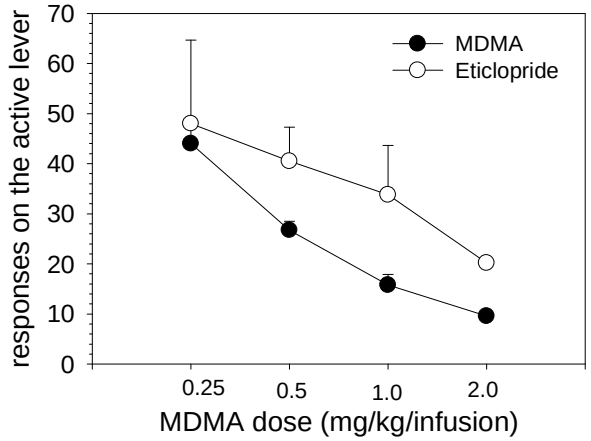


Figure 16. Dose dependant responding maintained by MDMA self-administration (0.25-2.0mg/kg/infusion; filled circles) and responding maintained by MDMA after eticlopride (0.05mg/kg; empty circles) administration. Symbols represent the mean number of responses (+/- SEM).

*Summary*MDMA self-administration was sensitive to dopaminergic manipulations. MDMA produced dose-dependant increases in basal locomotor activity. SCH23390 and eticlopride dose-dependently

decreased MDMA –induced locomotor activity. SCH23390 shifted the dose response curve for MDMA self-administration to the right, decreasing responding at low doses and increasing responding at high doses. Eticlopride pre-treatment failed to shift the dose effect curve; however, responding for the higher doses of MDMA increased.

Chapter 5- Experiment 3

Influence of conditioned stimuli on MDMA self-administration

The aim of the third experiment was to determine if MDMA self-administration produces conditioned responding. The transition from drug use to abuse is hypothesised to involve alterations in the processing of drug-associate stimuli (Leshner & Koob 1999, Robinson & Berridge 1993; 2000; 2001; 2003; Childress et al 1988, Childress et al 1986, Ehrman et al 1990, Haney et al 1999, O'Brien et al 1992, O'Brien et al 1992, Robinson & Berridge 1993). The effects of manipulation of the light and/or drug stimuli on responding were be measured.

Method

Procedure

A new group of rats were trained to self-administer MDMA (1.0mg/kg/infusion) as described above. Once 75 (+/- 5) infusions (range for meeting this criterion was 5-15 days) had been self-administered, the MDMA dose was reduced to 0.5 mg/kg/infusion for a further 150 (+/-10) infusions (range for meeting this criterion was 6-19 days). Responses per day and the number of days to criterion were recorded for each animal. This phase of self-administration training lasted an average of 19.2 days during which rats self-administered approximately 225 infusions of MDMA associated with a light stimulus.

The rats were then divided into groups (n=6/gp) to test the influence of the continued contingent presentation of the light stimulus or

the drug stimulus on operant responding. One group continued to receive a drug infusion (0.5 mg/kg/infusion) according to an FR1 schedule of reinforcement but the light stimulus that had been associated with drug infusions was omitted (DRUG ONLY group). Another group continued to receive the light stimulus that had been paired with self-administered drug infusions but the MDMA was replaced with the 3 U heparin/ml saline vehicle solution (LIGHT ONLY group). A final group received only vehicle solution, without the light stimulus (NO LIGHT/NO DRUG group). These conditions were maintained during an additional 15 daily 2 hr sessions. Total responses per session and temporal pattern of responding within each session were recorded for all subjects. A group of unoperated drug-naïve rats (n=7) was tested to determine whether the light stimulus was a reinforcer of operant responding when it had not been paired with MDMA infusions (NO DRUG/LIGHT). These rats were placed in the operant chambers for daily 2 hr tests. Responding on the active lever was reinforced by the 12 sec presentation of the light stimulus according to an FR1 schedule.

Data Analysis

Self-administration data were analysed using separate repeated measures ANOVA to examine changes in responding from baseline for the LIGHT ONLY, DRUG ONLY, and NO LIGHT/NO DRUG groups. The average number of responses produced during the last 5 days of the training period served as the baseline number of responses for each rat. A repeated measures ANOVA (Condition X Day) was conducted on the number of responses reinforced by the light stimulus only for the group

that had previously had the light paired with MDMA infusions (paired group) and for the group that had not previously had light/drug pairings (unpaired group). The temporal pattern of responding was summated for every ten minute period on baseline day and days 1,5,10,15, of extinction for each animal. Analysis was performed for every ten minute period for all groups across extinction days using three wayANOVA (time X extinction day X group). Post hoc tests were performed for days and group using tukey pot hoc test, and simple contrast were used to compare time periods.

Results

Figure 17 shows the average number of responses during baseline and on the subsequent 15 days of testing for the LIGHT ONLY, DRUG ONLY, NO LIGHT/NO drug groups. Separate ANOVA for each group revealed a significant decrease in responding as a function of days for the NO DRUG/ NO LIGHT group ($F(15,75) = 4.765$, $p<0.001$) and subsequent simple contrasts revealed that the decrease in operant responding was significant for all 15 test days ($p<0.01$). A decrease in responding as a function of days was also observed for the DRUG ONLY group ($F(15, 75) = 2.380$, $P<0.01$), with simple contrasts showing a significant difference from baseline on day 4 and following day 6 of test days ($p<0.01$). A decrease in responding for the Light ONLY group approached significance ($F(15, 75)= 1.771$, $p<0.055$) and simple contrasts revealed a significant decrease in responding from baseline, on day 6 and from day 8 to day 14 ($p<0.05$). Baseline responding did not vary between groups ($F(2,15)= 0.838$, $p< 0.452$).

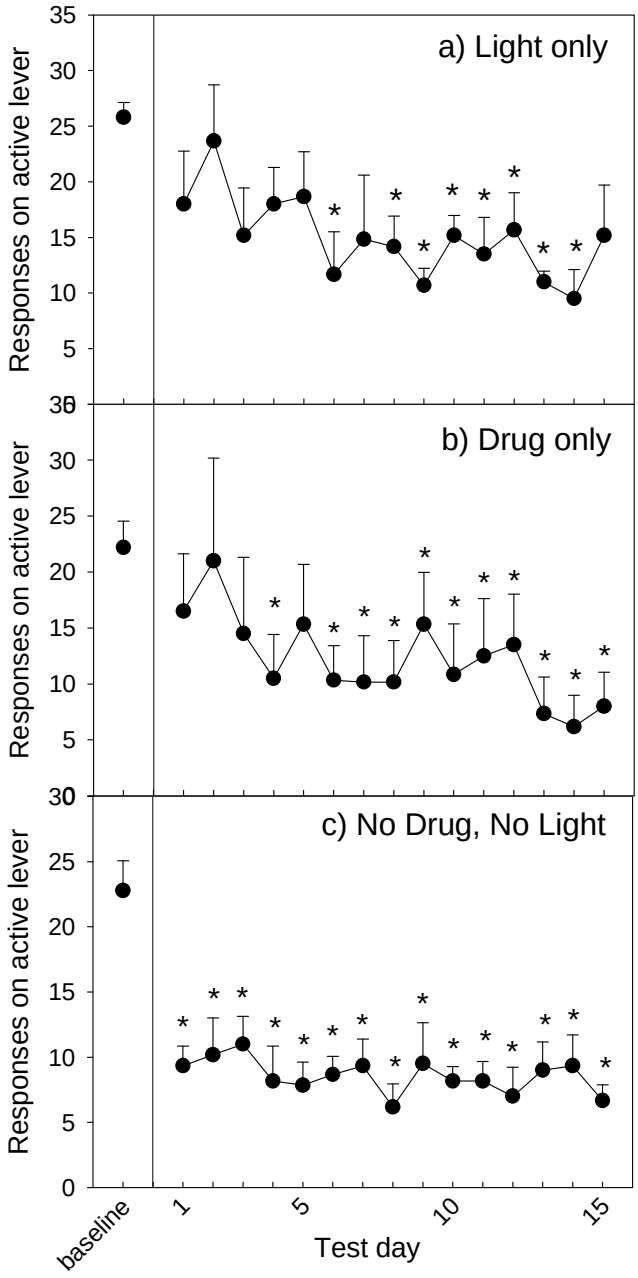


Figure 17. From Daniela et al, (2006). Effects of removal of light or/and drug stimuli on responding over 15 days. Symbols denote average (+/- SEM) daily response rates for baseline responding and extinction condition for each condition. * denotes significant differences from baseline responding.

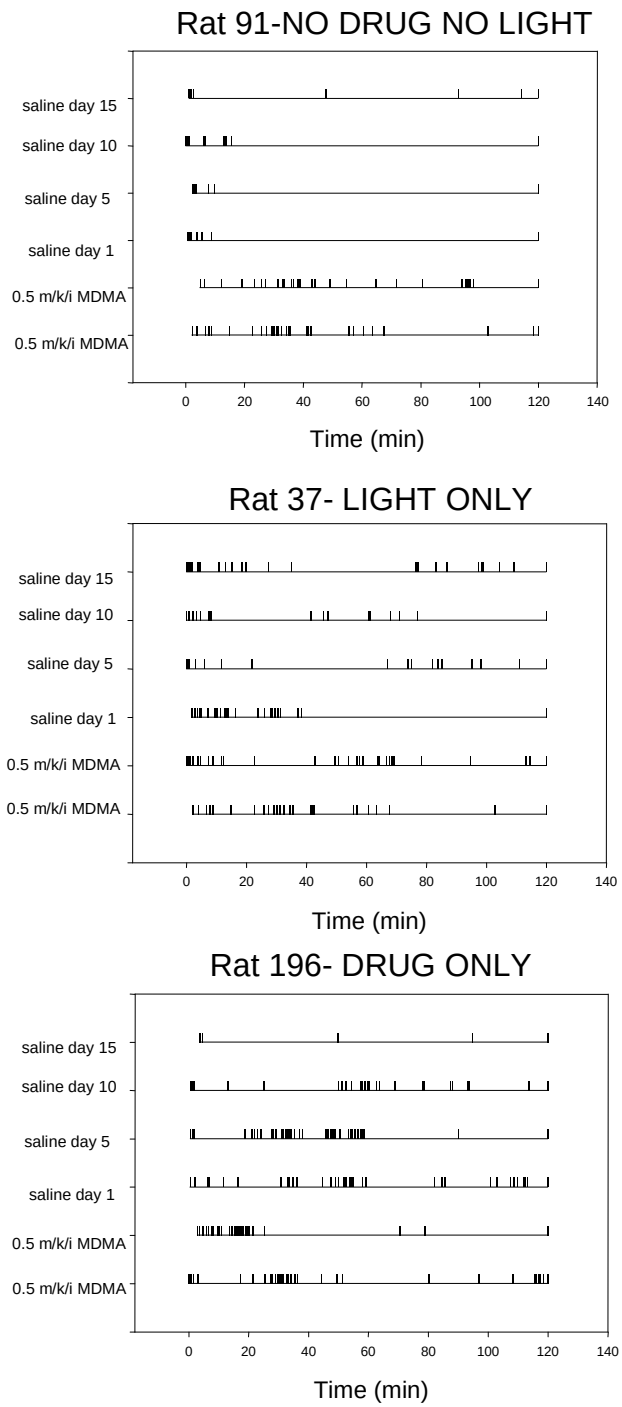


Figure 18. Temporal pattern of responding from a representative rat from each group, on baseline days 4 and 5, extinction days 1,5,10, 15. Each

vertical bar denotes a depression on the active lever. Despite individual variation, analyses revealed all groups to have comparable time course;

Figure 18 shows the temporal pattern of responding a representative rat from each group, on two baseline days, and extinction days 1, 5, 10, 15. Analyses revealed that all groups demonstrated the typical elevated responding in the first ten minutes followed by a reduction and low levels of responding throughout the session for all extinction days ($F(11,616)= 39.691$, $p<0.001$). No difference between extinction days was found ($p=0.594$). Figure 19 shows the average number of responses over the 4 extinction days (1,5,10,15) for each group. Responding maintained by either the light or drug stimuli produced elevated levels of responding through the session when compared to the No light, No drug group ($F (22,616) = 3.237$, $p<0.001$).

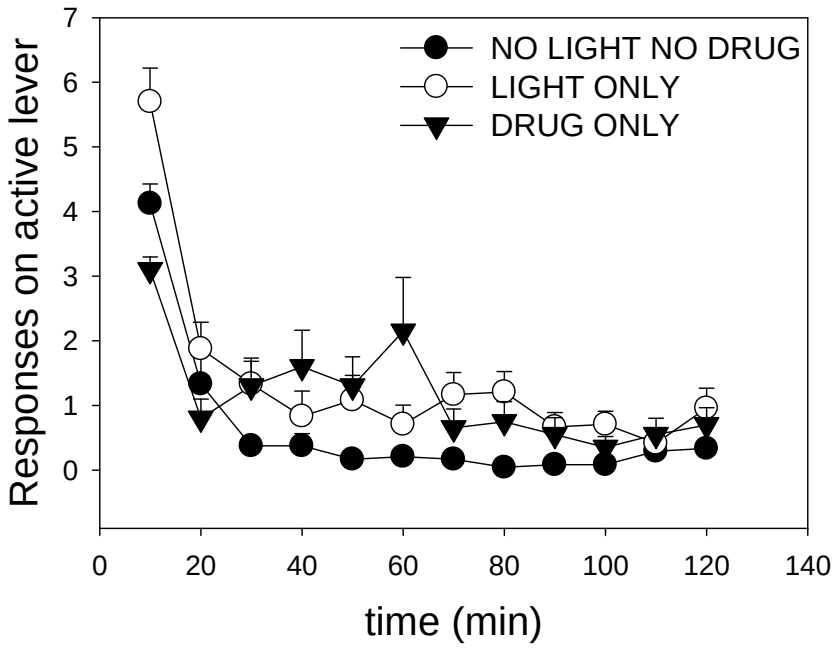


Figure 19. The average number of responses on the active lever every ten minutes for each group. Data averaged over extinction days 1,5,10, 15. Symbols denote (=/-SEM) average responses every ten minutes over 120 minutes.

Figure 20 shows the average number of responses when lever presses were reinforced by presentation of the light stimulus only. Data are from rats that had experienced the light stimulus paired with self-administered MDMA and for a group of drug naïve animals that had not experienced the light stimulus in any context. Responding maintained by the presentation of the light stimulus was higher for the group that had received prior MDMA/light pairings ($F(1,11)=36.733$, $p<0.01$), and subsequent simple contrasts revealed that the differences were significant across all days.

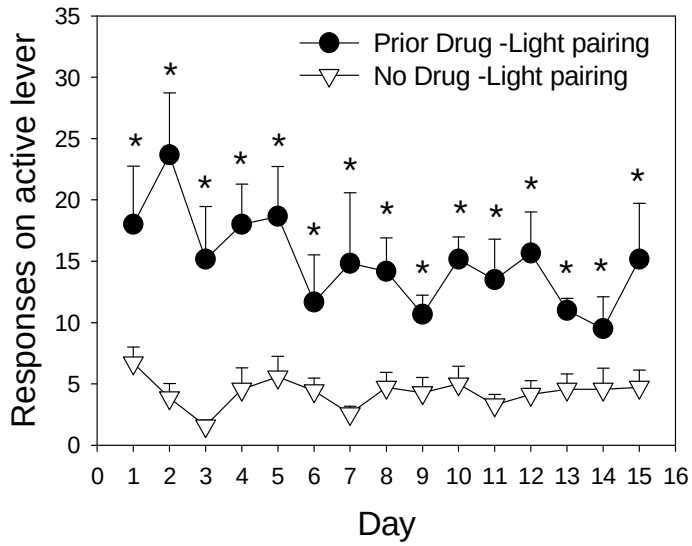


Figure 20. From Daniela et al, (2006). Effects of prior drug – light pairing on responding maintained by the presentation of a light stimulus. Symbols represent the average number of responses (+/-SEM) on the active lever for animals with prior MDMA self-administration experience (filled circles) and drug naïve animals (empty triangles). * denotes significant ($p<0.01$) group differences

Summary

Manipulation of the light and/or drug stimuli produced changes in self-administration behaviors. Removal of both stimuli dramatically reduced responding, while removal of the light produced a trend towards a reduction in responding, indicating that the light stimuli may have acquired conditioned reinforcing properties.

Chapter 6 – Experiment 4

Reinstatement of responding previously maintained by MDMA

The aim of the fourth experiment was to determine if MDMA administration will reinstate responding previously maintained by MDMA. Relapse after abstinence from abused substances is a common feature of addiction (Chang & Haning 2006, Mendelson & Mello 1996, O'Brien et al 1992, Shalev et al 2002). MDMA doses were administered to animals after a period of extinction, and responses were measured.

Method

Procedure

Rats were trained to self-administer MDMA using the procedure described in the general methods. Reinstatement of MDMA self-administration was assessed in a group of animals (N=8). However due to catheter patency, 3 animals did not complete this study. Following the acquisition, the schedule of reinforcement was increased to FR2. After stable responding (less than 20% variation over three consecutive days) was produced, the schedule of reinforcement was increased to FR5 and responding stabilised.

A recurring series of 6 hr daily tests comprised of baseline, extinction and reinstatement phases was conducted. Phase one consisted of at least two days of responding that was reinforced by an infusion of MDMA (FR5, 0.5 mg/kg/infusion) with the associated light stimulus. During Phase two (minimum two days), the MDMA solution was replaced with vehicle and the light stimulus that had been paired with self-administered MDMA infusions was omitted. These conditions were imposed for a minimum of two days and continued until there were less than 30 responses produced. At the start of phase three, rats received an injection of MDMA (0.0 – 10.0 mg/kg, IP). During these tests, responding continued to be reinforced by an infusion of vehicle and the light stimulus was illuminated according to an FR5 schedule of reinforcement. Drug seeking behaviour was defined as the number of responses on the active lever during phase three. Order of MDMA dose was randomised between animals, and no repetition effect was found.

Data Analysis

The responses from reinstatement days were analysed using a within subjects repeated measures ANOVA. Temporal responding from reinstatement data was also analysed using a between measures ANOVA for each hour of reinstatement (hrs X group).

Results

Figure 21 shows the average number of responses on the active lever for all animals during MDMA administration, extinction, and MDMA reinstatement doses. ANOVAs conducted for baseline and extinction days revealed no significant difference across baseline days ($P>0.28$) or extinction days ($P>0.5$). In contrast, a main effect for MDMA reinstatement dose was observed ($F(2,8) = 14.573$, $p<0.05$). Contrasts indicated that responding was significantly increased for the MDMA doses 5mg/kg ($F(1,4) = 33.5534$, $p<0.05$) and 10mg/kg ($F(1,4) = 15.76$, $p< 0.05$) compared to 0.0mg/kg MDMA.

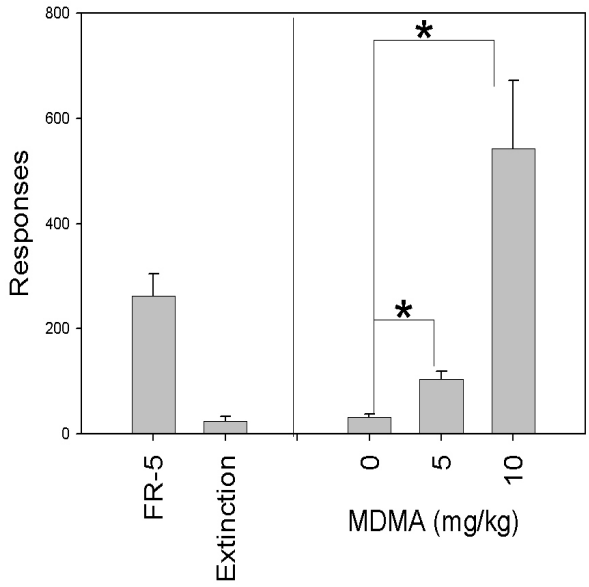


Figure 21. Effect of experimenter administered MDMA (0.0-10mg/kg) on responding in animals previously trained to self-administer MDMA. Bars denote number of depressions on active lever during testing phases. * denotes significant difference from 0.00mg/kg MDMA.

Figure 22 shows the temporal pattern of responding on the active lever during each hour of reinstatement. Responding during the 6 hour reinstatement phase varied as a function of MDMA dose ($F(10, 60) = 4.400$, $p<0.005$). Post hoc simple contrasts revealed that responding produced by 10mg/kg MDMA maintained elevated levels of responding when compared to 0.0mg/kg ($p<0.005$) and 5mg/kg ($p<0.002$). No difference in the temporal pattern of responding was found between 0.0mg/kg and 5mg/kg MDMA ($p=0.463$). Responding produced by 10mg/kg MDMA was elevated during the first three hours of responding ($p<0.05$).

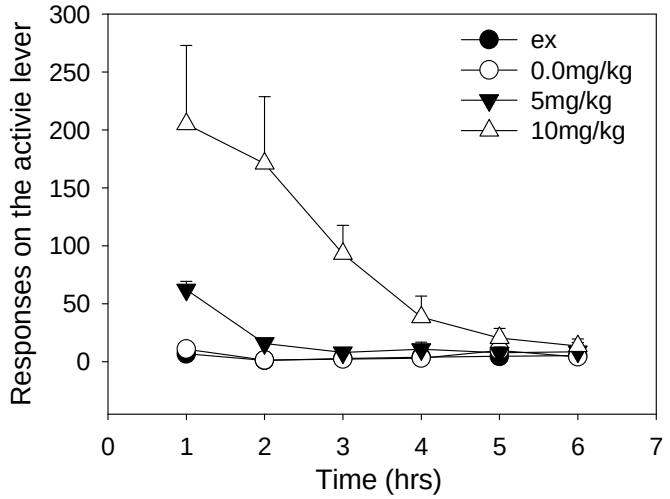


Figure 22. Effects of experimenter administered MDMA (0.0-10mg/kg) on responding previously maintained by MDMA. Symbols represent the mean (+/-SEM) responses as function of hour.

Summary

MDMA self-administration could also be reinstated after extinction of responding resulting from removal of the drug and light stimuli. Experimenter administration dose dependently increased responding on the active lever in the absence of self-administered MDMA.

Chapter 7- Discussion

The aim of the current thesis was to examine factors involved in the acquisition and maintenance of MDMA self-administration. MDMA was demonstrated to be reliably self-administered in drug-naïve and cocaine-trained animals. Responding was contingent to the active lever, reduced with vehicle substitution, sensitive to dose and schedule manipulation, and increased as demand increased. MDMA self-administration was also sensitive to dopaminergic manipulation. Pretreatment with SCH23390 produced a rightward shift in the dose response curve. Removal of the light and drug stimuli produced a rapid reduction in responding. In contrast, responding was reduced slowly when either the light or drug stimuli were removed, suggesting that the light and drug stimuli appeared to have comparable abilities to reinforce responding in animals with MDMA self-administration histories. Responding was also reinstated when animals previously experienced with MDMA self-administration were administered MDMA. The demonstration of reliable self-administration and subsequent determination of factors involved in MDMA self-administration is a novel contribution to the literature on MDMA, and has provided extensive support to the suggestion that MDMA may have abuse liability (see Schenk et al, 2003, Daniela et al, 2004; Daniela et al, 2006).

Reliable MDMA self-administration

Previous studies have indicated that MDMA self-administration is readily produced in laboratory animals that had a prior history of

cocaine self-administration (Beardsley et al 1986, Fantegrossi et al 2002, Fantegrossi 2002, Lamb & Griffiths 1987, Ratzenboeck et al 2001). In the present study, rats experienced with cocaine self-administration also readily acquired MDMA self-administration suggesting that prior exposure to cocaine may have sensitized animals to the reinforcing effects of MDMA. A wealth of studies have indicated that pretreatment with psychostimulants sensitizes rats to the behavioral effects of subsequent injections (Kalivas & Stewart 1991, Robinson & Becker 1986), while latency to acquisition by untrained drug naïve animals was delayed. Latency to acquisition of self-administration was decreased by pretreating rats with either the to-be self-administered drug or a variety of other drugs (Schenk & Gittings 2003, Schenk & Izenwasser 2002, Schenk & Partridge 1997, Schenk & Partridge 2000). Previous studies have indicated that some of the behavioral effects of MDMA are susceptible to sensitization. For example, acute exposure to MDMA resulted in locomotor activation that became sensitized following repeated exposures (Kalivas et al 1998, McCreary et al 1999, Spanos & Yamamoto 1989). Cross sensitization has also been demonstrated and rats that received treatment with MDMA became more responsive to the locomotor activating effects of amphetamine (Callaway & Geyer 1992), and cocaine (Kalivas et al 1998) as well as to the conditioned reinforcing effects of cocaine (Horan et al 2000). Of interest, rats that were pretreated with MDMA subsequently acquired self-administration of a low dose of cocaine with shorter latencies than rats that received saline pretreatment (Fletcher et al 2001). Consistent with these studies, the present results

indicate that neuronal mechanism common to both cocaine and MDMA may be mediating self-administration.

MDMA self-administration was gradually acquired with repeated daily tests in rats that had no prior self-administration training and were drug naïve. These data are comparable to data obtained when the acquisition of self-administration of other psychostimulant drugs was measured. Acquisition of cocaine (Schenk et al 1991, Schenk & Partridge 2000, Schenk et al 1993) and amphetamine (Carroll & Lac 1997, Piazza et al 1989, Pierre & Vezina 1997) self-administration occurred gradually over days. The gradual increase in the average number of responses as a function of test day resulted from the recruitment of subjects that reliably self-administered the drug over days.

Following acquisition, responding maintained by MDMA was dose-dependent, extinguished when saline was substituted for the drug and was reinstated when MDMA was reintroduced. The number of responses was an inverse function of MDMA dose. These results were comparable to those produced in early psychostimulant self-administration studies (Gotestam & Andersson 1975, Hoffmeister & Goldberg 1973, Smith et al 1976, Yokel & Pickens 1973, Yokel & Wise 1978). There was almost perfect compensatory responding that maintained drug intake at about 18-20 mg/kg during daily sessions. It has been suggested that changes in operant responding as function of dose are due to titration of drug effects (Hurd et al 1989, Neisewander et al 1996, Pettit & Justice 1989, Pettit & Justice 1991, Ranaldi et al 1999, Wise et al 1995, Wise et al 1995). Therefore, the dose dependant responding

demonstrated suggests that animals were actively titrating the effects of MDMA.

The relatively high dose of MDMA consumed in the current study is somewhat disparate to the doses typically consumed by humans (de la Garza et al, 2006). The average dose of MDMA in a MDMA pill varies considerably, and is estimated to be between 80 -150mg (Lesiter et al, 1992; Siegal et al, 1986; Parrott & Lasky, 1998). De la Garza et al (2006) reported that the mean consumption of MDMA in humans is 1.8mg/kg per session. In novice MDMA users, a single pill is consumed, however, heavy MDMA users typically show a pattern of maintenance dosing throughout an evening, and as previously mention can consume 10 or more pills in an evening (Winstock et al, 2001).

In the current experiments, animals that acquired MDMA self-administration consumed approximately 17-25mg/kg MDMA per day. While this appears to be a significant variation, it may not be, as animals were only included when they acquired MDMA self-administrations. Animals that did not meet acquisition criteria were excluded. It is possible that the results reported are more consistent with heavy MDMA use in humans, rather than mean MDMA consumption. An alternative explanation is that variation across species is to be expected, due to physiological factors such as speed of metabolism. Research into the neurotoxic effects of MDMA on serotonin neurons lead to the use of inter-species scaling for drug doses (Ricaurte et al, 2000). Due to smaller body mass and rapid drug clearance in rodents, equivalent drug doses in rodents are significantly higher than mg/kg doses used by humans.

Ricaurte et al (2000) argue that the dose of 20mg/kg in a rodent is equivalent to 1.28mg/kg in humans. This dose is comparable to the dose of MDMA self-administered in the present studies.

The demonstration of reliable, dose-dependent self-administration is consistent with characteristics of a drug that possesses high abuse liability (Ator & Griffiths 2003, Kozikowski et al 2003). This interpretation is strengthened by the finding that reliable self-administration persisted during a single 24 hr session. MDMA self-administration during this long session differed however, from what has previously been reported for cocaine self-administration (Covington & Miczek 2005, Mantsch et al 2004, Morgan et al 2002, Mutschler et al 2001, Schenk & Partridge 1997, Schenk & Partridge 2000). Continuous access to cocaine self-administration produced binge patterns of consumption, characterized by an initial 'loading up' phase and 'regulatory' phase (Tornatzky & Miczek 2000). During the regulatory phase, responding maintained by cocaine infusions persisted at a high hourly rate throughout the self-administration session (Mantsch & Goeders 2000, Mutschler et al 2001, Roberts et al 2002, Schenk et al 2001, Tornatzky & Miczek 2000). The pattern of temporal responding maintained by MDMA was characterized by an initial 'loading up' phase and then a prominent reduction in responding with periodic responses on the active lever at a low hourly rate. This may be due to the long duration of action of MDMA and/or the accumulation of an active metabolite. 3,4-methylenedioxyamphetamine (MDA), a major metabolite of MDMA is known to increase extracellular levels of serotonin and dopamine (Nash

& Nichols, 1991; Schmidt et al, 1987). It is possible that the increases in MDA after initial MDMA administration, may maintain elevated levels of dopamine over a prolonged duration of time decreasing the need for 'top up' responses. Furthermore, the secondary dopamine release that occurs as a consequence of 5-HT1B and 5-HT2A receptor activation may also prolong elevations in dopamine levels (Lucas & Spampinato, 2004). If animals are titrating the effects of MDMA through responses, then it would be expected that these mechanisms would reduce responding, as dopamine levels remain elevated. A methodology employing microdialysis would provide a more comprehensive answer to these suggestions.

When saline was substituted for MDMA after experience with MDMA self-administration, responding decreased for these more experienced rats. Saline-maintained responding was, however, higher than had been observed during acquisition and a preference for the active lever was demonstrated during these saline-reinforced trials. These findings suggest that these rats with an extensive history of MDMA use were more resistant to extinction than animals with limited MDMA self-administration experience. Of note, in this study, the light stimulus remained on, and may have functioned as a conditioned reinforcer maintaining responding.

Operant responding was dependant on contingent administration of MDMA, as demonstrated in the yoked experiment. Animals receiving non-contingent light and drug presentation, or non-contingent light and vehicle presentations produced low levels of responding on both the

active and inactive levers. Similar findings have been reported with a range of substances including, amphetamine (Di Ciano et al 1998, Ranaldi et al 1999, Stefanski et al 1999), cocaine (Hooks et al 1994, Meil et al 1995, Wilson et al 1994) morphine (Grasing & Miller 1989, Mierzejewski et al 2003, Smith et al 1982) and nicotine (Donny et al 1998). These results suggest that selective operant behavior was not a consequence of the motor-activating effects of MDMA alone, as animals' receiving non-contingent MDMA did not demonstrate elevated responding on the active lever. Furthermore, responding on either lever was not maintained by animals that received only non-contingent light presentation suggesting that the light stimulus alone failed to have any initial effect on self-administration behaviors. The demonstration of elevated levels of responding on the active lever by animals receiving contingent MDMA only is a strong demonstration that MDMA self-administration is a purposeful selective behavior performed by animals.

The effects of increasing demand on responding were assessed in two experiments. Initial manipulations demonstrated that an increase in FR schedule produced compensatory responding, that responding decreased when MDMA and the light stimulus were both removed and was reinstated when MDMA and the light stimulus were again made available for self-administration. These results are consistent with those produced in primate models (Fantegrossi et al 2002). The use of an FR schedule of reinforcement provided preliminary assessment of reinforcement; this schedule, however, did not assess the reinforcing efficacy of a substance (Arnold & Roberts, 1997; Richardson & Roberts, 1996). In the current

study, the maintenance of MDMA self-administration was sensitive to increasing demand. The implementation of a PR schedule of reinforcement produced an incremental increase in the number of infusions received, and breakpoint reached as a function of MDMA dose. The dose effect function produced under this condition was consistent with those produced by MDMA in the primate (Lile et al, 2004). The demonstration of increasing breakpoints, as MDMA dose increased suggests that as MDMA dose was increased, the maximal effort expended was also increased – reflective of reinforcing efficacy. Furthermore, the MDMA PR dose effect function produced was comparable to those produced in self-administration studies with other commonly abused substances (Hubner & Moreton 1991, Loh & Roberts 1990, Risner & Goldberg 1983, Roberts 1989, Roberts et al 1989, Szostak et al 1987). No direct comparison between MDMA and alternative reinforcers was assessed, and as such, the relative reinforcing efficacy of MDMA in the rodent is yet to be determined. Prior studies have indicated that MDMA maintained a lower breakpoint, at fewer doses when compared to cocaine PR (Lile et al, 2006; Trigio et al, 2006), indicating that MDMA may be a less efficacious reinforcer than other psychostimulants. Future research would benefit from comparing the reinforcing efficacy of MDMA and other abused substances.

While the current thesis has conclusively demonstrated that reliable MDMA self-administration can be produced, discrepancies between the current findings and other published studies has been raised (see De La Garza et al, 2006), leading to speculation that MDMA is not a reliable

reinforcer. Like previous attempts to demonstrate reliable nicotine and Δ-9- THC self-administration, explanation is likely to be due to experimental parameters, rather than the drug itself. Several major differences between other published MDMA self-administration studies and the current study are noted. Firstly, the infusion duration for drug delivery in the current study was relatively long at 12 seconds, compared to other rodent MDMA self-administration studies. For example, Ratzenboeck et al (2002) reported 6' infusion duration, while De la Garza et al (2006) reported a 4.5' infusion time. Increasing the infusion times for cocaine self-administration produced a reduction in responding (Panlilo et al, 1998; Balster & Schuster, 1973; Samaha & Robinson, 2005), indicating that infusion duration can affect the acquisition and maintenance of self-administration. In the current study, prolonging the infusion time may have had the opposite effect, perhaps due to the mechanisms of actions of MDMA. Initial experiences with MDMA have been reported to occasionally be aversive, due to the strong initial serotonergic effects (Green et al, 2003). Prolonging the infusion time and exposure to the light stimulus may result in lever depression being associated with 5-HT efflux and secondary DA efflux. The prolonged presentation of the light stimulus may have resulted in the light stimulus functioning as a predictive stimulus. Additionally, the volume of infusion used was less than those used in other studies. For example, Ratzenboeck et al (2002) reported infusions of 300µl over 6 seconds, compared to the 100µl over 12 seconds in the current study. It may be that large infusion

volumes of MDMA delivered in rapid infusions produced aversive effects.

Secondly, the absence of a time – out period in the current study may have facilitated acquisition of MDMA self-administration, by allowing rapid administration of sequential MDMA doses to produce maximal effects. The temporal pattern of responding seen when MDMA made available for self- administration, revealed a 'loading' phase at the beginning of self-administration sessions. The imposition of a time out phase may have reduced this 'loading' phase, thereby reducing acquisition.

Thirdly, animals in the current study did not have any prior operant training. Initial exposure to the self-administration environment only occurred when MDMA was available for self-administration, perhaps strengthening context – dependant learning. For example, it has been reported that associations between specific and contextual environmental stimuli and drug administration decreased the acquisition latency for other self-administered substances (Arroyo et al 1998, Caggiula et al 2002, Smith & Davis 1973).

Fourthly, acquisition of MDMA self-administration occurred during relatively long self-administration sessions. For example, De La Garza et al (2006) reported 3 hr daily sessions, in contrast to the 6hr daily sessions used currently. Previous studies have shown that longer access times to cocaine and amphetamine increased responding, and drug intake (Ahmed & Koob 1999, Mantsch et al 2003, Mantsch et al 2004). While this factor may increase acquisition, some animals were trained during

daily two hour sessions, indicating that session duration alone did not determine acquisition. Of note, animals trained during two hour sessions tended to have a longer acquisition periods, than those trained in 6 hour sessions. Systematic analysis of the effects of session duration on MDMA acquisition latency would determine if this observation has any significance.

The demonstration of MDMA self-administration in the current study may be due to some of these experimental conditions. It may also be due to other unqualified factors. For example, in the current study, all animals received a 'priming' injection of MDMA at the being of each acquisition session. This daily exposure to MDMA may have gradually sensitised animals to the effects of MDMA. Other published rodent MDMA studies do not report on priming, therefore comparisons are difficult. In order to determine the factors that assisted in MDMA self-administration, a methodical assessment of all the potential factors contributing to the acquisition of MDMA self-administration is required.

The first experiment of this thesis demonstrated reliable MDMA self-administration. Acquisition of MDMA self-administration was demonstrated in both drug naive and cocaine trained animals, whereas animals receiving non-contingent MDMA did not perform selective operant behaviour. Animals responded in a dose dependant manner, ceased when MDMA was replaced with vehicle solution, and was reinstated when MDMA was made available again. Furthermore, increasing the demand required for reinforcement produced schedule dependant increases in responding. These findings are novel

contributions (Schenk et al 2003) to understanding the mechanisms underlying MDMA use. The demonstration of MDMA self-administration provides a robust animal paradigm for further research into factors affecting MDMA consumption. The relative absence of published studies demonstrating MDMA self-administration and attempting to characterise psychopharmacology mechanisms underlying MDMA reinforcement may be due to conceptualisation of MDMA as a 5-HT agonist and potential neurotoxic substance (Bankson & Cunningham 2001, Battaglia & De Souza 1989, Cole & Sumnall 2003, Green et al 1995, Green et al 2003, Parrott 2002, Shulgin 1986). The concern over MDMA neurotoxicity has lead research to focus primarily on causes, modulators and protective factors – pharmacological and environmental for MDMA neurotoxicity. Given the wealth of evidence demonstrating toxicity, further investigation into the behavioural features of MDMA consumption is necessary in order to prevent and treat the effects of MDMA induced neurotoxicity.

Dopaminergic mechanisms in MDMA self-administration

The second experiment examined the role of dopamine in the behavioural effects of MDMA. MDMA –induced locomotion and self-administration was reduced with dopamine receptor antagonism. MDMA-produced hyperactivity was attenuated in a dose-dependent manner by pre-treatment with SCH 23390 and eticlopride at doses lower than those producing general disruption of motor activity (Millan et al, 2001; Meyer et al, 1993; Piggins & Merali, 1989). These findings contribute to the hypothesis that dopaminergic mechanisms underlie MDMA-produced

hyperactivity (Ball et al 2003, Bubar et al 2004, Fernandez et al 2003, Gold et al 1989). Furthermore, these findings are consistent with microdialysis and electrophysiology studies that have shown MDMA induced dopamine elevations. For example, administration of MDMA (10mg/kg) elevated locomotor activity levels and increased extracellular DA in the nucleus accumbens of Fisher rats (Fernandez et al 2003), while MDMA administration (5mg/kg) also resulted in elevated locomotor behaviour and excitation of neurons in the striatum (Ball et al 2003). SCH233390 (0.2mg/kg) delayed the locomotor activating effects of MDMA and excitation of striatal neurons, while eticlopride (0.2mg/kg) administration attenuated MDMA –induced locomotion and neuronal excitation (Ball et al 2003). The reduction in MDMA –induced locomotion seen after dopamine antagonism was also comparable to studies reporting DA antagonism of the locomotor activating effects of amphetamine and cocaine (Gold et al 1989, Kelley & Lang 1989, Piazza et al 1991, Wallace et al 1996).

The role of dopamine in the reinforcing effects of common psychostimulants has been demonstrated through the production of rightward shifts in the dose response curves. SCH23390 pre-treatment resulted in rightward shifts in the dose-response curve for self-administration of cocaine (Caine 1995, Caine & Koob 1994, Carelli & Deadwyler 1996, Corrigall & Coen 1991, Maldonado et al 1993) and amphetamine (Barrett et al 2004, Beninger et al 1989, Phillips et al 1994, Sziraki et al 1998). Antagonism of the D2-like receptors also shifted the dose response curves for cocaine and amphetamine self-administration in

a rightward direction(Barrett et al 2004, Bergman et al 1990, Caine & Koob 1994, Hemby et al 1996, Schenk & Gittings 2003).

In the current study, pre-treatment with SCH 23390 produced a rightward shift in the dose-effect curve for MDMA self-administration. In contrast, dose dependant MDMA self-administration was not significantly altered by eticlopride pre-treatment, although increases in responding were noted after eticlopride pre-treatment when the two highest doses of MDMA were made available for self-administration.

The production of a rightward shift in dose-response curves is consistent with a pharmacological blockade (Barrett et al 2004, Caine & Koob 1994, Hubner & Moreton 1991, Koob et al 1987). The shift in dose-response function has been attributed to variations in the neurological substrates involved and drug-receptor interactions (Kenakin, 1993). For example, the behavioral consequences of drug consumption may be due to the density of available receptors or the affinity for a receptor by a specific substance (Kenakin, 1993). Higher densities of available receptors would suggest an increased response to a low unit of drug, whereas, a drug with low affinity for available receptors would require a higher unit dose to order to achieve a maximal effect. It is likely that the increased responding evident after SCH23390 pretreatment was due to receptor blockade, therefore limiting available D1-like receptors requiring increased drug –intake to maintain comparable reinforcing effects.

Administration of eticlopride, a D2-like antagonist, surprisingly, failed to have any significant effect on an MDMA produced dose

response curve. Pre-treatment with haloperidol – a widely use D2-lke receptor antagonist blocked the subjective effects of positive mood and 'mania' produced by MDMA in humans (Liechti & Vollenweider 2000). While explanation may be found in the physiological differences between humans and rodents, or the discrepancies between operant responding and subjective experiences, a more likely explanation is that it is due to the experimental parameters of the current study. Eticlopride pre-treatment did increase responding at higher MDMA doses, but had no effect on responding maintained by low doses of self-administered MDMA. The within subject design utilized was a rigorous assessment of D2 –like receptor involvement, however, high variability and small sample size may have been causal factors in the absence of an effect. Therefore, theoretical interpretation of these results may be premature. Further assessment of the role of the D2-like receptor in MDMA self-administration is required before any valid interpretation can be made.

Though MDMA has behavioural activating effects consistent with other psychostimulants, the role of serotonin is less well clarified. Serotonin neurons innervate dopaminergic systems that underlie the reinforcing effects of drugs of abuse (Herve et al., 1987). Evidence is emerging that activation of some serotonin receptor subtypes facilitates dopamine effects (Bankson & Cunningham 2001, De Deurwaerdere 1999, De Deurwaerdere et al 2004, Di Giovanni 1999, Lucas et al 2000, McCreary et al 1999, Schmidt et al 1994, Yan 2000, Yan & Yan 2001). The acute elevations in 5-HT and subsequent activation of 5-HT post-synaptic receptors are implicated in the locomotor activating effects of

MDMA. For example, antagonism of the 5-HT1B and 5-HT2A receptors reduced MDMA induced locomotion, where as antagonism of the 5-HT2C increased MDMA induced locomotion (Bankson 2002, Bankson & Cunningham 2001, Fletcher et al 2002, McCreary et al 1999). Antagonism of the 5-HT1B and 5-HT2A reduced MDMA-produced dopamine increases (Lucas & Spampinato 2000, Schmidt et al 1994). Therefore, it is likely that change in locomotor behaviour seen after serotonergic pre-treatment's are due to interactions with dopaminergic systems. For example, antagonism of the 5-HT2A receptor attenuated MDMA induced excitation of striatal neurons and locomotion while SB 206553, a 5-HT2C/2B antagonist had no effect on either MDMA induced locomotion or neuronal response to MDMA (Ball & Rebec 2005).

Serotonergic mechanisms have also been implicated in the reinforcing effects of MDMA. Pretreatment with the 5-HT2 antagonist ketanserin, decreased MDMA self-administration by rhesus monkeys without altering cocaine self-administration (Fantegrossi et al 2002). Though no study has thus far determined whether the reported interactions between the serotonin and dopamine systems are applicable to self-administration studies, it is likely that the same mechanisms are activated by both self-administered MDMA and experimenter administered MDMA. Repeated MDMA-produced increases in serotonin might also repeatedly activate reward-relevant dopaminergic substrates. This repeated activation of dopamine might be expected to lead to neurochemical sensitization that becomes expressed in reliable self-administration. This effect of repeated MDMA would also explain its

ability to enhance the reinforcing and other behavioral effects of cocaine (Fletcher et al 2001, Horan et al 2000)(Fletcher et al., 2001; Horan et al., 2000; Kalivas et al., 1998), which has been attributed to sensitization of dopaminergic substrates.

During self-administration training and testing, rats received substantial exposure to MDMA. Repeated exposure to MDMA produces effects on brain chemistry that might play a role in the ability of MDMA to increase synaptic dopamine and produce positively reinforcing effects that maintain self-administration.

It is well-documented that exposure to MDMA produces toxicity in central serotonergic systems (Battaglia et al 1988, Reneman et al 2001, Reneman et al 2006, Ricaurte et al 2000, Schmidt et al 1990). There are complex interactions between serotonin and dopamine but several studies have shown that self-administration of cocaine (Czoty et al 2002, Fletcher et al 2002, Loh & Roberts 1990), morphine (Dworkin et al 1988) and amphetamine (Leccese & Lyness 1984) was altered following serotonin depletion, presumably as a result of decreased serotonin modulation of dopamine. It has also been reported that exposure to MDMA produced a persistent decrease in the density of 5-HT2c receptors (McGregor et al 2003). This might also contribute to the ability of MDMA to increase synaptic dopamine since activation of 5-HT2c receptors decreased dopamine release (Blackburn et al 2002, Di Giovanni et al 2002, Filip & Cunningham 2003). Following acute MDMA administration increases in 5-HT and the resulting activation of 5-HT2c receptors (Gudelsky & Yamamoto 2003) might be expected to limit MDMA-produced increased

dopamine. For example, Ramos et al (2005) reported attenuation of MDMA sensitization after administration of the 5-HT2c receptor agonist, MK-212, indicating a likely role for the 5-HT2c receptor in MDMA – induced behaviour.

Following repeated exposure, however, this inhibitory effect might be less influential because of decreased 5-HT2c receptor densities. The resulting disinhibition would contribute to the sensitized dopamine response produced following repeated MDMA exposures (Kalivas et al 1998). This sensitized neurochemical response would be expected to maintain MDMA self-administration and produce cross-sensitization in the behavioural effects of MDMA and other indirect dopamine agonists (Callaway & Geyer 1992, Cole et al 2003, Fletcher et al 2001, Itzhak et al 2003, Kalivas et al 1998).

In summary, MDMA locomotion and self-administration was demonstrated to be sensitive to blockade of the D1-like receptor. Blockade of the D2-like receptor dose dependently reduced MDMA induced locomotion, but had limited effects on MDMA self-administration. These findings are the first to demonstrate that the reinforcing effects of MDMA are dependant on dopaminergic activation (see Daniela et al 2004). Furthermore, the production of rightward shift in the MDMA dose-response curve after DA antagonism indicates that similar pharmacological mechanisms underlie the reinforcing properties of MDMA and other commonly abused substances.

Maintenance of responding by MDMA- associated stimulus

The third experiment evaluated the role of the drug and /or drug-associated light stimulus on responding. For rats that had extensive experience with MDMA self-administration removal of both the drug and the light stimulus that had been paired with intravenous drug infusions led to a dramatic and rapid decrease in operant responding. When operant responding continued to produce either the light stimulus or the drug infusion, the decrease in responding was delayed relative to when both stimuli were omitted. Thus, the light stimulus that had been paired with self-administered MDMA infusions was sufficient to reinforce responding for several days even in the absence of the MDMA infusion. Similarly, MDMA infusions were sufficient to maintain responding for several days once the drug-associated light stimulus had been removed. When either the drug or the light stimulus was removed however, responding eventually decreased to rates that were comparable to when both the drug and the light were removed. Because the light stimulus failed to reinforce responding for the group that had not received light/drug pairings, these data suggest that the light stimulus had acquired reinforcing properties through repeated pairings with self-administered MDMA infusions.

Previous studies have documented rapid extinction of self-administration of a number of drugs of abuse (DiCiano & Everritt 2004; Grimm et al. 2002; Neiswander et al. 1996; See et al. 1999) and presentation of drug-associated stimuli reinstated extinguished cocaine- (Deroche- Gamonent et al. 2003; Di Ciano et al. 2004) and methamphetamine- (Anggadiredja et al. 2004) taking behavior. In another

study (Schenk and Partridge 2001), the continued presentation of a light stimulus that had been associated with self-administered cocaine infusions was required for the maintenance of high rates of cocaine self-administration; removal of the stimulus that had been associated with self-administered cocaine resulted in a dramatic decrease in operant responding despite the continued availability of cocaine.

The present study demonstrates that an MDMA-associated stimulus is also required for continued self-administration of MDMA and is the first to demonstrate the development of similar conditioned reinforcing properties of a stimulus that had been associated with self-administered MDMA. Behaviour maintained in the absence of the drug stimuli may also indicate that the light stimulus is acting as a discriminative stimulus, consequently behaviour may be under stimulus control. Again, this phenomenon is noted for many other drugs of abuse, such as cocaine (Weiss et al, 2003), amphetamine (Davis & Smith, 1976), and morphine (Davis & Smith, 1976).

The discriminative ability of drug-associated stimuli to indicate the onset or availability of self-administration, resulted in drug- taking behaviour being controlled by these associated stimuli (Beninger et al, 1981; Van der Kooy, et al, 1983; Foltin & Haney, 2000). Typically in stimuli control studies the discriminative stimuli precede reinforcement; however, in the current study behaviour was maintained by a stimulus that co-occurred with the infusion of MDMA. Given the duration of infusion delivery / light presentation and the subjective response to

MDMA, the light stimulus may have been functioning as a discriminative stimulus.

The ability of drug-associated cues to acquire control over behaviour and to lead to drug seeking is a critical characteristic of drug abuse (Carter & Tiffany, 1999; Childress et al, 1986; 1988; 1992; 1993; 1999; O'Brien et al, 1992; Drummond et al, 1990; Foltin & Hanley, 2000). Accordingly, these data are consistent with the idea that MDMA is a drug with high abuse potential. In the present study, continued presentation of the light stimulus associated with self-administered MDMA infusions rendered rats resistant to extinction of self-administration behaviour.

With other drugs of abuse, the ability of drug-associated stimuli to control behaviour has been elegantly demonstrated through the use of second order schedules (Keheller, 1966; Goldberg, 1973; Goldberg et al, 1975; Goldberg & Gardner, 1981; Sanchez-Ramos & Schuster, 1977; Schindler et al, 2002; Arroyo et al, 1998; Everrit & Robbins, 2000; Parkinson et al, 2001; Diciano & Everrit, 2004). The demonstration of a resistance to extinction through presentation of a drug-associated stimulus indicates that MDMA may maintain a second-order schedule of reinforcement. This possibility remains an exciting avenue for future research.

The development of conditioned reinforcing effects of drug-associated stimuli might explain why MDMA self-administration by humans remains high despite reports of tolerance to the positive subjective effects of the drug (Parrott 2005; Verheyden et al 2003). Of

note, a majority of MDMA users will consume MDMA in specific environments and behavior does not generalize easily (Parrott, 2005). This might also explain the development of compulsive use among some MDMA users (Jansen 1999; Parrott 2005; Von Sydow et al. 2002) since stimuli associated with MDMA might maintain drug-taking behavior despite the development of tolerance to the positive effects of the drug. In some studies, the continued presentation of cues associated with self-administered drugs enhanced responding maintained by the drug alone (Panilio et al., 2000; Weiss et al., 2003; Palmatier et al., 2006). In the present study, the importance of the continued presentation of a stimulus associated with self-administered MDMA was also demonstrated and operant responding decreased dramatically when this drug-associated stimulus was omitted. In this manner, MDMA-self-administration by experienced subjects might come under the same level of stimulus control as has been demonstrated in cocaine-, nicotine- and heroin-experienced subjects (Panilio et al., 2000; Weiss et al., 2003; Palmatier et al., 2006; Chaudhri et al., 2005).

The fact that extinction of operant responding was delayed by the continued presentation of the MDMA-associated light stimulus and that MDMA infusions failed to continue to reinforce operant responding when the light stimulus was removed suggests a change in the ability of MDMA to activate substrates relevant to its reinforcing properties. In other studies (Schultz et al. 1992; Fontana et al. 1993; Duvauchelle et al. 2000; Ito et al. 2000; Carelli 2000; 2004; Schultz 2001), it has been demonstrated that following repeated pairings, there is a loss of the

capacity of a primary reinforcer to activate dopamine systems and an increased response of central dopamine systems to the presentation of the stimulus that had been paired with the primary reinforcer. These findings have profound implications for compulsive drug taking since they suggest that conditioned stimuli rather than primary reinforcers become the primary determinants of continued drug seeking.

Reinstatement of extinguished responding after MDMA prime

In the present study the ability of MDMA to reinstate extinguished MDMA self-administration behaviours was measured. Responding was produced as both dose-, and schedule-, dependant prior to reinstatement studies. Removal of both the light stimulus and drug stimulus produced a rapid reduction in responding. Experimenter administered MDMA reinstating extinguished responding. Responding on the inactive lever remained low and stable throughout the different phases of testing.

Several studies have reported that priming injections of a self-administered drug reinstates extinguished drug-taking behaviour. For example, experimenter administered cocaine, amphetamine and heroin reinstated extinguished responding for animals trained to self-administer cocaine (de Wit and Stewart, 1981; Slikker et al., 1984; Comer et al, 1993; Worley et al, 1994; Weissenborn et al, 1995), amphetamine (Stretch and Gerber, 1975; Ettenberg, 1990) and heroin (de Wit and Stewart, 1983; Shaham et al, 1996), respectively. MDMA has also been demonstrated to reinstate responding after amphetamine self-administration, only in animals previously exposed to MDMA (Morley et al 2004). In the current study, all animals had self-administered MDMA,

and reinstatement was robust. These findings indicate that MDMA may be able to reinstate responding for other substances. Given the high rates of poly drug use amongst MDMA users, MDMA use after a period of abstinence may initiate drug-seeking behaviours for a variety of substances. The possibility that MDMA use may promote relapse in poly-drug users needs further consideration.

The between session measurement of self-administration, extinction and reinstatement behaviours indicates that reinstatement is not due to the acute withdrawal effects (Shalev et al, 2002). In the current study, the use of 2-3 days of extinction training and attenuation of responding during this period suggests that animals were responding as a function of drug stimulus presentation. Responding produced after MDMA administration was dose dependant and 10mg/kg MDMA produced double the rate of baseline responding. Similar findings have been reported when other drugs of abuse were self-administered. For example, methamphetamine administration (1mg/kg) produced responding approximately double that maintained by 0.06mg/kg/infusion (Anggadiredja et al, 2004). The temporal pattern of responding was dose dependently elevated in the first half of the self-administration sessions. The production of dose-dependant reinstatement is consistent with other reports of drug-primed reinstatement (Self & Nestler, 1998; Stewart, 2000; Chiamuerla et al, 1996; Shaham et al, 1997; de Wit, 1996; De wit & Stewart, 1981). The use of drug doses higher than those used to maintain self-administration, have been regularly used to reinstate responding (de Wit, 1996). While the dose of 10mg/kg may have

increased motor activity, responding occurred selectivity on the active lever. The selectivity of this response suggests that animals may have been seeking MDMA.

The predictive utility of the reinstatement procedure has been well established, and therefore, clinical implications of this finding are profound. The reinstatement model is widely used to understand factors contributing to the 'relapse' process of addiction (Shalev et al, 2002; Katz et al, 2004). The return to compulsive drug taking after periods of abstinence is a determinant of addiction. Accordingly, the demonstration of MDMA reinstatement suggests that some individuals may be sensitive to relapse. It would be expected that in the future, current or abstinent MDMA users may experience relapse to either MDMA use, or poly drug use if exposed to MDMA again. In addition, given the commonalties between MDMA self-administration and the self-administration patterns and features produced by other commonly abused drugs; these data indicate that MDMA does have a significant abuse liability. Subsequent studies would benefit from evaluating the role of dopaminergic agonists in reinstating behaviour. Furthermore, given the wealth of data implicating cross-sensization, assessment of reinstatement with other substances is required in order to provide a strong understanding of widely reported poly drug use in MDMA users.

Validity of MDMA self-administration

Underpinning all interpretation is the assumption that MDMA self-administration models human MDMA use. The validity of the MDMA self-administration has been questioned due to several features of

human MDMA use that are not yet addressed in the MDMA self-administration literature, including, route of administration, patterns of consumption, and human polydrug use (de la Garza et al, 2006).

The self-administration paradigm employed used an indwelling intravenous catheter to deliver MDMA. It could be argued that intravenous delivery is not consistent with the widely reported oral consumption of MDMA (de la Garza et al, 2006). Intravenous delivery produces rapid effects when compared to oral administration, therefore increasing the likelihood that a substance be more reinforcing. MDMA is, however, administered intravenously by some people. For example, Topp et al, (1999) report 16% of MDMA users had used MDMA intravenously. Heavy MDMA users can differentiate the subjective effects of MDMA based on the route of administration (Solowij et al, 1992; Topp et al, 1999). The focus of the current thesis was to explore basic parameters of MDMA self-administration. Future studies may benefit from looking at oral MDMA self-administration.

The current results were produced over daily self-administration sessions; in contrast human MDMA consumption occurs predominantly in binge patterns (Topp et al, 1999; Winstock et al, 2001). It is highly likely that these parameters may have affected the results. Self-administration studies utilizing unlimited access over a long period of time and discrete access to MDMA may help to clarify patterns of consumption.

Poly drug use is very common amongst MDMA users (Solowij et al, 1992; Forsyth et al, 1996; Davidson & Parrott, 1997; Schifano et al,

1998; Topp et al, 1999; Parrott et al, 2000; von Sydow et al, 2002; Verheyden et al, 2003; Schooley et al, 2004). MDMA is rarely used alone; with one large study reporting 0.7% of MDMA users consuming MDMA alone (Verheyden et al, 2003). Concurrent acute drug use is typically alcohol, cannabis, and amphetamine (Topp et al, 1999; Verheyden et al, 2003). Approximately 40-45% of MDMA users concurrently use amphetamines (Solowij et al, 1992; Topp et al, 1999), while 45-55% of MDMA users concurrently use marijuana (Solowij et al, 1992; Topp et al, 1999). Smoking cannabis is reportedly to 'pick you up' and 'bring you down' in an attempt to prolong peak effects or to counteract insomnia (Solowij et al, 1992). The high use of benzodiazepines in the residual phase of MDMA use is also particularly common (Topp et al, 1999; Forsyth et al, 1996; Scholey et al, 2004). The current study did not attempt to address issues pertaining to poly drug use simply because basic clarification of MDMA self-administration was required. Subsequent research would benefit from systematically looking at self-administration of multiple compounds with MDMA and pre-treatment with other substances. Given the literature on cross-sensitisation, the interactions between MDMA and other drugs of abuse is a very important avenue for future research.

Consistency with dominant addictions theories

The MDMA self-administration data indicates that MDMA can produce behavioural features consistent with other commonly abused substances. These behavioural phenomena have been used as an index for the abuse potential of illicit substances, suggesting that MDMA is a drug with

abuse liability. Self-administration alone does not provide evidence of addiction; rather features of addiction are required to be demonstrated within a self-administration paradigm (Robinson, 2004; Deroche – Gamonet et al, 2004). At a basic level, the demonstration of reliable MDMA self-administration indicates that MDMA functions as a positive reinforcer. Positive reinforcement is an established feature in most scientific theories of addiction (Koob et al 2004, 1997; Robinson & Berridge, 2000; 2003; Wise & Bozarth, 1987).

In animals, self-administration of drugs of abuse is mediated by the natural reward pathways in the brain – primarily the mesolimbic system (Wise, 1981; Koob & Le Moal, 2001; Volkow et al, 1999). MDMA self-administration was sensitive to manipulation of the dopamine system, indicating that like other psychostimulants, MDMA use has a dopaminergic component. Several theories of addiction have focused on aberrations in dopaminergic processing and consequently learning, after repeated drug use (Wise, 1996; Koob et al, 1998; Di Chiara et al 1999). It has been clearly demonstrated that increases in dopamine are produced after MDMA self-administration (Fitzgerald & Reid, 1990). The demonstration of a rightward shift in the MDMA dose effect curve after dopaminergic antagonism provides evidence that the dopamine efflux produced during MDMA self-administration mediates some of the behavioural effects of MDMA.

Aberrant learning theories of addiction hypothesise that a lack of dopaminergic habituation produces these abnormally strong stimuli-drug associations (Di Chiara et al, 1999; Wolf, 2002). . The magnitude of the

drug- drug stimuli relationship has been proposed to increase the incentive motivational aspects of drug taking (Di Chiara et al, 1999; Wolf, 2002), and to increase sensitivity to drug associated stimuli. Repeated exposure to drug-associated stimuli is widely known to produce conditioned highs, conditioned withdrawals and conditioned craving (O'Brien et al, 1992; Childress et al, 1988; Eherman et al, 1992). MDMA self-administration was sensitive to manipulation of associated stimuli, providing an indication that repeated self-administration of MDMA produces conditioning effects, and an increase in the salience of environmental stimuli associated with MDMA use. Of interest, in humans MDMA consumption is largely context specific (Green et al, 2003). The sensitisation towards salient attentional stimuli is theorised to underpin the transition from wanting to craving, from abuse to dependence (Robinson & Berridge, 1993; 2000; 2001; 2003).

Alterations in the processing of drug associated stimuli and underlying neural substrates after chronic drug use has been suggested to render individuals sensitive to the resumption of drug taking behaviours after drug consumption has initially ceased (Wolf, 2002; Di Chiara, et al, 1999; Wise, 1996; Koob, 2006; Weiss, 2005; Nestler, 2002; Kalivas & Volkow, 2005). In the current study, MDMA reinstated responding previously maintained by MDMA. The reinstatement paradigm has been used to model aspects of the relapse process in addiction (Shalev et al, 2002); therefore, the demonstration of MDMA induced reinstatement implies that prior MDMA users may be sensitive to the resumption of MDMA use after a period of abstinence. No studies have adequately

assessed MDMA produced relapse in humans, however, von Sydow and colleagues (2002) did report that a small proportion of MDMA users had difficulty remaining abstinent from MDMA.

The development of tolerance, a behaviour reported with much drug addiction, and accounted for by most theories of addiction was not systematically investigated in the current study. Given the commonalties between MDMA self-administration and self-administration of other psychostimulants, and the applicability of drug addiction theories to MDMA self-administration, it would be expected that MDMA administration produces tolerance to the subjective effects. Tolerance after chronic MDMA use in humans (Shulgin, 1986; Pertrouka et al, 1988; Solowij et al, 1992; Davidson & Parrott, 1997; Winstock et al, 2001; Verhyeden et al, 2003; Parrott, 2005) in primate MDMA self-administration (Fantegrossi et al, 2004) has been reported. The role of tolerance to MDMA, and the consequential behaviours still need to be evaluated within the self-administration paradigm.

Much debate has occurred over the abuse liability of MDMA in the absence of a theoretical framework (De la Garza et al, 2006); rather the abuse potential has been measured by the paucity of MDMA self-administration studies, and consequential lack of behavioural markers of abuse potential. The demonstration of self-administration, and the sensitivity of MDMA self-administration to manipulation of pharmacological and environment stimuli is consistent with key features in all the major theories of addiction providing further evidence that MDMA has an abuse potential.

Given the commonalities outlined between MDMA and other psychostimulants, treatment of MDMA abuse and MDMA –poly drug abuse could be similar to empirically validated substance abuse treatments. For example, cue exposure is frequently used in rehabilitation centres to desensitise people to the conditioned effects of drug-associated stimuli (Seigel & Ramos, 2002; Childress et al, 1988; 1993). The conditioned effects reported here indicate that MDMA users would likely benefit from cue exposure treatments to stimuli associated with MDMA use. The use of relapse prevention models also may be beneficial in order to prevent relapse (Marlett & Gordon, 1985). Pharmacologically, the acute positive subjective effects of MDMA in humans can be blocked using dopamine antagonists (Leitchi & Vollenweider, 2000). The focus of this thesis was to look at factors affecting acquisition and maintenance of MDMA self-administration. These factors are consistent with a substance that has abuse liability, and potential to induce relapse. Therefore, before any specific treatments, MDMA use needs to firstly be specifically addressed in treatment with those who have used MDMA.

Conclusion

The results reported here provide support for the hypothesis that MDMA has an abuse potential, and shares common addictive properties with other abused substances. It is hypothesised that as MDMA consumption has increased so too is the likelihood that MDMA users may have symptoms of addiction.

MDMA consumption has been poorly characterised and query over the abuse potential of MDMA has existed. The central tenet of this thesis was to ascertain whether MDMA is self-administered and whether MDMA self-administration has features of addiction. Self-administration of MDMA was obtained and tested. Dopamine antagonism indicated that dopaminergic mechanisms are involved in the reinforcing effects of MDMA. Manipulation of drug and drug associated stimuli provided evidence that stimuli associated with MDMA acquire reinforcing properties. Reinstatement of responding previously maintained by MDMA was also obtained upon re-exposure to MDMA. The behaviours reported are comparable to those produced by other psychostimulants, and consistent with theories of addiction, and definitions of abuse potential. Given the increases in MDMA consumption over the past two decades, it is likely that problems associated specifically with MDMA will arise. As such, further investigation into MDMA self-administration is warranted and will provide further information for clinical and neuropsychological gain.

References

Achat-Mendes, C., Anderson, K.L., & Itzhak, Y. (2003). Methylphenidate and MDMA adolescent exposure in mice: long-lasting consequences on cocaine-induced reward and psychomotor stimulation in adulthood. *Neuropharmacology, 45(1),* 106-15.

Ahmed, S.H., & Koob, G.F. (1998). Transition from moderate to excessive drug intake: change in hedonic set point. *Science, 282,* 298-300

Ahmed, SH., & Koob, G.F. (1999). Long-lasting increase in the set point for cocaine self-.administration after escalation in rats. *Psychopharmacology (Berl), 146,* 303-12

Alderson, H.L., Robbins, T.W., & Everitt, B.J. (2000). Heroin self-administration under a second-order schedule of reinforcement: acquisition and maintenance of heroin-seeking behaviour in rats. *Psychopharmacology (Berl), 153,* 120-33

Alex, K.D., Yavanian, G.J., McFarlane, H.G., Pluto, C.P., & Pehek, E.A. (2005). Modulation of dopamine release by striatal 5-HT2C receptors. *Synapse, 55(4),* 242-51

Anderson, S.M., & Pierce, R.C. (2005). Cocaine-induced alterations in dopamine receptor signaling: implications for reinforcement and reinstatement. *Pharmacology & Therapeutics, 106,* 389-403

Anggadiredja, K., Sakimura, K., Hiranita, T., & Yamamoto, T. (2004). Naltrexone attenuates cue- but not drug-induced methamphetamine seeking: a possible mechanism for the dissociation of primary and secondary reward. *Brain Research,earch, 1021(2),* 272-6

Arnold, J.M., & Roberts, D.C. (1997). A critique of fixed and progressive ratio schedules used to examine the neural substrates of drug reinforcement. *Pharmacology Biochemistry & Behaviour, 57,* 441-7

Arroyo, M., Markou, A., Robbins, T.W., Everitt, B.J. (1998). Acquisition, maintenance and reinstatement of intravenous cocaine self-administration under a second-order schedule of reinforcement in rats: effects of conditioned cues and continuous access to cocaine. *Psychopharmacology (Berl), 140,* 331-44

Ator, N.A., & Griffiths. R.R. (1983). Nicotine self-administration in baboons. *Pharmacology, Biochemistry & Behaviour, 19,* 993-1003

Ator, N.A., & Griffiths, R.R. (2003). Principles of drug abuse liability assessment in laboratory animals. *Drug & Alcohol Dependence, 70,* S55-72

Baker, L.E., Broadbent, J., Michael, E.K., Matthews, P.K., & Metosh, C.A. (1995). Assessment of the discriminative stimulus effects of the optical isomers of ecstasy (3,4-methylenedioxymethamphetamine; MDMA). *Behavioural Pharmacology, 6,* 263-75

Ball, K.T., Budreau, D., & Rebec. G.V. (2003). Acute effects of 3,4-methylenedioxymethamphetamine on striatal single-unit activity and behavior in freely moving rats: differential involvement of dopamine D(1) and D(2) receptors. *Brain Research, 994,* 203-15

Ball, K.T., & Rebec, G.V. (2005). Role of 5-HT2A and 5-HT2C/B receptors in the acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on striatal single-unit

activity and locomotion in freely moving rats. *Psychopharmacology (Berl), 181,* 676-87

Balster, R.L. & Lukas, S.E. (1985). Review of self-administration. *Drug& Alcohol Dependence, 14,* 249-61

Balster, R.L., Mansbach, R.S., Gold, L., & Harris, L.S. (1992). Preclinical methods for the development of pharmacotherapies for cocaine abuse. *NIDA Research Monograph, 119,* 160-4

Balster, R.L., & Schuster, C.R. (1973). Fixed-interval schedule of cocaine reinforcement: effect of dose and infusion duration. *Journal of Experimental Analysis of Behaviour, 20,* 119-29

Bankson, M.G., & Cunningham, K.A. (2002). Pharmacological studies of the acute effects of (+)-3,4-methylenedioxymethamphetamine on locomotor activity: role of 5-HT(1B/1D) and 5-HT(2) receptors. *Neuropsychopharmacology, 26,* 40-52

Bankson, M.G, & Cunningham, K.A. (2001). 3,4-Methylenedioxymethamphetamine (MDMA) as a unique model of serotonin receptor function and serotonin-dopamine interactions. *Journal of Pharmacology & Experimental Therapeutics, 297,* 846-52

Bankson, M.G., & Cunningham, K.A. (2002). Pharmacological studies of the acute effects of (+)-3,4-methylenedioxymethamphetamine on locomotor activity: role of 5-HT(1B/1D) and 5-HT(2) receptors. *Neuropsychopharmacology, 26,* 40-52

Bankson, M.G., & Yamamoto, B.K. (2004). Serotonin-GABA interactions modulate MDMA-induced mesolimbic dopamine release. *Journal of Neurochemistry, 91,* 852-9

Bardo, M.T., Valone, J.M., & Bevins, R.A. (1999). Locomotion and conditioned place preference produced by acute intravenous amphetamine: role of dopamine receptors and individual differences in amphetamine self-administration. *Psychopharmacology (Berl), 143,* 39-46

Bari, A.A., & Pierce, R.C. (2005). D1-like and D2 dopamine receptor antagonists administered into the shell subregion of the rat nucleus accumbens decrease cocaine, but not food, reinforcement. *Neuroscience, 135,* 959-68

Barr, G.A., Sharpless, N.S., Cooper, S., Schiff, S.R., Paredes, W., & Bridger, W.H. (1983). Classical conditioning, decay and extinction of cocaine-induced hyperactivity and stereotypy. *Life Science, 33,* 1341-51

Barrett, A.C., Miller, J.R., Dohrmann, J.M., & Caine, S.B. (2004). Effects of dopamine indirect agonists and selective D1-like and D2-like agonists and antagonists on cocaine self-administration and food maintained responding in rats. *Neuropharmacology, 47, Suppl 1,* 256-73

Bassareo, V., Tanda, G., Petromilli, P., Giua, C., & Di Chiara, G. (1996). Non-psychostimulant drugs of abuse and anxiogenic drugs activate with differential selectivity dopamine transmission in the nucleus

accumbens and in the medial prefrontal cortex of the rat. *Psychopharmacology (Berl), 124,* 293-9

Battaglia, G., Brooks, B.P., Kulsakdinun, C., & De Souza, E.B. (1988). Pharmacologic profile of MDMA (3,4-methylenedioxymethamphetamine) at various brain recognition sites. *European Journal of Pharmacology, 149,* 159-63

Battaglia, G., & De Souza, E.B. (1989). Pharmacologic profile of amphetamine derivatives at various brain recognition sites: selective effects on serotonergic systems. *NIDA Research Monograph, 94,* 240-58

Battaglia, G., & Napier, T.C. (1998). The effects of cocaine and the amphetamines on brain and behavior: a conference report. *Drug& Alcohol Dependence, 52,* 41-8

Battaglia, G., Yeh, S.Y., & De Souza, E.B. (1988). MDMA-induced neurotoxicity: parameters of degeneration and recovery of brain serotonin neurons. *Pharmacology Biochemistry & Behaviour, 29,* 269-74

Beardsley, P.M., Balster, R.L., & Harris, L.S. (1986). Dependence on tetrahydrocannabinol in rhesus monkeys. *Journal of Pharmacology & Experimental Therapeutics, 239,* 311-9

Beardsley, P.M., Balster, R.L., & Harris, L.S. (1986). Self-administration of methylenedioxymethamphetamine (MDMA) by rhesus monkeys. *Drug & Alcohol Dependence, 18,* 149-57

Bellis, M.A., Hughes, K., Bennett, A., & Thomson, R. (2003). The role of an international nightlife resort in the proliferation of recreational drugs. *Addiction,* 98, 1713-21

Beninger, R.J. (1983). The role of dopamine in locomotor activity and learning. *Brain Research, 287,* 173-96

Beninger. R.J., Hoffman, D.C., & Mazurski, E.J. (1989). Receptor subtype-specific dopaminergic agents and conditioned behavior. *Neuroscience & Biobehavioural Review, 13,* 113-22

Beninger, R.J., Hanson, D.R., & Phillips, A.G. (1981). The acquisition of responding with conditioned reinforcement: effects of cocaine, (+)-amphetamine and pipradrol. *British Journal of Pharmacology,74(1),* 149-54.

Bergman, J., Kamien, J.B., & Spealman, R.D. (1990). Antagonism of cocaine self-administration by selective dopamine D(1) and D(2) antagonists. *Behavioural Pharmacology, 1,* 355-63

Bickel, W.K., DeGrandpre, R.J., Higgins, S.T., Hughes, J.R. (1990). Behavioral economics of drug self-administration. I. Functional equivalence of response requirement and drug dose. *Life Science, 47,* 1501-10

Bilsky, E.J., Hubbell, C.L., Delconte, J.D., & Reid, L.D. (1991). MDMA produces a conditioned place preference and elicits ejaculation in male rats: a modulatory role for the endogenous opioids. *Pharmacology, Biochemistry & Behaviour, 40,* 443-7

Bilsky, E.J., Hui, Y.Z., Hubbell, C.L., & Reid, L.D. (1990). Methylenedioxymethamphetamine's capacity to establish place

preferences and modify intake of an alcoholic beverage. *Pharmacology Biochemistry & Behaviour, 37,* 633-8

Blackburn, T.P., Minabe, Y., Middlemiss, D.N., Shirayama, Y., Hashimoto, K., Ashby, C.R., Jr. (2002). Effect of acute and chronic administration of the selective 5-HT2C receptor antagonist SB-243213 on midbrain dopamine neurons in the rat: an in vivo extracellular single cell study. *Synapse, 46,* 129-39

Blankenship, M.R., Finn, P.R., & Steinmetz, J.E. (2000). A characterization of approach and avoidance learning in high-alcohol-drinking (HAD) and low-alcohol-drinking (LAD) rats. *Alcoholism, Clinical & Experimental Research, 24(12),* 1778-84.

Bobes, J., Saiz, P.A., Gonzalez, M.P., Bascaran, M.T., & Bousono, M. (2002). Use of MDMA and other illicit drugs by young adult males in northern Spain. A five-year study. *European Addiction Research, 8,* 147-54

Bossert, J.M., Ghitza, U.E., Lu, L., Epstein, D.H., & Shaham, Y. (2005). Neurobiology of relapse to heroin and cocaine seeking: an update and clinical implications. *European Journal of Pharmacology, 526,* 36-50

Bozarth, M.A., & Wise, R.A. (1986). Involvement of the ventral tegmental dopamine system in opioid and psychomotor stimulant reinforcement. *NIDA Research Monograph, 67,* 190-6

Brady, J.V., & Griffiths, R.R. (1976). Behavioral procedures for evaluating the relative abuse potential of CNS drugs in primates. *Federal Proceedings, 35,* 2245-53

Braida, D., & Sala, M. (2002). Role of the endocannabinoid system in MDMA intracerebral self-administration in rats. *British Journal of Pharmacology, 136,* 1089-92

Brennan, K.A., & Schenk, S. (2006). Initial deficit and recovery of function after MDMA preexposure in rats. *Psychopharmacology (Berl), 184(2),* 239-46

Brown, E.E., & Fibiger, H.C. (1993). Differential effects of excitotoxic lesions of the amygdala on cocaine-induced conditioned locomotion and conditioned place preference. *Psychopharmacology (Berl), 113,* 123-30

Bubar, M.J., Pack, K.M., Frankel, P.S., & Cunningham, K.A. (2004). Effects of dopamine D1- or D2-like receptor antagonists on the hypermotive and discriminative stimulus effects of (+)-MDMA. *Psychopharmacology (Berl), 173,* 326-36

Cadoni, C., Solinas, M., Pisanu, A., Zernig, G., Acquas, E., Di Chiara, G. (2005). Effect of 3,4-methylendioxymethamphetamine (MDMA, "ecstasy") on dopamine transmission in the nucleus accumbens shell and core. *Brain Research, 1055,* 143-8

Caggiula, A.R., Donny, E.C., White, A.R., Chaudhri, N., & Booth, S. (2002). Environmental stimuli promote the acquisition of nicotine self-administration in rats. *Psychopharmacology (Berl), 163,* 230-7

Caine, S.B., Heinrichs, S.C., Coffin, V.L., & Koob, G.F. (1995). Effects of the dopamine D-1 antagonist SCH23390 microinjected into the accumbens, amygdala or striatum on cocaine self-administration in the rat. *Brain Research, 692,* 47-56

Caine, S.B., & Koob, G.F. (1994). Effects of dopamine D-1 and D-2 antagonists on cocaine self-administration under different schedules of reinforcement in the rat. *Journal of Pharmacology & Experimental Therapeutics, 270,* 209-18

Caine, S.B., & Koob, G.F. (1994). Effects of mesolimbic dopamine depletion on responding maintained by cocaine and food. *Journal of Experimental Analysis of Behaviour, 61,* 213-21

Calcagnetti, D.J., Keck, B.J., Quatrella, L.A., & Schechter, M.D. (1995). Blockade of cocaine-induced conditioned place preference: relevance to cocaine abuse therapeutics. *Life Science, 56,* 475-83

Callaway, C.W., & Geyer, M.A. (1992). Stimulant effects of 3,4-methylenedioxymethamphetamine in the nucleus accumbens of rat. *European Journal of Pharmacology, 214,* 45-51

Callaway, C.W., & Geyer, M.A. (1992). Tolerance and cross-tolerance to the activating effects of 3,4-methylenedioxymethamphetamine and a 5-hydroxytryptamine1B agonist. *Journal of Pharmacology & Experimental Therapeutics, 263,* 318-26

Callaway, C.W., Rempel, N., Peng, R.Y., & Geyer, M.A. (1992). Serotonin 5-HT1-like receptors mediate hyperactivity in rats induced by 3,4-methylenedioxymethamphetamine. *Neuropsychopharmacology, 7,* 113-27

Callaway, C.W., Wing, L.L., & Geyer, M.A. (1990). Serotonin release contributes to the locomotor stimulant effects of 3,4-methylenedioxymethamphetamine in rats. *Journal of Pharmacology & Experimental Therapeutics, 254,* 456-64

Cami, J., Farre, M., Mas, M., Roset, P.N., & Poudevida, S. (2000). Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. *Journal of Clinical Psychopharmacology, 20,* 455-66

Campbell, J., & Spear, L.P. (1999). Effects of early handling on amphetamine-induced locomotor activation and conditioned place preference in the adult rat. *Psychopharmacology (Berl), 143,* 183-9

Campbell, U.C., & Carroll, M.E. (2000). Acquisition of drug self-administration: environmental and pharmacological interventions. *Experimental & Clinical Psychopharmacology, 8,* 312-25

Canfield, D.R., Spealman, R.D., Kaufman, M.J., & Madras, B.K. (1990). Autoradiographic localization of cocaine binding sites by [3H]CFT ([3H]WIN 35,428) in the monkey brain. *Synapse, 6,* 189-95

Carelli, R.M., & Deadwyler, S.A. (1996). Dose-dependent transitions in nucleus accumbens cell firing and behavioral responding during cocaine self-administration sessions in rats. *Journal of Pharmacology & Experimental Therapeutics, 277,* 385-93

Carelli, R.M., & Ijames, S.G. (2000). Nucleus accumbens cell firing during maintenance, extinction, and reinstatement of cocaine self-administration behavior in rats. *Brain Research,earch, 866,* 44-54

Carelli, R.M. (2004). Nucleus accumbens cell firing and rapid dopamine signaling during goal-directed behaviors in rats. *Neuropharmacology, 47,Suppl 1,* 180-9

Carr, G.D., Phillips, A.G., & Fibiger, H.C. (1988). Independence of amphetamine reward from locomotor stimulation demonstrated by

conditioned place preference. *Psychopharmacology (Berl), 94,* 221-6

Carroll, M.E., & Lac, S.T. (1997). Acquisition of i.v. amphetamine and cocaine self-administration in rats as a function of dose. *Psychopharmacology (Berl), 129,* 206-14

Carter, B.L., & Tiffany, S.T. (1999). Meta-analysis of cue-reactivity in addiction research. *Addiction, 94,* 327-40

Casas, M., Guix T, Prat G, Ferre S, Cadafalch J, Jane F. (1988). Conditioning of rotational behavior after the administration of a single dose of apomorphine in rats with unilateral denervation of the dopaminergic nigrostriatal pathway: relevance to drug addiction. *Pharmacology, Biochemistry & Behaviour, 31(3),* 605-9

Cervo, L., & Samanin, R. (1996). Effects of dopaminergic and glutamatergic receptor antagonists on the establishment and expression of conditioned locomotion to cocaine in rats. *Brain Research,earch,731(1-2),* 31-8

Chang, L., & Haning, W. (2006). Insights from recent positron emission tomographic studies of drug abuse and dependence. *Current Opinions in Psychiatry, 19,* 246-52

Chaudhri, N., Caggiula, A.R., Donny, E.C., Booth, S., Gharib, M.A., Craven, L.A., Allen, S.S., Sved, A.F., & Perkins, K.A. (2005). Sex differences in the contribution of nicotine and nonpharmacological stimuli to nicotine self-administration in rats *Psychopharmacology (Berl), 180(2),* 258-66

Chiamulera, C., Borgo, C., Falchetto, S., Valerio, E., & Tessari, M. (1996). Nicotine reinstatement of nicotine self-administration after long-term extinction. *Psychopharmacology (Berl), 127(2),* 102-7

Childress, A., Ehrman, R., McLellan, A., & O'Brien, C. (1988). Update on behavioral treatments for substance abuse. *NIDA Research Monograph, 90,* 183-92

Childress, A., Ehrman, R., McLellan, A.T., & O'Brien, C. (1988). Conditioned craving and arousal in cocaine addiction: a preliminary report. *NIDA Research Monograph, 81,* 74-80

Childress, A.R., Hole, A.V., Ehrman, R.N., Robbins, S.J., McLellan, A.T., & O'Brien, C.P. (1993). Cue reactivity and cue reactivity interventions in drug dependence. *NIDA Research Monograph, 137,* 73-95

Childress, A.R., McLellan, A.T., Ehrman, R., & O'Brien, C.P. (1988). Classically conditioned responses in opioid and cocaine dependence: a role in relapse? *NIDA Research Monograph, 84,* 25-43

Childress, A.R., McLellan, A.T., & O'Brien, C.P. (1986). Conditioned responses in a methadone population. A comparison of laboratory, clinic, and natural settings. *Journal of Substance Abuse Treatment, 3,* 173-9

Childress, A.R., McLellan, A.T., & O'Brien, C.P. (1986). Role of conditioning factors in the development of drug dependence. *The Psychiatric Clinics of North America, 9,* 413-25

Chinen, C.C., & Frussa-Filho, R. (1999). Conditioning to injection procedures and repeated testing increase SCH 23390-induced catalepsy in mice. *Neuropsychopharmacology, 21(5),* 670-8.

Ciccocioppo, R., Martin-Fardon, R., & Weiss, F. (2002). Effect of selective blockade of mu(1) or delta opioid receptors on reinstatement of alcohol-seeking behavior by drug-associated stimuli in rats. *Neuropsychopharmacology, 27,* 391-9

Ciccocioppo, R., Sanna, P.P., & Weiss, F. (2001). Cocaine-predictive stimulus induces drug-seeking behavior and neural activation in limbic brain regions after multiple months of abstinence: reversal by D(1) antagonists. *Proceedings of the national Academy of Science U S A, 98,* 1976-81

Colado, M.I., Murray, T.K., & Green, A.R. (1993). 5-HT loss in rat brain following 3,4-methylenedioxymethamphetamine (MDMA), p-chloroamphetamine and fenfluramine administration and effects of chlormethiazole and dizocilpine. *British Journal of Pharmacology, 108,* 583-9

Cole, J.C., & Sumnall, H.R. (2003). The pre-clinical behavioural pharmacology of 3,4-methylenedioxymethamphetamine (MDMA). *Neuroscience and Biobehavioural Review, 27,* 199-217

Cole, J.C., Sumnall, H.R., O'Shea, E., & Marsden, C.A. (2003). Effects of MDMA exposure on the conditioned place preference produced by other drugs of abuse. *Psychopharmacology (Berl), 166,* 383-90

Comer, S.D., Lac, S.T., Curtis, L.K., & Carroll, M.E. (1993). Effects of buprenorphine and naltrexone on reinstatement of cocaine-

reinforced responding in rats. *Journal of Pharmacology and Experimental Therapeutics, 267(3),* 1470-7

Cornish, J.L., Shahnawaz, Z., Thompson, M.R., Wong, S., Morley, K.C. (2003). Heat increases 3,4-methylenedioxymethamphetamine self-administration and social effects in rats. *European Journal of Pharmacology, 482,* 339-41

Corrigall, W.A. (1999). Nicotine self-administration in animals as a dependence model. *Nicotine & Tobacco Research, 1,* 11-20

Corrigall, W.A., & Coen, K.M. (1989). Nicotine maintains robust self-administration in rats on a limited-access schedule. *Psychopharmacology (Berl), 99,* 473-8

Corrigall, W.A., & Coen, K.M. (1991). Cocaine self-administration is increased by both D1 and D2 dopamine antagonists. *Pharmacology, Biochemistry & Behaviour, 39,* 799-802

Corrigall, W.A, & Coen, K.M. (1991). Selective dopamine antagonists reduce nicotine self-administration. *Psychopharmacology (Berl), 104,* 171-6

Corrigall, W.A., Robertson, J.M., Coen, K.M., & Lodge, B.A. (1992). The reinforcing and discriminative stimulus properties of para-ethoxy- and para-methoxyamphetamine. *Pharmacology, Biochemistry & Behaviour, 41,* 165-9

Corrigall, W.A., & Vaccarino, F.J. (1988). Antagonist treatment in nucleus accumbens or periaqueductal grey affects heroin self-administration. *Pharmacology, Biochemistry & Behaviour, 30,* 443-50

Covington, H.E., & Miczek, K.A. (2005). Intense cocaine self-administration after episodic social defeat stress, but not after aggressive behavior: dissociation from corticosterone activation. *Psychopharmacology (Berl), 183,* 331-40

Crespi, D., Mennini, T., & Gobbi, M. (1997). Carrier-dependent and Ca(2+)-dependent 5-HT and dopamine release induced by (+)-amphetamine, 3,4-methylendioxymethamphetamine, p-chloroamphetamine and (+)-fenfluramine. *British Journal of Pharmacology, 121,* 1735-43

Criswell, H., Mueller, R.A., & Breese, G.R. (1988). Assessment of purine-dopamine interactions in 6-hydroxydopamine-lesioned rats: evidence for pre- and postsynaptic influences by adenosine. *Journal of Pharmacology & Experimental Therapeutics, 244,* 493-500

Crombag, H. S., A. Badiani, et al. (2001). The ability of environmental context to facilitate psychomotor sensitization to amphetamine can be dissociated from its effect on acute drug responsiveness and on conditioned responding. *Neuropsychopharmacology, 24(6),* 680-90.

Crombag, H. S., A. Badiani, et al. (2000). The role of contextual versus discrete drug-associated cues in promoting the induction of psychomotor sensitization to intravenous amphetamine. *Behaviour Brain Research,earch, 116(1),* 1-22

Cuddy, M.L. (2004). Common drugs of abuse--Part II. *Journal of Practical Nursing, 54,* 5-8, 25-31; quiz 17-9

Curran, H.V., Travill, R.A. (1997). Mood and cognitive effects of +/-3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): week-end 'high' followed by mid-week low. *Addiction, 92,* 821-31

Czoty, P.W., Ginsburg, B.C., & Howell, L.L. (2002). Serotonergic attenuation of the reinforcing and neurochemical effects of cocaine in squirrel monkeys. *Journal of Pharmacology & Experimental Therapeutics, 300,* 831-7

Daniela, E., Brennan, K., Gittings, D., Hely, L., & Schenk, S. (2004). Effect of SCH 23390 on (+/-)-3,4-methylenedioxymethamphetamine hyperactivity and self-administration in rats. *Pharmacology, Biochemistry & Behaviour, 77,* 745-50

Daniela, E., Gittings, D., & Schenk, S. (2006). Conditioning following repeated exposure to MDMA in rats: role in the maintenance of MDMA self-administration. *Behavioural Neuroscience, 120(5),* 1144-50

David, V., Durkin, T.P., & Cazala, P. (2002). Differential effects of the dopamine D2/D3 receptor antagonist sulpiride on self-administration of morphine into the ventral tegmental area or the nucleus accumbens. *Psychopharmacology (Berl), 160,* 307-17

Davis, W.M., & Smith, S.G. (1976). Role of conditioned reinforcers in the initiation, maintenance and extinction of drug-seeking behavior. *Pavlovian Journal of Biological Science,* 11, 222-36

De Deurwaerdere, P., & Spaminato, U. (1999). Role of serotonin2A and serotonin2B/2C receptor subtypes in the control of accumbal and

striatal dopamine release elicited in vivo by dorsal raphe nucleus electrical stimulation. *Journal of Neurochemistry, 73,* 1033-42

De Deurwaerdere, P., Navailles, S., Berg, K.A., Clarke, W.P., & Spampinato, U. (2004). Constitutive activity of the serotonin2C receptor inhibits in vivo dopamine release in the rat striatum and nucleus accumbens. *Journal of Neuroscience, 24,* 3235-41

De Vries, T.J., Schoffelmeer, A.N., Binnekade, R., Raaso, H., & Vanderschuren, L.J. (2002). Relapse to cocaine- and heroin-seeking behavior mediated by dopamine D2 receptors is time-dependent and associated with behavioral sensitization. *Neuropsychopharmacology, 26,* 18-26

De Vries, T.J., Schoffelmeer, A.N., Binnekade, R., & Vanderschuren, L.J. (1999). Dopaminergic mechanisms mediating the incentive to seek cocaine and heroin following long-term withdrawal of IV drug self-administration. *Psychopharmacology (Berl), 143,* 254-60

De Vries, T.J., Shaham, Y., Homberg, J.R., Crombag, H., & Schuurman, K. (2001). A cannabinoid mechanism in relapse to cocaine seeking. *National Medicine,* 7,1151-4

de Wit, H., & Stewart, J. (1981). Reinstatement of cocaine-reinforced responding in the rat. *Psychopharmacology (Berl), 75,* 134-43

de Wit, H., & Stewart, J. (1983). Drug reinstatement of heroin-reinforced responding in the rat. *Psychopharmacology (Berl), 79,* 29-31

Degenhardt, L., Copeland, J., & Dillon, P. (2005). Recent trends in the use of "club drugs": an Australian review. *Substance Use & Misuse, 40,* 1241-56

Deminiere, J.M., Piazza, P.V., Le Moal, M., & Simon, H. (1989). Experimental approach to individual vulnerability to psychostimulant addiction. *Neuroscience & Biobehavioural Reviews, 13,* 141-7

Deroche-Gamonet, V., Martinez, A., Le Moal, M., & Piazza, P.V. (2003). Relationships between individual sensitivity to CS- and cocaine-induced reinstatement in the rat. *Psychopharmacology (Berl), 168,* 201-7

Deroche-Gamonet, V., Piat, F., Le Moal, M., & Piazza, P.V. (2002). Influence of cue-conditioning on acquisition, maintenance and relapse of cocaine intravenous self-administration. *European Journal of Neuroscience, 15,* 1363-70

Deroche-Gamonet, V., Belin, D., & Piazza, P.V. (2004). Evidence for addiction-like behavior in the rat. *Science, 305(5686),* 1014-7

Dewey, S.L., Brodie, J.D., Gerasimov, M., Horan, B., Gardner, E.L, & Ashby, C.R. Jr. 1999. A pharmacologic strategy for the treatment of nicotine addiction. *Synapse, 31,* 76-86

Di Chiara, G. (1998). A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. *Journal of Psychopharmacology, 12,* 54-67

Di Chiara, G. (1999). Drug addiction as dopamine-dependent associative learning disorder. *European Journal of Pharmacology, 375,*13-30

Di Chiara, G., Acquas, E., Tanda, G., Cadoni, C. (1993). Drugs of abuse: biochemical surrogates of specific aspects of natural reward? *Biochemistry Society Symposium, 59,* 65-81

Di Chiara, G., Bassareo, V., Fenu, S., De Luca, M.A., & Spina, L. (2004). Dopamine and drug addiction: the nucleus accumbens shell connection. *Neuropharmacology, 47, Supl,* 227-41

Di Chiara, G., & Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Science, U S A, 85,* 5274-8

Di Chiara, G., Tanda, G., Bassareo, V., Pontieri, F., & Acquas E. (1999). Drug addiction as a disorder of associative learning. Role of nucleus accumbens shell/extended amygdala dopamine. *Annals of the New York Academy of Science*, 877, 461-85

Di Ciano, P., Blaha, C.D., & Phillips, A.G. (1998). Conditioned changes in dopamine oxidation currents in the nucleus accumbens of rats by stimuli paired with self-administration or yoked-administration of d-amphetamine. *European Journal of Neuroscience, 10,* 1121-7

Di Ciano, P., Blaha, C.D., & Phillips, A.G. (2001). Changes in dopamine efflux associated with extinction, CS-induced and d-amphetamine-induced reinstatement of drug-seeking behavior by rats. *Behaviour Brain Research, 120,* 147-58

Di Ciano, P., Coury, A., Depoortere, R.Y., Egilmez, Y., & Lane. J.D. (1995). Comparison of changes in extracellular dopamine concentrations in the nucleus accumbens during intravenous self-administration of cocaine or d-amphetamine. *Behavioural Pharmacology, 6,* 311-22

Di Ciano, P., & Everitt, B.J. (2002). Reinstatement and spontaneous recovery of cocaine-seeking following extinction and different durations of withdrawal. *Behavioural Pharmacology, 13,* 397-405

Di Ciano, P., Underwood, R.J., Hagan, J.J., & Everitt, B.J. (2003). Attenuation of cue-controlled cocaine-seeking by a selective D3 dopamine receptor antagonist SB-277011-A. *Neuropsychopharmacology, 28,* 329-38

Di Giovanni, G., Di Matteo, V., & Esposito, E. (2002). Serotonin/dopamine interaction--focus on 5-HT2C receptor, a new target of psychotropic drugs. *Indian Journal of Experimental Biology, 40,* 1344-52

Di Giovanni, G.D., De Deurwaerdere, P., Di Mascio, M., Di Matteo, V., Esposito, E., & Spampinato, U. 1999. Selective blockade of serotonin-2C/2B receptors enhances mesolimbic and mesostriatal dopaminergic function: a combined in vivo electrophysiological and microdialysis study. *Neuroscience, 91,* 587-97

Donny, E.C., Caggiula, A.R., Mielke, M.M., Jacobs, K.S., Rose, C., & Sved, A.F. (1998). Acquisition of nicotine self-administration in rats: the effects of dose, feeding schedule, and drug contingency. *Psychopharmacology (Berl), 136,* 83-90

Dougherty, J., Miller, D., Todd, G., & Kostenbauder, H.B. (1981). Reinforcing and other behavioral effects of nicotine. *Neuroscience & Biobehavioural Review, 5,* 487-95

Downing, J. (1986). The psychological and physiological effects of MDMA on normal volunteers. *Journal of Psychoactive Drugs, 18,* 335-40

Downs, D.A., & Woods, J.H. (1975). Fixed-ratio escape and avoidance-escape from naloxone in morphine-dependent monkeys: effects of naloxone dose and morphine pretreatment. *Journal of Experimental Analysis of Behaviour, 23,* 415-27

Drummond, D.C., Cooper, T., & Glautier, S.P. (1990). Conditioned learning in alcohol dependence: implications for cue exposure treatment. *British Journal of Addiction, 85,* 725-43

Drummond, D.C., Litten, R.Z., Lowman, C., & Hunt, W.A. (2000). Craving research: future directions. *Addiction, 95, Suppl 2,* S247-55

DSM-IV. 1994. *Diagnostic and statistical manual of mental disorders* Washington D.C.: American Psychiatric Association

Duarte, C., Lefebvre, C., Chaperon, F., Hamon, M., & Thiebot, M.H. (2003). Effects of a dopamine D3 receptor ligand, BP 897, on acquisition and expression of food-, morphine-, and cocaine-induced conditioned place preference, and food-seeking behavior in rats. *Neuropsychopharmacology, 28,* 1903-15

Duvauchelle, C.L., Ikegami, A., & Castaneda, E. (2000). Conditioned increases in behavioral activity and accumbens dopamine levels produced by intravenous cocaine. *Behavioural Neuroscience, 114(6),*1156-66

Dworkin, S., Guerin, G., Co, C., & Smith, J., Goeders, N. (1988). Effects of 5,7-dihydroxytryptamine lesions of the nucleus accumbens in rats responding on a concurrent schedule of food, water and intravenous morphine self-administration. *NIDA Research Monograph, 81,* 149-55

Dworkin, S.I., Guerin, G.F., Co, C., Goeders, N.E., & Smith, J.E. (1988). Lack of an effect of 6-hydroxydopamine lesions of the nucleus accumbens on intravenous morphine self-administration. *Pharmacology Biochemistry & Behaviour, 30,* 1051-7

Dworkin, S.I., Guerin, G.F., Goeders, N.E., Cherek, D.R., Lane, J.D, & Smith, J.E. (1984). Reinforcer interactions under concurrent schedules of food, water, and intravenous morphine. *Psychopharmacology (Berl), 82,* 282-6

Ehrman, R.N., Robbins, S.J., Childress, A.R., McLellan, A.T., & O'Brien, C.P. (1991). Responding to drug-related stimuli in humans as a function of drug-use history. *NIDA Research Monograph,* 231-44

Ehrman, R.N., Robbins, S.J., Childress, A.R., O'Brien, C.P. (1992). Conditioned responses to cocaine-related stimuli in cocaine abuse patients. *Psychopharmacology (Berl), 107,* 523-9

Ehrman, R.N., Robbins, S.J., MacRae, J.R., & Childress, A.R. (1990). Specificity of conditional responding to naturalistic stimuli in humans with different drug-use histories. *NIDA Research Monograph, 105,* 282-3

Eidelberg, E., & Erspamer, R. (1975). Dopaminergic mechanisms of opiate actions in brain. *Journal of Pharmacology & Experimental Therapeutics, 192,* 50-7

Epstein, D.H., Preston, K.L., Stewart, J., & Shaham, Y. (2006). Toward a model of drug relapse: an assessment of the validity of the reinstatement procedure. *Psychopharmacology (Berl), 189,*1-16

Erb, S., Shaham, Y., & Stewart, J. (1996). Stress reinstates cocaine-seeking behavior after prolonged extinction and a drug-free period. *Psychopharmacology (Berl), 128,* 408-12

Ettenberg, A., MacConell, L.A., & Geist, T.D. (1996). Effects of haloperidol in a response-reinstatement model of heroin relapse. *Psychopharmacology (Berl), 124,* 205-10

Everitt, B.J., & Robbins, T.W. (2000). Second-order schedules of drug reinforcement in rats and monkeys: measurement of reinforcing efficacy and drug-seeking behaviour. *Psychopharmacology (Berl), 153,* 17-30

Fantegrossi, W.E. (2007). Reinforcing effects of methylenedioxy amphetamine congeners in rhesus monkeys: are intravenous self-administration experiments relevant to MDMA neurotoxicity? *Psychopharmacology (Berl), 189,* 471-82

Fantegrossi, W.E., Ullrich, T., Rice, K.C., Woods, J.H., & Winger, G. (2002). 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") and its stereoisomers as reinforcers in rhesus monkeys: serotonergic involvement. *Psychopharmacology (Berl), 161,* 356-64

Fantegrossi, W.E., Woods, J.H., & Winger, G. (2004). Transient reinforcing effects of phenylisopropylamine and indolealkylamine hallucinogens in rhesus monkeys. *Behavioural Pharmacology, 15,* 149-57

Fantegrossi, W.E., Woolverton, W.L., Kilbourn, M., Sherman, P., & Yuan, J. (2004). Behavioral and neurochemical consequences of long-term

intravenous self-administration of MDMA and its enantiomers by rhesus monkeys. *Neuropsychopharmacology, 29,* 1270-81

Fernandez, F., Porras, G., Mormede, P., Spampinato, U., & Chaouloff, F. (2003). Effects of 3,4-methylenedioxymethamphetamine on locomotor activity and extracellular dopamine in the nucleus accumbens of Fischer 344 and Lewis rats. *Neuroscience Letter, 335,* 212-6

Fibiger, H.C., Phillips, A.G., & Brown, E.E. (1992). The neurobiology of cocaine-induced reinforcement. *Ciba Foundation Symposium, 166,* 96-111; discussion -24

Filip, M., & Cunningham, K.A. (2003). Hyperlocomotive and discriminative stimulus effects of cocaine are under the control of serotonin(2C) (5-HT(2C)) receptors in rat prefrontal cortex. *Journal of Pharmacology & Experimental Therapeutics, 306,* 734-43

Fischman, M.W., & Schuster, C.R. (1978). Drug seeking: a behavioral analysis in animals and humans. *NIDA Research Monograph, 4,* 23

Fisher, L.A., Elias, J.W., & Ritz, K. (1998). Predicting relapse to substance abuse as a function of personality dimensions. *Alcoholism, Clinical and Experimental Research, 22,* 1041-7

Fletcher, P.J., Grottick, A.J, & Higgins, G.A. (2002). Differential effects of the 5-HT(2A) receptor antagonist M100907 and the 5-HT(2C) receptor antagonist SB242084 on cocaine-induced locomotor activity, cocaine self-administration and cocaine-induced reinstatement of responding. *Neuropsychopharmacology, 27,* 576-86

Fletcher, P.J., Korth, K.M., Robinson, S.R., & Baker, G.B. (2002). Multiple 5-HT receptors are involved in the effects of acute MDMA treatment: studies on locomotor activity and responding for conditioned reinforcement. *Psychopharmacology (Berl), 162,* 282-91

Fletcher, P.J., Robinson, S.R., & Slippoy, D.L. (2001). Pre-exposure to (+/-)3,4-methylenedioxy-methamphetamine (MDMA) facilitates acquisition of intravenous cocaine self-administration in rats. *Neuropsychopharmacology, 25,* 195-203

Foltin, R.W., & Haney, M. (2000). Conditioned effects of environmental stimuli paired with smoked cocaine in humans. *Psychopharmacology (Berl), 149,* 24-33

Fontana, D.J., Post, R.M., & Pert, A. (1993). Conditioned increases in mesolimbic dopamine overflow by stimuli associated with cocaine. *Brain Research, 629(1),* 31-9

Ford, R.D., & Balster, R.L. (1976). Schedule-controlled behavior in the morphine-dependent rat. *Pharmacology, Biochemistry & Behaviour, 4,* 569-73

Forsyth, A.J. (1996). Places and patterns of drug use in the Scottish dance scene. *Addiction, 91,* 511-21

Foster, G.A., Roberts, M.H., Wilkinson, L.S., Bjorklund, A., & Gage, F.H. (1989). Structural and functional analysis of raphe neurone implants into denervated rat spinal cord. *Brain Research Bulletin, 22,* 131-7

Fox, H.C., McLean, A., Turner, J.J., Parrott, A.C., Rogers, R., & Sahakian, B.J. (2002). Neuropsychological evidence of a relatively selective

profile of temporal dysfunction in drug-free MDMA ("ecstasy") polydrug users. *Psychopharmacology (Berl), 162,*203-14

Franken, I.H., Hendriks, V.M., Stam, C.J., & Van den Brink, W. (2004). A role for dopamine in the processing of drug cues in heroin dependent patients. *European Neuropsychopharmacology, 14,* 503-8

Fuchs,R.A., Evans, K.A., Parker, M.P., & See, R.E. (2004). Differential involvement of orbitofrontal cortex subregions in conditioned cue-induced and cocaine-primed reinstatement of cocaine seeking in rats. *Journal of Neuroscience, 24,* 6600-10

Gardner, E.L. (2000). What we have learned about addiction from animal models of drug self-administration. *American Journal of Addiction, 9,* 285-313

Gerber, G.J., & Stretch, R. (1975). Drug-induced reinstatement of extinguished self-administration behavior in monkeys. *Pharmacology, Biochemistry & Behaviour, 3,* 1055-61

Gold, L.H., Geyer, M.A., & Koob, G.F. (1989). Neurochemical mechanisms involved in behavioral effects of amphetamines and related designer drugs. *NIDA Research Monograph, 94,* 101-26

Gold, L.H., Hubner, C.B., & Koob, G.F. (1989). A role for the mesolimbic dopamine system in the psychostimulant actions of MDMA. *Psychopharmacology (Berl), 99,* 40-7

Gold, L.H., & Koob, G.F. (1988). Methysergide potentiates the hyperactivity produced by MDMA in rats. *Pharmacology, Biochemistry & Behaviour, 29,* 645-8

Gold, L.H., & Koob, G.F. (1989). MDMA produces stimulant-like conditioned locomotor activity. *Psychopharmacology (Berl), 99,* 352-6

Gold. L.H., Koob, G.F., & Geyer, M.A. (1988). Stimulant and hallucinogenic behavioral profiles of 3,4-methylenedioxymethamphetamine and N-ethyl-3,4-methylenedioxyamphetamine in rats. *Journal of Pharmacology & Experimental Therapeutics, 247,* 547-55

Gold, L.H., Swerdlow, N.R., & Koob, G.F. (1988). The role of mesolimbic dopamine in conditioned locomotion produced by amphetamine. *Behavioural Neuroscience, 102,* 544-52

Goldberg, S.R. (1973). Comparable behavior maintained under fixed-ratio and second-order schedules of food presentation, cocaine injection or d-amphetamine injection in the squirrel monkey. *Journal of Pharmacology & Experimental Therapeutics, 186,* 18-30

Goldberg, S.R., & Gardner, M.L. (1981). Second-order schedules: extended sequences of behavior controlled by brief environmental stimuli associated with drug self-administration. *NIDA Research Monograph, 37,* 241-70

Goldberg, S.R., & Henningfield, J.E. (1988). Reinforcing effects of nicotine in humans and experimental animals responding under intermittent schedules of i.v. drug injection. *Pharmacology, Biochemistry & Behaviour, 30,* 227-34

Goldberg, S.R., Kelleher, R.T., & Goldberg, D.M. (1981). Fixed-ratio responding under second-order schedules of food presentation or

cocaine injection. *Journal of Pharmacology & Experimental Therapeutics, 218,* 271-81

Goldberg, S.R., Kelleher, R.T., & Morse, W.H. (1975). Second-order schedules of drug injection. *Federal Proceedings, 34,* 1771-6

Goldberg, S.R., & Tang, A.H. (1977). Behavior maintained under second-order schedules of intravenous morphine injection in squirrel and rhesus monkeys. *Psychopharmacology (Berl), 51,* 235-42

Goldberg, S.R., Woods, J.H., & Schuster, C.R. (1969). Morphine: conditioned increases in self-administration in rhesus monkeys. *Science, 166,* 1306-7

Gong, W., Neill, D., & Justice, J.B., Jr. (1996). Conditioned place preference and locomotor activation produced by injection of psychostimulants into ventral pallidum. *Brain Research, 707,* 64-74

Gong, W., Neill D., & Justice, J.B., Jr. (1997). 6-Hydroxydopamine lesion of ventral pallidum blocks acquisition of place preference conditioning to cocaine. *Brain Research, 754,* 103-12

Gotestam, K.G., & Anderson, B.E. (1975). Self-administration of amphetamine analogues in rats. *Pharmacology, Biochemistry & Behaviour, 3,* 229-33

Grasing, K.W., & Miller, N.E. (1989). Self-administration of morphine contingent on heart rate in the rat. *Life Science, 45,* 1967-76

Green, A.R., Cross, A.J., & Goodwin, G.M. (1995). Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy"). *Psychopharmacology (Berl), 119,* 247-60

Green, A.R., Mechan, A.O., Elliott, J.M., O'Shea, E., & Colado, M.I. (2003). The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacological Review, 55,* 463-508

Greer, G., & Tolbert, R. (1986). Subjective reports of the effects of MDMA in a clinical setting. *Journal of Psychoactive Drugs, 18,* 319-27

Griffiths, R., Brady, J.V., & Bradford, L.D. (1979). Predicting the abuse liability of drugs with animal drug self-administration procedures: Psychomotor stimulants and hallucinogens. In *Advances in Behavioural Pharmacology,* ed. T Thompson, PB dews, pp. 163-208. New York: Academic press

Griffiths, R.R., & Balster, R.L. (1979). Opioids: similarity between evaluations of subjective effects and animal self-administration results. *Clinical Pharamcology & Therapeutics, 25,* 611-7

Griffiths, R.R., Bigelow, G.E., & Liebson, I. (1978). Experimental drug self-administration: generality across species and type of drug. *NIDA Research Monograph*: *24,* 43

Griffiths, R.R., Brady, J.V., & Bigelow, G.E. (1981). Predicting the dependence liability of stimulant drugs. *NIDA Research Monograph, 37,* 182-96

Griffiths, R.R., Brady, J.V., & Snell, J.D. (1978). Progressive-ratio performance maintained by drug infusions: comparison of cocaine, diethylpropion, chlorphentermine, and fenfluramine. *Psychopharmacology (Berl), 56,* 5-13

Griffiths, R.R., Winger, G., Brady, J.V., Snell, J.D. (1976). Comparison of behavior maintained by infusions of eight phenylethylamines in baboons. *Psychopharmacology (Berl), 50,* 251-8

Grimm, J.W., Shaham, Y., & Hope, B.T. (2002). Effect of cocaine and sucrose withdrawal period on extinction behavior, cue-induced reinstatement, and protein levels of the dopamine transporter and tyrosine hydroxylase in limbic and cortical areas in rats. *Behavioural Pharmacology, 13,* 379-88

Grob, C., Bravo, G., & Walsh, R. (1990). Second thoughts on 3,4-methylenedioxymethamphetamine (MDMA) neurotoxicity. *Archives of General Psychiatry, 47,* 288-9

Grob, C.S., Poland, R.E., Chang, L., & Ernst, T. (1996). Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations. *Behaiour Brain Research, 73,* 103-7

Gudelsky, G.A., & Nash, J.F. (1996). Carrier-mediated release of serotonin by 3,4-methylenedioxymethamphetamine: implications for serotonin-dopamine interactions. *Journal of Neurochemistry, 66,* 243-9

Gudelsky, G.A., & Yamamoto, B.K. (2003). Neuropharmacology and neurotoxicity of 3,4-methylenedioxymethamphetamine. *Methods of Molecular Medicine,* 79, 55-73

Gudelsky, G.A., Yamamoto, B.K., & Nash, J.F. (1994). Potentiation of 3,4-methylenedioxymethamphetamine-induced dopamine release and

serotonin neurotoxicity by 5-HT2 receptor agonists. *European Journal of Pharmacology, 264,* 325-30

Haile, C.N., & Kosten, T.A. (2001). Differential effects of D1- and D2-like compounds on cocaine self-administration in Lewis and Fischer 344 inbred rats. *Journal of Pharmacology & Experimental Therapeutics, 299,* 509-18

Haney, M., Collins, E.D., Ward, A.S., Foltin, R.W., & Fischman, M.W. (1999). Effect of a selective dopamine D1 agonist (ABT-431) on smoked cocaine self-administration in humans. *Psychopharmacology (Berl), 143,* 102-10

Haney, M., Comer, S.D., Ward, A.S., Foltin, R.W., & Fischman, M.W. (1997). Factors influencing marijuana self-administration by humans. *Behavioural Pharmacology, 8,* 101-12

Hanson, H.M., Ivester, C.A., & Morton, B.R. (1979). Nicotine self-administration in rats. *NIDA Research Monograph*, 70-90

Harrigan, S.E., & Downs, D.A. (1978). Self-administration of heroin, acetylmethadol, morphine, and methadone in rhesus monkeys. *Life Science, 22,* 619-23

Harris, D.S., Batki, S.L., & Berger, S.P. (2004). Fluoxetine attenuates adrenocortical but not subjective responses to cocaine cues. *American Journal of Drug and Alcohol Abuse, 30,* 765-82

Hegadoren, K.M., Baker, G.B., & Bourin, M. (1999). 3,4-Methylenedioxy analogues of amphetamine: defining the risks to humans. *Neuroscience and Biobehavioural Review, 23,* 539-53

Helzer, J. (1988). Psychiatric diagnoses and substance abuse in the general population: the ECA data. *NIDA Research Monograph 81*:405-15

Hemby, S.E., Co, C., Koves, T.R., Smith, J.E., & Dworkin, S.I. (1997). Differences in extracellular dopamine concentrations in the nucleus accumbens during response-dependent and response-independent cocaine administration in the rat. *Psychopharmacology (Berl), 133,* 7-16

Hemby, S.E., Jones, G.H., Hubert, G.W., Neill, D.B., & Justice, J.B., Jr. (1994). Assessment of the relative contribution of peripheral and central components in cocaine place conditioning. *Pharmacology, Biochemistry & Behaviour, 47,* 973-9

Hemby, S.E., Smith, J.E., & Dworkin, S.I. (1996). The effects of eticlopride and naltrexone on responding maintained by food, cocaine, heroin and cocaine/heroin combinations in rats. *Journal of Pharmacology & Experimental Therapeutics, 277,* 1247-58

Higgins, G.A., Wang, Y., Corrigall, W.A., & Sellers, E.M. (1994). Influence of 5-HT3 receptor antagonists and the indirect 5-HT agonist, dexfenfluramine, on heroin self-administration in rats. *Psychopharmacology (Berl), 114,* 611-9

Hinson, R.E., & Poulos, C.X. (1981). Sensitization to the behavioral effects of cocaine: modification by Pavlovian conditioning. *Pharmacology, Biochemistry & Behaviour, 15,* 559-62

Hinson, R.E., & Siegel, S. (1983). Anticipatory hyperexcitability and tolerance to the narcotizing effect of morphine in the rat. *Behavioural Neuroscience, 97,* 759-67

Hoffman, D.C., Dickson, P.R., & Beninger, R.J. (1988). The dopamine D2 receptor agonists, quinpirole and bromocriptine produce conditioned place preferences. *Progress in Neuropsychopharmacology and Biological Psychiatry, 12,* 315-22

Hoffmeister, F., & Goldberg, S.R. (1973). A comparison of chlorpromazine, imipramine, morphine and d-amphetamine self-administration in cocaine-dependent rhesus monkeys. *Journal of Pharmacology & Experimental Therapeutics, 187,* 8-14

Hooks, M.S., Duffy, P., Striplin, C., & Kalivas, P.W. (1994). Behavioral and neurochemical sensitization following cocaine self-administration. *Psychopharmacology (Berl), 115,* 265-72

Horan, B., Gardner, E.L., & Ashby, C.R, Jr. (2000). Enhancement of conditioned place preference response to cocaine in rats following subchronic administration of 3, 4-methylenedioxymethamphetamine (MDMA). *Synapse, 35,* 160-2

Howell, L.L., & Byrd, L.D. (1991). Characterization of the effects of cocaine and GBR 12909, a dopamine uptake inhibitor, on behavior in the squirrel monkey. *Journal of Pharmacology & Experimental Therapeutic*s, 258, 178-85

Hubner, C.B., & Moreton, J.E. (1991). Effects of selective D1 and D2 dopamine antagonists on cocaine self-administration in the rat. *Psychopharmacology (Berl), 105,* 151-6

Hurd, Y.L., Weiss, F., Koob, G.F., & Ungerstedt U. (1989). Cocaine reinforcement and extracellular dopamine overflow in rat nucleus

accumbens: an in vivo microdialysis study. *Brain Research, 498,* 199-203

Hutchison, K.E., Rutter, M.C., Niaura, R., Swift, R.M., Pickworth, W.B., & Sobik, L. 2004. Olanzapine attenuates cue-elicited craving for tobacco. *Psychopharmacology (Berl), 175,* 407-13

Hyman, S.E., & Malenka, R.C. (2001). Addiction and the brain: the neurobiology of compulsion and its persistence. *Nature reviews: Neuroscience,* 2, 695-703

Iannone, M., Bulotta, S., Paolino, D., Zito, M.C., & Gratteri, S., (2006). Electrocortical effects of MDMA are potentiated by acoustic stimulation in rats. *BMC Neurosciecnce,* 7, 13

Imperato, A., Mele, A., Scrocco, M.G., & Puglisi-Allegra, S. (1992). Chronic cocaine alters limbic extracellular dopamine. Neurochemical basis for addiction. *European Journal of Pharmacology, 212,* 299-300

Imperato, A., Obinu, M.C., Casu, M.A., Mascia, M.S., Carta, G., & Gessa, G.L. (1996). Chronic morphine increases hippocampal acetylcholine release: possible relevance in drug dependence. *European Journal of Pharmacology, 302,* 21-6

Ingersoll, K.S., Lu, I.L., & Haller, D.L. (1995). Predictors of in-treatment relapse in perinatal substance abusers and impact on treatment retention: a prospective study. *Journal of Psychoactive Drugs, 27,* 375-87

Irwin, S., & Armstrong, P.M. (1961). Conditioned locomotor response with drug as the unconditioned stimulus: Individual differences. In:

Rothlin, E.,ed. *Neuropsychopharmacology: Proceedings of the Second Meeting of the Colleqium Internationale Neuro-psychopharmacologicum*. Amsterdam: Elsevier, *1961*. pp. 151-157.

Ito, R., Dalley, J.W., Howes, S.R., Robbins, T.W., & Everitt, B.J. (2000). Dissociation in conditioned dopamine release in the nucleus accumbens core and shell in response to cocaine cues and during cocaine-seeking behavior in rats. *Journal of Neuroscience, 20(19),* 7489-95.

Itzhak, Y., Ali, S.F., Achat, C.N., & Anderson, K.L. (2003). Relevance of MDMA ("ecstasy")-induced neurotoxicity to long-lasting psychomotor stimulation in mice. *Psychopharmacology (Berl), 166,* 241-8

Itzhak, Y., & Martin, J.L. (2000). Blockade of alcohol-induced locomotor sensitization and conditioned place preference in DBA mice by 7-nitroindazole. *Brain Research, 858,* 402-7

Izzo, E., Orsini, C., Koob, G.F., & Pulvirenti, L. (2001). A dopamine partial agonist and antagonist block amphetamine self-administration in a progressive ratio schedule. *Pharmacology, Biochemistry & Behaviour, 68,* 701-8

Jansen, K.L. (1999). Ecstasy (MDMA) dependence. *Drug Alcohol Dependenc*e, *53,* 121-4

Johnson, M.P., Hoffman, A.J., & Nichols, D.E. (1986). Effects of the enantiomers of MDA, MDMA and related analogues on [3H]serotonin and [3H]dopamine release from superfused rat brain slices. *European Journal of Pharmacology, 132,* 269-76

Kalivas, P.W., Duffy, P., & White, S.R. (1998). MDMA elicits behavioral and neurochemical sensitization in rats. *Neuropsychopharmacology, 18,* 469-79

Kalivas, P.W., & McFarland, K. (2003). Brain circuitry and the reinstatement of cocaine-seeking behavior. *Psychopharmacology (Berl), 168,* 44-56

Kalivas, P.W., Pierce, R.C., Cornish, J., & Sorg, B.A. (1998). A role for sensitization in craving and relapse in cocaine addiction. *Journal of Psychopharmacology, 12,* 49-53

Kalivas, P.W., & Stewart, J. (1991). Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. *Brain Research Reviews, 16,* 223-44

Kamat, K.A., Dutta, S.N., & Pradhan, S.N. (1974). Conditioning of morphine-induced enhancement of motor activity. *Research Communications in Chemical Pathology and Pharmacology, 7,* 367-73

Katz, J.L., & Higgins, S.T. (2003). The validity of the reinstatement model of craving and relapse to drug use. *Psychopharmacology (Berl), 168,* 21-30

Kehne, J.H., Ketteler, H.J., McCloskey, T.C., Sullivan, C.K., Dudley, M.W., & Schmidt C.J. (1996). Effects of the selective 5-HT2A receptor antagonist MDL 100,907 on MDMA-induced locomotor stimulation in rats. *Neuropsychopharmacology, 15,* 116-24

Kelleher, R.T. (1966). Conditioned reinforcement in second-order schedules. *Journal of Experimental Analysis of Behaviour, 9,* 475-85

Kelley, A.E., & Lang, C.G. (1989). Effects of GBR 12909, a selective dopamine uptake inhibitor, on motor activity and operant behavior in the rat. *European Journal of Pharmacology, 167,* 385-95

Khroyan, T.V., Baker, D.A., & Neisewander, J.L. (1995). Dose-dependent effects of the D3-preferring agonist 7-OH-DPAT on motor behaviors and place conditioning. *Psychopharmacology (Berl), 122,* 351-7

Khroyan, T.V., Barrett-Larimore, R.L., Rowlett, J.K., & Spealman, R.D. (2000). Dopamine D1- and D2-like receptor mechanisms in relapse to cocaine-seeking behavior: effects of selective antagonists and agonists. *Journal of Pharmacology & Experimental Therapeutics, 294,* 680-7

Kling-Petersen, T., Ljung, E., Wollter, L., & Svensson, K. (1995). Effects of dopamine D3 preferring compounds on conditioned place preference and intracranial self-stimulation in the rat. *Journal of Neural Transmission,General Section, 101,* 27-39

Koch, S., & Galloway, M.P. (1997). MDMA induced dopamine release in vivo: role of endogenous serotonin. *Journal of Neural Transmission, 104,* 135-46

Koeltzow, T.E., & Vezina, P. (2005). Locomotor activity and cocaine-seeking behavior during acquisition and reinstatement of operant

self-administration behavior in rats. *Behav Brain Research, 160,* 250-9

Koob, G.F. (1992). Neural mechanisms of drug reinforcement. *Annals of New York Academy of Science, 654,*171-91

Koob, G.F. (2006). The neurobiology of addiction: a neuroadaptational view relevant for diagnosis. *Addiction, 101, Suppl 1,*23-30

Koob, G.F., & Hubner, C.B. (1988). Reinforcement pathways for cocaine. *NIDA Research Monograph, 88,* 137-59

Koob, G.F., Le, H.T., & Creese, I. (1987). The D1 dopamine receptor antagonist SCH 23390 increases cocaine self-administration in the rat. *Neuroscience Letter,79,* 315-20

Koob, G.F., & Le Moal, M. (1997). Drug abuse: hedonic homeostatic dysregulation. *Science,* 278, 52-8

Koob, G.F, & Weiss, F. (1990). Pharmacology of drug self-administration. *Alcohol, 7,* 193-7

Koob, G.F., Caine, S.B., Parsons, L., Markou, A., & Weiss, F. (1997). Opponent process model and psychostimulant addiction. *Pharmacology, Biochemistry & Behaviour., 57(3),* 513-21.

Kosten, T.A., & Nestler, E.J. (1994). Clozapine attenuates cocaine conditioned place preference. *Life Science, 55,* PL9-14

Kozikowski, A.P., Johnson, K.M., Deschaux, O., Bandyopadhyay, B.C., & Araldi, G.L., (2003). Mixed cocaine agonist/antagonist properties of (+)-methyl 4beta-(4-chlorophenyl)-1-methylpiperidine-3alpha-carboxylate, a piperidine-based analog of cocaine. *Journal of Pharmacology & Experimental Therapeutics, 305,* 143-50

Kuczenski, R., Segal, D.S., & Todd, P.K. (1997). Behavioral sensitization and extracellular dopamine responses to amphetamine after various treatments. *Psychopharmacology (Berl), 134*, 221-9

Kurtz, S.P., Inciardi, J.A., Surratt, H.L., & Cottler, L. (2005). Prescription drug abuse among ecstasy users in Miami. *Journal of Addictive Diseases, 24*, 1-16

Lacosta, S., & Roberts, D.C. (1993). MDL 72222, ketanserin, and methysergide pretreatments fail to alter breaking points on a progressive ratio schedule reinforced by intravenous cocaine. *Pharmacology, Biochemistry & Behaviour, 44*, 161-5

Lamb, R.J., & Griffiths, R.R. (1987). Self-injection of d,1-3,4-methylenedioxymethamphetamine (MDMA) in the baboon. *Psychopharmacology (Berl), 91*, 268-72

Lang, W.J., Latiff, A.A., McQueen, A., & Singer, G. (1977). Self administration of nicotine with and without a food delivery schedule. *Pharmacology, Biochemistry & Behaviour, 7*, 65-70

Le Foll, B., & Goldberg, S.R. (2005). Control of the reinforcing effects of nicotine by associated environmental stimuli in animals and humans. *Trends in Pharmacological Sciences, 26*, 287-93

Le Foll, B., Sokoloff, P., Stark, H., & Goldberg, S.R. (2005). Dopamine D3 receptor ligands block nicotine-induced conditioned place preferences through a mechanism that does not involve discriminative-stimulus or antidepressant-like effects. *Neuropsychopharmacology, 30*, 720-30

Leccese, A.P., & Lyness, W.H. (1984). The effects of putative 5-hydroxytryptamine receptor active agents on D-amphetamine self-administration in controls and rats with 5,7-dihydroxytryptamine median forebrain bundle lesions. *Brain Research, 303,* 153-62

Leccese, A.P., & Lyness WH. (1987). Lesions of dopamine neurons in the medial prefrontal cortex: effects on self-administration of amphetamine and dopamine synthesis in the brain of the rat. *Neuropharmacology, 26,* 1303-8

Lemaire, G.A., & Meisch, R.A. (1984). Pentobarbital self-administration in rhesus monkeys: drug concentration and fixed-ratio size interactions. *Journal of Experimental Analysis of Behaviour, 42,* 37-49

Lemaire, G.A., & Meisch, R.A. (1985). Oral drug self-administration in rhesus monkeys: interactions between drug amount and fixed-ratio size. *Journal of Experimental Analysis of Behaviour, 44,* 377-89

Leshner, A.I., & Koob, G.F. (1999). Drugs of abuse and the brain. *Proc Assoc Am Physicians, 111,* 99-108

Levy, K.B., O'Grady, K.E., Wish, E.D., & Arria, A.M. (2005). An in-depth qualitative examination of the ecstasy experience: results of a focus group with ecstasy-using college students. *Substance use and misuse, 40,* 1427-41

Lew, E.O., & Richardson, J.S. (1981). Neurochemical and behavioural correlates of the interaction between amphetamine and delta 9-tetrahydrocannabinol in the rat. *Drug and Alcohol Dependence, 8,* 93-101

Li, D.H., Depoortere, R.Y., & Emmett-Oglesby, M.W. (1994). Tolerance to the reinforcing effects of cocaine in a progressive ratio paradigm. *Psychopharmacology (Berl), 116,* 326-32

Li,N., He, S., Parrish, C., Delich, J., & Grasing, K. (2003). Differences in morphine and cocaine reinforcement under fixed and progressive ratio schedules; effects of extinction, reacquisition and schedule design. *Behavioural Pharmacology, 14,* 619-30

Liechti, M.E. (2003). ["Ecstasy" (MDMA): pharmacology, toxicology, and treatment of acute intoxication]. *Dtsch Med Wochenschr, 128,* 1361-6

Liechti, M.E., Baumann, C., Gamma, A., & Vollenweider, F.X. (2000a). Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") are attenuated by the serotonin uptake inhibitor citalopram. *Neuropsychopharmacology, 22,* 513-21

Liechti, M.E., Gamma, A., & Vollenweider, F.X. (2001). Gender differences in the subjective effects of MDMA. *Psychopharmacology (Berl), 154,* 161-8

Liechti, M.E., Saur, M.R., Gamma, A., Hell, D., & Vollenweider, F.X. (2000b). Psychological and physiological effects of MDMA ("Ecstasy") after pretreatment with the 5-HT(2) antagonist ketanserin in healthy humans. *Neuropsychopharmacology, 23,* 396-404

Liechti, M.E., & Vollenweider, F.X. (2000). Acute psychological and physiological effects of MDMA ("Ecstasy") after haloperidol

pretreatment in healthy humans. *European Neuropsychopharmacology, 10,* 289-95

Lile, J.A., Ross, J.T., & Nader, M.A. (2005). A comparison of the reinforcing efficacy of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") with cocaine in rhesus monkeys. *Drug and Alcohol Dependence, 78,* 135-40

Lin, H.Q., Atrens, D.M., Christie, M.J., Jackson, D.M., & McGregor, I.S. (1993). Comparison of conditioned taste aversions produced by MDMA and d-amphetamine. *Pharmacology, Biochemistry & Behaviour, 46,* 153-6

Lin, H.Q., McGregor, I.S., Atrens, D.M., Christie, M.J., & Jackson, D.M. (1994). Contrasting effects of dopaminergic blockade on MDMA and d-amphetamine conditioned taste aversions. *Pharmacology, Biochemistry & Behaviour,* 47, 369-74

Liu, X., & Weiss, F. (2002). Additive effect of stress and drug cues on reinstatement of ethanol seeking: exacerbation by history of dependence and role of concurrent activation of corticotropin-releasing factor and opioid mechanisms. *Journal of Neuroscience, 22,* 7856-61

Llorente del Pozo, J.M., Fernandez Gomez, C., Gutierrez Fraile, M., & Vielva Perez, I. (1998). Psychological and behavioural factors associated with relapse among heroin abusers treated in therapeutic communities. *Addictive behaviours, 23,* 155-69

Loh, E.A., & Roberts, D.C. (1990). Break-points on a progressive ratio schedule reinforced by intravenous cocaine increase following

depletion of forebrain serotonin. *Psychopharmacology (Berl), 101,* 262-6

London, E.D., Ernst, M., Grant, S., Bonson, K., & Weinstein, A. (2000). Orbitofrontal cortex and human drug abuse: functional imaging. *Cerebral Cortex, 10,* 334-42

Lucas, G., De Deurwaerdere, P., Caccia, S., & Umberto, S. (2000). The effect of serotonergic agents on haloperidol-induced striatal dopamine release in vivo: opposite role of 5-HT(2A) and 5-HT(2C) receptor subtypes and significance of the haloperidol dose used. *Neuropharmacology, 39,* 1053-63

Lucas, G., & Spampinato, U. (2000). Role of striatal serotonin2A and serotonin2C receptor subtypes in the control of in vivo dopamine outflow in the rat striatum. *Journal of Neurochemistry, 74,* 693-701

Lyness, W.H., Friedle, N.M., & Moore, K.E. (1979). Destruction of dopaminergic nerve terminals in nucleus accumbens: effect on d-amphetamine self-administration. *Pharmacology, Biochemistry & Behaviour, 11,* 553-6

Maldonado, R., Robledo, P., Chover, A.J., Caine, S.B., & Koob, G.F. (1993). D1 dopamine receptors in the nucleus accumbens modulate cocaine self-administration in the rat. *Pharmacology, Biochemistry & Behaviour, 45,* 239-42

Mann, N.R., Charuvastra, V.C., Murthy, V.K. (1984). A diagnostic tool with important implications for treatment of addiction: identification of factors underlying relapse and remission time distributions. *International Journal of Addiction, 19,* 25-44

Mansbach, R.S., Markou, A., & Patrick, G.A. (1994). Lack of altered startle responding in rats following termination of self-administered or noncontingently infused cocaine. *Pharmacology, Biochemistry & Behaviour, 48,* 453-8

Mantsch, J.R., & Goeders, N.E. (2000). Effects of cocaine self-administration on plasma corticosterone in rats: relationship to hippocampal type II glucocorticoid receptors. *Progress in Neuropsychopharmacology and Biological Psychiatry, 24,* 633-46

Mantsch, J.R., Yuferov, V., Mathieu-Kia, A.M., Ho, A., & Kreek, M.J. (2003). Neuroendocrine alterations in a high-dose, extended-access rat self-administration model of escalating cocaine use. *Psychoneuroendocrinology, 28,* 836-62

Mantsch, J.R., Yuferov, V., Mathieu-Kia, A.M., Ho, A., & Kreek, M.J. (2004). Effects of extended access to high versus low cocaine doses on self-administration, cocaine-induced reinstatement and brain mRNA levels in rats. *Psychopharmacology (Berl), 175,* 26-36

Marlatt, G. A., & Gordon, J.R. (Ed.). (1985). *Relapse Prevention: Maintenance strategies in the treatment of addictive behaviors.* New York: Guilford Press.

Marona-Lewicka, D., Rhee, G.S., Sprague, J.E., & Nichols, D.E. (1996). Reinforcing effects of certain serotonin-releasing amphetamine derivatives. *Pharmacology, Biochemistry & Behaviour, 53,* 99-105

Martin-Iverson, M.T., Szostak, C., & Fibiger, H.C. (1986). 6-Hydroxydopamine lesions of the medial prefrontal cortex fail to

influence intravenous self-administration of cocaine. *Psychopharmacology (Berl), 88,* 310-4

Martin, T.J., Walker, L.E., Sizemore, G.M., Smith, J.E., & Dworkin, S.I. (1996). Within-session determination of dose-response curves for heroin self-administration in rats: Comparison with between-session determination and effects of naltrexone. *Drug and Alcohol Dependence, 41,* 93-100

Mayerhofer, A., Kovar, K.A., Schmidt, W.J. (2001). Changes in serotonin, dopamine and noradrenaline levels in striatum and nucleus accumbens after repeated administration of the abused drug MDMA in rats. *Neuroscience Letter, 308,* 99-102

Mazurski, E.J., & Beninger, R.J. (1991). Effects of selective drugs for dopaminergic D1 and D2 receptors on conditioned locomotion in rats. *Psychopharmacology (Berl), 105,* 107-12

McCann, U.D., Slate, S.O., & Ricaurte, G.A. (1996). Adverse reactions with 3,4-methylenedioxymethamphetamine (MDMA; 'ecstasy'). *Drug Safe, 15,*107-15

McCreary, A.C., Bankson, M.G., & Cunningham, K.A. (1999). Pharmacological studies of the acute and chronic effects of (+)-3, 4-methylenedioxymethamphetamine on locomotor activity: role of 5-hydroxytryptamine(1A) and 5-hydroxytryptamine(1B/1D) receptors. *Journal of Pharmacology & Experimental Therapeutics, 290,* 965-73

McFarland, K., & Ettenberg, A. (1997). Reinstatement of drug-seeking behavior produced by heroin-predictive environmental stimuli. *Psychopharmacology (Berl),* 131, 86-92

McGregor, A., Baker, G., & Roberts, D.C. (1996). Effect of 6-hydroxydopamine lesions of the medial prefrontal cortex on intravenous cocaine self-administration under a progressive ratio schedule of reinforcement. *Pharmacology, Biochemistry & Behaviour, 53,* 5-9

McGregor, A., & Roberts, D.C. (1995). Effect of medial prefrontal cortex injections of SCH 23390 on intravenous cocaine self-administration under both a fixed and progressive ratio schedule of reinforcement. *Behav Brain Research, 67,* 75-80

McGregor, I.S., Clemens, K.J., Van der Plasse, G., Li, K.M., Hunt, G.E., et al. (2003). Increased anxiety 3 months after brief exposure to MDMA ("Ecstasy") in rats: association with altered 5-HT transporter and receptor density. *Neuropsychopharmacology, 28,* 1472-84

McKenna, D.J., & Peroutka, S.J. (1990). Neurochemistry and neurotoxicity of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Journal of Neurochemistry, 54,* 14-22

Mechan, A.O., Moran, P.M., Elliott, M., Young, A.J., Joseph, M.H., & Green. R. (2002). A study of the effect of a single neurotoxic dose of 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy") on the subsequent long-term behaviour of rats in the plus maze and open field. *Psychopharmacology (Berl), 159,* 167-75

Meil, W.M., Roll, J.M., Grimm, J.W., Lynch, A.M., & See, R.E. (1995). Tolerance-like attenuation to contingent and noncontingent cocaine-induced elevation of extracellular dopamine in the ventral striatum following 7 days of withdrawal from chronic treatment. *Psychopharmacology (Berl), 118,* 338-46

Meil, W.M., & See, R.E. (1996). Conditioned cued recovery of responding following prolonged withdrawal from self-administered cocaine in rats: an animal model of relapse. *Behavioural Pharmacology, 7,* 754-63

Meisch, R.A., & Stewart, R.B. (1994). Ethanol as a reinforcer: a review of laboratory studies of non-human primates. *Behavioural Pharmacology, 5,* 425-40

Mendelson, J.H., & Mello, N.K. (1996). Management of cocaine abuse and dependence. *New England Journal of Medicine, 334,* 965-72

Merck. (1989). *The Merck Index: An Encyclopaedia of Chemicals, Drugs, and Biologicals*: Merck & Co.

Meyer, A., Mayerhofer, A., Kovar, K.A., & Schmidt, W.J. (2002). Rewarding effects of the optical isomers of 3,4-methylenedioxy-methylamphetamine ('Ecstasy') and 3,4-methylenedioxy-ethylamphetamine ('Eve') measured by conditioned place preference in rats. *Neuroscience Letter, 330,* 280-4

Mierzejewski, P., Koros, E., Goldberg, S.R., Kostowski, W., & Stefanski, R. (2003). Intravenous self-administration of morphine and cocaine: a comparative study. *Polish Journal of Pharmacology, 55,* 713-26

Milkman. H., Weiner, S.E., & Sunderwirth, S. (1983). Addiction relapse. *Advances in Alcohol & Substance Abuse, 3,* 119-34

Miller, N.S., Ninonuevo, F.G., Klamen, D.L., Hoffmann, N.G., & Smith, D.E. (1997). Integration of treatment and posttreatment variables in predicting results of abstinence-based outpatient treatment after one year. *Journal of Psychoactive Drugs, 29,* 239-48

Morgan, D., Brebner, K., Lynch, W.J., & Roberts, D.C. (2002). Increases in the reinforcing efficacy of cocaine after particular histories of reinforcement. *Behavioural Pharmacology, 13,* 389-96

Morley, K.C., Arnold, J.C., & McGregor, I.S. (2005). Serotonin (1A) receptor involvement in acute 3,4-methylenedioxymethamphetamine (MDMA) facilitation of social interaction in the rat. *Progress in Neuropsychopharmacology & Biological Psychiatry, 29,* 648-57

Morley, K.C., Cornish, J.L., Li, K.M., & McGregor, I.S. (2004). Preexposure to MDMA ("Ecstasy") delays acquisition but facilitates MDMA-induced reinstatement of amphetamine self-administration behavior in rats. *Pharmacology, Biochemistry & Behaviour, 79,* 331-42

Mutschler, N.H., Covington, H.E. 3rd., & Miczek, K.A. (2001). Repeated self-administered cocaine "binges" in rats: effects on cocaine intake and withdrawal. *Psychopharmacology (Berl), 154,* 292-300

Nader, M.A., & Mach, R.H. (1996). Self-administration of the dopamine D3 agonist 7-OH-DPAT in rhesus monkeys is modified by prior cocaine exposure. *Psychopharmacology (Berl), 125,* 13-22

Nash, J.F., & Brodkin, J. (1991). Microdialysis studies on 3,4-methylenedioxymethamphetamine-induced dopamine release: effect of dopamine uptake inhibitors. *Journal of Pharmacology & Experimental Therapeutics, 259,* 820-5

Navailles, S., Moison, D., Ryczko, D., & Spampinato, U. (2006). Region-dependent regulation of mesoaccumbens dopamine neurons in vivo by the constitutive activity of central serotonin2C receptors. *Journal of Neurochemistry, 99(4),* 1311-9.

Neisewander, J.L., O'Dell, L.E., Tran-Nguyen, L.T., Castaneda, E., & Fuchs, R.A. (1996). Dopamine overflow in the nucleus accumbens during extinction and reinstatement of cocaine self-administration behavior. *Neuropsychopharmacology, 15,* 506-14

Newton, T.F., Roache, J.D., De La Garza, R, 2nd., Fong, T., Wallace, C.L., et al. (2006). Bupropion reduces methamphetamine-induced subjective effects and cue-induced craving. *Neuropsychopharmacology, 31,* 1537-44

Nichols, D.E. (1986). Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. *Journal of Psychoactive Drugs, 18,* 305-13

Norman, A.B., Norman, M.K., Hall, J.F., & Tsibulsky, V.L. (1999). Priming threshold: a novel quantitative measure of the reinstatement of cocaine self-administration. *Brain Research, 831,* 165-74

O'Brien, C.P., Childress, A.R., Ehrman, R., & Robbins, S.J. (1998). Conditioning factors in drug abuse: can they explain compulsion? *Journal of Psychopharmacology, 12,*15-22

O'Brien, C.P., Childress, A.R., & McLellan, A.T. (1991). Conditioning factors may help to understand and prevent relapse in patients who are recovering from drug dependence. *NIDA Research Monograph, 106,* 293-312

O'Brien, C.P., Childress, A.R., McLellan, A.T., & Ehrman, R. (1992a). Classical conditioning in drug-dependent humans. *Annals of New York Academy of Science, 654,* 400-15

O'Brien, C.P., & Gardner, E.L. (2005). Critical assessment of how to study addiction and its treatment: human and non-human animal models. *Pharmacology & Therapeutics, 108,* 18-58

O'Brien, C.P., McLellan, A.T., Alterman, A., & Childress, A.R. (1992b). Psychotherapy for cocaine dependence. *Ciba Foundation Symposium, 166,* 207-16; discussion 16-23

O'Loinsigh, E.D., Boland, G., Kelly, J.P., & O'Boyle, K.M. (2001). Behavioural, hyperthermic and neurotoxic effects of 3,4-methylenedioxymethamphetamine analogues in the Wistar rat. *Progress in Neuropsychopharmacology & Biological Psychiatry, 25,* 621-38

O'Regan, M.C., & Clow, A. (2004). Decreased pain tolerance and mood in recreational users of MDMA. *Psychopharmacology (Berl), 173,* 446-51

O'Shea, E., Escobedo, I., Orio, L., Sanchez, V., Navarro, M., et al. (2005). Elevation of ambient room temperature has differential effects on MDMA-induced 5-HT and dopamine release in striatum and nucleus accumbens of rats. *Neuropsychopharmacology, 30,* 1312-23

Oberlender, R., & Nichols, D.E. (1988). Drug discrimination studies with MDMA and amphetamine. *Psychopharmacology (Berl), 95,* 71-6

Palmatier, M.I., Evans-Martin, F.F., Hoffman, A., Caggiula, A.R., Chaudhri, N., & Donny, E.C. (2006). Dissociating the primary reinforcing and reinforcement-enhancing effects of nicotine using a rat self-administration paradigm with concurrently available drug and environmental reinforcers. *Psychopharmacology (Berl), 184(3-4),* 391-400

Panlilio, L.V., Weiss, S.J., & Schindler, C.W. (1996). Cocaine self-administration increased by compounding discriminative stimuli. *Psychopharmacology (Berl), 125,* 202-8

Panlilio, L.V., Weiss, S.J., & Schindler, C.W. (2000). Effects of compounding drug-related stimuli: escalation of heroin self-administration. *Journal of Experimental Analysis of Behaviour, 73,* 211-24

Panlilio, L.V., Yasar, S., Nemeth-Coslett, R., Katz, J.L., Henningfield, J.E., et al. (2005). Human cocaine-seeking behavior and its control by drug-associated stimuli in the laboratory. *Neuropsychopharmacology, 30,* 433-43

Parker, L.A. (1992). Place conditioning in a three- or four-choice apparatus: role of stimulus novelty in drug-induced place conditioning. *Behavioural Neuroscience, 106,* 294-306

Parkinson, J.A., Crofts, H.S., McGuigan, M., Tomic, D.L., Everitt, B.J., & Roberts, A.C. (2001). The role of the primate amygdala in conditioned reinforcement. *Journal of Neuroscience, 21(19),* 7770-80.

Parks, K.A., & Kennedy, C.L. (2004). Club drugs: reasons for and consequences of use. *Journal of Psychoactive Drugs, 36,* 295-302

Parrott, A. (2003). Cognitive deficits and cognitive normality in recreational cannabis and Ecstasy/MDMA users. *Human Psychopharmacology, 18*, 89-90

Parrott, A.C. (2001). Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research. *Human Psychopharmacology, 16*, 557-77

Parrott, A.C. (2002). Recreational Ecstasy/MDMA, the serotonin syndrome, and serotonergic neurotoxicity. *Pharmacology, Biochemistry & Behaviour, 71,* 837-44

Parrott, A.C. (2004). Is ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity. *Psychopharmacology (Berl), 173,* 234-41

Parrott, A.C. (2004). MDMA (3,4-Methylenedioxymethamphetamine) or ecstasy: the neuropsychobiological implications of taking it at dances and raves. *Neuropsychobiology, 50,* 329-35

Parrott, A.C. (2005). Chronic tolerance to recreational MDMA (3,4-methylenedioxymethamphetamine) or Ecstasy. *Journal of Psychopharmacology, 19,* 71-83

Patel, V.B., Watson, L., Mathias, C.J., Richardson, P.J., & Preedy, V.R. (1996). The involvement of catecholamines, in hypertension, alcohol and ACE-inhibition. *Biochemical Society Transactions, 24,* 262S

Paulus, M.P., & Geyer, M.A. (1992). The effects of MDMA and other methylenedioxy-substituted phenylalkylamines on the structure of rat locomotor activity. *Neuropsychopharmacology, 7,* 15-31

Peltier, R., & Schenk, S. (1991). GR38032F, a serotonin 5-HT3 antagonist, fails to alter cocaine self-administration in rats. *Pharmacology, Biochemistry & Behaviour, 39,* 133-6

Peroutka, S.J., Newman, H., & Harris, H. (1988). Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. *Neuropsychopharmacology, 1,* 273-7

Pert, A. (1994). Neurobiological mechanisms underlying the acquisition and expression of incentive motivation by cocaine-associated stimuli: relationship to craving. *NIDA Research Monograph, 145,* 163-90

Pert, A., Post, R., & Weiss, S.R. (1990). Conditioning as a critical determinant of sensitization induced by psychomotor stimulants. *NIDA Research Monograph, 97,* 208-41

Pettit, H.O., & Justice, J.B. Jr., (1989). Dopamine in the nucleus accumbens during cocaine self-administration as studied by in vivo

microdialysis. *Pharmacology, Biochemistry & Behaviour, 34,* 899-904

Pettit, H.O., & Justice, J.B. Jr., (1991). Effect of dose on cocaine self-administration behavior and dopamine levels in the nucleus accumbens. *Brain Research, 539,* 94-102

Pfeffer, A.O., & Samson, H.H. (1985). Oral ethanol reinforcement: interactive effects of amphetamine, pimozide and food-restriction. *Alcohol & Drug Research, 6,* 37-48

Phillips, A.G., & Fibiger, H.C. (1990). Role of reward and enhancement of conditioned reward in persistence of responding for cocaine. *Behavioural Pharmacology, 1,* 269-82

Phillips, G.D., Robbins, T.W., & Everitt, B.J. (1994). Bilateral intra-accumbens self-administration of d-amphetamine: antagonism with intra-accumbens SCH-23390 and sulpiride. *Psychopharmacology (Berl), 114,* 477-85

Phillips, P.E., Stuber, G.D., Heien, M.L., Wightman, R.M., & Carelli, R.M. (2003). Subsecond dopamine release promotes cocaine seeking. *Nature, 422,* 614-8

Piazza, P.V., Deminiere, J.M., Le Moal, M., & Simon, H. (1989). Factors that predict individual vulnerability to amphetamine self-administration. *Science, 245,* 1511-3

Piazza, P.V., Rouge-Pont, F., Deminiere, J.M., Kharoubi, M., Le Moal, M., & Simon, H. (1991). Dopaminergic activity is reduced in the prefrontal cortex and increased in the nucleus accumbens of rats

predisposed to develop amphetamine self-administration. *Brain Research, 567,* 169-74

Pich, E.M., & Epping-Jordan, M.P. (1998). Transgenic mice in drug dependence research. *Annals of Medicine, 30,* 390-6

Pickens, R., & Harris, W.C. (1968). Self-administration of d-amphetamine by rats. *Psychopharmacologia, 12,* 158-63

Pickens, R.W., & Crowder, W.F. (1967). Effects of CS-US interval on conditioning of drug response, with assessment of speed of conditioning. *Psychopharmacologia, 11,* 88-94

Pierce, P.A., & Peroutka, S.J. (1988). Ring-substituted amphetamine interactions with neurotransmitter receptor binding sites in human cortex. *Neuroscience Letter, 95,* 208-12

Pierre, P.J., & Vezina, P. (1997). Predisposition to self-administer amphetamine: the contribution of response to novelty and prior exposure to the drug. *Psychopharmacology (Berl), 129,* 277-84

Pierre, P.J., & Vezina, P. (1998). D1 dopamine receptor blockade prevents the facilitation of amphetamine self-administration induced by prior exposure to the drug. *Psychopharmacology (Berl), 138,* 159-66

Pilotto, R., Singer, G., & Overstreet, D. (1984). Self-injection of diazepam in naive rats: effects of dose, schedule and blockade of different receptors. *Psychopharmacology (Berl), 84,* 174-7

Porrino, L.J., Ritz, M.C., Goodman, N.L., Sharpe, L.G., Kuhar, M.J., & Goldberg, S.R. (1989). Differential effects of the pharmacological manipulation of serotonin systems on cocaine and amphetamine self-administration in rats. *Life Science, 45,* 1529-35

Post, R.M., Kopanda, R.T., & Black, K.E. (1976). Progressive effects of cocaine on behavior and central amine metabolism in rhesus monkeys: relationship to kindling and psychosis. *Biological Psychiatry, 11,* 403-19

Pucilowski, O., Plaznik, A., & Overstreet, D.H. (1995). Isradipine suppresses amphetamine-induced conditioned place preference and locomotor stimulation in the rat. *Neuropsychopharmacology, 12,* 239-44

Pulvirenti, L., & Koob, G.F. (1990). The neural substrates of drug addiction and dependence. *Functional Neurology, 5,* 109-19

Quinlan, M.G., Sharf, R., Lee, D.Y., Wise, R.A., & Ranaldi, R. (2004). Blockade of substantia nigra dopamine D1 receptors reduces intravenous cocaine reward in rats. *Psychopharmacology (Berl), 175,* 53-9

Ramos, M., Goni-Allo, B., & Aguirre, N. (2004). Studies on the role of dopamine D1 receptors in the development and expression of MDMA-induced behavioral sensitization in rats. *Psychopharmacology (Berl), 177,* 100-10

Ranaldi, R., Pocock, D., Zereik, R., & Wise, R.A. (1999). Dopamine fluctuations in the nucleus accumbens during maintenance, extinction, and reinstatement of intravenous D-amphetamine self-administration. *Journal of Neuroscience, 19,* 4102-9

Ranaldi, R., & Wise, R.A. (2001). Blockade of D1 dopamine receptors in the ventral tegmental area decreases cocaine reward: possible role

for dendritically released dopamine. *Journal of Neuroscience, 21,* 5841-6

Ratzenboeck, E., Saria, A., Kriechbaum, N., & Zernig, G. (2001). Reinforcing effects of MDMA ("ecstasy") in drug-naive and cocaine-trained rats. *Pharmacology, 62, 1*38-44

Reid, L.D., Glick, S.D., Menkens, K.A., French, E.D., Bilsky, E.J., & Porreca, F. (1995). Cocaine self-administration and naltrindole, a delta-selective opioid antagonist. *Neuroreport, 6,* 1409-12

Reneman, L., Booij, J., Majoie, C.B., Van Den Brink, W., & Den Heeten, G.J. (2001). Investigating the potential neurotoxicity of Ecstasy (MDMA): an imaging approach. *Human Psychopharmacology, 16,* 579-88

Reneman, L., de Win, M.M., van den Brink, W., Booij, J., & den Heeten, G.J. (2006). Neuroimaging findings with MDMA/ecstasy: technical aspects, conceptual issues and future prospects. *Journal of Psychopharmacology, 20*, 164-75

Reveron, M.E., Maier, E.Y., & Duvauchelle, C.L. (2006). Experience-dependent changes in temperature and behavioral activity induced by MDMA. *Physiology & Behaviour, 89(3),* 358-63.

Ricaurte, G.A., McCann, U.D., Szabo, Z., & Scheffel, U. (2000). Toxicodynamics and long-term toxicity of the recreational drug, 3, 4-methylenedioxymethamphetamine (MDMA, 'Ecstasy'). *Toxicology Letters, 112-113*, 143-6

Risinger, R.C., Salmeron, B.J., Ross, T.J., Amen, S.L., Sanfilipo, M., et al. (2005). Neural correlates of high and craving during cocaine self-administration using BOLD fMRI. *Neuroimage, 26,* 1097-108

Risner, M.E., & Goldberg, S.R. (1983). A comparison of nicotine and cocaine self-administration in the dog: fixed-ratio and progressive-ratio schedules of intravenous drug infusion. *Journal of Pharmacology & Experimental Therapeutics, 224,* 319-26

Risner, M.E., & Jones, B.E. (1975). Self-administration of CNS stimulants by dog. *Psychopharmacologia, 43,* 207-13

Risner, M.E., & Jones, B.E. (1980). Intravenous self-administration of cocaine and norcocaine by dogs. *Psychopharmacology (Berl), 71,* 83-9

Ritz, M.C., Lamb, R.J., Goldberg, S.R., & Kuhar, M.J. (1987). Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science, 237,* 1219-23

Ritz, M.C., Lamb, R.J., Goldberg, S.R., & Kuhar, M.J. (1988). Cocaine self-administration appears to be mediated by dopamine uptake inhibition. *Progressions in Neuropsychopharmacology & Biological Psychiatry, 12,* 233-9

Roberts, D.C. (1989). Breaking points on a progressive ratio schedule reinforced by intravenous apomorphine increase daily following 6-hydroxydopamine lesions of the nucleus accumbens. *Pharmacology, Biochemistry & Behaviour, 32,* 43-7

Roberts, D.C. (1993). Self-administration of GBR 12909 on a fixed ratio and progressive ratio schedule in rats. *Psychopharmacology (Berl), 111,* 202-6

Roberts, D.C., & Bennett, S.A. (1993). Heroin self-administration in rats under a progressive ratio schedule of reinforcement. *Psychopharmacology (Berl), 111,* 215-8

Roberts, D.C., Brebner, K., Vincler, M., & Lynch, W.J. (2002). Patterns of cocaine self-administration in rats produced by various access conditions under a discrete trials procedure. *Drug and Alcohol Dependence, 67,* 291-9

Roberts, D.C., Corcoran, M.E., & Fibiger, H.C. (1977). On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. *Pharmacology, Biochemistry & Behaviour, 6,* 615-20

Roberts, D.C., & Koob, G.F. (1982). Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats. *Pharmacology, Biochemistry & Behaviour, 17,* 901-4

Roberts, D.C., Loh, E.A., & Vickers, G. (1989). Self-administration of cocaine on a progressive ratio schedule in rats: dose-response relationship and effect of haloperidol pretreatment. *Psychopharmacology (Berl), 97,* 535-8

Roberts, D.C., Phelan, R., Hodges, L.M., Hodges, M.M., Bennett, B., et al. (1999). Self-administration of cocaine analogs by rats. *Psychopharmacology (Berl), 144,* 389-97

Robinson, T.E. (2004). Neuroscience. Addicted rats. *Science, 305(5686),* 951-3

Robinson, T.E., & Becker, J.B. (1986). Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Research, 396,* 157-98

Robinson, T.E., & Berridge, K.C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Research, Brain Research, Review, 18,* 247-91

Robinson, T.E., & Berridge, K.C. (2000). The psychology and neurobiology of addiction: an incentive-sensitization view. *Addiction, 95 Suppl 2,* S91-117

Robinson, T.E., & Berridge, K.C. (2001). Incentive-sensitization and addiction. *Addiction, 96,* 103-14

Robinson, T.E., & Berridge, K.C. (2003). Addiction. *Annual Review of Psychology, 54,* 25-53

Rochester, J.A., & Kirchner, J.T. (1999). Ecstasy (3,4-methylenedioxymethamphetamine): history, neurochemistry, and toxicology. *Journal of the American Board of Family Practice, 12,* 137-42

Rodriguez De Fonseca, F., Rubio, P., Martin-Calderon, J.L., Caine, S.B., & Koob, G.F., Navarro, M. (1995). The dopamine receptor agonist 7-OH-DPAT modulates the acquisition and expression of morphine-induced place preference. *European Journal of Pharmacology, 274,* 47-55

Rose, J.E., & Corrigall, W.A. (1997). Nicotine self-administration in animals and humans: similarities and differences. *Psychopharmacology (Berl), 130*, 28-40

Rudnick, G., & Wall, S.C. (1992). The molecular mechanism of "ecstasy" [3,4-methylenedioxy-methamphetamine (MDMA)]: serotonin transporters are targets for MDMA-induced serotonin release. *Proceedings of the National Academy of Science, U S A, 89*, 1817-21

Sabol, K.E., & Seiden, L.S. (1998). Reserpine attenuates D-amphetamine and MDMA-induced transmitter release in vivo: a consideration of dose, core temperature and dopamine synthesis. *Brain Research, 806*, 69-78

Sahakyan, L., & Kelley, C.M. (2002). A contextual change account of the directed forgetting effect. *Journal of Experimental Psychology; Learning, Memory, & Cognition, 28*, 1064-72

Salamone, J.D., & Correa, M. (2002). Motivational views of reinforcement: implications for understanding the behavioral functions of nucleus accumbens dopamine. *Behaviour & Brain Research, 137*, 3-25

Sanchez-Ramos, J.R., & Schuster, C.R. (1977). Second-order schedules of intravenous drug self-administration in rhesus monkeys. *Pharmacology, Biochemistry & Behaviour, 7(5)*, 443-50.

Schenk, S., & Gittings, D. (2003). Effects of SCH 23390 and eticlopride on cocaine-seeking produced by cocaine and WIN 35,428 in rats. *Psychopharmacology (Berl), 168*, 118-23

Schenk, S., Gittings, D., Johnstone, M., & Daniela, E. (2003). Development, maintenance and temporal pattern of self-administration maintained by ecstasy (MDMA) in rats. *Psychopharmacology (Berl), 169*, 21-7

Schenk, S., Horger, B.A., Peltier, R., & Shelton, K. (1991). Supersensitivity to the reinforcing effects of cocaine following 6-hydroxydopamine lesions to the medial prefrontal cortex in rats. *Brain Research, 543*, 227-35

Schenk, S., & Izenwasser, S. (2002). Pretreatment with methylphenidate sensitizes rats to the reinforcing effects of cocaine. *Pharmacology, Biochemistry & Behaviour, 72*, 651-7

Schenk, S., & Partridge, B. (1997). Sensitization and tolerance in psychostimulant self-administration. *Pharmacology, Biochemistry & Behaviour, 57*, 543-50

Schenk, S., & Partridge, B. (1999). Cocaine-seeking produced by experimenter-administered drug injections: dose-effect relationships in rats. *Psychopharmacology (Berl), 147*, 285-90

Schenk, S., & Partridge, B. (2000). Sensitization to cocaine's reinforcing effects produced by various cocaine pretreatment regimens in rats. *Pharmacology, Biochemistry & Behaviour, 66*, 765-70

Schenk, S., & Partridge, B. (2001). Influence of a conditioned light stimulus on cocaine self-administration in rats. *Psychopharmacology (Berl), 154*, 390-6

Schenk, S., Partridge, B., & Shippenberg, T.S. (2001). Effects of the kappa-opioid receptor agonist, U69593, on the development of

sensitization and on the maintenance of cocaine self-administration. *Neuropsychopharmacology, 24,* 441-50

Schenk, S., Valadez, A., Worley, C.M., & McNamara, C. (1993). Blockade of the acquisition of cocaine self-administration by the NMDA antagonist MK-801 (dizocilpine). *Behavioural Pharmacology, 4,* 652-9

Schifano, F., Di Furia, L., Forza, G., Minicuci, N., & Bricolo, R. (1998). MDMA ('ecstasy') consumption in the context of polydrug abuse: a report on 150 patients. *Drug and Alcohol Dependence, 52,* 85-90

Schildein, S., Agmo, A., Huston, J.P., & Schwarting, R.K. (1998). Intraaccumbens injections of substance P, morphine and amphetamine: effects on conditioned place preference and behavioral activity. *Brain Research, 790,* 185-94

Schindler, C.W., Panlilio, L.V., & Goldberg, S.R. (2002). Second-order schedules of drug self-administration in animals. *Psychopharmacology (Berl), 163(3-4),* 327-44

Schmidt, C., Sullivan, C., & Fadayel, G. (1994). Blockade of striatal 5-hydroxytryptamine2 receptors reduces the increase in extracellular concentrations of dopamine produced by the amphetamine analogue 3,4-methylenedioxymethamphetamine. *Journal of Neurochemistry, 62,* 1382-9

Schmidt, C., Abbate, G.M., Black, C.K., & Taylor, V.L. (1990). Selective 5-hydroxytryptamine2 receptor antagonists protect against the neurotoxicity of methylenedioxymethamphetamine in rats. *Journal of Pharmacology & Experimental Therapeutics, 255,* 478-83

Schmidt, C.J., Levin, J.A., & Lovenberg, W. (1987). In vitro and in vivo neurochemical effects of methylenedioxymethamphetamine on striatal monoaminergic systems in the rat brain. *Biochemical Pharmacology, 36,* 747-55

Schmidt, C.J., Sullivan, C.K., & Fadayel, G.M. (1994). Blockade of striatal 5-hydroxytryptamine2 receptors reduces the increase in extracellular concentrations of dopamine produced by the amphetamine analogue 3,4-methylenedioxymethamphetamine. *Journal of Neurochemistry, 62,* 1382-9

Schmidt, C.J., & Taylor, V.L. (1990). Reversal of the acute effects of 3,4-methylenedioxymethamphetamine by 5-HT uptake inhibitors. *European Journal of Pharmacology, 181,* 133-6

Schmidt, C.J., Wu, L., & Lovenberg, W. (1986). Methylenedioxymethamphetamine: a potentially neurotoxic amphetamine analogue. *European Journal of Pharmacology, 124,* 175-8

Scholey, A.B., Parrott, A.C., Buchanan, T., Heffernan, T.M., Ling, J., & Rodgers, J. (2004). Increased intensity of Ecstasy and polydrug usage in the more experienced recreational Ecstasy/MDMA users: a WWW study. *Addictive behaviours, 29,* 743-52

Shulgin, A. T. (1986). The background and chemistry of MDMA. *Journal of Psychoactive Drugs, 18(4),* 291-304.

Schuster, P., Lieb, R., Lamertz, C., & Wittchen, H.U. (1998). Is the use of ecstasy and hallucinogens increasing? Results from a community study. *European Addiction Research, 4,* 75-82

Schultz, W. (2001). Reward signaling by dopamine neurons. *Neuroscientist, 7(4),* 293-302.

Schultz, W., Apicella, P., Scarnati, E., & Ljungberg, T. (1992). Neuronal activity in monkey ventral striatum related to the expectation of reward. *Journal of Neuroscience, 12(12),* 4595-610.

See, R.E. (2002). Neural substrates of conditioned-cued relapse to drug-seeking behavior. *Pharmacology, Biochemistry & Behaviour, 71,* 517-29

See, R.E., Fuchs, R.A., Ledford, C.C., & McLaughlin, J. (2003). Drug addiction, relapse, and the amygdala. *Annals of New York Academy of Science, 985,* 294-307

Segal, M., Deneau, G.A., Seevers, M.H. (1972). Levels and distribution of central nervous system amines in normal and morphine-dependent monkeys. *Neuropharmacology, 11,* 211-22

Siegel, S., & Ramos, B.M. (2002). Applying laboratory research: drug anticipation and the treatment of drug addiction. *Experimental & Clinical Psychopharmacology, 10(3),* 162-83

Self, D.W., Barnhart, W.J., Lehman, D.A., & Nestler, E.J. (1996). Opposite modulation of cocaine-seeking behavior by D1- and D2-like dopamine receptor agonists. *Science, 271,* 1586-9

Self, D.W., & Nestler, E.J. (1998). Relapse to drug-seeking: neural and molecular mechanisms. *Drug Alcohol Dependence, 51(1-2),* 49-60

Self, D.W., & Stein, L. (1992). Receptor subtypes in opioid and stimulant reward. *Pharmacology & Toxicology, 70,* 87-94

Shaham, Y., Erb, S., & Stewart, J. (2000). Stress-induced relapse to heroin and cocaine seeking in rats: a review. *Brain Research, Brain Research, Review, 33*, 13-33

Shaham, Y., & Hope, B.T. (2005). The role of neuroadaptations in relapse to drug seeking. *Nature: Neuroscience, 8*, 1437-9

Shaham, Y., Rodaros, D., & Stewart, J. (1994). Reinstatement of heroin-reinforced behavior following long-term extinction: implications for the treatment of relapse to drug taking. *Behavioural Pharmacology, 5*, 360-4

Shaham, Y., Shalev, U., Lu, L., De Wit, H., & Stewart, J. (2003). The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology (Berl), 168*, 3-20

Shaham, Y., & Stewart, J. (1994). Exposure to mild stress enhances the reinforcing efficacy of intravenous heroin self-administration in rats. *Psychopharmacology (Berl)*, 114, 523-7

Shaham, Y., & Stewart, J. (1996). Effects of opioid and dopamine receptor antagonists on relapse induced by stress and re-exposure to heroin in rats. *Psychopharmacology (Berl), 125*, 385-91

Shaham, Y., Shufman, Scher, Barel, Zlotogorski, Cohen. (1991). Methadone maintenance and clonidine detoxification in the treatment of opiate addicts in Israel: suggesting evidence for cultural differences in the effectiveness of treatment modalities for opiate addiction. *Israeli Journal of Psychiatry & Related Science, 28*, 45-57

Shalev, U., Grimm, J.W., & Shaham, Y. (2002). Neurobiology of relapse to heroin and cocaine seeking: a review. *Pharmacological Review, 54,* 1-42

Shalev, U., Highfield, D., Yap, J., & Shaham, Y. (2000). Stress and relapse to drug seeking in rats: studies on the generality of the effect. *Psychopharmacology (Berl), 150,* 337-46

Shankaran, M., & Gudelsky, G.A. (1998). Effect of 3,4-methylenedioxymethamphetamine (MDMA) on hippocampal dopamine and serotonin. *Pharmacology, Biochemistry & Behaviour, 61,* 361-6

Shippenberg, T.S., & Elmer, G.I. (1998). The neurobiology of opiate reinforcement. *Critical Review of Neurobiology, 12,* 267-303

Shulgin, A.T. (1986). The background and chemistry of MDMA. *Journal of Psychoactive Drugs, 18,* 291-304

Sinha, R. (2001). How does stress increase risk of drug abuse and relapse? *Psychopharmacology (Berl), 158,* 343-59

Slifer, B.L., & Balster, R.L. (1983). Reinforcing properties of stereoisomers of the putative sigma agonists N-allylnormetazocine and cyclazocine in rhesus monkeys. *Journal of Pharmacology & Experimental Therapeutics, 225,* 522-8

Slikker, W. Jr., Brocco, M.J., & Killam, K.F. Jr. (1984). Reinstatement of responding maintained by cocaine or thiamylal. *Journal of Pharmacology & Experimental Therapeutics, 228(1),* 43-52

Smith, J.E., Co, C., Freeman, M.E., & Lane, J.D. (1982). Brain neurotransmitter turnover correlated with morphine-seeking

behavior of rats. *Pharmacology, Biochemistry & Behaviour, 16,* 509-19

Smith, J.E., Guerin, G.F., Co, C., Barr, T.S., & Lane, J.D. (1985). Effects of 6-OHDA lesions of the central medial nucleus accumbens on rat intravenous morphine self-administration. *Pharmacology, Biochemistry & Behaviour, 23,* 843-9

Smith, S.G., & Davis, W.M. (1973). Behavioral control by stimuli associated with acquisition of morphine self-administration. *Behavioural Biology, 9,* 777-80

Smith, S.G., Werner, T.E., & Davis, W.M. (1976). Effect of unit dose and route of administration on self-administration of morphine. *Psychopharmacology (Berl), 50,* 103-5

Solowij, N., Hall, W., & Lee, N. (1992). Recreational MDMA use in Sydney: a profile of 'Ecstacy' users and their experiences with the drug. *British Journal of Addiction, 87,* 1161-72

Spanos, L.J., & Yamamoto, B.K. (1989). Acute and subchronic effects of methylenedioxymethamphetamine [(+/-)MDMA] on locomotion and serotonin syndrome behavior in the rat. *Pharmacology, Biochemistry & Behaviour, 32,* 835-40

Spealman, R.D., Barrett-Larimore, R.L., Rowlett, J.K., Platt, D.M., & Khroyan, T.V. (1999). Pharmacological and environmental determinants of relapse to cocaine-seeking behavior. *Pharmacology, Biochemistry & Behaviour, 64,* 327-36

Spealman, R.D., & Goldberg, S.R. (1978). Drug self-administration by laboratory animals: control by schedules of reinforcement. *Annual Reviews of Pharmacology & Toxicology, 18,* 313-39

Spealman, R.D., & Kelleher, R.T. (1981). Self-administration of cocaine derivatives by squirrel monkeys. *Journal of Pharmacology & Experimental Therapeutics, 216,* 532-6

Spina, L., Fenu, S., Longoni, R., Rivas, E., & Di Chiara, G. (2006). Nicotine-conditioned single-trial place preference: selective role of nucleus accumbens shell dopamine D1 receptors in acquisition. *Psychopharmacology (Berl), 184,* 447-55

Stefanski, R., Ladenheim, B., Lee, S.H., Cadet, J.L., & Goldberg, S.R. (1999). Neuroadaptations in the dopaminergic system after active self-administration but not after passive administration of methamphetamine. *European Journal of Pharmacology, 371*, 123-35

Stewart, J. (1983). Conditioned and unconditioned drug effects in relapse to opiate and stimulant drug self-adminstration. *Progress in Neuropsychopharmacology & Biological Psychiatry, 7,* 591-7

Stewart, J. (2000). Pathways to relapse: the neurobiology of drug- and stress-induced relapse to drug-taking. *Journal of Psychiatry & Neuroscience, 25,* 125-36

Stone, D.M., Stahl, D.C., Hanson, G.R., & Gibb, J.W. (1986). The effects of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) on monoaminergic systems in the rat brain. *European Journal of Pharmacology, 128,* 41-8

Stone, D.M., Merchant, K.M., Hanson, G.R., & Gibb, J.W. (1987). Immediate and long-term effects of 3,4-methylenedioxymethamphetamine on serotonin pathways in brain of rat. *Neuropharmacology, 26,* 1677-83

Stretch, R., & Gerber, G.J. (1973). Drug-induced reinstatement of amphetamine self-administration behaviour in monkeys. *Canadian Journal of Psychology, 27(2),* 168-77.

Sumnall, HR., O'Shea, E., Marsden, C.A., & Cole, J.C. (2004). The effects of MDMA pretreatment on the behavioural effects of other drugs of abuse in the rat elevated plus-maze test. *Pharmacology, Biochemistry & Behaviour, 77,* 805-14

Suzuki, T., & Misawa, M. (1995). Sertindole antagonizes morphine-, cocaine-, and methamphetamine-induced place preference in the rat. *Life Science, 57,* 1277-84

Swerdlow, N.R., Hauger, R., Irwin, M., Koob, G.F., Britton, K.T., & Pulvirenti, L. (1991). Endocrine, immune, and neurochemical changes in rats during withdrawal from chronic amphetamine intoxication. *Neuropsychopharmacology, 5,* 23-31

Swerdlow, N.R., & Koob, G.F. (1984). Restrained rats learn amphetamine-conditioned locomotion, but not place preference. *Psychopharmacology (Berl), 84,* 163-6

Sziraki, I., Sershen, H., Benuck, M., Hashim, A., & Lajtha, A. (1998). Receptor systems participating in nicotine-specific effects. *Neurochemistry International, 33,* 445-57

Szostak, C., Finlay, J.M., & Fibiger, H.C. (1987). Intravenous self-administration of the short-acting benzodiazepine midazolam in the rat. *Neuropharmacology, 26,* 1673-6

Takahashi, R.N., & Singer, G. (1979). Self-administration of delta 9-tetrahydrocannabinol by rats. *Pharmacology, Biochemistry & Behaviour, 11,* 737-40

Takahashi, R.N., & Singer, G. (1981). Cross self-administration of delta 9-tetrahydrocannabinol and D-amphetamine in rats. *Brazilian Journal of Medicine and Biological Research, 14,* 395-400

Tancer, M., & Johanson, C.E. (2003). Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP. *Drug and Alcohol Dependence, 72,* 33-44

Tanda, G., & Goldberg, S.R. (2003). Cannabinoids: reward, dependence, and underlying neurochemical mechanisms--a review of recent preclinical data. *Psychopharmacology (Berl), 169,* 115-34

Tanda, G., Loddo, P., & Di Chiara, G. (1999). Dependence of mesolimbic dopamine transmission on delta9-tetrahydrocannabinol. *European Journal of Pharmacology, 376,* 23-6

Tanda, G., Munzar, P., & Goldberg, S.R. (2000). Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. *Nature: Neuroscience, 3,* 1073-4

ter Bogt, T.F., Engels, R.C., & Dubas, J.S. (2006). Party people: personality and MDMA use of house party visitors. *Addictive behaviours, 31,* 1240-4

TF, MtB., & Engels, R.C. (2005). "Partying" hard: party style, motives for and effects of MDMA use at rave parties. *Substance use and misuse, 40,* 1479-502

Thompson, T. (1981). Behavioral mechanisms and loci of drug dependence: an overview. *NIDA Research Monograph, 37,* 1-10

Tilson, H.A., & Rech, R.H. (1973). Prior drug experience and effects of amphetamine on schedule controlled behavior. *Pharmacology, Biochemistry & Behaviour, 1,* 129-32

Topp, L., Barker, B., & Degenhardt, L. (2004). The external validity of results derived from ecstasy users recruited using purposive sampling strategies. *Drug and Alcohol Dependence, 73,* 33-40

Topp, L., Hando, J., Dillon, P., Roche, A., & Solowij, N. (1999). Ecstasy use in Australia: patterns of use and associated harm. *Drug and Alcohol Dependence, 55,* 105-15

Tornatzky, W., & Miczek, K.A. (2000). Cocaine self-administration "binges": transition from behavioral and autonomic regulation toward homeostatic dysregulation in rats. *Psychopharmacology (Berl), 148,* 289-98

Tran-Nguyen, L.T., Fuchs, R.A., Coffey, G.P., Baker, D.A., O'Dell, L.E., & Neisewander, J. L. (1998). Time-dependent changes in cocaine-seeking behavior and extracellular dopamine levels in the amygdala during cocaine withdrawal. *Neuropsychopharmacology, 19,* 48-59

Tzschentke, T.M., Bruckmann, W., & Friderichs, E. (2002). Lack of sensitization during place conditioning in rats is consistent with the low abuse potential of tramadol. *Neuroscience Letter, 329,* 25-8

Tzschentke, T.M., Magalas, Z., & De Vry, J. (2006). Effects of venlafaxine and desipramine on heroin-induced conditioned place preference in the rat. *Addiction & Biology, 11*, 64-71

UNODC. (2004). *World Drug Report.* United Nations.

Van der Kooy, D., Swerdlow, N.R., & Koob, G.F. (1983). Paradoxical reinforcing properties of apomorphine: effects of nucleus accumbens and area postrema lesions. *Brain Research, 259(1),* 111-8.

Verheyden, S.L., Henry, J.A., & Curran, H.V. (2003). Acute, sub-acute and long-term subjective consequences of 'ecstasy' (MDMA) consumption in 430 regular users. *Human Psychopharmacology, 18*, 507-17

Vezina, P., & Stewart, J. (1987). Conditioned locomotion and place preference elicited by tactile cues paired exclusively with morphine in an open field. *Psychopharmacology (Berl), 91,* 375-80

Vezina, P., & Stewart, J. (1987). Morphine conditioned place preference and locomotion: the effect of confinement during training. *Psychopharmacology (Berl), 93*, 257-60

Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Ding, Y.S., et al. (2001). Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *American Journal of Psychiatry, 158,* 2015-21

Volkow, N.D., Fowler, J.S., & Wang, G.J. (2002). Role of dopamine in drug reinforcement and addiction in humans: results from imaging studies. *Behavioural Pharmacology, 13*, 355-66

Volkow, N.D., Fowler, J.S., Wang, G.J., Hitzemann, R., Logan, J., et al. (1993). Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse, 14,* 169-77

Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Gatley, S.J., et al. (1999). Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels. *American Journal of Psychiatry, 156,* 1440-3

Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Gatley, S.J., et al. (1997). Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature, 386,* 830-3

Vollenweider, F.X., Gamma, A., Liechti, M., & Huber, T. (1998). Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers. *Neuropsychopharmacology, 19,* 241-51

von Sydow, K., Lieb, R., Pfister, H., Hofler, M., & Wittchen, H.U. (2002). Use, abuse and dependence of ecstasy and related drugs in adolescents and young adults-a transient phenomenon? Results from a longitudinal community study. *Drug and Alcohol Dependence, 66,* 147-59

Wallace, D.R., Mactutus, C.F., & Booze, R.M. (1996). Repeated intravenous cocaine administration: locomotor activity and dopamine D2/D3 receptors. *Synapse, 23,* 152-63

Wang, B., Luo, F., Ge, X., Fu, A., Han, J. (2003). Effect of 6-OHDA lesions of the dopaminergic mesolimbic system on drug priming

induced reinstatement of extinguished morphine CPP in rats. *Beijing Da Xue Xue Bao, 35,* 449-52

Ward, A.S., Li, D.H., Luedtke, R.R., & Emmett-Oglesby, M.W. (1996). Variations in cocaine self-administration by inbred rat strains under a progressive-ratio schedule. *Psychopharmacology (Berl), 127,* 204-12

Ward, A.S., Haney, M., Fischman, M.W., & Foltin, R,W. (1997). Binge cocaine self-administration by humans: smoked cocaine. *Behavioural Pharmacology, 8(8),* 736-44

Wareing, M., Fisk, J.E., Murphy, P., & Montgomery, C. (2004). Verbal working memory deficits in current and previous users of MDMA. *Human Psychopharmacology, 19,* 225-34

Wareing, M., Fisk, J.E., Murphy, P., & Montgomery, C. (2005). Visuo-spatial working memory deficits in current and former users of MDMA ('ecstasy'). *Human Psychopharmacology, 20,* 115-23

Wareing, M., Fisk, J.E., & Murphy, P.N. (2000). Working memory deficits in current and previous users of MDMA ('ecstasy'). *British Journal of Psychology, 91 (Pt 2),* 181-8

Washton, A.M. (1988). Preventing relapse to cocaine. *Journal of Clinical Psychiatry, 49, Suppl,* 34-8

Weed, M.R., & Woolverton, W.L. (1995). The reinforcing effects of dopamine D1 receptor agonists in rhesus monkeys. *Journal of Pharmacology & Experimental Therapeutics, 275,* 1367-74

Weed, M.R., Woolverton, W.L., & Paul, I.A. (1998). Dopamine D1 and D2 receptor selectivities of phenyl-benzazepines in rhesus monkey striata. *European Journal of Pharmacology, 361,* 129-42

Weeks, J.R. (1962). Experimental morphine addiction: method for automatic intravenous injections in unrestrained rats. *Science, 138,* 143-4

Weeks, J.R., & Collins, R.J. (1978). Self-administration of morphine in the rat: relative influence of fixed ratio and time-out. *Pharmacology, Biochemistry & Behaviour, 9,* 703-4

Weiss, F., Ciccocioppo, R., Parsons, L.H., Katner, S., Liu, X., et al. (2001a). Compulsive drug-seeking behavior and relapse. Neuroadaptation, stress, and conditioning factors. *Annals of New York Academy of Science, 937,* 1-26

Weiss, F., Martin-Fardon, R., Ciccocioppo, R., Kerr, T.M., Smith, D.L., Ben-Shahar, O. (2001). Enduring resistance to extinction of cocaine-seeking behavior induced by drug-related cues. *Neuropsychopharmacology, 25,* 361-72

Weiss, S.J., Kearns, D.N., Cohn, S.I., Schindler, C.W., & Panlilio, L.V. (2003). Stimulus control of cocaine self-administration. *Journal of Experimental Analysis of Behaviour, 79,* 111-35

Weissenborn, R., Yackey, M., Koob, G.F., & Weiss, F. (1995). Measures of cocaine-seeking behavior using a multiple schedule of food and drug self-administration in rats. *Drug Alcohol Dependence, 38(3),* 237-46.

White, S.R., Duffy, P., & Kalivas, P.W. (1994). Methylenedioxymethamphetamine depresses glutamate-evoked neuronal firing and increases extracellular levels of dopamine and serotonin in the nucleus accumbens in vivo. *Neuroscience, 62*, 41-50

White, S.R., Obradovic, T., Imel, K.M., & Wheaton, M.J. (1996). The effects of methylenedioxymethamphetamine (MDMA, "Ecstasy") on monoaminergic neurotransmission in the central nervous system. *Progress in Neurobiology, 49*, 455-79

Wilkins, C., Bhatta, K., Pledger, M., & Casswell, S. (2003). Ecstasy use in New Zealand: findings from the 1998 and 2001 National Drug Surveys. *New Zealand Medical Journal, 116,* U383

Williams, H.. Dratcu, L., Taylor, R., Roberts, M., & Oyefeso, A. (1998). "Saturday night fever": ecstasy related problems in a London accident and emergency department. *Journal of Accident & Emergency Medicine, 15*, 322-6

Wilson, J.M., Nobrega, J.N., Corrigall W, Shannak K, Deck JH, Kish SJ. 1992. Influence of chronic cocaine on monoamine neurotransmitters in human brain and animal model: preliminary observations. *Annals of New York Academy of Science 654:* 461-3

Wilson, J.M., Nobrega, J.N., Corrigall, W.A., Coen, K.M., Shannak, K., & Kish, S.J. (1994). Amygdala dopamine levels are markedly elevated after self- but not passive-administration of cocaine. *Brain Research, 668,* 39-45

Wilson, M.C., Hitomi, M., & Schuster, C.R. (1971). Psychomotor stimulant self administration as a function of dosage per injection in the rhesus monkey. *Psychopharmacologia, 22,* 271-81

Wilson, M.C., & Schuster, C.R. (1972). The effects of chlorpromazine on psychomotor stimulant self-administration in the rhesus monkey. *Psychopharmacologia, 26,* 115-26

Winger, G., Palmer, R.K., & Woods, J.H. (1989). Drug-reinforced responding: rapid determination of dose-response functions. *Drug and Alcohol Dependence, 24,* 135-42

Winstock, A.R. (1991). Chronic paranoid psychosis after misuse of MDMA. *British Medical Journal, 302,* 1150-1

Winstock, A.R., Wolff, K., & Ramsey, J. (2001). Ecstasy pill testing: harm minimization gone too far? *Addiction, 96,* 1139-48

Wise, R.A. (1984). Neural mechanisms of the reinforcing action of cocaine. *NIDA Research Monograph, 50,* 15-33

Wise, R.A. (1987). The role of reward pathways in the development of drug dependence. *Pharmacology & Therapeutics, 35,* 227-63

Wise, R.A. (1998). Drug-activation of brain reward pathways. *Drug and Alcohol Dependence, 51,* 13-22

Wise, R.A., & Bozarth, M.A. (1982). Action of drugs of abuse on brain reward systems: an update with specific attention to opiates. *Pharmacology, Biochemistry & Behaviour, 17,* 239-43

Wise, R.A., & Bozarth, M.A. (1985). Brain mechanisms of drug reward and euphoria. *Psychiatry & Medicine, 3,* 445-60

Wise, R.A., Leone, P., Rivest, R., & Leeb, K. (1995a). Elevations of nucleus accumbens dopamine and DOPAC levels during intravenous heroin self-administration. *Synapse, 21,* 140-8

Wise, R.A., Murray, A., & Bozarth, M.A. (1990). Bromocriptine self-administration and bromocriptine-reinstatement of cocaine-trained and heroin-trained lever pressing in rats. *Psychopharmacology (Berl), 100,* 355-60

Wise, R.A., Newton, P., Leeb, K., Burnette, B., Pocock, D., & Justice JB, Jr. (1995b). Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. *Psychopharmacology (Berl), 120,* 10-20

Wise, R.A., Yokel, R.A., Hansson, P.A., & Gerber, G.J. (1977). Concurrent intracranial self-stimulation and amphetamine self-administration in rats. *Pharmacology, Biochemistry & Behaviour, 7,* 459-61

Wolf, M.E. (2002). Addiction: making the connection between behavioral changes and neuronal plasticity in specific pathways. *Molecular Interventions, 2,* 146-57

Woods, J., Medzihradsky, F., Smith, C., Winger, G., & France, C. (1988). Evaluation of new compounds for opioid activity. *NIDA Research Monograph, 90,* 421-67

Woolverton, W.L., Goldberg, L.I., & Ginos, J.Z. (1984). Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. *Journal of Pharmacology & Experimental Therapeutics, 230,* 678-83

Woolverton, W.L., Shybut, G., & Johanson, C.E. (1980). Structure-activity relationships among some d-N-alkylated amphetamines. *Pharmacology, Biochemistry & Behaviour, 13,* 869-76

Woolverton, W.L., & Virus, R.M. (1989). The effects of a D1 and a D2 dopamine antagonist on behavior maintained by cocaine or food. *Pharmacology, Biochemistry & Behaviour, 32,* 691-7

Worley, C.M., Valadez, A., & Schenk, S. (1994). Reinstatement of extinguished cocaine-taking behavior by cocaine and caffeine. *Pharmacology, Biochemistry & Behaviour, 48(1),* 217-21

Yamamoto, B.K., Nash, J.F., & Gudelsky, G.A. (1995). Modulation of methylenedioxymethamphetamine-induced striatal dopamine release by the interaction between serotonin and gamma-aminobutyric acid in the substantia nigra. *Journal of Pharmacology & Experimental Therapeutics, 273,* 1063-70

Yamamoto, B.K., & Spanos, L.J. (1988). The acute effects of methylenedioxymethamphetamine on dopamine release in the awake-behaving rat. *European Journal of Pharmacology, 148,* 195-203

Yan, Q.S. (2000). Activation of 5-HT2A/2C receptors within the nucleus accumbens increases local dopaminergic transmission. *Brain Research Bulletin, 51,* 75-81

Yan, Q.S., Yan, S.E. (2001). Activation of 5-HT(1B/1D) receptors in the mesolimbic dopamine system increases dopamine release from the nucleus accumbens: a microdialysis study. *European Journal of Pharmacology, 418,* 55-64

Yokel, R.A., & Pickens, R. (1973). Self-administration of optical isomers of amphetamine and methylamphetamine by rats. *Journal of Pharmacology & Experimental Therapeutics, 187*, 27-33

Yokel, R.A., & Pickens, R. (1974). Drug level of d- and l-amphetamine during intravenous self-administration. *Psychopharmacologia, 34*, 255-64

Yokel, R.A., & Wise, R.A. (1976). Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. *Psychopharmacology (Berl), 48*, 311-8

Yokel, R.A., & Wise, R.A. (1978). Amphetamine- type reinforcement by dopaminergic agonists in the rat. *Psychopharmacology (Berl), 58*, 289-96

Yui, K., Ishiguro, T., Goto, K., & Ikemoto, S. (1997). Precipitating factors in spontaneous recurrence of methamphetamine psychosis. *Psychopharmacology (Berl), 134*, 303-8

Ziedonis, D.M., & Kosten, T.R. (1991). Pharmacotherapy improves treatment outcome in depressed cocaine addicts. *Journal of Psychoactive Drugs, 23*, 417-25