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Review

Endocannabinoids and 3,4-methylenedioxymethamphetamine (MDMA) interaction

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Contents

1. Introduction

The lay population, the media, and health professionals are becoming increasingly alarmed about patterns of polydrug use among young people and the growth of recreational drug consumption, particularly 3,4-methylene-dioxy-methamphetamine (MDMA).

MDMA, popularly known as “ecstasy” or “adam”, is a synthetic (man-made) drug that causes both visual hallucinations and stimulant effects (Green et al., 2003). The drug was developed in Germany in the early twentieth century as an appetite suppressant, but today MDMA is classified as an entactogen. The acute psychological effects include feelings of euphoria, elevated self-confidence, and heightened sensory awareness (Vollenweider et al., 1998; Liechti et al., 2000). MDMA users also consume MDMA for its stimulant properties, which enable them to dance for hours at all-night parties and nightclubs. Lenton et al. (1997) reported that MDMA was the only drug that was used in association with the raves (85.7%) more than in situations that were not rave-related.

Acute adverse effects include moderate de-realization and depersonalization, cognitive disturbances, elevated anxiety, and trismus (Liechti et al., 2000). Hyperthermia is one of the major symptoms of acute MDMA toxicity (Green et al., 2004). This can lead to other, often fatal, toxicological problems including rhabdomyolysis, disseminated intravascular coagulation and acute renal failure, which is potentially fatal in rodents, primates, and humans (Green et al., 2003). Other acute physiological effects after MDMA ingestion include elevated blood pressure and heart rate (McCann et al., 1996). Potentially fatal neurological effects can arise after ingestion of MDMA, including subarachnoid

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hemorrhage, intracranial hemorrhage, or cerebral infarction (McCann et al., 1996).

MDMA is generally agreed to be a potent indirect monoaminergic agonist, raising synaptic levels of monoamines by at least three different mechanisms: increased release, inhibited uptake (both related to action on the transporters), and MAO inhibition (Morgan, 1998; Green et al., 2003; Escobedo et al., 2005). A major mechanism by which MDMA may affect neuronal excitability in the brain is therefore by raising extracellular levels of serotonin (5-HT), dopamine (DA), and norepinephrine (NE). MDMA enhanced DA release in rodents, investigated in vivo using microdialysis techniques (Yamamoto and Spanos, 1988; Yamamoto et al., 1995; Colado et al., 1999, 2004; Nixdorf et al., 2001).

The stimulant and rewarding properties of MDMA are thought to arise in part from its ability to enhance DA release in the ventral tegmental area (VTA) that projects to the nucleus accumbens (NAC) (Bankson and Yamamoto, 2004). DA release in response to MDMA appears to be the primary cause of hyperthermia in rats although it is influenced by dose, ambient temperature, and other housing conditions (Colado et al., 2004).

Cannabis is the most widely consumed illegal drug and self-reported consumption has continued to grow through the 1990s (Farrell et al., 1998). The main feature of the recreational use of cannabis is that it produces a euphoric effect or 'high' (Webb et al., 1996, 1998). Cannabis combines many of the properties of alcohol, tranquilizers, opiates, and hallucinogens: it is anxiolytic, sedative, analgesic, and psychedelic; it stimulates appetite and has many systemic effects. Accompanying the 'high', and often contributing to it, cannabis produces perceptual changes. Hallucinations may occur with high doses. However, cannabis can also produce dysphoric reactions, including severe anxiety and panic, paranoia and psychosis (Ashton, 2001). These reactions are dose-related and more common in naïve users, anxious subjects and psychologically vulnerable individuals (Johns, 2001). Cannabis use in young people moderately increases the risk of developing psychotic symptoms (Henquet et al., 2005).

Cannabinoids exert their effect by interactions with specific endogenous CB_1 and CB_2 cannabinoid receptors (Devane et al., 1988; Munro et al., 1993) present in mammalian tissues. The presence of specific cannabinoid receptors led to the discovery of endogenous, specific cannabinoid ligands that activate these receptors. The term 'endocannabinoid' – originally coined in the mid-1990s after the discovery of membrane receptors for the psychoactive principle in cannabis, Δ^9-tetrahydrocannabinol and their endogenous ligands (anandamide, 2-arachidonoyl glycerol and 2-arachidonyl glyceryl ether) – indicates a whole signaling system that comprises cannabinoid receptors, endogenous ligands and enzymes for ligand biosynthesis and inactivation (Howlett et al., 2004).

2. Cannabis/MDMA: human studies

Numerous reports have indicated that MDMA users consume other psychoactive drugs too, either legal (alcohol or nicotine) or illicit (cannabis, amphetamine, LSD, and opiates). Among the illicit drugs, cannabis is the most useful when taken with MDMA. It has even been suggested that trying MDMA and cannabis is now a teenage rite-of-passage, almost as casual as alcohol and cigarettes were in the past. The main reason for using cannabis with MDMA is that it helps bring on the high and mellows the intense rushes, making MDMA more psychedelic (The Good Drugs Guide, 2004).

The drug most commonly used in association with (either before, during, or after) the last rave is cannabis (51.8%) according to Lenton et al. (1997) and the prevalence of polydrug (MDMA and cannabis) use is higher among young people in dance club settings than in other settings, particularly in combinations of alcohol, cannabis, and stimulant drugs (Calafat et al., 1999; ESPAD, 2000). Table 1 summarizes various reported percentages of users of concomitant MDMA and other substances of abuse. Despite the wide range (between 20 and 13,958) and the type of subjects recruited (students, 18-year-old military personnel, employees, dancers), the findings on concomitant abuse of MDMA and cannabis are similar in different countries, ranging between 73% and 100%. This shows that cannabis is the drug most widely consumed with MDMA followed by alcohol, stimulants, and LSD (Boys et al., 1997; Lenton et al., 1997).

The main results of studies on users of MDMA/cannabis, either together or separately, can be summarized as follows:

1) MDMA and cannabis use is higher among young people in dance club settings than in other settings, particularly the combination(s) of cannabis, alcohol, and stimulant drugs (Calafat et al., 1999; ESPAD, 2000). However other environments such as the home or a friend's house have been reported too (Degenhardt et al., 2004);
2) there is also evidence that, across Europe in general, the prevalence of multiple recreational drug use (MDMA + cannabis) is higher among males and regular users of cannabis than among females and cannabis experimenters, although there are geographical differences (Calafat et al., 1999);
3) almost all the young people who used MDMA in the past year also used marijuana, while students who used marijuana in the past year were 13 times more likely to use MDMA (Strote et al., 2002). This can be explained considering that cannabis and alcohol are the most common drugs used to help reduce the *comedown* (agitation, insomnia) associated with MDMA use (Topp et al., 1999; Strote et al., 2002; Winstock et al., 2001) or to alleviate the negative feelings experienced when the MDMA-related euphoria is diminishing (Croft et al., 2001);

Table 1
Percentage distribution of ecstasy users[a] in association with other substances

Reference	Recruited MDMA users[a] (no.)	Country	MDMA+cannabis users (no.)	MDMA+stimulants users (no.)	MDMA+LSD users (no.)	MDMA+alcohol users (no.)
Schifano et al., 1998	150	Italy	78/66[b]	63/56[b]	30/57[b]	23/47[b]
Topp et al., 1999	329	Australia	98.8	94.2	93.3	99.7
Parrott et al., 2000	28	Ireland	87/100[c]	69/83[c]	69/83[c]	92/100[c]
Siliquini et al., 2001	145	Italy	91	–	53.1	–
Daumann et al., 2001	28	Germany	78	–	–	–
Winstock et al., 2001	1106	U.K.	82	83	30	88
Fox et al., 2002	20	U.K.	100	90	75	70
Strote et al., 2002	13,958	U.S.A.	92.1	–	–	–
National Drug Strategy Household Survey (2002)	1.000.000	Australia	66	50	–	76
Daumann et al., 2004	60	Germany	73	73	28	–
Degenhardt et al., 2004	127/425[d]	Australia	54.6/63.8[d]	27.3/21.8[d]	–	54.4/74.7

–: not detected.
[a] Data collected from 1991 to 2004 on subjects with an age ranging from 14 to 29 years.
[b] Problematic (with at least one psychopathological disturbance) users/non-problematic (free from any psychiatric diagnosis) users.
[c] Light (20 or less occasions) MDMA users/Heavy (more than 20 occasions) MDMA users.
[d] 14–19/20–29 years old.

4) patterns of MDMA use among younger (14–19 years) and older (20–29 years) youngsters do not appear to be significantly different, although MDMA use by the older group tends to be in a context of greater polydrug use (Degenhardt et al., 2004);
5) prolonged use of MDMA and cannabis together may be associated with a variety of psychological problems, including elevated impulsiveness, anxiety, somatic complaints, obsessive–compulsive patterns, and psychotic behavior (Daumann et al., 2001). These results are in line with other reports indicating a broad range of subclinical abnormalities in MDMA, polydrug, and cannabis users (Morgan, 1998; Gamma et al., 2000; McCann et al., 2000; Milani et al., 2000);
6) regular cannabis use seems essential for the development and maintenance of psychopathological symptoms in MDMA users.

Abstinence from cannabis and not MDMA seems to be a useful predictor for remission of psychological complaints in MDMA users, most notably anxiety, depression, interpersonal sensitivity and obsessive–compulsive behavior. There is also striking evidence of a significant relationship between the duration of regular cannabis exposure and various psychopathological symptoms (Daumann et al., 2004).

The most common drugs (other than alcohol) found in fatally injured drivers have been cannabis, benzodiazepines, amphetamine-like stimulants (MDMA) and opioids (Drummer et al., 2003). The majority of all drug-positive cases involved more than one impairing substance. The largest group was combinations with alcohol (9.3%), cannabis with opioids (1.1%), cannabis with stimulants (0.8%), and benzodiazepines (0.7%).

The contribution of MDMA and cannabis to fatal motor vehicle accidents are scant. Kruger and Vollrath (2000) analyzed the driving performance of 66 subjects who had consumed drugs in discotheques in three large cities in Germany, using a driving-simulator which evaluated the ability to maintain lateral position and speed tests, peripheral and central attention and risk-taking behavior; consumption of cannabis and amphetamines/MDMA alone did not adversely affect driving behavior. However, other studies found that cannabis was one of the drugs most likely to be involved in car accidents and traffic fatalities (Ameri, 1999; Ashton, 2001). The combination of the two substances with or without alcohol led to a substantial impairment of driving and performance in secondary tasks. In addition, a recent communication by Rizzo et al. (2003) reported an additive adverse effect on visual perception in MDMA/Δ^9-THC users (42 licensed drivers aged 21–42 years), suggesting that residual effects may impair performance on driving-related tasks.

MDMA/cannabis users also had a poorer performance in tests of memory, learning, word fluency, speed of processing, and manual dexterity in comparison with the no-drug controls and cannabis alone (Croft et al., 2001). In contrast, however, Dafters et al. (2004) and Gouzoulis-Mayfrank et al. (2000), using a similar group design, found no difference between the cannabis users and no-drug controls in any task, but significant differences between users of MDMA and cannabis.

It is still not clear whether the deleterious neurocognitive effects of cannabis and MDMA are best conceptualized in additive terms or should be seen as alternatives (Parrott et al., 2003, 2004). This is illustrated by a study involving 490 participants, of whom 192 were cannabis users and 155 had taken MDMA (Rodgers et al., 2001). Each drug was significantly associated with a different type of self-rating memory impairment. Cannabis was associated with reports of "here-and-now" cognitive problems in short-term and internally cued prospective memory, whereas MDMA was

associated with reports of long-term memory problems, related more to storage and retrieval difficulties. These effects are reasonably consistent with functional impairment in the hippocampus – an area rich in cannabinoid receptors – for cannabis users (Herkenham et al., 1990), and with frontal lobe serotonergic deterioration for MDMA users (Reneman et al., 2000). Those who had used both reported impairments in all these areas.

Finally, an important methodological problem of most studies arises from the frequent polydrug habits of MDMA users and the poor paralleling of control samples as regards the use of other drugs (Curran, 2000). For instance, cannabis influences prolactin secretion, and almost every MDMA user smokes cannabis regularly (Fernandez-Ruiz et al., 1997; Rodriguez et al., 1999).

MDMA causes significant elevations of rat serum corticosterone and prolactin concentrations 30 min post-injection (Nash et al., 1988). Aldosterone and renin secretion also increased in rats given MDMA (Burns et al., 1996). In vitro studies using isolated hypothalamic tissue found that MDMA and some of its metabolites stimulated the release of both oxytocin and vasopressin in a dose-dependent manner (Forsling et al., 2001, 2002). Endocrine abnormalities in MDMA users have been closely related to their using cannabis too (Gouzoulis-Mayfrank et al., 2002). The prolactin response to D-fenfluramine was decreased in abstinent MDMA users who concomitantly used cannabis. Thus, cannabis use may be an important confounder in endocrinological studies of MDMA users and should be looked for systematically in future studies.

3. Cannabis/MDMA in animals

Few studies have systematically examined the pharmacological effects of concomitant treatment with cannabinoids and MDMA in laboratory animals.

3.1. Neurotoxicity

A recent study investigated whether co-administered cannabinoids and MDMA affected the long-term neurotoxic properties of MDMA through either a hypothermic action, an antioxidant action, or both (Morley et al., 2004). There was a significant hyperthermic effect of MDMA and hypothermic effects of the MDMA/Δ^9-THC combination in Wistar rats given repeated injections for two days. The Δ^9-THC group also presented significant hypothermia compared to the vehicle group but not to the same extent as the MDMA/Δ^9-THC group. In the same study, MDMA caused pronounced locomotor stimulation while co-administration of Δ^9-THC or CP 55,940, a potent synthetic cannabinoid agonist, significantly reversed this. In addition, the MDMA/Δ^9-THC combination offered some protection against the long-term anxiogenic effects of MDMA in the emergence test.

These findings indicate that co-administration of the main psychoactive constituent of cannabis (Δ^9-THC) or the synthetic cannabinoid CP 55,940 prevents the hyperthermia and partially attenuates the long-term 5-HT depletion produced by MDMA. The selective CB_1 receptor antagonist SR 141716, while reversing the cannabinoid agonist effects on MDMA-induced hyperthermia, did not affect the prevention of 5-HT depletion.

The mechanism of neuroprotection may be due to the cannabinoids' antioxidant properties, mediated by their phenolic moiety, independently of CB_1 receptor mediation, possibly by counteracting MDMA-induced oxidative stress. In many animal experiments MDMA reduced the antioxidant capacity in the brain, lowering levels of antioxidants such as vitamin C and vitamin E, aggravating oxidative stress, and leaving the way free for oxidative damage and lipoperoxidative damage resulting from excessive free radical formation and abnormal free radical reactions (Green et al., 2003).

These results do not suggest, however, as indicated by Morley et al. (2004), that human MDMA users should resort to Δ^9-THC consumption to minimize harm. Firstly, the protective doses of Δ^9-THC and CP 55,940 used in that study were high and these effects are unlikely to be obtained with the relatively small amounts of Δ^9-THC typically consumed during recreational cannabis use. Secondly, the effect of cannabinoids on MDMA-induced neurotoxicity in cannabinoid-tolerant animals is not known; thus, protection from the neurotoxic effects of MDMA may not necessarily be obtained in frequent cannabis users. Finally, it should be stressed that the neuroprotective effects of Δ^9-THC and CP 55,940 were by no means complete, and were in fact only partial in all brain regions examined.

3.2. Reward and reinforcement

Until now, very few studies have been designed to clarify the consequences of chronic exposure to concomitant cannabinoids and MDMA and their abuse liability.

3.2.1. Drug discrimination

Subjective effects of cannabinoids/MDMA have been reported in drug discrimination studies. Drug discrimination studies in animals are widely considered a model for subjective drug effects in humans. In drug discrimination research, animals faced with two possible responses, one of which results in reinforcement delivery, are trained to detect whether they received an active drug or a placebo – such as the vehicle – in order to establish through drug effects which response is correct. The discrimination between drug and vehicle is based on the presence or absence of subjective and perceptible CNS effects (Schuster and Johanson, 1988; Balster, 1990). Drug discrimination studies have shown that cannabinoid agonists and MDMA, given separately, produce subjective drug effects in rats (Schechter, 1988; Balster and Prescott, 1992; Wiley et al.,

1993, 1995a,b; Baker et al., 1995, 1997; Baker and Taylor, 1997; Barrett et al., 1995; Virden and Baker, 1999) and monkeys (Kamien et al., 1986; Wiley et al., 1993, 1995a,b).

Numerous psychoactive compounds have been evaluated in substitution studies (opioids, barbiturates and other anticonvulsant agents, neuroleptics, benzodiazepines and other γ-aminobutyric acid agents, adrenergic and serotonergic ligands, cholinergic compounds, antidepressants, psychostimulants, hallucinogens, antihistaminergics, and corticoids), but the majority showed no cross-discrimination with cannabinoids (Barrett et al., 1995; Balster and Prescott, 1992; Wiley and Martin, 1999). A partial overlap in the discriminative stimulus effects of Δ^9-THC and diazepam has been reported (Barrett et al., 1995; Wiley and Martin, 1999), but this partial substitution is not mediated by diazepam's action at CB_1 cannabinoid receptors, and is consistent with a γ-aminobutyric acid component to cannabinoid drug discrimination (Wiley and Martin, 1999).

Two other psychoactive compounds, phencyclidine and MDMA (2.5 mg/kg i.p.), have also shown some cross-discriminative stimulus effects with cannabinoids but partial substitution with these compounds and Δ^9-THC (3 mg/kg i.p.) was less important than with diazepam at a dose of 3 mg/kg i.p. (67%) (Barrett et al., 1995). Although MDMA produced 50% of Δ^9-THC-level responding, this partial substitution occurred only at a high dose that substantially affected rates of responding. Thus, it is likely that MDMA's effects in this study reflected disruption of the discrimination rather than any overlap of its discriminative stimulus effects with Δ^9-THC.

3.2.2. Self-administration and self-stimulation

The reinforcing potential of a drug as evaluated in a self-administration paradigm in animals is probably the clearest indication of its addictive potential in humans (Deneau and Seevers, 1964). Animals are given the opportunity to self-administer a drug by making an operant response such as pressing a lever or inserting their nose into a hole (a "nosepoke"), which activates a syringe to deliver the drug through different routes. Reliable and persistent self-administration behavior has been demonstrated in laboratory animals for almost all drugs abused by humans. For instance, MDMA was self-administered i.v. by rhesus monkeys (Beardsley et al., 1986; Thompson et al., 1987; Fantegrossi et al., 2002), baboons (Lamb and Griffiths, 1987), rats (Li et al., 1989; Nagilla et al., 1998; Meyer et al., 2002), mice (Rosecrans and Glennon, 1987; Miczek and Haney, 1994), and chickens (Bronson et al., 1994) and sustained i.c.v. self-administration in rats (Braida and Sala, 2002). MDMA also enhanced lever pressing for rewarding brain stimulation (Reid et al., 1996; Hubner et al., 1988).

During the past three decades, different research groups have modified the parameters of self-administration procedures in unsuccessful attempts to demonstrate reliable and persistent reinforcing effects of Δ^9-THC or synthetic cannabinoids experimentally in animals (Kaymakcalan, 1972, 1973; Pickens et al., 1973; Harris et al., 1974; Leite and Carlini, 1974; Carney et al., 1977; Van Ree et al., 1978; Mansbach et al., 1994). In none of these studies, however, Δ^9-THC or synthetic cannabinoids clearly maintained self-administration behavior that was persistent, dose-related, and susceptible to vehicle extinction and subsequent reinstatement. Only recently has the possibility that monkeys will actively self-administer i.v. Δ^9-THC been re-examined, using a primate species, dosage, and vehicle and injection speed parameters not previously employed (Tanda et al., 2000; Justinova et al., 2003). CP 55,940 had a dose-dependent reinforcing effect, with an inverted U-shaped curve, also in rats using i.c.v. self-administration. This responding was blocked by SR 141716, suggesting CB1 receptor mediation. This method (Braida et al., 1998) presents advantages such as a durable preparation, the possibility of simultaneous choice between the addicting drug and vehicle, and the avoidance of peripheral side effects.

Since it is common for MDMA users to consume cannabis to alleviate negative experience that arise as the MDMA-related euphoria wears off (Croft et al., 2001), this group investigated the involvement of the endocannabinoid system in MDMA self-administration in rats through the i.c.v. route (Braida and Sala, 2002). I.c.v. self-administration of MDMA or the cannabinoid agonist CP 55,940 alone, at the maximal reinforcing unit dose, significantly increased the number of drug-associated and reduced the number of vehicle-associated lever pressings in comparison with vehicle (Fig. 1). The combination of CP 55,940 with the maximal reinforcing unit dose of MDMA (10 ng/rat), simultaneously delivered by pressing the same lever, significantly lowered the mean number of drug-associated lever pressings in comparison with the drug alone. Pretreatment with SR 141716A significantly increased MDMA-associated lever pressings and reduced vehicle-associated pressings in comparison with the drug alone. These findings demonstrate, for the first time, that the cannabinoid agonist alters i.c.v. MDMA self-administration, significantly reducing MDMA intake. The decrease in response seemed to mimic the effect of changes in the unit dose of the reinforcer, suggesting a synergistic action of cannabinoid agonists on the reinforcing properties of MDMA and other drugs of abuse.

The increase of operant responding induced by SR 141716A on MDMA self-administration indicated a decrease in the sensitivity to the motivation, suggesting that the endogenous cannabinoid system influences the mechanism regulating MDMA's reinforcing effect.

However, these findings have not been supported by microdialysis studies in mesolimbic structures which might further define this interaction. This approach appears fundamental, as suggested by Parolaro and Rubino (2002), since other papers with different animal models reported opposite results. Cossu et al. (2001),

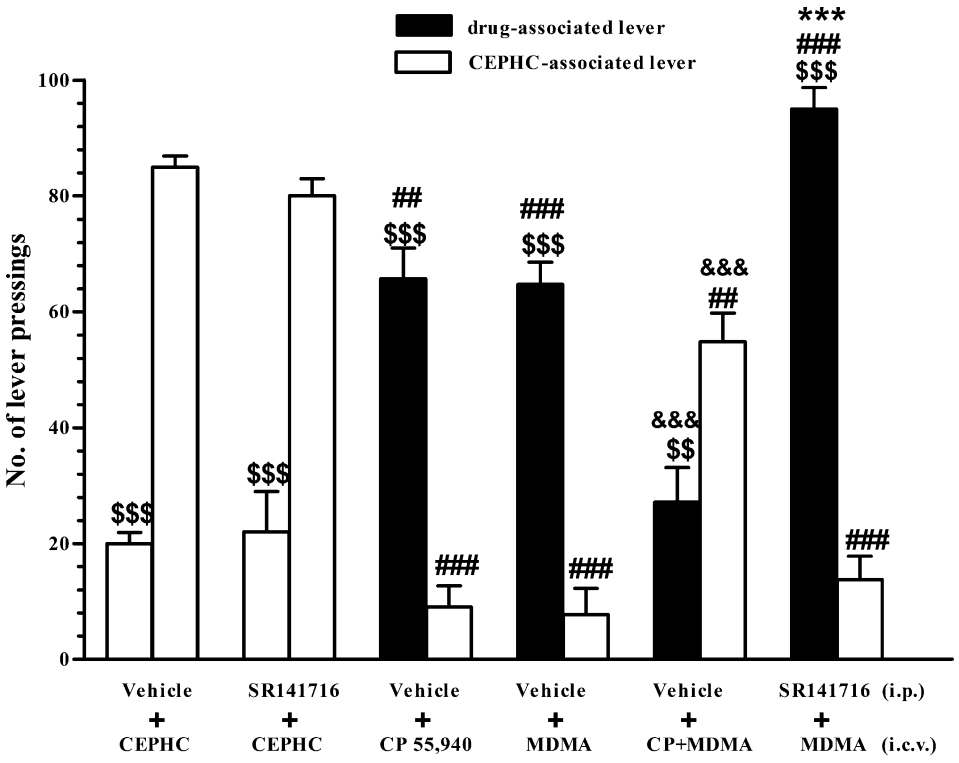

Fig. 1. Mean operant responding (±S.E.) in a free-choice situation to drug and vehicle lever-pressing during the last five stable daily sessions of 15–20 days of acquisition of six animals per group. Each drug lever-pressing delivered 1 μg/2 μL/infusion of MDMA or 0.4 μg/2 μL/infusion of CP 55,940, or both. CEPHC was the vehicle. SR 141716A vehicle or SR 141716A (0.5 mg/kg) was given i.p. 15 min before each daily session. $^{\$\$}p<0.01$, $^{\$\$\$}p<0.001$ vs. the corresponding vehicle associated-lever pressing; $^{\#\#}p<0.01$; $^{\#\#\#}p<0.001$ vs. the corresponding vehicle and SR 141716A; $^{***}p<0.001$ vs. corresponding MDMA alone; $^{\&\&\&}p<0.001$ vs. corresponding CP 55,940 and MDMA alone, and SR 141716A+MDMA (ANOVA followed by post-hoc Tukey's test).

using CB1 receptor knockout mice, found that cocaine, D-amphetamine, and nicotine were i.v. self-administered by both CB_1 knockout and CB_1 wild-type mice. These authors refer to unpublished data (Cossu et al., 2001), showing that cocaine stimulated DA release to the same extent in the nucleus accumbens of CB_1 receptor knockout mice and the wild-type. For example, CB1 knockout mice are a different model from SR 141716A pretreated animals, and the genetic manipulation may have led to the development of compensatory mechanisms absent in wild-type animals; differences in species and administration route are also likely. However, in a previous paper (Fattore et al., 1999), the same group reported that pretreatment with WIN 55,212-2, a CB1 cannabinoid receptor agonist, significantly reduced cocaine intake, suggesting that activation of the CB1 receptor had reinforcing effects additional to those induced by cocaine.

The mechanism by which MDMA and cannabinoids interact is hard to explain. MDMA rapidly increases DA release from cerebral tissue, as has been shown by in vivo microdialysis (Yamamoto and Spanos, 1988; Nixdorf et al., 2001) and in vitro studies using tissue slices (Johnson et al., 1986; Crespi et al., 1997), inhibiting uptake, and by MAO inhibition (Morland, 2000). After peripheral administration of MDMA there was dose-dependent release of DA in the caudate nucleus and nucleus accumbens.

Cannabinoids also participate in the regulation of DA synthesis, release, and turnover (Gardner and Vorel, 1998). The overlapping expression of cannabinoid and DA receptors found in some brain areas, including the nucleus accumbens (Hermann et al., 2002), raises the possibility that stimulation of cannabinoid receptors might produce additional effects to MDMA reinforcing properties.

The positive interaction of concurrent CP 55,940 and MDMA might possibly account for the combined use of marijuana and MDMA by polydrug users in order to overcome the unpleasant effects that often arise as the initial euphoria wears off (Croft et al., 2001).

3.2.3. Conditioned place preference (CPP)

CPP is a widely accepted secondary reinforcement paradigm to predict potential for abuse in humans, which allows animals to be tested in a drug-free state so as to determine the appetitive value of a drug, while avoiding any interference with motor skills.

MDMA, administered peripherally, established CPP in rats (0.2–20 mg/kg) (Bilsky et al., 1991; Schechter, 1991; Marona-Lewicka et al., 1996; Horan et al., 2000; Ratzenboeck et al., 2001; Fone et al., 2002; Meyer et al., 2002; Cole et al., 2003) and mice (Salzmann et al., 2003; Robledo et al., 2004). It therefore appears that MDMA has strong rewarding properties. The proposed mechanism is a synaptic

Table 2
Antagonism by SR 141716A ,naloxone and tropisetron on the establishment of MDMA-induced CPP in rats

Pretreatment	Dose	Treatment	Dose	Pre-conditioning	Post-conditioning
Vehicle	–	Saline	–	75.75±23.37	110.30±28.09
Naloxone	2.0 mg kg^{-1}	Saline	–	106.00±30.87	145.20±28.29
SR 141716A	0.5 mg kg^{-1}	Saline	–	66.60±9.19	113.10±37.34
Tropisetron	1.0 mg kg^{-1}	Saline	–	64.50±13.31	92.00±28.75
Vehicle	–	MDMA	10 ng/rat	58.33±29.27	376.00±33.53***,$$$
Naloxone	2.0 mg kg^{-1}	MDMA	10 ng/rat	59.80±23.15	210.50±38.83#,$$
SR 141716A	0.5 mg kg^{-1}	MDMA	10 ng/rat	73.20±31.53	163.70±47.18###
Tropisetron	1.0 mg kg^{-1}	MDMA	10 ng/rat	81.60±4.41	245.00±23.63#,$$

Time (mean±S.E.M.) spent in the white compartment during pre and post conditioning on the test day. Naloxone and SR 141716A were injected intraperitoneally 10 min, while tropisetron subcutaneously, 30 min before i.c.v. MDMA. Vehicle=pool of 8 rats, 2 receiving saline i.p., 3 receiving vehicle i.p. and 3 receiving tropisetron vehicle s.c. Asterisks indicate a significant difference compared with vehicle group during post-conditioning (***$P<0.001$); dollar signs indicate a significant difference compared with corresponding pre-conditioning time ($^{\$\$}P<0.01$; $^{\$\$\$}P<0.01$); pound signs indicate a significant difference compared with MDMA alone during post-conditioning ($^{\#}P<0.05$, $^{\#\#\#}P<0.001$, Bonferroni's test).

increase of DA through direct inhibition of the DA transporter (Bilsky et al., 1998) and secondary to its ability to increase synaptic 5-HT (Bilsky and Reid, 1991).

The opioidergic system has also been found to influence MDMA's reinforcing properties through the release of DA (Bilsky et al., 1991). Reinforcing properties were also found when MDMA was administered centrally (Braida et al., 2005) at doses between 1 and 1000 ng/rat/i.c.v., compared to a control group. Pretreatment with the selective CB_1 receptor antagonist SR 141716 antagonized MDMA-induced CPP, suggesting that the endocannabinoid system is involved in MDMA's reinforcing properties (Braida et al., 2005) (Table 2).

4. Summary

Cannabis and MDMA are two of the most widely used recreational drugs. This review considered their neuropsychological effects, when taken singly or in combination, in humans or animals. In humans, prolonged use of MDMA and cannabis together is associated with a variety of psychological problems, including elevated impulsiveness, anxiety, somatic complaints, obsessive–compulsive patterns, and psychotic behavior. It is not clear to what extent the combination of MDMA and cannabis contributes to fatal motor vehicles accidents though an additive adverse effect on visual perception in MDMA/Δ^9-THC users has been reported. Neurocognitive deficits (memory, learning, word fluency, speed of processing, and manual dexterity) in several brain areas (hippocampus, frontal lobe) have been reported in those taking both drugs. Endocrine abnormalities in MDMA users have been closely related to their use of cannabis too. A recent study investigated whether co-administered cannabinoids and MDMA in rats affected the long-term neurotoxic properties of MDMA through a hypothermic action, an antioxidant action, or both. Very few studies have set out to clarify the consequences of chronic exposure to concomitant cannabinoids and MDMA for their abuse liability in animals. MDMA showed some cross-discriminative stimulus effects with cannabinoids (Δ^9-THC), and it has been demonstrated in rats that the endocannabinoid system is involved in MDMA self-administration. However, these findings have not been confirmed by microdialysis studies in mesolimbic structures which might further clarify this interaction.

These findings may help explain the use of marijuana and MDMA together by polydrug users in order to overcome the unpleasant effect which often arise as the initial euphoria dissipates. It has recently been confirmed, using a CPP task, that the endocannabinoid system is involved when the reinforcing properties of MDMA, given centrally, were blocked by pretreatment with SR 141716.

References

Ameri A. The effects of cannabinoids on the brain. Prog Neurobiol 1999;58:315–48.

Ashton CH. Pharmacology and effects of cannabis: a brief review. Br J Psychiatry 2001;178:181–6.

Baker LE, Taylor MM. Assessment of the MDA and MDMA optical isomers in a stimulant-hallucinogen discrimination. Pharmacol Biochem Behav 1997;57:737–48.

Baker LE, Broadbent J, Michael EK, Matthews PK, Metosh CA, Saunders RB, et al. Assessment of the discriminative stimulus effects of the optical isomers of ecstasy (3,4-methylenedioxymethamphetamine; MDMA). Behav Pharmacol 1995;6:263–75.

Baker LE, Virden TB, Miller ME, Sullivan CL. Time course analysis of the discriminative stimulus effects of the optical isomers of 3,4-methylenedioxymethamphetamine (MDMA). Pharmacol Biochem Behav 1997;58:505–16.

Balster RL. Perception of drug effects. In: Berkley MA, Stebbins WC, editors. Comparative perception. Basic mechanisms, vol. 1. New York: John Wiley and Sons; 1990. p. 127–54.

Balster RL, Prescott WR. Delta 9-tetrahydrocannabinol discrimination in rats as a model for cannabis intoxication. Neurosci Biobehav Rev 1992;16:55–62.

Bankson MG, Yamamoto BK. Serotonin–GABA interactions modulate MDMA-induced mesolimbic dopamine release. J Neurochem 2004;91:852–9.

Barrett RL, Wiley JL, Balster RL, Martin BR. Pharmacological specificity of delta 9-tetrahydrocannabinol discrimination in rats. Psychopharmacology 1995;118:419–24.

Beardsley PM, Balster RL, Harris LS. Self-administration of methylene dioxymethamphetamine (MDMA) by rhesus monkeys. Drug Alcohol Depend 1986;18:149–57.

Bilsky EJ, Reid LD. MDL72222, a serotonin 5-HT3 receptor antagonist, blocks MDMA's ability to establish a conditioned place preference. Pharmacol Biochem Behav 1991;39:509–12.

Bilsky EJ, Hubbell CL, Delconte JD, Reid LD. MDMA produces a conditioned place preference and elicits ejaculation in male rats: a modulatory role for the endogenous opioids. Pharmacol Biochem Behav 1991;40:443–7.

Bilsky EJ, Montegut MJ, Nichols ML, Reid LD. CGS 10746B, a novel dopamine release inhibitor, blocks the establishment of cocaine and MDMA conditioned place preferences. Pharmacol Biochem Behav 1998;59:215–20.

Boys A, Lenton S, Norcross K. Polydrug use at raves by a Western Australian sample. Drug Alcohol Rev 1997;16:227–34.

Braida D, Sala M. Role of the endocannabinoid system in MDMA intracerebral self-administration in rats. Br J Pharmacol 2002;136:1089–92.

Braida D, Virag W, Ottonello F, Inghilterra S, Gori E, Sala M. A novel method for self-administering addicting drugs intracerebroventricularly in a free-choice procedure. Brain Res Protoc 1998;3:135–41.

Braida D, Iosuè S, Pegorini S, Sala M. 3,4 methylenedioxymethamphetamine-induced Conditioned Place Preference (CPP) is mediated by endocannabinoid system. Pharmacol Res 2005;51:177–82.

Bronson ME, Jiang W, Clark CR, DeRuiter J. Effects of designer drugs on the embryo and 1-day-old chicken. Brain Res Bull 1994;34:143–50.

Burns N, Olverman HJ, Kelly PA, Williams BC. Effects of ecstasy on aldosterone secretion in the rat in vivo and in vitro. Endocr Res 1996;22:601–6.

Calafat A, Bohrn K, Juan M, Kokkevi A, Maalsté N, Mendes F, et al. Night life in Europe and recreative drug use. Valencia: Irefrea and European Commission; 1999.

Carney JM, Uwaydah IM, Balster RL. Evaluation of a suspension system for intravenous self-administration of water insoluble substances in the rhesus monkey. Pharmacol Biochem Behav 1977;7:357–64.

Colado MI, O'Shea E, Granados R, Esteban B, Martín AB, Green AR. Studies on the role of dopamine in the degeneration of 5-HT nerve endings in the brain of Dark Agouti rats following 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") administration. Br J Pharmacol 1999;126:911–24.

Colado MI, O'Shea E, Green AR. Acute and long-term effects of MDMA on cerebral dopamine biochemistry and function. Psychopharmacology 2004;173:249–63.

Cole JC, Sumnall HR, O'Shea E, Marsden CA. Effects of MDMA exposure on the conditioned place preference produced by other drugs of abuse. Psychopharmacology 2003;166:383–90.

Cossu G, Ledent C, Fattore L, Imperato A, Bohme GA, Parmentier M, et al. Cannabinoid CB_1 receptor knockout mice fail to self-administer morphine but not other drugs of abuse. Behav Brain Res 2001;118:61–5.

Crespi D, Mennini T, Gobbi M. Carrier-dependent and Ca(2+)-dependent 5-HT and dopamine release induced by (+)-amphetamine, 3,4-methylendioxymethamphetamine, *p*-chloroamphetamine and (+)-fenfluramine. Br J Pharmacol 1997;121:1735–43.

Croft RJ, Mackay AJ, Mills ATD, Gruzieler JGH. The relative contribution of ecstasy and cannabis to cognitive impairment. Psychopharmacology 2001;153:373–9.

Curran HV. Is MDMA ('Ecstasy') neurotoxic in humans? An overview of evidence and of methodological problems in research. Neuropsychobiology 2000;42:34–41.

Dafters RI, Hoshi R, Talbot AC. Contribution of cannabis and MDMA ("ecstasy") to cognitive changes in long-term polydrug users. Psychopharmacology 2004;173:405–10.

Daumann J, Pelz S, Becker S, Tuchtenhagen F, Gouzoulis-Mayfrank E. Psychological profile of abstinent recreational ecstasy (MDMA) users and significance of concomitant cannabis use. Hum Psychopharmacol 2001;16:627–33.

Daumann J, Hensen G, Thimm B, Rezk M, Till B, Gouzoulis-Mayfrank E. Self-reported psychopathological symptoms in recreational ecstasy (MDMA) users are mainly associated with regular cannabis use: further evidence from a combined cross-sectional/longitudinal investigation. Psychopharmacology 2004;173:398–404.

Degenhardt L, Barker B, Topp L. Patterns of ecstasy use in Australia: findings from a national household survey. Addiction 2004;99:187–95.

Deneau GA, Seevers MH. Pharmacological aspects of drug dependence. Adv Pharmacol 1964;55:267–83.

Devane WA, Dysarz FA, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 1988;34:605–13.

Drummer OH, Gerostamoulos J, Batziris H, Chu M, Caplehorn JR, Robertson MD, et al. The incidence of drugs in drivers killed in Australian road traffic crashes. Forensic Sci Int 2003;134:154–62.

Escobedo I, O'shea E, Orio L, Sanchez V, Segura M, de la Torre R, et al. A comparative study on the acute and long-term effects of MDMA and 3,4-dihydroxymethamphetamine (HHMA) on brain monoamine levels after ip or striatal administration in mice. Br J Pharmacol 2005;144:231–41.

ESPAD. The 1999 alcohol and other drug use among students in 30 European countries, Swedish council for information on alcohol and other drugs (CAN). The Pompidou Group of the Council of Europe; 2000.

Fantegrossi WE, Ullrich T, Rice KC, Woods JH, Winger G. 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") and its stereoisomers as reinforcers in rhesus monkeys: serotonergic involvement. Psychopharmacology 2002;161:356–64.

Farrell M, Howes S, Taylor C, Lewis G, Jenkins R, Bebbington P, et al. Substance misuse and psychiatric comorbidity: an overview of the OPCS national psychiatric morbidity survey. Addict Behav 1998;23:909–18.

Fattore L, Martellotta MC, Cossu G, Mascia MS, Fratta W. CB_1 cannabinoid receptor agonist WIN 55,212-2 decreases intravenous cocaine self-administration in rats. Behav Brain Res 1999;104:141–6.

Fernandez-Ruiz JJ, Munoz RM, Romero J, Villanua MA, Makriyannis A, Ramos JA. Time course of the effects of different cannabimimetics on prolactin and gonadotrophin secretion: evidence for the presence of CB_1 receptors in hypothalamic structures and their involvement in the effects of cannabimimetics. Biochem Pharmacol 1997;53:1919–27.

Fone KC, Beckett SR, Topham IA, Swettenham J, Ball M, Maddocks L. Long-term changes in social interaction and reward following repeated MDMA administration to adolescent rats without accompanying serotonergic neurotoxicity. Psychopharmacology 2002;159:437–44.

Forsling M, Fallon JK, Kicman AT, Hutt AJ, Cowan DA, Henry JA. Arginine vasopressin release in response to the administration of 3,4-methylenedioxymethamphetamine ("ecstasy"): is metabolism a contributory factor? J Pharm Pharmacol 2001;53:1357–63.

Forsling ML, Fallon JK, Shah D, Tilbrook GS, Cowan DA, Kicman AT, et al. The effect of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') and its metabolites on neurohypophysial hormone release from the isolated rat hypothalamus. Br J Pharmacol 2002;135:649–56.

Fox HC, McLean A, Turner JJ, Parrott AC, Rogers R, Sahakian BJ. Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ("ecstasy") polydrug users. Psychopharmacology 2002;16:203–14.

Gamma A, Frei E, Lehmann D, Pascual-Marqui RD, Hell D, Vollenweider FX. Mood state and brain electric activity in ecstasy users. Neuroreport 2000;11:157–62.

Gardner EL, Vorel SR. Cannabinoid transmission and reward-related events. Neurobiol Dis 1998;5:502–33.

Gouzoulis-Mayfrank E, Daumann J, Tuchtenhagen F, Pelz S, Becker S, Kunert HJ, et al. Impaired cognitive performance in drug free users of

recreational ecstasy (MDMA). J Neurol Neurosurg Psychiatry 2000;68:719–25.
Gouzoulis-Mayfrank E, Becker S, Pelz S, Tuchtenhagen F, Daumann J. Neuroendocrine abnormalities in recreational ecstasy (MDMA) users: is it ecstasy or cannabis? J Biol Psychiatry 2002;51:766–9.
Green AR, Mechan AO, Elliott JM, O'shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4 methylenedyoxymethamphetamine (MDMA, "Ecstasy"). Pharmacol Rev 2003;55:463–508.
Green AR, O'shea E, Colado MI. A review of the mechanisms involved in the acute MDMA (ecstasy)-induced hyperthermic response. Eur J Pharmacol 2004;500:3–13.
Harris RT, Waters W, McLendon D. Evaluation of reinforcing capability of Δ^9-tetrahydrocannabinol in monkeys. Psychopharmacologia 1974;37:23–9.
Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen H-U, et al. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. BMJ 2005;330:11–5.
Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, et al. Cannabinoid receptor localization in brain. Proc Natl Acad Sci U S A 1990;87:1932–6.
Hermann H, Marsicano G, Lutz B. Coexpression of the cannabinoid receptor type 1 with dopamine and serotonin receptors in distinct neuronal subpopulations of the adult mouse forebrain. Neuroscience 2002;109:451–60.
Horan B, Gardner EL, Ashby Jr CR. Enhancement of conditioned place preference response to cocaine in rats following subchronic administration of 3, 4-methylenedioxymethamphetamine (MDMA). Synapse 2000;35:160–2.
Howlett AC, Breivogel CS, Childers SR, Deadwyler SA, Hampson RE, Porrino LJ. Cannabinoid physiology and pharmacology: 30 years of progress. Neuropharmacology 2004;47(Suppl. 1):345–58.
Hubner CB, Bird M, Rassnick S, Kornetsky C. The threshold lowering effects of MDMA (ecstasy) on brain-stimulation reward. Psychopharmacology 1988;95:49–51.
Johns A. Psychiatric effects of cannabis. Br J Psychiatry 2001;178:116–22.
Johnson MP, Hoffman AJ, Nichols DE. Effects of the enantiomers of MDA, MDMA and related analogues on [^{3}H]serotonin and [^{3}H]dopamine release from superfused rat brain slices. Eur J Pharmacol 1986;132:269–76.
Justinova Z, Tanda G, Redhi GH, Goldberg SR. Self administration of Δ^9-tetrahydrocannabinol (THC) by drug naive squirrel monkeys. Psychopharmacology 2003;169:135–40.
Kamien JB, Johanson CE, Schuster CR, Woolverton WL. The effects of (+/−)-ethylenedioxy methamphetamine and (+/−)-methylenedioxy amphetamine in monkeys trained to discriminate (+)-amphetamine from saline. Drug Alcohol Depend 1986;18:139–47.
Kaymakcalan S. Physiology and psychological dependence on THC in rhesus monkeys. In: Paton WDM, Crown J, editors. Cannabis and its derivatives. Oxford: University Press; 1972. p. 142–9.
Kaymakcalan S. Tolerance to and dependence on cannabis. Bull Narc 1973;25:39–47.
Kruger HP, Vollrath M. Effects of cannabis and amphetamines on driving simulator performance of recreational drug users under natural conditions. 15th International Conference on Alcohol, Drugs and traffic Safety (T2000), Stockholm, Sweden: May 22nd–26th, 2000.
Lamb RJ, Griffiths RR. Self-injection of D,1-3,4-methylenedioxymethamphetamine (MDMA) in the baboon. Psychopharmacology 1987;9:268–72.
Leite JR, Carlini EA. Failure to obtain "cannabis directed behavior" and abstinence syndrome in rats chronically treated with cannabis sativa extracts. Psychopharmacologia 1974;36:133–45.
Lenton S, Boys A, Norcross K. Raves, drugs and experience: drug use by a sample of people who attend raves in Western Australia. Addiction 1997;92:1327–37.
Li AA, Marek GJ, Vosmer G, Seiden LS. Long-term central 5-HT depletions resulting from repeated administration of MDMA enhances the effects of single administration of MDMA on schedule-controlled behavior of rats. Pharmacol Biochem Behav 1989;33:641–8.
Liechti ME, Saur MR, Gamma A, Hell D, Vollenweider FX. Psychological and physiological effects of MDMA ("Ecstasy") after pretreatment with the 5-HT(2) antagonist ketanserin in healthy humans. Neuropsychopharmacology 2000;23:396–404.
Mansbach RS, Nicholson KL, Martin BR, Balster RL. Failure of Δ^9-tetrahydrocannabinol and CP 55,940 to maintain intravenous self-administration under a fixed-interval schedule in rhesus monkeys. Behav Pharmacol 1994;5:219–25.
Marona-Lewicka D, Rhee GS, Sprague JE, Nichols DE. Reinforcing effects of certain serotonin-releasing amphetamine derivatives. Pharmacol Biochem Behav 1996;53:99–105.
McCann UD, Slate SO, Ricaurte GA. Adverse reactions with 3,4-methylenedioxymethamphetamine (MDMA; 'ecstasy'). Drug Saf 1996;15:107–15.
McCann UD, Eligulashvili V, Ricaurte GA. (+/−) 3,4-Methylenedioxy methamphetamine ('Ecstasy')-induced serotonin neurotoxicity: clinical studies. Neuropsychobiology 2000;42:11–6.
Meyer A, Mayerhofera A, Kovara K, Schmidt WJ. 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. Neurosci Lett 2002;330:280–4.
Miczek KA, Haney M. Psychomotor stimulant effects of Damphetamine, MDMA and PCP: aggressive and schedule-controlled behavior in mice. Psychopharmacology 1994;115:358–65.
Milani R, Turner JJD, Parrott AC, Parmar R. Recreational drug use and psychobiological problems, collaborative UK/Italy study (5): ecstasy (MDMA) polydrug user findings. J Psychopharmacol 2000;14:A15.
Morgan MJ. Recreational use of "ecstasy" (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology 1998;19:252–64.
Morland J. Toxicity of drug abuse-amphetamine designer drugs (ecstasy): mental effects and consequences of single dose use. Toxicol Lett 2000;112–113:147–52.
Morley KC, Li KM, Hunt GE, Mallet PE, McGregor IS. Cannabinoids prevent the acute hyperthermia and partially protect against the 5-HT depleting effects of MDMA ("Ecstasy") in rats. Neuropharmacology 2004;46:954–65.
Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993;365:61–5.
Nagilla R, Newland MC, Snyder J, Bronson ME. Effect of once weekly treatment with 3,4-methylenedioxy methamphetamine on schedule-controlled behavior in rats. Eur J Pharmacol 1998;358:1–8.
Nash Jr JF, Meltzer HY, Gudelsky GA. Elevation of serum prolactin and corticosterone concentrations in the rat after the administration of 3,4-methylenedioxy methamphetamine. J Pharmacol Exp Ther 1988;245:873–9.
National Drug Strategy Household Survey, 2002. http://www.aihw.gov.au/publications/phe/ndshs01sts/ndshs01sts.pdf.
Nixdorf WI, Burrows KB, Gudelsky GA, Yamamoto BK. Enhancement of 3,4-methylenedioxymethamphetamine neurotoxicity by the energy inhibitor malonate. J Neurochem 2001;77:647–54.
Parolaro D, Rubino T. Is cannabinoid transmission involved in rewarding properties of drugs of abuse? Br J Pharmacol 2002;136:1083–4.
Parrott AC, Sisk E, Turner JJ. Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users. Drug Alcohol Depend 2000;60:105–10.
Parrott AC, Fox H, Milani RM. Cannabis, ecstasy/MDMA and memory: a commentary on Simon and Mattick's recent study. Addiction 2003;98:1003–5.
Parrott A, Gouzoulis-Meyfrank E, Rodgers J, Solowij N. Ecstasy/MDMA and cannabis: the complexities of their interactive neuropsychobiological effects. J Psychopharmacol 2004;18:572–5.
Pickens R, Thompson T, Muchow DC. Cannabis and phencyclidine self-administered by animals. In: Goldfarb L, Hoffmeister F, editors. Psychic dependence. Bayer-Symposiumvol. IV. Berlin: Springer; 1973. p. 78–86.

Ratzenboeck E, Saria A, Kriechbaum N, Zernig G. Reinforcing effects of MDMA ("ecstasy") in drug-naive and cocaine-trained rats. Pharmacology 2001;62:138–44.

Reid LD, Hubbell CL, Tsai J, Fishkin MD, Amendola CA. Naltrindole, a delta-opioid antagonist, blocks MDMA's ability to enhance pressing for rewarding brain stimulation. Pharmacol Biochem Behav 1996;53:477–80.

Reneman L, Booij J, Schmand B, van den Brink W, Gunning B. Memory disturbances in "Ecstasy" users are correlated with an altered brain serotonin neurotransmission. Psychopharmacology 2000;148:322–4.

Rizzo M, Lamers CTJ, Skaar N, Sauer CW, Ramaekers J, Andersen GJ. Perception of heading in abstinent MDMA and THC users. J Vis 2003;3:410a.

Robledo P, Balerio G, Berrendero F, Maldonado R. Study of the behavioural responses related to the potential addictive properties of MDMA in mice. Naunyn Schmiedebergs Arch Pharmacol 2004;369:338–49.

Rodgers J, Buchanan T, Scholey AB, Heffernan TM, Ling J, Parrott A. Differential effects of Ecstasy and cannabis on self-reports of memory ability: a web-based study. Hum Psychopharmacol 2001;16:619–25.

Rodriguez DF, Wenger T, Navarro M, Murphy LL. Effects of Δ^9-THC on VIP-induced prolactin secretion in anterior pituitary cultures: evidence for the presence of functional cannabinoid CB_1 receptors in pituitary cells. Brain Res 1999;841:114–22.

Rosecrans JA, Glennon RA. The effect of MDA and MDMA (ecstasy) isomers in combination with pirenpirone on operant responding in mice. Pharmacol Biochem Behav 1987;28:39–42.

Salzmann J, Marie-Claire C, Le Guen S, Roques BP, Noble F. Importance of ERK activation in behavioral and biochemical effects induced by MDMA in mice. Br J Pharmacol 2003;140:831–8.

Schechter MD. Serotonergic–dopaminergic mediation of 3,4-methylene dioxymethamphetamine (MDMA, "ecstasy"). Pharmacol Biochem Behav 1988;31:817–24.

Schechter MD. Effect of MDMA neurotoxicity upon its conditioned place preference and discrimination. Pharmacol Biochem Behav 1991;38:539–44.

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

Schuster CR, Johanson CE. Relationships between the discriminative stimulus properties and subjective effects of drugs. In: Colpaert FC, Balster RL, editors. Transduction mechanisms of drug stimuli. Berlin: Springer-Verlag; 1988. p. 161–75.

Siliquini R, Faggiano F, Geninatti S, Versino E, Mitola B, Ippolito R. Patterns of drug use among young men in Piedmont (Italy). Drug Alcohol Depend 2001;64:329–35.

Strote J, Lee JE, Wechsler H. Increasing MDMA use among college students: results of a national survey. J Adolesc Health 2002;30:64–72.

Tanda G, Munzar P, Goldberg SR. Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. Nat Neurosci 2000;3:1073–4.

The Good Drugs Guide: http://www.thegooddrugsguide.com/articles/e_politics.htm.

Thompson DM, Winsauer PJ, Mastropaolo J. Effects of phencyclidine, ketamine and MDMA on complex operant behavior in monkeys. Pharmacol Biochem Behav 1987;26:401–5.

Topp L, Hando J, Dillon P, Roche A, Solowij N. Ecstasy use in Australia: patterns of use and associated harm. Drug Alcohol Depend 1999;55:105–15.

Van Ree JM, Slangen JL, de Wied D. Intravenous self administration of drugs in rats. J Pharmacol Exp Ther 1978;204:547–57.

Virden TB, Baker LE. Disruption of the discriminative stimulus effects of *S*(+)-3,4-methylenedioxymethamphetamine (MDMA) by (+/−)-MDMA neurotoxicity: protection by fluoxetine. Behav Pharmacol 1999;10:195–204.

Vollenweider FX, Gamma A, Liechti M, Huber T. Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers. Neuropsychopharmacology 1998;19:241–51.

Webb E, Ashton CH, Kelly P, Kamali F. Alcohol and drug use in UK university students. Lancet 1996;348:922–5.

Webb E, Ashton CH, Kelly P, Kamali F. An update on British medical students' lifestyles. Med Educ 1998;32:325–31.

Wiley JL, Martin BR. Effects of SR141716A on diazepam substitution for Δ^9-tetrahydrocannabinol in rat drug discrimination. Pharmacol Biochem Behav 1999;64:519–22.

Wiley JL, Barrett RL, Britt DT, Balster RL, Martin BR. Discriminative stimulus effects of delta 9-tetrahydrocannabinoland delta 9-11-tetrahydrocannabinol in rats and rhesus monkeys. Neuropharmacology 1993;32:359–65.

Wiley JL, Huffman JW, Balster RL, Martin BR. Pharmacological specificity of the discriminative stimulus effects of Δ^9-tetrahydrocannabinol in rhesus monkeys. Drug Alcohol Depend 1995a;40:81–6.

Wiley JL, Lowe JA, Balster RL, Martin BR. Antagonism of the discriminative stimulus effects of delta 9-tetrahydrocannabinol in rats and rhesus monkeys. J Pharmacol Exp Ther 1995b;275:1–6.

Winstock AR, Griffiths P, Stewart D. Drugs and the dance music scene: a survey of current drug use patterns among a sample of dance music enthusiasts in the UK. Drug Alcohol Depend 2001;64:9–17.

Yamamoto BK, Spanos LJ. The acute effects of methylenedioxymethamphetamine on dopamine release in the awake-behaving rat. Eur J Pharmacol 1988;148:195–203.

Yamamoto BK, Nash JF, Gudelsky GA. Modulation of methylenedioxymethamphetamine-induced striatal dopamine release by the interaction between serotonin and γ-aminobutyric acid in the substantia nigra. J Pharmacol Exp Ther 1995;273:1063–70.