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Review

The pre-clinical behavioural pharmacology of 3,4-methylenedioxymethamphetamine (MDMA)

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Abstract

3,4-Methylenedioxymethamphetamine (MDMA) is a relatively novel drug of abuse and as such little is currently known of its behavioural pharmacology. This review aims to examine whether MDMA represents a novel class of abused drug. MDMA is known as a selective serotonergic neurotoxin in a variety of animal species but acutely it is a potent releaser and/or reuptake inhibitor of presynaptic serotonin, dopamine, noradrenaline, and acetylcholine. Interaction of these effects contributes to its behavioural pharmacology, in particular its effects on body temperature. Drug discrimination studies indicate that MDMA and related drugs produce unique interoceptive effects which have led to their classification as entactogens. This is supported by results from other behavioural paradigms although there is evidence for dose dependency of MDMA-specific effects. MDMA also produces conditioned place preference but is not a potent reinforcer in self-administration studies. These unique behavioural effects probably underlie its current popularity. MDMA is found in the street drug ecstasy but it may not be appropriate to equate the two as other drugs are routinely found in ecstasy tablets

Keywords: Serotonin; Dopamine; MDMA; Ecstasy; Dependence; Drug discrimination

Contents

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA) is currently one of the most popular drugs of abuse in Europe. Its increasing popularity over the last 15 years has led to concerns over possible short- and long-term adverse effects

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on users. Reports of short-term adverse reactions emerged shortly after the introduction of MDMA into the pharmacopoeia of controlled drugs. Despite widespread use, however, these adverse reactions remain rare and the death rate from MDMA intoxication is no higher than that from comparable drugs of abuse and lower than that of alcohol [55]. Of more concern from the Public Health perspective is the possible neurotoxic effects of MDMA. Like other amphetamines, MDMA has been shown to produce neurotoxic damage in a variety of animal species using high dose regimens (reviewed in Refs. [69,123,138, 223,250]). Whether this neurotoxic damage occurs in human users of MDMA is uncertain as studies investigating this phenomena suffer from a host of methodological confounds [55,127,139,159,166,192,207,245]. What is certain from the literature is that human users of MDMA are ingesting sufficient quantities to produce behavioural effects. This review will examine the pre-clinical behavioural pharmacology of MDMA, with a focus upon rodent data, in order to determine if MDMA represents a novel class of abused drug. The relevance of such studies to human use of MDMA will then be discussed.

2. Pre-clinical pharmacokinetics and metabolism

Pharmacokinetic data after systemic injection of MDMA has been described in Sprague Dawley rats [92,49]. Forty-five minutes after a single injection of 20 mg/kg [^{3}H]MDMA, comparable concentrations of drug were detected in various brain regions, whilst higher levels were measured in the liver [23]. Distribution half-life varied between animals from 2 to 26 min whilst, assuming a first-order process, terminal plasma half-life was approximately 2.5 h for R(−)MDMA and 2.2 h for S(+)MDMA. Half-life in the brain was approximately 1.5 h [79]. Following a racemic dose of (±)MDMA, the area under the curve for R(−)MDMA was greater than that of S(+)MDMA [49,92].

Approximately 8% of the MDMA dose is excreted unchanged in rats but this rises to 50% in humans [49,72]. The main metabolic products are 3,4-methylenedioxyamphetamine (MDA) and 3,4-dihydroxymethamphetamine (DHMA) [49,72]. These undergo further metabolism (possibly via catechol-*O*-methyl transferase mediated reactions) to form 4-hydroxy-3-methoxymethamphetamine (HMMA) and 4-hydroxy-3-methoxyamphetamine (HMA), respectively. Oxidation of the methylenedioxy group takes place via enzymatic hydroxylation, or non-enzymatic processes involving hydroxyl radicals [144,167,178,180, 296]. In rats, the AUC for S(+)MDA is approximately 2.5 times greater than for the R(−) isomer, indicating the presence of long lasting (active) metabolites [92]. Stereoselective formation of S(+)MDA may account for the more rapid clearance of S(+)MDMA. Irreversible oxidation of MDMA also produces methamphetamine-quinone, which is further (reversibly) oxidised to 3,4-DHMA [150]. Metabolic species are excreted after appropriate glucorinide and sulphate conjugation, which may produce neurotoxicants [12,203]. The increased formation of metabolites in rats may indicate a greater susceptibility to neurotoxicity compared to humans.

MDMA is demethylenated to catechol metabolites in the brain and liver by, amongst other enzymes, the cytochrome P450 isoenzyme debrisoquine 4-hydroxylase (CYP 2D6) [144,168,181,296]. Approximately 5–9% of Caucasians show an absence of this isoenzyme as a result of autosomal recessive inheritance of gene mutations and are classed as 'poor debrisoquine metabolisers' [117]. Female Dark Agouti rats have been proposed as a model of the human 'poor debrisoquine metaboliser' polymorphism [33]. These rats show a greater hyperthermic response to 10 mg/kg MDMA i.p. at room temperature than males ('extensive debrisoquine metabolisers' corresponding to the majority of the Caucasian population), in the absence of significant differences in plasma MDMA concentration [53]. Some authors have speculated that severe toxic reactions seen after single doses of ecstasy (e.g. [143]) may be idiosyncratic and related to the metabolic status of the user [53,57, 163,296]. Concomitant use of CPY2D6 inhibiting drugs (e.g. fluoxetine) with MDMA may increase the toxic risks to all MDMA users [136,142].

3. Pre-clinical pharmacology

In vivo and in vitro studies suggest that MDMA is a potent releaser and/or reuptake inhibitor of presynaptic 5-HT, DA, noradrenaline (NA) and acetylcholine (ACh) (Fig. 1; [2,44,63,89,121,129,151,194,213,219,286,302,304, 309,310]. Interaction of these systems underlies the unique behavioural effects of MDMA (see sections below).

MDMA has a high affinity for the serotonin transporter (SERT) ($K_i = 610$ nM) and in accordance with the 'exchange-diffusion' model [90] may facilitate fluoxetine-sensitive 5-HT release by stimulating both Ca^{2+}-dependent and -independent 5-HT/MDMA exchange (i.e. dependent and independent of neuronal firing) through reversal of vesicular and plasma membrane transporters [63,140,151, 258,260,268,304]. MDMA thus behaves as a SERT substrate, promoting carrier-mediated neurotransmitter release [17,176]. However, recent fast cyclic voltammetry data suggests that in some brain regions, inhibition of 5-HT uptake ($EC_{50} = 0.35$ μM [63]) is a more important factor than direct transmitter release in increasing extracellular 5-HT concentration [150]. In all brain regions, inhibition of MAO_A and MAO_B contributes to the rise in extracellular monoamine concentrations [128,173].

MDMA inhibits the firing of both dorsal (DRN) and median (MRN) raphé nuclei with equal potency by direct (receptor interaction, see below) or indirect (5-HT release) activation of somatodendritic 5-HT_{1A} autoreceptors [22,68, 202,238,284]. MDMA is distinguished from the classic

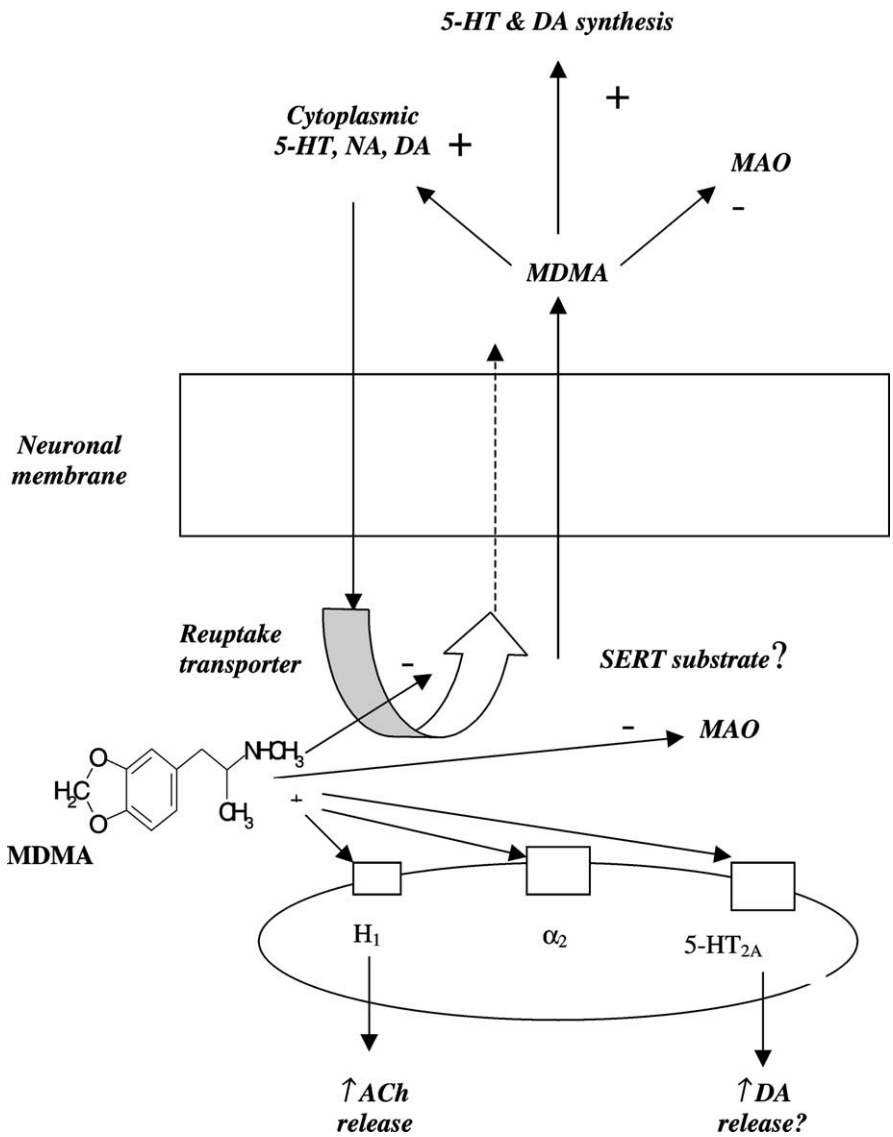

Fig. 1. Schematic representation of the main pharmacological effects of MDMA as described in the text. Extracellular monoamine concentration is elevated by increased intraneuronal synthesis, reuptake inhibition, monoamine oxidase inhibition and carrier-mediated exchange. Direct and indirect postsynaptic histamine and 5-HT receptor activation mediates ACh and DA release. There is speculation that MDMA may enter the nerve terminal as part of a vesicle exchange-diffusion process.

5-HT hallucinogens, which also share this electrophysiological property, by additional inhibitory activity in regions such as the medial prefrontal cortex [233,234]. This work also suggests that in contrast to administration of neurotoxic regimens [10], there is no difference in the sensitivity of DRN and MRN terminal regions to the acute serotonergic effects of MDMA.

5-HT synthesis rate is acutely increased one hour after i.v. infusion, only to be halved 5 h post-administration [221]. MDMA rapidly (<1 h) inactivates tryptophan hydroxylase by sulphydryl oxidation and this may be one of the earliest markers of more prolonged neurotoxic effects [165,269,274,277,288].

Although MDMA has higher affinity for the SERT there is a greater *total* efflux of DA than 5-HT at behaviourally active doses [257,303]. This involves both carrier- and impulse-mediated processes, and may also include the reversal and reuptake inhibition of the DA transporter (DAT) [63,160,199,258,310]. Extracellular DA levels are enhanced and maintained by a rapid and reversible inhibition of reuptake accompanied by an increase in DA synthesis and decrease in turnover [63,150,172,199,214,260,286,289]. DA release has been shown in the hippocampus, an area sparsely innervated by DA fibres [279]. It has been proposed that this occurs through an increase in the efflux of cytosolic DA from NA neurons via the NA transporter (NAT) [279]. Microdialysis studies indicate that blocking MDMA-induced 5-HT release by neurotoxic lesion, or utilisation of pharmacological antagonists at the SERT or 5-HT_{2A} receptors, significantly decreases

subsequent DA release [129,160,276,309]. Increases in MDMA-induced DA efflux occur in parallel with a decrease in ventral substantia nigra GABA release [309]. Taken alongside the observation that local infusion of 5-HT_{2A} receptor antagonists or the systemic administration of $GABA_A$ receptor antagonists significantly attenuates the rise in extracellular striatal DA [51,212] it has been hypothesised that direct or indirect activation of 5-HT_{2A} receptors localised upon GABA interneurones, may disrupt nigrostriatal GABA negative feedback control such that there is a subsequent disinhibition of DA release [276]. DA release may also be 'state-dependent', i.e. a phasic response that is only of pharmacological significance during states of high 5-HT and DA transmission [19,273]. For example, endogenous 5-HT enhances the release of DA in the striatum, only when nigro-striatal DA transmission is also activated [182]. MDMA administration may facilitate these state-dependent requirements through extensive 5-HT and DA release. However, the exact mechanism underlying DA release, particularly the role played by the DAT, has yet to be clarified [258].

MDMA releases NA with greater potency than DA [257]. The drug has strong inhibitory effects on the firing rate of NA neurons in the locus coeruleus which may be due to 5-HT and/or NA mechanisms [91,171,257,288]. MDMA potentiates NA-induced smooth muscle contraction, which is blocked by the presence of cocaine but not isoprenaline [7]. As isoprenaline is not a substrate for the NAT, reuptake blockade rather than transmitter release may underlie MDMA effects on NA neurons. NA release may be responsible for many of the amphetamine-like psychostimulant effects of MDMA.

MDMA elicits cortical and striatal ACh release at doses that also stimulate spontaneous behaviour, and may be controlled by histamine H_1 receptor activation [2,89]. Similar cholinergic effects have been reported for cocaine and amphetamine and whilst they may underlie some of the psychomotor stimulant properties of MDMA, the importance of this effect is unknown [71,149].

Extracellular brain concentrations of MDMA are reported in the high micromolar range after systemic administration to rats [313]. At these concentrations MDMA has moderate affinity for a variety of central receptor sites including 5-HT uptakes sites ($K_i = 610$ nM), 5-HT_{2A} receptors ($K_i = 5.1$ μM), histamine H_1 receptors ($K_i = 5.7$ μM) and muscarinic M_1 ($K_i = 5.8$ μM) and M_2 ($K_i = 15.1$ μM) receptors [22,294]. Whilst direct receptor interactions undoubtedly contribute to the behavioural pharmacology of MDMA, increases in extracellular transmitter concentrations are probably more important.

Both rat and human studies have shown an acute increase in concentrations of prolactin, arginine vasopressin and peripheral markers of hypothalamic-pituitary-adrenal (HPA) axis activation, namely corticosterone, cortisol, and adrenal ascorbic acid [62,73,195,215,231]. Oxytocin and vasopressin are dose-dependently released by MDMA and its metabolites from rat hypothalamic preparations, with HMMA being the most potent releaser [94]. Sex and metabolic status may therefore predict susceptibility to the more serious side effects of hyponatraemia after MDMA-ingestion [131,301]. Administration of MDMA produced rapid and pronounced changes in immune function [57–61,147,230]. This included a reduction in the number of circulating lymphocytes, a suppression of T-lymphocyte proliferation and immunoglobulin production, changes in cytokine production and an impairment of the ability to respond to an in vivo bacterial lipopolysaccharide challenge. In humans, there is a general trend towards baseline immunological response 24 h post drug. It is possible that prolonged administration of MDMA could reduce host resistance to disease.

4. Pre-clinical toxicology

The acute LD_{50} of MDMA reported for Swiss-Webster mice is 97 mg/kg i.p., and 49 mg/kg i.p. for the Sprague Dawley rat [134]. Serum MDMA levels assayed in humans have approached, or in some cases exceeded, the non-human primate LD_{50} of 22 mg/kg i.p. [253]. MDMA is less toxic in rats via the oral route, with an LD_{50} of 325 mg/kg [113], although deaths have occurred in female Sprague Dawley rats over a range of lower oral doses (40–320 mg/kg), including $>66\%$ of animals dying within 4 h of administration of >160 mg/kg MDMA at 20 °C [50]. Death was thought to have resulted from a combination of hyperthermia and the 'serotonin syndrome' (see below). Toxicity also seems strain dependent, at least in female rats. The female Dark Agouti rat died after 10 mg/kg i.p. administered at ambient temperatures of 31 °C, but this dose was not lethal to the female Sprague Dawley [188]. Some individuals may therefore be more sensitive to acute MDMA toxicity at high ambient temperatures. Chronic administration to beagle dogs ($n = 24$) using oral doses of ≤ 15 mg/kg (once daily for 28 days) resulted in a single death, and there was evidence of testicular atrophy and prostatic enlargement in some animals [98]. Concurrent studies in the rat (≤ 15 mg/kg per day) were without notable pathological consequence. However, more recent work found that daily administration of MDMA to rats for 28 days produced significant myocardial pathology, which resembled the necrotic and inflammatory responses observed in some human fatalities [204,222,298]. Like other substituted amphetamines, aggregation toxicity is observed with MDMA [70]. Housing mice in groups of at least five produced a 5-fold decrease in the i.p. LD_{50} compared with individually housed animals.

Pre-natal methamphetamine and *d*-amphetamine exposure in mice and rabbits is associated with dose-dependent increases in physiological abnormalities in offspring [239]. Pre-natal studies have shown that MDMA releases [^{3}H]5-HT from cortical synaptosomes harvested

from rat embryos as early as 17 days old [162]. This is notable as some actions of 5-HT are considered teratogenic, partly through modulation of uterine blood flow [78,164, 205]. However, rodent teratological studies have found no abnormalities in gestational duration, neonatal birth weights or physical appearance after MDMA [285], and only a modest reduction in litter size (which the authors admit may have been a chance finding considering a higher than average litter size in control animals) [52]. Other workers investigating the neurotoxic effects of pre-natal MDMA administration have not reported physical abnormalities [5, 36,37]. In contrast, a single 8 mg/kg MDMA injection into 14 day old chick embryos and 1 day old chicks results in decreased body and brain weight, and decreased motility [38].

5. Cardiovascular effects

Acute MDMA administration produces cardiac stimulation and tachycardia, and facilitates vasoconstriction in rats and rabbits [91,236]. Such vascular changes, together with cerebral hyperperfusion, forced cerebrovascular dilation and coagulapothy may be responsible for cases of intracerebral haemorrhage in some human users [91,104, 135]. In common with cocaine and other amphetamine analogues, clinical reports indicate MDMA use is associated with cardiovascular toxicity, most likely through acute sympathomimetic activation [7,91,100,175]. Cardiovascular changes are compounded by acute MDMA-induced renin release, leading to an increase in angiotensin II (AII) production [39]. AII is the effector peptide of the renin–angiotensin system, which in addition to its vasoconstrictive effects promotes aldosterone release from the adrenal cortex, leading to an increase in blood pressure. Neurotoxic effects of some MDMA regimens [251] may also alter cardiovascular or cardiovascular reflex function through actions on descending central or peripheral 5-HT systems [222]. The drug also has agonist activity at central $\alpha_{2A/D}$ adrenoceptors (see below; [171]) and produces short-lived, pressor responses at low to medium doses (1–5 mg/kg) followed by a more prolonged depressor response [297]. Of the limited number of studies performed in humans investigating cardiovascular activity after MDMA, only Downing has reported similar observations [77], although this may be explained by the relatively short time frame of investigation of other work.

6. Hyperthermia and thermoregulation

At room temperatures MDMA produces an abrupt rise in body temperature ($\approx$1.5 °C) that is sensitised to chronic administration [48,66,67,120,215,271]. Oral administration produces a more prolonged elevation in core temperature than the i.p. route [195], although in human volunteer studies oral MDMA does not reliably increase body temperature, and any observed increases do not exceed 0.5 °C. In the rat, core temperature changes induced by the administration of MDMA are dependent upon environmental variables, such as cage type, housing conditions, water availability, and ambient temperature [65,66,119,184]. High doses of MDMA administered at high ambient temperatures produce hyperthermia, low doses at low ambient temperatures produce hypothermia, and intermediate doses produce a biphasic response, initially hypothermia followed by hyperthermia [67]. Different types of cages have also been shown to affect the hyperthermic properties of MDMA, with acrylic cages producing an increase of over 2 °C and metal cages producing no hyperthermia [185]. In the rat, hyperthermia is accentuated by an increase in metabolic rate and reduced blood flow to the tail [120]. Despite inducing a rise in rectal temperature, there was no corresponding increase in the tail, indicating that MDMA may inhibit heat dissipation in the rat [196]. Cutaneous vasoconstriction coincides with acute hyperthermia indicating impaired heat loss in MDMA treated animals [91,236].

Until recently, 5-HT release and activation of post-synaptic 5-$HT_{2A/2C}$ receptors were thought to be essential prerequisites for MDMA-induced temperature change [123,225,270]. Work in the Dark Agouti rat has indicated that it is more likely that the D_1 receptor mediates hyperthermia [196]. Furthermore, increasing the availability of DA by administration of high doses (>25 mg/kg i.p.) of the DA precursor *l*-dihydroxyphenylalanine (L-DOPA) 2 h after MDMA administration (15 mg/kg i.p.) led to a severe, prolonged, and often fatal hyperthermia in male Dark Agouti rats [51]. Hyperthermia may also potentiate MDMA-induced depletion of glutathione, increasing the risk of hepatocytic exposure to pro-oxidant toxicants [47,281].

7. Locomotor response

Peripheral and central administration of MDMA dose-dependently enhanced locomotor activity in the open field test [27,41,44,65,116,247,262,283]. In contrast to undrugged animals, those receiving MDMA initially exhibited immobilisation, which may be related to the anxiogenic properties of the drug (see below) [114]. Whilst administration of doses of cocaine and amphetamine that produced a similar amount of activity increased locomotion throughout the test chamber, MDMA characteristically resulted in focused 'straight-line patterns' in which movement of the animal was confined to the periphery [43,115, 247,262]. This has been described as 'rotation within the chamber' [24] but may more accurately represent a thigmotactic response [115], a property shared with the classic 5-HT hallucinogens. Familiarity with the testing environment failed to change the pattern of activity, indicating that 'centre-avoidance' was not due to

the aversive properties of the open spaces of the arena [43]. Higher doses evoked repetitive stereotypical movements, although the majority of behaviours showed greater resemblance to elements of the serotonin syndrome [169, 283]. In keeping with its effects on 5-HT release, S(+)MDMA was more potent in eliciting stereotypy/serotonin syndrome behaviour [145]. Repeated administration of low to medium doses (2.5–7.5 mg/kg i.p. every other day for 6 and 12 days) produced locomotor sensitisation [283]. Pairing MDMA with a distinct odour produced enhanced locomotion upon presentation of the odour alone, indicating that like other psychostimulants, it can produce conditioned activity [116]. Interestingly, and of great relevance for the development of new anti-parkinsonian drugs, MDMA dose-dependently reversed haloperidol-induced catalepsy in rats. There was a supraadditive effect of administration of the individual enantiomers, indicating that multiple sites of action were involved [278].

Neuropharmacological analysis has indicated an important role for DA in the mediation of the locomotor effects of MDMA, as might be expected of an amphetamine-like drug [19,41,42,114,310] (comprehensively reviewed in Ref. [20]). However, 6-hydroxydopamine (6-OHDA) lesions of the mesolimbic DA system only partially attenuated MDMA-induced locomotion [114]. As 5-HT release alone is insufficient to increase locomotor activity [9], an interaction between DA and 5-HT may underlie the qualitative differences between amphetamine- and MDMA-induced locomotion [19]. 5-HT_{1B} receptor agonists elicit locomotor hyperactivity similar to MDMA [247] and transgenic mice lacking the SERT or 5-HT_{1B} receptor show no or reduced MDMA-induced locomotion and a behavioural pattern qualitatively reminiscent of other amphetamines [262,27]. Prior 5-HT depletion or pre-treatment of animals with SSRIs or 5-HT_{1B} receptor antagonists block low dose MDMA hyperkinesis [42,44]. Activation of this receptor subtype may be fundamental in defining MDMA-specific locomotor activity. The 5-HT_{2A} antagonist MDL 100,907 blocked high dose (20 mg/kg) but not low dose (3 mg/kg) MDMA-induced locomotion [157].5-HT_{2C} receptor antagonists potentiated locomotor activation after low dose MDMA [20,115]. It has been proposed that unmasking of 5-HT_{1B} receptor-mediated hyperactivity via 5-HT_{2C} antagonism is only possible in the presence of the elevated DA and 5-HT concentrations seen after MDMA [19].

8. Anxiety, aggression and social behaviour

Medium to high doses of MDMA (8–20 mg/kg i.p.) reduced aggressive behaviours (sideways threats and attack) in social encounters between individually housed male mice without affecting immobility [187,216]. However, these were also accompanied by decreases in social investigation, body care, and digging behaviours. Furthermore, MDMA significantly increased avoidance and submissive behaviours in a similar manner to the anxiogenic benzodiazepine receptor ligand, FG 7142, suggesting that mice treated with MDMA exhibit anxiogenic-like behaviour in agonistic encounters. In contrast, whilst 0.3–10 mg/kg MDMA dose-dependently reduced the combined frequency of attacks and sideways threats in the resident-intruder model, there were no reported effects upon other characteristic postures [201]. Aggressive behaviour was reduced in pairs of *Gymnotus carapo*, considered the most aggressive of all weakly electrical fish species [45]. In contrast with effects reported in mice, acute injection (1 or 5 mg/kg MDMA) to this species was associated with an increase in non-aggressive social interaction. Responses to novel visual stimuli were enhanced suggesting that diminished aggression was not due to general behavioural suppression. In Charles Foster rats, 5 or 10 mg/kg MDMA reduced the total time spent in social interaction [28], whilst 5 mg/kg decreased aggressive behaviours and facilitated a longer duration of social interaction in inbred Wistar rats [208]. The difference in behaviour produced at the overlapping dose of these two studies (i.e. 5 mg/kg) may have been due to strain variation and/or degree of familiarity towards the testing environment [193].

In the rat elevated plus maze, 5–10 mg/kg i.p. produced a dose-dependent increase in fear-like behaviour [28]. Total arm entries, and open arm entries and time are decreased, with a concomitant increase in closed arm preference. Over a range of lower doses (<5 mg/kg), and in contrast to the effects on social interaction, MDMA also increased anxiety-like behaviour on the plus maze [208]. This dose range decreased open arm time and increased closed arm time. In contrast, there was no effect on the expression of a variety of risk assessment behaviours (head dips, rears, and stretched attend postures). Similar increases in anxiety were obtained from the emergence and cat odour avoidance tests [208]. In the emergence test, <5 mg/kg decreased the frequency of emergence and caused a concomitant increase in emergence latency, whilst 5 mg/kg produced a significant decrease in approach time towards a worn cat collar. There was a dose-dependent reduction in the number of vocalisations produced by footshock [208].

Dose-related effects have been reported on the murine plus maze [179,217]. 4–8 mg/kg MDMA reduced% open arm entries and increased closed arm entries, 12 mg/kg produced no significant effects, whilst 15–20 mg/kg increased% open arm time without affecting other traditional indices of behaviour. An anxiogenic behavioural profile, signified by a significant reduction in rearings and transitions, is also reported in mice at medium to high doses (8–15 mg/kg i.p.) in the light-dark box [186]. Repeated testing on the plus maze revealed the anxiogenic effects of a low dose of MDMA (1 mg/kg), which was not present acutely [217]. In contrast, high dose anxiolysis is diminished after sub-chronic dosing. Binge users of ecstasy may therefore experience an increase in unpleasant subjective effects across time.

In comparison with saline treated animals, which actively explore new environments, MDMA initially reduced locomotor activity when animals were introduced into an open field arena [115]. Moreover, both wild type and 5-HT_{1B} receptor knockout mice exhibited reduced rearings and nose pokes (3.3–30 mg/kg i.p.) after introduction to a modified open field arena [262], suggesting that reductions in exploratory behaviour are preserved across different behavioural models.

The pharmacological processes underlying the anxiogenic and social effects of MDMA have not yet been described. The dose dependent nature of effects suggests that multiple mechanisms underlie the behavioural pharmacology. Acute 5-HT release may make the animal more responsive to the aversive properties of the plus-maze environment, although increasing 5-HT function in the absence of threat does not cause fear-like behaviour in itself [132]. Like fenfluramine, some reports suggest that treatment with low doses of fluoxetine suppresses plus maze open arm exploration in rats, which mirrors acute anxiogenic effects in humans [133] (but see [125]). Both these drugs share the pharmacological ability with MDMA to increase extracellular 5-HT concentration. 5-$HT_{2A/2C}$ receptor agonists such as *meta*-chlorophenylpiperazine (*m*CPP) exert strong anxiogenic effects in a variety of animal models of anxiety [102,198]. MDMA shows micromolar affinity for the 5-HT_{2A} receptor, and 5-HT released by MDMA may interact with 5-$HT_{2A/2C}$ receptor sites (see above). This property, perhaps in combination with HPA axis and sympathomimetic activation, both potent anxiogenic stimuli, may underlie the effects of MDMA in the plus maze [3,161,254]. However, there have been no reports of increased social interaction after acute treatment with either fenfluramine or fluoxetine [85,124] and another SSRI, citalopram, has been shown to reduce social behaviours in rats [75]. In contrast, pro-social and anti-aggressive effects have been reported with the 5-HT_{1A} and 5-HT_{2B} receptor agonist buspirone [237]. Interaction with these receptor subtypes at low doses may underlie the unique social effects of MDMA. Finally, and worthy of further investigation, are the possible links between vasopressin and oxytocin release and pro-social behaviours induced by MDMA at low doses (see Section 3; <5 mg/kg). For example, administration of these neurohormones ordinarily facilitates social approach and recognition, whilst oxytocin and vasopressin receptor knockout mice show unique social deficits (e.g. [311]) Furthermore, stress-reduction in rats exposed to an oxytocin-injected cage-mate [4] may underlie accounts of gregariousness reported by drug-free humans at social events where MDMA is consumed by others [141].

9. Reward and reinforcement

In the cocaine substitution paradigm, MDMA was self-administered by rats, Rhesus macaques, and baboons and appeared to be under 5-HT_{2A} control [26,82,170,244]. Compared to cocaine, MDMA was administered at a lower response rate and served as a reinforcer in a smaller percentage of animals. Cocaine substitution may reflect the DA stimulus properties of MDMA (see Section 12), as 5-HT hallucinogens are rarely self-administered [21,197]. However, i.v. MDMA has been self-administered by drug naïve rats [244]. Prior experience with MDMA produced sensitisation to itself, although in contrast to other behavioural and neurochemical responses [146,155,206], did not produce cross-sensitisation to cocaine [244]. In common with other drugs of abuse, MDMA dose dependently lowered the threshold and increased the response rate of medial forebrain bundle and nucleus accumbens self-stimulation, and reduced the response rate in operant schedules of reinforcement [148,180,246,256,293].

MDMA and its isomers readily establish conditioned place preference (CPP) in rats and chickens [30,31,38,86,191]. Failure, or difficulty in demonstrating CPP (e.g. [93]) appears related to the housing status of the test animals, in common with the effects of many other abused drugs, a more profound place preference is observed in socially isolated animals compared with group housed rats [200]. Unsurprisingly, considering the well-documented role of DA in reward circuitry [287], CGS 10746B, a DA uptake inhibitor prevented the acquisition of MDMA CPP [31]. The non-specific 5-HT receptor antagonists methysergide and LY 53857 blocked the self-stimulation-response-rate increasing effects of MDMA, but not the threshold lowering effects [180]. This indicated that 5-HT plays less of a role in the rewarding properties than the performance effect of MDMA self-stimulation. However, MDL 72222, a 5-HT_3 receptor antagonist completely blocked the acquisition of MDMA CPP [32]. Consistent within their localisation within limbic areas, 5-HT_3 receptors modulate DA transmission, but fail to attenuate amphetamine CPP [46]. Alternatively, there is good evidence to suggest transmitter interactions between 5-HT and DA [116,229]. As 5-HT has been shown to have an inhibitory effect upon self-stimulation reward threshold, possibly through negative modulation of DA activation, the reversal of 5-HT-induced inhibition may be expected to increase DA activity. Finally, naltrexone, a non-specific opioid receptor antagonist prevented the acquisition of MDMA CPP [29]. In common with its effects upon cocaine CPP and self-stimulation, the opioid δ receptor antagonist natrindole prevented the increase in MDMA-induced self-stimulation response rate [246]. These data suggest that MDMA has rewarding properties but is only a weak reinforcer and is therefore unlikely to be a drug of dependence.

10. Sensorimotor gating

Pre-pulse inhibition (PPI) is the unlearned suppression of startle when the startling stimulus is preceded by

a weaker pre-stimulus, and has been used as a laboratory measure of sensorimotor gating [99]. Patients with symptoms of schizophrenia fail to filter or gate most of the sensory stimuli they receive, leading to sensory overload and fragmented thinking. PPI is deficient in symptomatic patients and can be modelled and reproduced in rats treated with DA drugs such as *d*-amphetamine [189]. MDMA (0.3–20 mg/kg) produced a reduction in auditory and visual PPI in rats that was reversed by fluoxetine pre-treatment or with the selective 5-HT_{2A} receptor antagonist MDL 100,907 [158,189,232,300]. This effect may therefore be attributable to presynaptic 5-HT release. The importance of 5-HT_{2A} receptors in the mechanism of action of many atypical antipsychotic drugs is well recognised [275]. Use of MDMA within PPI may serve as a useful animal model of psychosis. However, despite PPI showing a high degree of cross species homology, clinical administration of 1.7 mg/kg p.o. MDMA produced opposite effects in MDMA-naïve humans, PPI was *increased*, although acoustic startle habituation was consistent with rat studies [99,300]. This is congruous with the fact that MDMA and related entactogens are not considered psychotomimetics in humans [122].

11. Operant behaviour

Acute MDMA decreases responding on multiple schedule fixed ratio and conditional discrimination procedures, and increases response rates and reduces reinforcement under interresponse-time-greater-than-*t* schedules in rats, mice, pigeons and non-human primates [173,209,210,256,259, 293]. This is comparable to the effects of both *d*-amphetamine and MDA [101,174,240,292], although the rate reducing effects of MDMA and MDA are antagonised by different monoamine antagonists [209]. Response rates under fixed ratio schedules of reinforcement are increased at low doses and decreased at high doses compared to control animals [201,210,177]. Like other behavioural effects, tolerance quickly develops to chronic dosing (>5 days) but intermittent or once weekly administration of low to medium doses results in sensitisation to the acute effects [177,210].

In an operant test battery which assessed complex brain function, non-human primates were more sensitive to disruptions in functions of time estimation, motivation and learning than short-term memory, colour- and position-discrimination [96]. Residual behavioural tolerance developed after chronic MDMA (1–20 mg/kg i.m. twice daily for 14 days in ascending order for several months in repeated cycles) but operant responding returned to pre-drug values a few weeks after chronic treatment had ended, indicating that cognitive disruptions are not long-lasting [95,97].

12. Drug discrimination

Parameters underlying stimulus control have been explored in rats trained to discriminate (±)MDMA from saline. (±)MDMA discrimination peaks at 20–60 min post injection (mirroring onset time in human volunteers) and stimulus generalisation occurs with both isomers, the S(+) isomer being more potent than R(−)MDMA but shorter acting [15,16,263]. Cross substitution occurs between the individual stereoisomers, but this seems dependent upon the training schedule and drugs doses used [13,16]. For example, increasing the training dose of MDMA allows for greater cross-generalisation between isomers [16]. Fenfluramine almost produces complete substitution in (±)MDMA trained rats [118] as would be expected of a 5-HT releaser, but *d*-amphetamine and cocaine do not [13, 110,228]. Blockade of MDMA stimulus control by pre-treatment with the 5-HT depletor *para*-chlorophenylalanine [265], a neurotoxic regimen of fenfluramine (4 mg/kg every 12 h for 96 h) [14], or fluoxetine [220] indicates that these behaviours are mediated by serotonin release rather than direct postsynaptic receptor actions. Interestingly, systemic administration of several putative metabolites of MDMA failed to produce stimulus generalisation [109]. The polar nature of many of these agents may have precluded blood brain barrier (BBB) penetration, although non-hydroxylated derivatives (lipophillic agents, able to cross the BBB) were also without MDMA-like activity. However, no systematic work has yet been done examining stimulus effects after direct i.c.v. administration of MDMA metabolites. Considering the role of MDMA-metabolites in neurotoxicity [12] it would be useful to further investigate the role of these species in discriminative stimulus control.

Two-choice drug discrimination procedures have shown that (±)MDMA and its individual stereoisomers produce similar discriminative stimulus effects to *d*-amphetamine in pigeons and rhesus monkeys [80,156]. In rats, generalisation of the *d*-amphetamine cue to (±)MDMA was only observed at doses that severely disrupted response rates [16, 227] and using a three-lever choice paradigm Baker and Taylor [15] failed to show full stereoselective MDMA substitution for *d*-amphetamine. Some workers, using standard two-lever operant procedures, have suggested that at short test drug injection intervals (20 min) the *d*-amphetamine cue will generalise to S(+)MDMA but not R(−)MDMA [108]. This may be related to the former enantiomer's greater potency in facilitating [^{3}H]DA release [151,194]. However, this effect is lost at slightly longer injection intervals (30 min) [16,227]. As there is little difference in caudate and nucleus accumbens DA release between these two time intervals in the awake rat [310] it is likely that methodological variables such as the schedule of reinforcement used may be a likely determinant of results. Rats can be trained to discriminate (±)MDMA from *d*-amphetamine, indicating that the two drugs produce dissociable interoceptive states [118]. This does not mean

that their effects are mutually exclusive. In pigeons trained to discriminate *d*-amphetamine and the 5-HT releaser fenfluramine from saline, (±)MDMA produced some responding on both drug levers [81] suggesting that (±)MDMA possesses complex stimulus properties that involve both 5-HT and DA mechanisms. Rats trained to discriminate DA and 5-HT drugs such as norfenfluramine, fenfluramine, 8-OH DPAT, tetrahydro-β-carboline or *l*-cathinone from saline, consistently show drug-appropriate responding when tested with (±)MDMA [111,263]. Schechter [264,266] has hypothesised that the mixed DA-5-HT effects may lie on a continuum with lower doses of (±)MDMA being more DA-like, higher doses possessing substantial 5-HT activity and intermediate doses producing both effects. D_2 receptor antagonists have little effect upon drug-appropriate responding in animals trained to discriminate (±)MDMA at 20 min post-injection, but significantly reduced drug-appropriate responding in animals trained at the 105 min interval [264]. DA mediated cues therefore become more conspicuous as the discrimination session progresses. This may also explain why some authors have had difficulty showing amphetamine-appropriate responding at short time intervals after injection but show partial substitution when tested at longer intervals, which coincide with peak DA release [16,310].

MDA will substitute for (±)MDMA and vice versa [106,34], but whereas both LSD and 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) substituted for MDA, attempts to identify a substantial 5-HT hallucinogen-like component to the (±)MDMA cue have generally failed [40,105,218]. However, a low dose of LSD (60 μg/kg), completely [15], or partially [16], substituted for R(−)MDMA, and using a more complex operant procedure, whereby the differences between 5-HT and DA stimulus components were made more salient, (±)MDMA substituted for LSD [8]. Mescaline produced full stimulus generalisation to (±)MDMA [35,40], although only R(−)MDMA shared similar discriminative stimulus effects in mescaline-trained rats [15]. It is interesting to speculate whether this is related to stereoselective affinity for $5HT_{2A}$ receptors, which also reflects hallucinogenic potency in man [183,291]. R(−)MDMA shows moderate micromolar affinity for $5\text{-}HT_{2A}$ receptors in the rat brain whilst K_i for S(+)MDMA was approximately 5 fold lower. Accordingly, S(+)MDMA may be more 'amphetamine-like' and R(−)MDMA more 'hallucinogen like'. Synergistic interaction exists between (±)MDMA and LSD. In rats trained to discriminate 1.5 mg/kg (±) MDMA from saline, co-administration of sub-threshold doses of (±)MDMA and LSD produced a maximal (±)MDMA-like response [267].

Glennon and colleagues [107,112] have summarised much of the existing work on the discriminative stimulus properties of MDMA and conclude that it lies in the intersect between *d*-amphetamine and *N*-methyl-1-(4-methoxyphenyl)-2-aminopropane (PMMA; a compound producing dissociable behavioural effects from DOM and amphetamine). However, whilst there is full stimulus generalisation of MDMA with PMMA (indeed as with all entactogens, see below), as has been discussed earlier in this section, generalisation to the amphetamine cue is dependent upon factors such as racemic form, training schedule, dose, and time interval. Furthermore, it is possible to show hallucinogen-like properties at low doses, so interoceptive stimuli produced by MDMA may be more complex than imagined.

Great similarities between the discriminative stimulus properties of MDMA and other structurally related drugs have been described, most notably *N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB), 5,6-methylene-dioxy-2-aminoindan (MDAI), and 3,4-methylenedioxyethamphetamine (MDEA) [34,110,190,228]. These drugs produce few interoceptive cues similar to LSD, DOM or *d*-amphetamine which suggests that they all possess homogenous components that are qualitatively different to both stimulant and hallucinogenic drugs. This has led to their classification as entactogens [1,218].

13. Miscellaneous behavioural effects

MDMA acutely reduced food intake at medium to high doses but chronic administration did not result in prolonged hypophagia [74,98,248]. Neurotoxicology studies have reported transitory weight loss but the rate of subsequent weight gain generally does not differ from controls [38,282,305]. 1–2.5 mg/kg of MDMA elicited amphetamine-like rotation in a round chamber [167]. MDMA showed cross-tolerance with the behavioural effects of methamphetamine but not MDA in a milk drinking task [312]. This is surprising considering that MDA is an active metabolite of MDMA and that it generalises to MDMA in drug discrimination studies [35,92]. However, whilst both are equipotent 5-HT, DA and NA releasers, MDA but not MDMA substitutes for classic hallucinogens and DOM substitutes for MDA but not MDMA [105,106,218,286]. Both MDA and MDMA enhance conditioned and unconditioned responding, an effect not shared by classical hallucinogens [255].

MDMA dose-dependently (0.2–20 mg/kg s.c.) reduced fluid intake, including sweetened ethanol in fluid deprived rats [30]. MDMA did not produce dipsogenic effects, despite increasing plasma renin and aldosterone, and may actually *inhibit* thirst in rats [18,39]. In humans, potentially harmful polydipsia may be caused by a direct result of exhaustion and dehydration through energetic dancing rather than through indirect endocrine effects [87,131]. Acute or subchronic administration of 5 mg/kg MDMA attenuated ethanol (10% w/v) consumption in two strains of alcohol preferring rats [248]. Alcohol preference can be suppressed by drugs that enhance 5-HT function, and Fawn Hooded rats, which express dysfunction in central 5-HT transmission, exhibited a high preference for ethanol

[56,103,211,249]. Finally, in common with other amphetamine derivatives such as fenfluramine and *para*-chloroamphetamine (*p*CA), MDMA produced 5-HT mediated non-reflexive antinociception [64].

14. MDMA and ecstasy

Recent community surveys of the illegal use of controlled drugs in the UK have reported that approximately 4% of 16–59 year olds have ever taken ecstasy [242,243]. This figure represents over two million people. Comparable figures have been reported from the USA and the rest of Europe [126,154,295]. Whilst levels of use have remained stable in Europe, between 1997 and 1999 there was a 69% increase in self-reported ecstasy use in USA college students [290]. Within the 'rave' dance music culture the percentage of individuals reporting use rises to 90%, although it is not known exactly how many people, and what percentage of the general population this actually represents [25,252,306].

Research into the effects of MDMA refer to the contents of ecstasy tablets as MDMA. These tablets have readily identifiable features, such as colours and imprinted designs (See Fig. 2). This has led to the notion of brand name ecstasy tablets as numerous designs mimic real brand names, such as *Calvin Klein* and *Mitsubishi*. As with all illegally purchased controlled drugs the contents of these tablets are highly variable. *White doves* have been found to contain between 19–140 mg of MDMA, 94–125 mg of MDEA and 185–197 mg of ketamine [54,280,307]. *Mitsubishi* tablets have been found to contain between 40–109 mg of MDMA and some also contained MDEA [54]. Other drugs which have been found in ecstasy tablets include dextromethorphan (DXM), MDA, 4-bromo-2, 5-dimethoxyphenethylamine (2CB), MBDB, methamphetamine, 4-methylthioamphetamine (4-MTA), paramethoxyamphetamine (PMA), ephedrine, salicylates, and over the counter painkillers [11,204,224,241,261]. As a consequence of this variation the World Health Organisation has concluded that the term 'ecstasy' is generic for a wide range of compounds [308]. In this context it is probably not appropriate to equate ecstasy solely with MDMA and discussion of its effects must also take this into consideration.

An essential difference between pre-clinical studies and human patterns of ecstasy use is polydrug use, i.e. the use of a variety of drugs and drug combinations [55,235]. Several lines of evidence suggest that combined use of drugs of abuse may modulate the neurotoxic effects of MDMA, possibly through thermoregulation. 5-HT_{2A} receptor agonists, for example, augment 5-HT neurotoxicity when administered in combination with MDMA [130]. It has been postulated that 5-HT acting at 5-HT_{2A} receptors partly underlies the hyperthermic effects of MDMA [271]. Antagonists acting at 5-HT_{2A} receptors also provide protection against neurotoxicity [83]. Use of LSD, a potent 5-HT_{2A} receptor agonist, is common amongst members of the rave scene in an ecstasy combination called 'candy-flipping' [267]. Preliminary evidence suggests that co-administration of *d*-amphetamine with MDMA potentiates the neurotoxic response through thermoregulatory means [225,226]. Furthermore, analogues of MDMA or sub-neurotoxic doses of MDMA can be rendered neurotoxic by co-administration of *d*-amphetamine or the DA precursor L-DOPA [152,153,272]. Again, co-use of amphetamines with ecstasy is a common practice (e.g. [6,252,306]). NMDA receptor antagonists, perhaps analogous to co-use of ketamine in humans, and ethanol, lower core body temperature, thereby offering protection against neurotoxic effects [76,84,88]. Many human users appear aware of strategies discussed in the scientific literature to reduce potential neurotoxicity. To date there has been

Fig. 2. Example of an ecstasy tablet (*White Dove*) from a batch with a mean MDMA content of 78.8 mg [54].

little pre-clinical work specifically modelling the acute behavioural and toxicological effects of these patterns of poly drug use (although the discriminative stimulus properties of the MDMA/LSD combination have been investigated [111]). If users are engaging in strategies to minimise neurotoxicity then it is essential that the behavioural effects of these drug combinations are thoroughly investigated in the laboratory.

There has been much debate over inter species dose scaling in the literature, particularly for the purposes of establishing a threshold neurotoxic dose in humans (e.g. [192,299]). Essentially, it has been argued that neurotoxic doses used in animal work (generally >10 mg/kg) are comparable to those ingested by human users. These claims have been countered by other authors on the basis that there are discrepancies between what is known about the pharmacokinetics and metabolism of MDMA and its neurotoxicity in rats and man. A more suitable dose for interspecies scaling may be that which has distinct behavioural effects. In rats, the ED_{50} of MDMA in standard drug discrimination studies is approximately 0.8 mg/kg after injection. Using the same principles of inter species dose scaling, this is equivalent to a dose of approximately 0.15 mg/kg in a 70 kg man. More typically, a dose of 1.5 mg/kg is used for discrimination training. This is equivalent to approximately 0.28 mg/kg after substitution into the scaling calculation. Harris and colleagues [137] reported that a dose of 0.5 mg/kg MDMA produced no discernible subjective effects in humans, suggesting that there may be some problems in interspecies dose calculations when applied to MDMA.

It is important that there is some means of equating doses used in pre-clinical studies and those ingested by humans. The overlap between effective doses in drug discrimination studies and those used in volunteer administrations suggests that, in the absence of a reliable dose scaling model, a straightforward dose–dose comparison may be appropriate between rats and humans. By this simple criteria, the relevance of behavioural studies which utilise very high dosing protocols (e.g. >15 mg/kg MDMA) is questionable. Such work provides useful insights into the actions of MDMA and increases understanding of the neurochemistry underlying various behaviours, but may reveal little about drug effects in humans.

15. Conclusions

MDMA has a complex pre-clinical pharmacology that involves a number of neurotransmitter systems and its behavioural effects have not been extensively characterised. Drug discrimination studies indicate that MDMA and related compounds form a distinct group, the entactogens. This relatively unique combination of stimulus properties probably underlies its current popularity among human drug users. It is also evident that a great many behavioural effects are dose dependent. With the doses used in the rat studies reviewed ranging from 0.2 to 20 mg/kg it is difficult to determine the precise mechanisms involved until the pharmacology of MDMA has been more extensively characterised in this species.

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