MDMA, methamphetamine and their combination: possible lessons for party drug users from recent preclinical research

KELLY J. CLEMENS¹, IAIN S. MCGREGOR¹, GLENN E. HUNT², & JENNIFER L. CORNISH³

¹School of Psychology & ²Department of Psychological Medicine, University of Sydney, and ³Department of Psychology, Macquarie University, Sydney, New South Wales, Australia

Abstract

The substituted amphetamines 3,4-methylenedioxyamphetamine (MDMA, ‘Ecstasy’) and methamphetamine (METH, ‘ice’, ‘speed’) are increasingly popular drugs amongst party-drug users. Studies with humans have investigated the acute and possible long-term adverse effects of these drugs, yet outcomes of such studies are often ambiguous due to a variety of confounding factors. Studies employing animal models have value in determining the acute and long-term effects of MDMA and METH on brain and behaviour. Self-administration studies show that intravenous METH is a particularly potent reinforcer in rats and other species. In contrast, MDMA appears to have powerful effects in enhancing social behaviour in laboratory animals. Brief exposure to MDMA or METH may produce long-term reductions in dopamine, serotonin and noradrenaline in the brain and alterations in the density of various receptor and transporter proteins. However it is still unclear, particularly in the case of MDMA, whether this reflects a ‘neurotoxic’ effect of the drug. Lasting alterations in social behaviour, anxiety, depressive symptoms and memory have been demonstrated in laboratory rats given MDMA or METH and this matches long-term changes reported in some human studies. Recent laboratory studies suggest that MDMA/METH combinations may produce greater adverse neurochemical and behavioural effects than either drug alone. This is of some concern given recent evidence that party drug users may be frequently exposed to this combination of drugs. [Clemens KJ, McGregor IS, Hunt GE, Cornish JL. MDMA, methamphetamine and their combination: possible lessons for party drug users from recent preclinical research. Drug Alcohol Rev 2007;26:9 – 15]

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Introduction

Amphetamines have been used in the clinic for many years to treat obesity, narcolepsy and attention deficit hyperactivity disorder (ADHD) [1,2]. The illicit consumption of amphetamines also occurs in most countries, irrespective of race, wealth or geographical location, and this illicit use often outstrips the medical use of these compounds [3].

Recreational use of amphetamines, particularly methamphetamine (METH), has developed through their capacity to induce feelings of euphoria, heightened self-confidence and sustained high energy levels among users [4]. However the transition from occasional recreational use to compulsive high dose METH use presents an increasingly worrying trend in many countries. The increased clandestine production and availability of high purity crystalline forms of METH has led to increasing reports of dependence and the onset of severe psychotic symptoms in some individuals [5], as well as reports of adverse effects on the brain and behaviour of users [6].

The substituted amphetamine 3,4-methylenedioxy-methamphetamine (MDMA; Ecstasy, E, M, Adam, XTC, Eccies or ‘The Love Drug’) has basic stimulant effects similar to METH. However MDMA has evolved as the drug of choice among club and rave attendees due to its ability to elicit strong and unique feelings of empathy and closeness to others. The illicit production and consumption of MDMA continues to grow or has stabilised at high levels in many countries [3]. Scores of research papers over the past 20 years however have raised concern about the capacity of MDMA to cause lasting adverse effects on the brain, mood and behaviour of users, although this important issue still appears far from resolved [7,8].

Of recent concern is the trend for users to combine the ingestion of MDMA and METH within the same drug-taking episode. This can occur intentionally or inadvertently through the presence of large proportions
of METH in tablets sold as ‘Ecstasy’ [9–11]. As both MDMA and METH have been independently linked to long-term adverse neural and behavioural effects, it is conceivable that the combination of the two drugs may be particularly harmful.

In this brief review, we discuss recent findings concerning the acute and long-term effects of MDMA and METH in laboratory animals, and discuss the possible implications of these results for human users.

**MDMA and METH: acute effects and pharmacology**

MDMA and METH have similar actions in the brain, elevating levels of the monoamine neurotransmitters dopamine, noradrenaline and serotonin (5-HT). The major difference is that MDMA primarily inhibits 5-HT reuptake and stimulates 5-HT release, while METH primarily inhibits dopamine reuptake and stimulates dopamine release [12]. Levels of synaptic monoamines are further elevated by MDMA and METH through the inhibition of enzymes responsible for metabolising these monoamines, and also through the expulsion of monoamines from intracellular storage vesicles [13,14]. This massive release of monoamines leads to a temporary deficit or depletion of monoamine stores that may take many days to replenish – hence the frequently reported ‘3-day dip’ or ‘eccy Monday’ following a weekend of sustained drug use [15].

The differential release of 5-HT and dopamine following MDMA or METH respectively may account for the unique positive subjective effects attributed to each drug. Acute 5-HT release contributes to the unique subjective effects of MDMA including euphoria, mild hallucinations and feelings of closeness to others [16]. In comparison, the elevated dopamine produced by METH may underlie the feelings of confidence, energy, sexual stimulation and euphoria produced by the drug, and may also be responsible for its considerable addictive potential [17]. The subjective experience produced by METH/MDMA combinations is not well characterised in the literature but potentially synergistic euphoric and prosocial effects may explain its popularity.

**Animal models of compulsive METH use and relapse**

The increased availability of highly potent forms of METH (crystal, ice) has produced a marked increase in rates of METH dependence and psychosis [5]. This appears to relate to the much greater purity of ice (80%) versus powder (10%), and also the method of ingestion (smoking or intravenous versus oral or nasal), leading to a much more rapid and intense high.

Unfortunately, treatment options for dependent METH users appear to be severely limited [18]. While medications such as disulfiram or naltrexone show some promise in the treatment of cocaine addicts [19], few treatment options are currently available for METH users. Many researchers have therefore focused on animal models of addiction to further understand this phenomenon and to develop novel treatment options.

Intravenous drug self-administration is a standard method for assessing the neurobiology of drug use and abuse potential, drug withdrawal, relapse and craving for drug use. In this model, animals (rodents or primates) learn to make a response (e.g. a lever press or nose poke) to gain intravenous infusion of a drug.

Comparison of intravenous MDMA and METH self-administration in rats demonstrates a clear difference in the reinforcing efficacy of these drugs, a disparity that is largely congruent with human reports of dependence. As Figure 1 shows, doses of METH and MDMA that produce maximal responding (asymptote of inverted-U dose response curve measured following stimulant self-administration), lead to different levels of intravenous intake in rats, with METH supporting much higher response rates.

Acquisition of MDMA self-administration is relatively slow, and is facilitated by first training the animal to self-administer cocaine or some other highly reinforcing drug [20,21]. Interestingly however, MDMA self-administration in rats can be facilitated by conducting test sessions in a hot environment (e.g. 30°C).
[22], and this temperature dependence of MDMA rewarding effects may explain the frequent use of the drug by humans in hot, crowded environments.

By comparison with MDMA, the acquisition of intravenous METH self-administration is rapid and robust, reflecting the greater addictive potential of this drug (see Figure 1). Intravenous self-administration of METH is reported in mice [23], rats [24], Rhesus monkeys [25] and humans [4]. Similar to MDMA, we have recently shown that METH self-administration is also enhanced at high ambient temperatures (unpublished data).

Analogous to human reports of relapse to drug seeking following a period of abstinence, rodents and non-human primates can also display reinstatement of methamphetamine-seeking behaviour after a period during which the drug is not available. A resumption of persistent drug-seeking behaviour is typically elicited by (i) drug-associated stimuli or contexts, (ii) stress, (iii) after brief exposure to the drug itself, or (iv) exposure to a different drug with a similar pharmacological action (e.g. cocaine or other amphetamines) [26, 27]. The reinstatement model lends itself to the development of pharmacotherapies that may prevent this relapse.

Surprisingly, while MDMA and METH combinations (either intentionally or unintentionally through tablet purity) are high amongst recreational drug users, our recent research suggests that combined administration of MDMA dampens the reinforcing effect of METH in rats tested in the self-administration paradigm [28]. This is not wholly unexpected given the lower rates of self-administration that MDMA supports (Figure 1). On the other hand, injections of MDMA stimulate METH seeking behaviour in abstinent rats that have previously self-administered METH (unpublished data). This suggests that combined METH/MDMA in humans may partly arise from an ability of one drug to trigger craving for the other.

A reduction in the self-administration of METH is also apparent following the administration of fenfluramine, a 5-HT releaser with effects similar to MDMA [29]. This suggests that drugs with 5-HT releasing properties may act as something of a ‘brake’ on METH intake. This is also supported by preliminary clinical evidence indicating that the selective serotonin reuptake inhibitor (SSRI) paroxetine, may reduce craving in METH users [30]. Further investigation into the potential of SSRIs in alleviating METH craving is warranted.

**Animal models of the positive social effects of MDMA**

The pattern of use of MDMA in humans seems largely ‘non-compulsive’, with most users taking the drug relatively infrequently and at relatively low doses [31]. MDMA produces few apparent signs of physical dependence in humans or laboratory animals [32]. It is likely that MDMA use is driven by the profound prosocial (entactogenic) effects of the drug, and this effect is apparent in studies with laboratory animals as well as humans. Rats administered moderate doses of MDMA show a substantial increase in social interaction, evident as a greater amount of time spent in close proximity between two rats meeting for the first time [33]. Interestingly, this characteristic appears to be specific to MDMA, as other stimulant drugs such as METH show the opposite effect.

Our recent research has linked the MDMA-elicted increase in social behaviour in rats to a specific 5-HT receptor known as the 5-HT<sub>1A</sub> receptor [33]. This receptor plays a role in control the release of the neurohormone oxytocin in mammalian species and MDMA causes powerful activation of oxytocin containing neurons in the brain [34]. This hormone plays a key role in social bonding, attachment and trust and appears to be elevated in the bloodstream of Ecstasy users tested at dance parties [35]. Future research into the role of oxytocin and other neurohormones in the recurring use of MDMA may prove important in understanding why MDMA remains so popular amongst party drug users.

**MDMA and METH: possible neurotoxicity**

The acute administration of MDMA or METH clearly causes a massive release of the neurotransmitters 5-HT and dopamine respectively. However, it is the capacity of these drugs to ‘exhaust’ serotonergic and dopaminergic neurons, causing long-term deficits in these systems that has attracted much attention and concern.

Administration of MDMA (>10 mg/kg) to various species of laboratory animals produces long-lasting depletions of basal levels of 5-HT [36–39], decreases in 5-HT transporter and 5-HT<sub>2A/2C</sub> receptor density [38], and inhibition of the 5-HT synthesising enzyme tryptophan hydroxylase [40]. For the most part however, these effects occur with doses that exceed those that human users would typically take (1–4 mg/kg) and despite the frequent use of the term ‘neurotoxicity’ to describe MDMA effects there are few studies to support the notion that MDMA causes neuronal cell death. Rather MDMA appears to damage only the terminal regions of 5-HT neurons, possibly in a reversible way [7].

Analogous to the effects of MDMA on 5-HT neurons, exposure to METH (>10 mg/kg) leads to long-term reductions in brain dopamine content [41–43] and dopamine transporter density in rats [44, 45] and other laboratory species [46]. With higher doses of METH (>40 mg/kg), long-term changes in
the 5-HT system may also become apparent. Again, these effects are typically measured at doses much higher than the typical human dose (0.05–1 mg/kg), and there is some debate as to whether effects observed reflect irreversible neurotoxic effects. In general, there is considerably more evidence in favour of long-term neural damage following METH use than there is with MDMA use [47].

Although the outcome of MDMA and METH exposure is different in terms of the systems affected, it is likely that an underlying cause in both cases may be the formation of free radical reactive oxygen and nitrogen species [48]. Such chemicals are thought to be produced as metabolic by-products following excessive monoamine release [48], or in response to exhausted energy stores [49]. As both MDMA and METH have these effects, combining these drugs within a single session may increase the likelihood of adverse neuronal effects.

When administered in combination, MDMA with METH may produce a wider pattern of dopamine and 5-HT depletion than is seen with equivalent doses of either drug alone, as well as a unique noradrenaline depletion [50,51]. Such results suggest that ingestion of MDMA with METH may be a particularly dangerous combination for party-drug users.

**Long-term behavioural changes in rodents after MDMA and METH**

Because of the inherent ambiguity in the results of functional studies involving human MDMA and METH users, studies of laboratory animals are of use in describing the possible functional deficits associated with exposure to pure MDMA or METH. Such studies have tested various aspects of behaviour including social anxiety, generalised anxiety (e.g. ‘elevated plus maze’), depressive-like symptoms (e.g. ‘forced swim’ test) and working memory (‘object recognition’ or ‘water maze’) after MDMA, and to a lesser extent, METH administration.

Months after 5-HT depleting injections of MDMA, rats exhibit dose-dependent increases in anxiety on the emergence test, the elevated plus maze, and (opposite to acute drug effects) a reduction in social interaction [38,52]. High dose MDMA treatment also increases depressive-like symptoms on the forced swim test [53], and causes some disruption of object recognition memory and spatial memory [39,54,55]. Performance does not appear to be affected on simple instrumental or passive avoidance tasks [56,57].

Although 5-HT depletion appears to be the most obvious explanation for these functional deficits, it is important to note that impaired memory [55], increased anxiety [38,39] and decreased social interaction [38] can be seen in rats that are given low doses of MDMA that cause little detectable 5-HT depletion. This indicates possible involvement of non-serotonergic systems in determining lasting behavioural changes following MDMA.

Behavioural deficits in laboratory animals have also been identified following exposure to METH. Similar to MDMA, METH administration leads to long-term decreases in social anxiety [50,51], impairments on object recognition and spatial memory tasks [58] and deficits in sequential learning on the radial arm maze [59]. Some of these effects may be reversible: impairment on the water-maze place task detected 65 days after METH administration was no longer detectable at 79 and 165 days post-injection [60].

The combination of MDMA and METH in rats has a tendency to produce a greater range and degree of behavioural deficits (social anxiety, emergence anxiety, depressive symptoms) than individual drug treatment [50,51]. The combined effect does not require the simultaneous administration of both drugs as it is also evident when these drugs are presented sequentially within a single session [50].

**Clinical relevance**

The results of the above preclinical studies help to clarify some of the effects obtained in parallel human studies. For example, studies of MDMA users, particularly heavy users, have sometimes reported an increased risk of depression, and poorer function on cognitive tests involving working memory and executive function [8,61–63]. Similarly, METH users demonstrate specific deficits in tasks of auditory discrimination, auditory vigilance [64], working memory and word recall [65–67]. However, such studies are often unable to draw strong conclusions surrounding MDMA and METH related harms, due to ubiquitous polydrug use in MDMA and METH using subjects and the possibility of pre-existing psychopathology predisposing to MDMA or METH use. For this reason, preclinical studies addressing realistic drug scenarios (e.g. combined MDMA/METH use) are particularly valuable.

Studies of the possibly neurotoxic effects of MDMA and METH have highlighted the importance of various environmental factors in the adverse behaviour and neurochemical effects of MDMA and METH. Particularly relevant to clinicians are studies reporting the ability of high environmental temperatures to modulate MDMA-related monoamine depletion [68]. There is also the possibility that exposure to MDMA may cause persistent deficits in the ability of animals to thermoregulate in hot environments [69].

In addition, intravenous self-administration models advance our understanding of the mechanisms involved in the prevention and treatment of human drug
addiction. In particular, the drug-self administration paradigm provides a valid indication of the abuse potential of illicit drugs, but also provides a platform for the development and testing of novel pharmacotherapies targeting relapse. As limited treatment options are available for dependent METH users, such research is particularly relevant.

It must also be acknowledged that questions have been raised regarding the applicability of pre-clinical findings to humans. Objections often relate to the very high doses that are used in studies with laboratory animals. These objections can be countered by pointing to a growing number of studies in which deficits are found using much lower doses of MDMA [38,70].

Conclusions

The present review indicates that substantial progress has been made in recent years in employing animal models to characterise both the acute and the lasting effects of MDMA and METH on brain and behaviour. Important recent findings made with animal models that inform the human situation include (i) the greater tendency towards compulsive use of METH compared to MDMA, (ii) the unique prosocial effects of MDMA and the neuroendocrine basis of this effect, (iii) the ability of high ambient temperatures to modulate the rewarding properties of MDMA and METH, (iv) the functional and emotional impairments observed in rats previously exposed to MDMA or METH, even in the absence of monoamine depletion, and (v) the likely synergistic adverse effects of combining MDMA and METH.

While it is acknowledged that animal models are not exact replicas of the human condition, we hope that the present review underscores the utility of such models in elucidating the neural substrates and environmental factors that drive MDMA and METH use and in providing a clear and realistic appraisal of the likely long-term hazards arising from exposure to these drugs.

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