ELSEVIER

Pharmacology, Biochemistry and Behavior 71 (2002) 837–844

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Recreational Ecstasy/MDMA, the serotonin syndrome, and serotonergic neurotoxicity

A.C. Parrott*

Department of Psychology, University of East London, London E15 4LZ, UK

Received 7 May 2001; received in revised form 7 September 2001; accepted 18 September 2001

Abstract

The ring-substituted amphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA) or "Ecstasy" is widely used a recreational drug. It stimulates the release and inhibits the reuptake of serotonin (5-HT) and other neurotransmitters such as dopamine to a lesser extent. The acute boost in monoamine activity can generate feelings of elation, emotional closeness, and sensory pleasure. In the hot and crowded conditions of raves/dances, mild versions of the serotonin syndrome often develop, when hyperthermia, mental confusion, and hyperkinesia predominate. Rest in a cooler environment generally reverses these problems, although they can develop into medical emergencies, which occasionally prove fatal. This acute serotonergic overactivity is exacerbated by the high ambient temperatures, overcrowding (aggregate toxicity), and use of other stimulant drugs. The on-drug experience is generally followed by negative moods, with 80–90% of weekend Ecstasy users reporting 'midweek blues', due probably to monoaminergic depletion. Single doses of MDMA can cause serotonergic nerve damage in laboratory animals, with repeated doses causing extensive loss of distal axon terminals. Huether's explanatory model for this 5-HT neurotoxicity will be briefly described. There is an increasing body of evidence for equivalent neuropsychobiological damage in humans. Abstinent regular Ecstasy users often show: reduced cerebrospinal 5-HIAA, reduced density of 5-HT transporters, blunted response to a fenfluramine challenge, memory problems, higher cognitive deficits, various psychiatric disorders, altered appetite, and loss of sexual interest. Functional deficits may remain long after drug use has ceased and are consistent with serotonergic axonal loss in higher brain regions.

Keywords: Ecstasy; MDMA; Drug; Serotonin; Serotonin syndrome; Neurotoxicity; Memory; Cognition; Mood; Pleasure; Sex

1. Introduction

Over the past 15 years, 3,4-methylenedioxymethamphetamine (MDMA) or Ecstasy has become one of the most popular of the illicit recreational drugs. Its use is strongly associated with the dance-club scene, with 64% of Dutch ravers/clubbers reporting they had taken it the previous night (Wijngaart et al., 1999). There are, however, many concerns over its short-term and long-term effects. One of the core aims of this paper is to overview the human literature on the psychobiological problems and deficits reported by recreational users. The other main aim is debate the role of serotonin (5-HT) in these changes. Many of the acute behavioural and physiological effects are consistent with the 'massive' 5-HT release induced by MDMA. The functional disorders in drug-free regular Ecstasy/MDMA users are also consistent with serotonergic neurotoxicity, which was first demonstrated in laboratory animals. One of several possible explanatory models for how this serotonergic damage might be occurring will also be briefly described. However, it should be emphasized that MDMA is neurochemically 'messy', affecting a range of transmitters in addition to 5-HT (e.g., dopamine). Thus, many neurotransmitters may be contributing to the psychobiological findings being described here.

2. Acute neurochemical and behavioural effects of MDMA/Ecstasy

MDMA or Ecstasy is a ring-substituted amphetamine derivative. It is an indirect monoaminergic agonist, stimulating the release and inhibiting the reuptake of 5-HT. Thus, McDowell and Kleber (1994, p. 129) noted:

* Tel.: +44-208-2234505.
E-mail address: a.c.parrott@uel.ac.uk (A.C. Parrott).

0091-3057/02/$ – see front matter
PII: S0091-3057(01)00711-0

"MDMA's primary mode of action is as an indirect serotonergic agonist." However, they also noted: "In addition it has affinities for a number of other transmitter binding sites. MDMA is a messy drug, affecting 5-HT and dopamine-containing neurones as well as a host of other neurotransmitter systems." Ecstasy is widely used as a recreational drug in many westernized countries (Cohen, 1998; Saunders, 1995; Schifano et al., 1998; Solowij et al., 1992). Thirteen percent of British university students have taken it (Webb et al., 1996), as have 59% of Italian disco-clubbers (Schifano, 2000), while the age of first use has gradually declined (Schuster et al., 1998). The popularity of MDMA/Ecstasy is due to its very positive effects upon mood and well-being: "All I wanted to do was smile, I was so wide awake, and I felt in love for everything and everyone" ... "Very intense. I felt as if nothing could go wrong or make me unhappy" ... "Touching was wonderful. Kissing was great. I kissed someone I was in love with and almost felt as if I was going to pass out from the intensity" (quotations from American clubbers in: Cohen, 1998, pp. 80–81). There has been debate over whether these positive mood changes reflect serotonergic or dopaminergic stimulation (McCann and Ricaurte, 1993; Gerra et al., 1998). Liechti and Vollenweider (2001) investigated the effects of neuroreceptor pretreatments (citalopram, ketanserin, and haloperidol) on the psychobiological effects of MDMA in human volunteers. They concluded that the overall psychological effects (included positive moods) were related to 5-HT release, whereas the stimulant/euphoric effects were related to dopamine. MDMA has been recommended for use in psychotherapy, where the surge of pleasant feelings and emotional insights are said to be beneficial (Greer and Tolbert, 1998). However, not every Ecstasy experience is positive, with 25% of users reporting having had at least one adverse reaction, when unpleasant feelings and bodily sensations predominated (Davison and Parrott, 1997).

There are indications that the positive effects of MDMA may subside with repeated use. Alexander Shulgin, the Californian research chemist who resynthesized MDMA during the 1970s, is reputed to have commented that its positive effects decline after the first seven experiences. Peroutka et al. (1988) uncovered similar personal reports of declining effectiveness in a survey of a hundred American recreational users, whose maximum lifetime Ecstasy consumption was 38 occasions. During the late 1980s and early 1990s, the archetypal usage pattern was of single tablets, taken at preplanned raves every few weeks. Meilman et al. (1990) reported that hardly any of their American college users took it more frequently than once a month. This pattern of self-administration allowed time for a degree of serotonergic recovery to occur, and may have minimized the development of adverse reactions. However, in more recent years, the typical usage pattern has intensified. During the late 1990s, regular users often took two to three tablets per occasion, with some needing four to six tablets to achieve the desired level of effect (unpublished UEL data). The frequency of use is also greater, with most regular users now taking it every weekend, while some take it additionally during the week. Many users also complain that the tablets are getting "weaker" (Turner and Godolphin Parrott, 1999). Taken together, this informal evidence is suggestive of chronic pharmacodynamic tolerance, although there is a paucity of empirical data on this question.

The pharmacological constituents of "Ecstasy" tablets have been investigated in a few surveys. Biochemical analyses of Italian samples, found that they generally contained MDMA (90%), or closely related ring-substituted amphetamine derivatives, such as 3,4-methylenedioxyamphetamine (MDA), or 3,4-methylenedioxyethylamphetamine (MDE); furthermore, the tablets were largely free from impurities (Schifano et al., 1998). Surveys in London have confirmed that while Ecstasy tablets generally contain MDMA, they may also comprise other ring-substituted amphetamine derivatives, but again are rarely contaminated by impurities (King, 2000). However, a minority of 'Ecstasy' tablets contained ketamine, sometimes combined with amphetamine, cocaine, or caffeine, while some tablets may be pharmacologically inert (King, 2000). There will be marked differences across time and place. Uncertainty over the chemical constituents of 'Ecstasy' tablets is thus an important confounding factor for this area of research. There are also several administration routes: oral, injection, smoking, and nasal. Topp et al. (1999) noted the use of all these modes in their Australian survey, although 94% of users favored the oral route, various problems with injecting were described, while smoking generally involved mixtures with cannabis. I am not aware of any published studies for Ecstasy powders, although one experienced user informed me that the nasal hit was far more rapid and intense, while their skin felt 'hot to the touch'. Indeed, the dance club where these powders had been sold arranged for club employees to circulate amongst the dancers, spraying them all with water from plastic bottles to cool them down.

The physiological effects of MDMA can indeed be very powerful. Homeostatic control of body temperature is adversely affected due to altered hypothalamic control. Gordon et al. (1991) found that MDMA-treated laboratory rats cooled down excessively in a cold environment, but overheated under a high ambient temperature. The metabolic rate of the MDMA-treated rats was twice that for the saline controls under the high-temperature condition. Malberg and Seiden (1998) found that an increase in ambient temperature of 2 °C led to a marked increase in core body temperature for the MDMA-treated rats, but not the saline-treated rats. Furthermore, the increase in core body temperature led to increased serotonergic neurotoxicity (see later sections). Around 85–90% of recreational Ecstasy users report an increase in body temperature, increased sweating, and dehydration (Davison and Parrott, 1997). Most dancers are aware of the dangers of overexertion and hyperthermia,

and visit 'chill-out' rooms to rest and cool down. This should help reverse the hyperthermia, but some users also report feeling cold and shivering. Fluid control is also important. Dancers need to maintain a steady fluid intake to reverse the fluid loss from sweating while dancing. Unfortunately, excessive fluid intake can cause hyponatraemia — dilution of electrolytes such as sodium and potassium in the systemic circulation. Both conditions are potentially fatal. So that while some Ecstasy users have died of hyperthermia, others develop hyponatraemia, which may prove fatal (Green et al., 1995; Henry et al., 1992). The British teenager Leah Betts, whose tragic death was widely publicized in the national press, died of hyponatraemia. She had been so concerned about hyperthermia that she drank several litres of water, which proved fatal; the postmortem analysis revealed that she had taken uncontaminated MDMA. Further acute causes of death include acute renal, hepatic, or cardiac failure, rhabdomyolysis, and disseminated intravascular coagulation (Cohen, 1998). Other physiological changes include tachycardia and increased blood pressure. Some users perceive this as exciting, but novice users may become concerned at their 'racing' heart and need reassurance. Physical reactions include trismus (jaw clenching), and bruxism (teeth grinding), which is why many ravers/dancers chew gum.

3. The serotonin syndrome and Ecstasy/MDMA

"The serotonin syndrome is caused by drug induced excess of intrasynaptic 5-hydroxytryptamine" (Gillman, 1999, p. 100). The symptoms include behavioural hyperactivity, mental confusion, agitation, hyperreflexia, hyperpyrexia (fever), tachycardia, shivering, clonus, myoclonus, ocular oscillations, and tremor (Gillman, 1999; Huether et al., 1997). The serotonin syndrome is often conceptualized as an unusual or atypical severe adverse drug reaction. However, Gillman (1998) argued that it was neither rare nor idiosyncratic but represented a continuum of responses from mild to severe. The mild serotonin syndrome (three symptoms from above list) generally require no direct medical intervention; stronger responses (four or more symptoms) would often necessitate medical supervision; while severe reactions (most symptoms from list) could prove fatal. One crucial aspect is the speed of onset and progression, so that mild cases may become severe within an hour or so (Gillman, 1998, 1999; Huether et al., 1997). Mild cases are best treated by rest in a cool environment, with recovery facilitated by the decline in pharmacological activity over time. However, severe serotonin syndromes require immediate and aggressive medical intervention: physical cooling, paralysis, and the use of 5-HT_2/5-HT_{1a} blocking drugs such as cyproheptadine or chlorpromazine in order to facilitate recovery and prevent death (Gillman, 1999). The serotonin syndrome is generally caused by the inadvertent combination of serotonergic drugs such as monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs). However, hundreds of psychoactive drugs in current use affect 5-HT, including many over-the-counter antihistamines, such as chlorpheniramine, and herbal remedies such as St. John's Wort (hypericum) and ginseng (Gillman, 1998, 1999). Thus, there are numerous potential sources of serotonergic drug combinations.

Inspection of the above symptom list shows that many Ecstasy-using clubbers can be seen to display mild signs of the serotonin syndrome. Hyperactivity, mental confusion, hyperthermia, and trismus (jaw clenching) are typical on-drug experiences for most Ecstasy users (Davison and Parrott, 1997; Parrott and Lasky, 1998). These physiological responses are perceived as normal drug reactions and are not generally seen as problematical. Indeed, without them, many clubbers might believe that they had not been sold real MDMA. However, Ecstasy users sometimes develop stronger signs of serotonergic overactivity (Cohen 1998; Demirkiran et al., 1997; Green et al., 1995; Henry et al., 1992). It is difficult to estimate the morbidity of these more severe reactions, since distressed clubbers often receive help from their friends, or assistance from volunteer paramedics at the larger clubs or raves. However, many inner-city hospitals report that the treatment of adverse drug reactions in clubbers has become part of the usual Saturday night routine. This raises the question of which factors influence the development of serotonergic overactivity. One crucial factor is dosage, while others include: individual sensitivity, variations in drug metabolism, and tolerance. Another factor is the concomitant use of other psychoactive drugs, which affect 5-HT either directly or indirectly, including cocaine (Milani et al., 2000), prescribed antidepressants (MAOIs and SSRIs), herbal remedies (hypericum, ginseng), and many others (Gillman, 1998). Alcohol, cannabis, and tobacco/nicotine are widely consumed, while recreational stimulants such as amphetamine and cocaine (also MDMA) boost dopamine and noradrenaline. This catecholaminergic stimulation is probably very important, both contributing to general arousal, and heightening the serotonergic response (Huether et al., 1997). These pharmacological factors also interact with environmental influences, such as overcrowding, high temperature, loud music, and prolonged dancing to make the strength of the individual psychophysiological response quite unpredictable.

4. Immediate after-effects of MDMA: midweek blues

The days following Ecstasy are typified by a period of poor moods, when feelings of anhedonia and lethargy predominate. In a questionnaire survey of 469 Ecstasy users, Curran (2000) found that 83% reported midweek low moods, while 80% complained of concentration difficulties or memory problems. This confirmed the findings from their earlier prospective study of young clubbers, when the

Ecstasy users felt comparatively better than the controls while on-drug, but comparatively worse 4 days afterwards; indeed, some of the recovering Ecstasy users reported clinically borderline levels of midweek depression (Curran and Travill, 1997). In another prospective study, mood states and cognitive performance were monitored before, during, and after a Saturday night out clubbing (Parrott and Lasky, 1998). At the dance club, there were no significant mood differences between those who had taken Ecstasy and those who had not. Everyone reported having had a good time, irrespective of which drugs they had taken. Two days afterwards, the Ecstasy users reported feeling significantly more depressed, unpleasant, sad, abnormal, and unsociable than the nonuser controls; 7 days later, the mood states of all groups had returned to baseline (Parrott and Lasky, 1998). Topp et al. (1999) noted various problems during the post-Ecstasy recovery period, including energy loss, irritability, muscle aches, and trouble sleeping. These mood and other psychobiological problems in the days following Ecstasy are probably due to monoaminergic depletion.

5. Repeated MDMA: neurochemical and neuroanatomic effect

The long-term serotonergic damage caused by MDMA was first demonstrated in laboratory animals during the mid 1980s. When rats were treated with successive doses of MDMA or MDA, they developed a pronounced loss of 5-HT axon terminal markers, while other monoaminergic neural systems were generally spared (Ricaurte et al., 1985; Schmidt et al., 1986). Serotonergic changes have been shown on a variety of indices, with dose-dependent reductions in 5-HT, 5-HIAA, tryptophan hydroxylase, and 5-HT uptake sites or neuronal transporters. They have been found across a variety of animal species, and are long-lasting. Neuroanatomic studies show that the cell bodies are spared, while the long 5-HT axonal projections into the higher brain regions are markedly reduced. The loss of distal axon terminals in the neocortex and hippocampus is accompanied by a proliferation of axons more proximal to the cell body, or 'neuronal pruning' (Fisher et al., 1995). Temperature is a key factor, with greater neurotoxicity under high ambient temperatures and cooler conditions providing a degree of neuroprotection (Malberg and Seiden, 1998). Neuronal recovery occurs over several months in laboratory rats, whereas monkeys and primates show only partial recovery even after an extended period (Ricaurte et al., 2000). Serotonergic neuronal damage in the laboratory is a robust phenomenon, but the doses involved are quite high, especially for mammals lower on the phylogenetic scale. This has raised questions over their relevance for humans (Saunders, 1995). However, when standard pharmaceutical industry formulae for interspecies scaling are applied, the dose-equivalents are within the range used by humans (Ricaurte et al., 2000). The animal literature is summarized in the following reviews (Green et al., 1995; Hegadoren et al., 1998; Ricaurte et al., 2000).

There are numerous indications of serotonergic damage in humans. In a PET scan study, McCann et al. (1998) documented a reduced density of 5-HT transporter sites, which correlated with the extent of past Ecstasy use; moreover, these serotonergic deficits were found across a wide range of brain regions. In another neuroimaging study, Semple et al. (1999) similarly found a reduced density of 5-HT transporter sites in the cerebral cortex. Significantly lower levels of cerebrospinal 5-HIAA have also been found in abstinent Ecstasy users (McCann et al., 1994). They uncovered an intriguing gender effect, with females showing a comparatively greater 5-HIAA reduction (-46%) than males (-20%). Furthermore, there was a significant reduction in female HVA levels, while males showed a nonsignificant trend towards reduced HVA. This suggests that the regular use of Ecstasy may be perturbing dopaminergic neurones in humans and raises the topic of differential gender effects. McCann et al. (1994) also investigated the prolactin response to an L-tryptophan challenge and found no differences from the control group. Other studies have, however, discovered impairments in neuroendocrine indices of serotonergic functioning. Verkes et al. (2001) also found a significant reduction in cortisol response to fenfluramine in both moderate and heavy Ecstasy users; their control group being regular ravers/clubbers who had never taken Ecstasy. They also assessed prolactin responses to fenfluramine but found high within-group variances. Price et al. (1987) is often cited as having found a reduced prolactin response to intravenous L-tryptophan, but the group difference was statistically only borderline. Gerra et al. (1998, p. 6) used a restricted inclusion policy aimed at excluding many of the heavier illicit polydrug users from the Ecstasy group. Prolactin and cortisol responses to a fenfluramine challenge were significantly reduced in the Ecstasy users, which was interpreted as support for: "... the hypothesis of a persistent 5-HT_{2C} receptor downregulation caused by long-term 5-HT hyposecretion" (De Souza et al., 1990). In a follow-up study of Ecstasy users who had been abstinent for 12 months, prolactin responses remained significantly reduced, whereas the cortisol responses had recovered significantly (Gerra et al., 2000).

6. Repeated MDMA: memory and neurocognitive effects

Memory deficits on a neurocognitive test battery were first reported in a small group of heavy Ecstasy users who had taken it for around 5 years (Krystal et al., 1992). On most tasks, their performance levels were as expected, but on the Weschsler Adult Intelligence (WAIS) memory subscales, five of the nine participants produced scores much lower than age-matched norms. There were, however, methodological limitations with this study: Many participants had

a psychiatric history, most had an extensive illicit drug history, they had all been administered a tryptophan challenge 3 h prior to the cognitive testing, and there was no control group. Parrott 1996; Parrott et al., 1998) found significant memory deficits in young Ecstasy users compared to similarly aged controls. On most tasks, the Ecstasy users and controls were very similar, but in immediate and delayed word recall, both novice and regular Ecstasy users recalled significantly less words than the nonuser controls (Parrott et al., 1996, 1998). Verbal memory deficits were confirmed in a follow-up study, with both novice and regular users (Parrott and Lasky, 1998). The important control group of regular polydrug users who had never taken Ecstasy was included by Morgan (1999). On the Rivermead Behavioural Memory test, abstinent Ecstasy users recalled significantly fewer prose points than both control groups, whereas the memory scores for the polydrug user and non-drug user controls were very similar (Morgan, 1999).

Memory and other cognitive impairments have been demonstrated by many different research groups, using a variety of assessment tasks and a range of methodological and statistical controls for potentially confounding variables. Verkes et al. (2001) found significant deficits in word recognition, Corsi Block span, and figure recognition in recreational Ecstasy users compared to nonuser controls. Word recognition was also significantly worse in heavy compared to moderate Ecstasy users. Furthermore, the heavy users showed significantly longer response times on tasks of simple and complex reaction time, in comparison to controls. The three groups comprised regular visitors to 'rave parties' and were broadly similar on most demographic variables. However, they differed in certain factors, including more extensive illicit drug histories for the Ecstasy users; but analysis of covariance showed that none of these confounding variables affected the significant memory deficits (Verkes et al., 2001). Gouzoulis-Meyfrank et al. (2000) administered a comprehensive cognitive test battery to three groups: non-drug users, moderate/regular Ecstasy users who also generally took cannabis, and a cannabis control group who were matched with the Ecstasy users on past cannabis use. There were no performance differences between the cannabis user and nonuser control groups. On most cognitive tasks, the Ecstasy users were significantly worse than the nonuser controls. They were also significantly worse than both cannabis user and nonuser controls on tests involving learning, memory, problem solving, and strategic planning. The only tasks where the abstinent Ecstasy users showed no impairment were measures of basic alertness such as simple reaction time. Finally, although the cannabis group was not cognitively impaired, the use of cannabis by the Ecstasy users was associated with stronger cognitive deficits, which illustrates the importance of considering polydrug combinations. Rodgers (2000) compared Ecstasy/cannabis users, with regular cannabis users and non-drug users. In this study, both the Ecstasy/cannabis users and the cannabis users showed significant impairments on some of the memory/learning tasks. However, the Ecstasy/cannabis user group was significantly worse than the cannabis user group on two memory measures: delayed recall of verbal paired associates and delayed recall of visual paired associates. It should be noted that the use of cannabis had been quite heavy, with an average frequency of 4 days/week for 10 years, whereas Ecstasy use was comparatively light, with an average of 20 occasions over 5 years (Rodgers, 2000).

Reneman et al. (2000) conducted a single photon emission computed tomography (SPECT) investigation of 5-HT_{2A} receptor density and cognitive test performance. Five regular Ecstasy users (average lifetime consumption 218 tablets) demonstrated a significant increase in 5-HT_{2A} receptor density at the occipital cortex. This was interpreted as postsynaptic receptor upregulation, following drug-induced serotonergic depletion. There was also a significant impairment in the sole cognitive test, Rey Auditory Verbal Learning (RAVLT), where the Ecstasy users recalled an average of 8.1 words, compared to 12.3 for controls. Furthermore, "In the MDMA group, but not in the controls, mean cortical binding was highly correlated with recall (Spearman's $r = +.98$, $< .005$)". Heffernan et al. (2000) assessed self-rated prospective memory — the ability to remember to do things in the near future. Ecstasy users reported higher error scores, which remained significant after covarying for the use of other drugs. Although able to describe their memory problems, they did not report using more practical strategies to aid remembering. Fox et al. (2001) assessed 20 users who complained of cognitive and/or psychobiological problems, which they attributed to their past use of Ecstasy, also a group of regular users who stated that they not developed any Ecstasy-related problems, and a control group of nonusers. There were no significant differences in the cognitive performance between those Ecstasy users who complained of problems and those who did not. Significant deficits were evident on some cognitive tasks (e.g., spatial working memory, Tower of London planning), whereas other cognitive tasks were unimpaired. The degree of cognitive deficit was significantly related to past Ecstasy usage in both groups. Thus, heavy Ecstasy users were the most impaired, and light users least impaired, irrespective of whether they complained of drug-related problems. This suggests that neuropsychobiological damage may occur in some users without their conscious awareness (Fox et al., 2001). Several studies have concluded that basic cognitive functions remain normal, whereas more difficult cognitive tasks are impaired (e.g., higher executive decision making, complex information processing; Morgan, 2000). The memory deficits may reflect serotonergic changes in the hippocampus, while the higher cognitive/executive deficits may reflect frontal cortical damage (Morgan, 1998; Parrott, 2000, 2001; Verkes et al., 2001). However, using the Cambridge Neuropsychological Test Battery (CANTAB), Fox et al. (2000) reported that cognitive deficit profiles for heavy Ecstasy users, were closest to those of temporal lobe neurosurgical patients.

7. Regular use of MDMA: psychiatric and psychobiological aspects

In a nonpharmacological review of 5-HT, Naughton et al. (2000, p. 402) noted that: ''Serotonin is involved in the regulation of mood, sleep, vigilance, memory and learning, feeding and sexual behaviour'', also psychiatric disorders including depression, anxiety, impulsivity, obsessive compulsive disorder, and schizophrenia. Numerous case studies of major depression, panic disorder, psychotic breakdown, aggressiveness, phobic anxiety, and various eating disorders have been described in recreational Ecstasy users (McCann et al., 2000; Morgan, 1998; Schifano, 2000; Turner et al., 1998). The first reports appeared in the late 1980s soon after MDMA first became popular. In some cases, the individual had no known psychiatric history, whereas in others a psychiatric predisposition was exacerbated by drug use (McCann et al., 1996; McGuire, 2000; Schifano et al., 1998; Schifano, 2000). An important limitation of evidence based upon individual reactions is that they may be seen as uncharacteristic or idiosyncratic. McCann et al. (1996, p. 108) noted that: ''Individual case studies might be perceived as anecdotal and can therefore be ignored or trivialized''. In order to gauge how normal or atypical these psychiatric disorders are, systematic survey data is required.

Schifano et al., (1998) administered a battery of psychiatric and psychobiological assessment measures to young attendees at a drug treatment centre. An analysis of the 150 who had taken Ecstasy uncovered the following problems in descending order of frequency: depression, psychotic disorder, cognitive impairment, bulimia, impulse control disorder, and panic disorder. Those with Ecstasy-related problems had a higher lifetime drug usage (mean 47 tablets) than those reporting no problems (mean 3 tablets). One limitation of the study was that it involved attendees at a drug clinic, who may have been atypical. Topp et al. (1999) described a wide range of problems in a nonclinical survey of Australian users, including depression, irritability, confusion, trouble sleeping, anxiety, and paranoia, although they did not have control group values. In another nonclinical study, Parrott et al. (2000) assessed 50 young adults in an Irish town where drug use was very prevalent. On the standard psychiatric self-rating questionnaire (SCL-90), heavy Ecstasy users reported significantly higher scores than nonusers on the following factors: general anxiety, phobic anxiety, hostility, obsessionality, paranoid ideation, psychoticism, somatisation, altered appetite, restless sleep, and impulsiveness. One problem was that the Ecstasy users had taken many different psychoactive drugs, so in a follow-up study we assessed a wider range of drug usage groups.

Over 760 young adults from Great Britain and Italy were categorised into six subgroups: non-drug users, legal drug users (alcohol and/or nicotine), cannabis users, illicit polydrug but not Ecstasy users, light Ecstasy polydrug users, and heavy Ecstasy polydrug users (Milani et al., 2000; Parrott et al., in press). The SCL-90 psychiatric symptom inventory was supplemented by 30 questions covering positive life experiences. The six groups did not differ on any of the four positive life factors. Whereas on the psychiatric self-rating scales, symptom scores increased with greater drug use, so that the illicit polydrug user groups reported the highest scores. Heavy Ecstasy users also reported significantly higher rates of ''loss of sexual interest or pleasure'' (14%) than the non-drug users (4%). There were, however, only slight differences between those polydrug users who taken Ecstasy and those who had not (Parrott et al., in press). Thus, Ecstasy is only one of many psychoactive drugs to be positively associated with psychiatric distress. Recreational users of cocaine, amphetamine, LSD, and magic mushrooms also report adverse psychiatric symptoms. We therefore investigated the influence of these other illicit drugs upon the symptom scores reported by the Ecstasy polydrug users. As expected, cocaine and amphetamine contributed to several of the adverse symptom profiles. However, the worst codrug for Ecstasy users was nicotine, which was positively associated with most of the psychiatric symptom scales. The incidence of cigarette smoking amongst Ecstasy users is often very high, raising the question of why their combined use is both popular yet troublesome (Parrott, 1999, 2001).

8. Serotonin syndrome and neurotoxicity: are they related?

Huether et al. (1997, p. 771) has proposed an explanatory model for the relationship between the 'massive and prolonged' stimulation of 5-HT induced by MDMA and the deleterious effects of repeated drug administration. The explanation was based upon energy metabolism within the presynaptic terminal. Acute MDMA causes the active carrier systems to remain at a permanently activated state, and this is exacerbated by hyperthermia. This leads to impaired ATP cell metabolism, so that the normal metabolic processes of recovery and repair become overstressed and exhausted. This causes cellular damage within the presynaptic region, and the loss of axonal terminals. A number of other explanations have been proposed (e.g., Schmidt, 1987; Sprague et al., 1988), with oxidative damage often conceptualized as a core factor. Huether et al., (1997) incorporates this as one process by which the cellular damage may be occurring. These different explanatory models are largely based upon animal data, where MDMA is administered under controlled conditions of dosage and temperature (Huether et al., 1997; Schmidt, 1987; Sprague et al., 1988). However, they also consistent with the more limited human data (see below), reinforcing Ricaurte et al.'s (2000) observation that Ecstasy/MDMA is a prime example of how animal and human research are often complementary.

In humans, the massive boost in 5-HT and other monoamines induced by MDMA causes euphoric mood states,

together with hyperactivity, hyperreflexia, and hyperthermia. Although the marked psychophysiological arousal may facilitate repetitive dancing, the acute serotonergic overactivity may be crucial for causing long-term neurotoxicity. The duration of MDMA's stimulatory effects may last only by a few hours, and most recreational users probably believe that this could not cause any long-lasting damage. However, the animal models suggest that these brief acute drug experiences will each contribute to the longer-lasting neurobiological damage, particularly when accompanied by heat and physical exertion (Huether et al., 1997; Sprague et al., 1988). The working hypothesis is that the long-term neuropsychobiological changes in humans will be a direct function of the acute serotonergic overactivity. There is plenty of empirical evidence that lifetime Ecstasy consumption is related to the incidence of neuropsychobiological problems, whether indicated by markers for serotonergic loss, cognitive/memory deficits, psychiatric symptoms, reduced sexual interest/pleasure, and a range of other serotonergic problems (see previous sections). However, there is very little data on the incidence and severity of the acute drug reactions in relation to the development of later problems. One possibility is that each period of acute 5-HT overactivity contributed to the later problems. Alternatively, it might be that high-dose periods have a disproportionate effect. Finally, there is the crucial question of neuronal recovery. Will the serotonergic system recover, either partially or completely, after recreational Ecstasy use has ceased?

References

Cohen RS. The love drug: marching to the beat of ecstasy New York: Haworth Medical Press, 1998.

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

Curran HV, Travill RA. Mood and cognitive effects of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"): weekend "high" followed by mid-week "low". Addiction 1997;92:821–31.

Davison D, Parrott AC. Ecstasy in recreational users: self-reported psychological and physiological effects. Hum Psychopharmacol 1997;12:91–7.

Demirkiran M, Jankovic J, Dean JM. Ecstasy intoxication: an overlap between the serotonin syndrome and neuroleptic malignancy syndrome. Clin Neuropharmacol 1997;19:157–64.

De Souza EB, Battaglia G, Insel TL. Neurotoxic effects of MDMA on brain serotonin neurones: evidence from neurochemical and radioligand binding studies. Ann NY Acad Sci 1990;600:682–97.

Fisher CA, Hatzidimitriou G, Katz JL, Ricaurte GA. Reorganization of ascending serotonin axon projections in animals previously exposed to the recreational drug 3,4-methylenedioxymethamphetamine. J Neurosci 1995;15:5476–85.

Fox H, Turner JJD, Parrott AC, Sahakian BJ, McLean A, Rogers R. Neuropsychological cognitive profiles of heavy MDMA ("Ecstasy") users. Int J Neuropsychopharmacol 2000;3:s325.

Fox H, Parrott AC, Turner JJD. Ecstasy/MDMA related cognitive deficits: a function of dosage rather than awareness of problems. J Psychopharmacol 2001;15:273–81.

Gerra G, Kaimovic A, Guicastro G, Maestri D, Monica C, Sartori R, Caccavari R, Delsignore R. Serotonergic function after 3,4-methylenedioxymethamphetamine. Int Clin Psychopharmacol 1998;13:1–9.

Gerra G, Kaimovic A, Ferri M, Zambelli U, Timpano M, Neri E, Marzocchi GF, Delsignore R, Brambilla F. Long-lasting effects of 3,4-methylenedioxymethamphetamine (Ecstasy) on serotonin system function in humans. Biol Psychiatry 2000;47:127–36.

Gillman PK. Serotonin syndrome: history and risk. Fundam Clin Pharmacol 1998;12:482–91.

Gillman PK. The serotonin syndrome and its treatment. J Psychopharmacol 1999;13:100–9.

Gordon CJ, Watkinson WP, O'Callaghan JP, Miller DB. Effects of 3,4-methylenedioxymethamphetamine on autonomic thermoregulatory responses of the rat. Pharmacol, Biochem Behav 1991;38:339–44.

Gouzoulis-Meyfrank E, Daumann J, Tuchtenhagen F, Pelz S, Becker S, Kunert HJ, Fimm B, Sass H. Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). J Neurol Neurosurg Psychiatry 2000;68:719–25.

Green AR, Cross AJ, Goodwin GM. Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or ecstasy). Psychopharmacology 1995;119:247–60.

Greer G, Tolbert R. A method of conducting therapeutic sessions with MDMA. J Psychoact Drugs 1998;30:371–9.

Heffernan TM, Ling J, Scholey A. Subjective ratings of prospective memory deficits in MDMA ('ecstasy') users. Human Psychopharmacol 2001;16:607–12.

Hegadoren KM, Baker GB, Bourin M. 3,4-Methylenedioxy analogues of amphetamine: defining the risks to humans. Neurosci Biobehav Rev 1998;23:539–53.

Henry JA, Jeffries KJ, Dawling S. Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("Ecstasy"). Lancet 1992;340:384–7.

Huether G, Zhou D, Ryuther E. Causes and consequences of the loss of serotonergic presynapses elicited by the consumption of 3,4-methylenedioxymethamphetamine (MDMA, ''ecstasy'') and its congeners. J Neural Transm 1997;104:771–94.

King LA. Was it MDMA? Neuropsychobiology 2000;42:45–6.

Krystal JH, Price LH, Opsahl C, Ricaurte GA, Heninger GR. Chronic 3,4-methylenedioxymethamphetamine (MDMA) use: effects on mood and neuropsychological function? Am J Drug Alcohol Abuse 1992;18:331–41.

Liechti ME, Vollenweider FX. Which neurotransmitters mediate the effects of MDMA in humans: a summary of mechanistic studies. Hum Psychopharmacol 2001;16:589–98.

Malberg JE, Seiden LS. Small changes in ambient temperature cause large changes in 3,4-methylenedioxymethamphetamine (MDMA)-induced serotonin neurotoxicity and core body temperature in the rat. J Neurosci 1998;18:5086–94.

McCann UD, Ricaurte GA. Reinforcing subjective experience of (±) 3,4-methylenedioxymethamphetamine ("ecstasy") may be separable from its neurotoxic actions: clinical evidence. J Clin Psychopharmacol 1993;13:214–7.

McCann UD, Ridenour A, Shaham Y, Ricaurte GA. Serotonin neurotoxicity after (±) 3,4-methylenedioxymethamphetamine (MDMA; 'Ecstasy'): a controlled study in humans. Neuropsychopharmacology 1994;20:129–38.

McCann UD, Slate SO, Ricaurte GA. Adverse reactions with 3,4-methylenedioxymethamphetamine (MDMA; ''Ecstasy''). Drug Saf 1996;15:107–15.

McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA. Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurones in human beings. Lancet 1998;352:1433–7.

McCann UD, Eligulashvili V, Ricaurte GA. (±) 3,4-Methylenedioxymethamphetamine ('Ecstasy')-induced serotonin neurotoxicity: clinical studies. Neuropsychobiology 2000;42:11–6.

McDowell DM, Kleber HD. MDMA: its history and pharmacology. Psychiatr Ann 1994;24:127–30.

McGuire P. Long term psychiatric and cognitive effects of MDMA use. Toxicol Lett 2000;112–113:153–6.

Meilman PW, Gaylor MS, Turco JH, Stone JE. Drug use amongst undergraduates: current use and 10 year trends. Int J Addict 1990;25:1025–36.

Milani R, Turner JJD, Parrott AC. Recreational drug use and psychobiological problems, collaborative UK/Italy study (2): Rome and Padua findings. J Psychopharmacol 2000;14:a14.

Morgan MJ. Recreational use of "ecstasy" (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology 1998;19:252–64.

Morgan MJ. Memory deficits associated with recreational use of "ecstasy" (MDMA). Psychopharmacology 1999;141:30–6.

Morgan MJ. Ecstasy (MDMA): a review of its possible persistent psychological effects. Psychopharmacology 2000;152:230–48.

Naughton M, Mulrooney JB, Leonard BE. A review of the role of serotonin receptors in psychiatric disorders. Hum Psychopharmacol 2000;15: 397–416.

Parrott AC. MDMA, mood and memory: the agnosia of the Ecstasy. Paper presented at the BPS Psychobiology Section Annual Scientific Meeting, September 1996. BPS Psychobiology Section Newsletter, 1996.

Parrott AC. Does cigarette smoking cause stress? Am Psychol 1999;54: 817–20.

Parrott AC. Human research on MDMA (3,4-methylenedioxymethamphetamine) neurotoxicity: cognitive and behavioral indices of change. Neuropsychobiology 2000;42:17–24.

Parrott AC. Human neuropsychopharmacology of Ecstasy/MDMA: a review of fifteen years of empirical research. Hum Psychopharmacol 2001;16:557–77.

Parrott AC, Lasky J. Ecstasy (MDMA) effects upon mood and cognition; before, during, and after a saturday night dance. Psychopharmacology 1998;139:261–8.

Parrott AC, Lees A, Garnham NJ, Jones M, Wesnes K. Cognitive performance in recreational users of MDMA or "ecstasy": evidence for memory deficits. J Psychopharmacol 1998;12:79–83.

Parrott AC, Sisk E, Turner J. Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users. Drug Alcohol Depend 2000;60:105–10.

Parrott AC, Milani R, Parmar R, Turner JJD. Recreational Ecstasy/MDMA and other drug users from Britain and Italy: psychiatric symptoms and psychobiological problems. Psychopharmacology (in press).

Peroutka SJ, Newman H, Harris H. Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. Neuropsychopharmacology 1988;1:273–7.

Price LH, Ricaurte GA, Krystal JH, Heninger GR. Neuroendocrine and mood responses to intravenous tryptophan in of 3,4-methylenedioxymethamphetamine (MDMA) users. Arch Gen Psychiatry 1987;46:20–2.

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

Ricaurte GA, Bryan G, Strauss L, Seiden LS, Schuster CR. Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. Science 1985;229:986–8.

Ricaurte GA, Yuan J, McCann UD. (±)3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy")-induced serotonin neurotoxicity: studies in animals. Neuropsychobiology 2000;42:5–10.

Rodgers J. Cognitive performance amongst recreational users of "ecstasy". Psychopharmacology 2000;151:19–24.

Saunders N. Ecstasy and the dance culture London: Neal's Yard Desktop Publishing, 1995.

Schifano F. Potential human neurotoxicity of MDMA ('Ecstasy"): subjective self-reports, evidence form an Italian drug addiction centre and clinical case studies. Neuropsychobiology 2000;42:25–33.

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.

Schmidt CJ, Wu L, Lovenberg W. Methylenedioxymethamphetamine: a potentially neurotoxic amphetamine analog. Eur J Pharmacol 1986; 124:175–8.

Schmidt CJ. Neurotoxicity of the psychedelic amphetamine methylenedioxymethamphetamine. J Pharmacol Exp Ther 1987;240:1–7.

Schuster P, Lieb R, Lamertz C, Wittchen HU. Is the use of ecstasy and hallucinogens increasing? Eur Addict Res 1998;4:75–82.

Semple DM, Ebmeier KP, Glabus MF, O'Carroll RE, Johnstone EC. Reduced in vivo binding to serotonin transporters in the cerebral cortex of MDMA ("Ecstasy") users. Br J Psychiatry 1999;175:63–9.

Solowij N, Hall W, Lee N. Recreational MDMA, use in Sydney: a profile of ecstasy users and their experiences with the drug. Br J Addiction 1992; 87:1161–72.

Sprague JE, Everman SL, Nichols DE. An integrated hypothesis for the serotonergic axonal loss induced by 3,4-methylenedioxymethamphetamine. Neurotoxicology 1988;19:427–41.

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

Turner JJD, Godolphin Parrott AC. Cognitive task performance profiles of current and former "Ecstasy" (MDMA) users. J Psychopharmacol 1999;13:a24.

Turner JJD, Nicolas L, Parrott AC. Reduced calorie intake in the week following weekend MDMA (ecstasy) use. J Psychopharmacol 1998; 12:a43.

Verkes RJ, Gigsman HJ, Pieters MSM, Schoemaker RC, de Visser S, Kuijpers M. Cognitive performance and serotonergic function in users of ecstasy. Psychopharmacology 2001;153:196–202.

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

Wijngaart van de GM, Braam R, de Bruin D, Fris M, Maalste NJM, Verbraeck, HT. Ecstasy and the Dutch rave scene: a socio-epidemiological study. Journal of Drug Issues 1999;19:697–702.