

MDMA: Neurohormonal, Neurocognitive, and Psychobiological Aspects of Recreational Ecstasy

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Abstract: This Ecstasy/MDMA symposium was held at the Annual Conference of the Australian Psychological Society, Hobart, Tasmania, in September 2008. The Australian government has been funding research into MDMA for many years, and hence there are several Australian groups at the forefront of international research in this field. Included in the studies reported here, were collaborations with universities from other countries. The main focus was on human studies, although animal psychopharmacology findings were also presented. The topics covered within this half-day symposium included Ecstasy dependence, the problems reported by recreational users, the influence of other psychoactive drugs, the Internet as a research tool, the contributory role of neurohormones such as oxytocin and cortisol, and the energetic stress model for recreational Ecstasy/MDMA.

Louisa Degenhardt and Raimondo Bruno noted how the use of MDMA had been increasing worldwide in recent years, and Australia was consistent with this trend [1, 2]. Research in Australia had benefited from the collation of multiple state and national data sources through the National Illicit Drug Indicators Project, which provided detailed information about trends in usage, and drug-related harm. Their paper was mainly concerned with the epidemiology of Ecstasy in Australia, focusing on sentinel groups of regular users, who had been recruited for the Ecstasy and related Drugs Reporting System (EDRS). They described recent trends in ecstasy markets, patterns of use, and the incidence of drug-attributed harms [2]. They also summarized how the EDRS had examined the associations between ecstasy usage patterns, risk behaviours, and adverse consequences, including overdose, social problems and mental health problems. One notable trend had been a substantial increase in co-incident binge alcohol consumption, with many regular Ecstasy users drinking alcohol at levels harmful to health, and strongly contributing to the experience of adverse consequences, such as overdose [2]. These findings were broadly similar to those reported in Norway, where many Ecstasy users drank alcohol at very high and dangerous levels [3]. The frequent use of other psychoactive drugs, was

also consistent with findings from the USA household survey, which had involved over 50,000 interviewees [4]. Amongst the subgroup of recent Ecstasy/MDMA users, 70% reported another substance use disorder in the past year, with the most frequent co-drugs being alcohol (41%), cannabis (31%), and cocaine (10%).

Raimondo Bruno debated the notion of 'Ecstasy/MDMA addiction'. Bruno and co-workers concluded that it provided an interesting variant of drug dependence – but 'not as we know it' [5]. There has been an extensive debate over whether a *true* dependence syndrome existed with ecstasy, since few users present at drug treatment services, and animal studies suggested few signs of physical dependence. Despite this, some users do experience problems with MDMA, and Ecstasy dependence can be diagnosed using both the hallucinogen dependence and amphetamine dependence categories of the DSM-IV-TR. The authors had also investigated the characteristics of Ecstasy/MDMA dependence, using the Severity of Dependence Scale in a large cohort of frequent ecstasy consumers, obtained from the Ecstasy and related Drugs Reporting System (see above). These findings revealed that the latent structure of dependence symptoms for Ecstasy was not homogeneous, in contrast to that for other drugs. However Ecstasy dependence still demonstrated a degree of validity, with greater symptoms of dependence related to higher overall MDMA usage, more engagement in risky behaviours, and a greater incidence of drug-related problems.

Andy Scholey outlined a series of Internet-based studies into cognitive aspects of Ecstasy/MDMA and other

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psychosocial drugs. The programme represented collaboration between Swinburne University in Australia, and several British universities. Jacqui Rodgers from Newcastle University in the UK had originally established this multi-faceted group, with experts in human psychopharmacology, cognition, multivariate statistics, and Internet research. The other contributors comprised Tom Buchanan from Westminster University, Jonathan Ling from Keele University, Tom Heffernan from Northumbria University, and Andy Parrott from Swansea University. The programme of Internet studies had involved strict data screening procedures, and large drug groups. The first investigation involved over 700 participants, and revealed an interesting pattern of self-reported neurocognitive deficits. In particular, cannabis was significantly associated with problems in everyday memory, whereas Ecstasy/MDMA was significantly linked with self-reported deficits in prospective memory [6]. This has been confirmed by subsequent Australian research, where deficits in prospective memory again emerged with Ecstasy/MDMA users [7], and German research showing episodic memory deficits following cannabis and MDMA [8]. The next Internet study involved 206 recreational MDMA users, when extensive dancing while 'on-Ecstasy' was statistically linked with more subjective complaints of memory problems, feelings of depression, and concentration/organizational difficulties [9]. Some of these psychobiological problems were also associated with self-rated thermal distress, defined as feeling 'hot or overheated'. As noted earlier, polydrug recreational usage was widespread [10], so that alcohol and nicotine can both contribute to these neurocognitive/memory problems [11, 12]. In conclusion, the Internet was recommended as an efficient means for undertaking psychopharmacology research, especially with large sample sizes. However potential difficulties were also noted (e.g. duplicate data entry, fraudulent responses), so that methods for optimizing data accuracy and purity were also described [13]. The most recent study by this international collaborative group, will involve on-line performance tests designed by Brian Tiplady (see: 14, for the types of test involved). The emergent findings should help to further illuminate the nature of the cognitive/memory deficits found in Ecstasy/MDMA and other polydrug users.

Kate Morefield described a recent empirical investigation into the psychobiological impact of illicit ecstasy/MDMA in the recreational environment. The fellow collaborators from Adelaide University included: M. Keane, P. Felgate, J.M. White, and R. Irvine. In this large field study, data were gathered at parties from 41 experienced ecstasy users. Blood samples, physiological measures and subjective reports were collected prior to ecstasy consumption and hourly for five hours thereafter. Participants consumed between 1 and 5 ecstasy pills, ingesting doses often exceeding and in some cases tripling the maximum doses administered to humans in laboratory studies [15]. Maximum MDMA plasma concentrations averaged 336 ng/mL, and a quarter of party-goers had MDMA plasma concentrations in the 'toxic to lethal' range - according to forensic guidelines [16]. Peak cardiovascular and thermodynamic effects also tended to exceed those found in clinical studies. Heart rates increased by a mean of 24 bpm, systolic blood pressure by 22 mmHg and diastolic blood pressure by 14 mmHg. Core and skin

temperatures also rose by 1.1 °C and 1.8 °C respectively. It was apparent that recreational ecstasy users often consume considerably higher doses of the drug, and experienced greater psychophysiological sequelae than those reported in controlled clinical research. The plasma concentrations were also very high, indeed sometimes similar to those reported in case studies involving toxicity; although Kate pointed out that the participants seemed able to physically tolerate these high drug levels. The laboratory analyses of neurohormones such as oxytocin and cortisol were still underway, and will be reported at a future meeting.

Jillian Broadbear, with coauthor Katherine Beringer, debated the potential role of oxytocin as a mediator of the unique interoceptive effects of 3, 4-methylenedioxymethamphetamine in the rat. Jillian pointed out that MDMA or 'Ecstasy' resulted in distinctive mood changes, most likely due to its combined enhancement of serotonin (5HT) and dopamine (DA) release. Features that exemplify MDMA's effects include the pro-social mood and behavioral changes that users report [17]. This was similar to some of the behavioural effects of the neurohormone oxytocin, which is thought to play a central role in social interaction [18]. Activation of 5HT-1A postsynaptic receptors has been reported to stimulate the release of oxytocin in the central nervous system [19], where it regulates mood and behaviour. Using a drug discrimination paradigm, Broadbear and colleagues examined how alterations in oxytocin levels can affect conditioned behavioural responses. Male and female Sprague Dawley rats (n=24) were trained to differentiate between MDMA (1.5 mg/kg) and a related stimulant, amphetamine (1.0 mg/kg), and saline using a three lever drug discrimination paradigm. In their study, the extent to which operant responding generalized to the training drugs following administration of carbetocin (an oxytocin analogue) or atosiban (oxytocin receptor antagonist) or combinations of these drugs was evaluated. The results supported the hypotheses that the addition of an oxytocin analogue (carbetocin) would partially substitute for the MDMA training drug, whereas blocking oxytocin receptors with atosiban resulted in some disruption to MDMA-appropriate responding, with responding shifting to the amphetamine and saline appropriate levers. It was concluded that oxytocin receptor activation is involved in MDMA-specific interoceptive cues, and that this is one of the features of MDMA that distinguishes it subjectively from amphetamine [20].

Andy Parrott noted that MDMA (3, 4-methylenedioxymethamphetamine), was a powerful indirect monoaminergic agonist, stimulating the release and inhibiting the reuptake of serotonin (5-HT) and other neurotransmitters [21]. This boost in neurotransmitter activity can generate intense feelings of elation and pleasure, along with hyperactivity and hyperthermia [22-24]. Several days after taking Ecstasy many users report rebound depression and lethargy which is thought to reflect monoaminergic depletion [25]. Many of these positive and negative drug sequelae reflect drug-induced changes in neuropsychophysiological arousal, and these may be exacerbated by high ambient temperature and prolonged dancing [26]. Some of these effects may also reflect neurohormonal changes. The putative role of oxytocin was

debated by Gillian Broadbear in the previous paragraph. Here the energetic stress neurohormone cortisol was debated [27]. In a recent study of Ecstasy using dance clubbers, where MDMA was biochemically confirmed, an 800% increase in cortisol emerged. This was significantly greater than the slight increase when these same clubbers went dancing during MDMA abstinence [28]. An 800% increase in cortisol has also been found in a follow up study of party goers, and contrasts with the 150% increase in cortisol post-MDMA in the laboratory [15]. The psychobiological problems of regular Ecstasy/MDMA use include selective deficits in learning/memory, higher cognitive processing, sleep, appetite, psychiatric wellbeing, and sexual function. Various drug and non-drug factors can influence these deficits. Novice users often remain relatively unimpaired, whereas most heavy users report psychobiological problems. Prolonged dancing and feeling hot at dances and raves are also associated with a higher incidence of psychobiological problems [9]. This is consistent with the animal literature, where high ambient temperature and other metabolic stimulants boost the acute effects of MDMA, and cause greater serotonergic neurotoxicity [21, 29]. These multiple influences have been integrated within a bioenergetic stress model for recreational MDMA [24, 27]. According to this model, metabolic cellular activity is increased by MDMA and other CNS stimulants. This drug-induced activation is further enhanced by environmental co-stimulants; these may make the drug more rewarding, but which also increase cellular distress. Hence according to the bioenergetic stress model, the longer term neuropsychobiological consequences will reflect a complex amalgam of drug and non-drug factors [24, 27].

In summary, MDMA displays an unusual neurochemical and neurohormonal profile, with stimulant and hallucinogenic properties. Since it displays attributes from both drug classes, this may help to explain its different patterns of usage in comparison with the other recreational stimulants. It also complicates any conclusions that can be offered regarding its harmfulness to well-being. For many years MDMA enjoyed a reputation as a 'party' drug with connotations of low risk and social acceptability [5]. However in psychobiological terms its use is associated with an array of deficits in memory, cognition, planning, social intelligence, sleeping rhythm and apnea, immunocompetence, and psychiatric distress [22-24, 30, 31]. Its use is also strongly associated with other problematic drugs, such as alcohol, nicotine, and cannabis [2, 4]. Its pro-social properties may support its positive reputation [32], but these may also mask the multiple risks associated with its recreational usage. After the conference, the speakers therefore eschewed the jitterbug halls and dance clubs of downtown Hobart, and met instead at Drunken Admiral Tavern on the Hobart waterfront. Rather than overstress our fading cortisol levels with excessive dancing, we retired to the T42^o bar nearby, where our oxytocin levels and feelings of pleasure increased. This reflected the excellent company, the refined Pinot Noir wines from Tasmania, and the wonderful sea foods from the icy waters of the nearby Southern Ocean.

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