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The confounding problem of polydrug use in recreational ecstasy/MDMA users: a brief overview

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Abstract

The popular dance drug ecstasy (3,4-methylenedioxy-methamphetamine = MDMA) is neurotoxic upon central serotonergic neurons in laboratory animals and possibly also in humans. In recent years, several studies reported alterations of serotonergic transmission and neuropsychiatric abnormalities in ecstasy users which might be related to MDMA-induced neurotoxic brain damage. To date, the most consistent findings associate subtle cognitive, particularly memory, deficits with heavy ecstasy use. However, most studies have important inherent methodological problems. One of the most serious confounds is the widespread pattern of polydrug use which makes it difficult to relate the findings in user populations to one specific drug. The present paper represents a brief overview on this issue. The most commonly co-used substances are alcohol, cannabis and stimulants (amphetamines and cocaine). Stimulants are also neurotoxic upon both serotonergic *and* dopaminergic neurons. Hence, they may act synergistically with MDMA and enhance its long-term adverse effects. The interactions between MDMA and cannabis use may be more complex: cannabis use is a well-recognized risk factor for neuropsychiatric disorders and it was shown to contribute to psychological problems and cognitive failures in ecstasy users. However, at the cellular level, cannabinoids have neuroprotective actions and they were shown to (partially) block MDMA-induced neurotoxicity in laboratory animals. In future, longitudinal and prospective research designs should hopefully lead to a better understanding of the relation between drug use and subclinical psychological symptoms or neurocognitive failures and, also, of questions around interactions between the various substances of abuse.

Keywords

ecstasy, MDMA, neurotoxicity, serotonin, memory, amphetamines, stimulants, cannabis, neuroprotection

Introduction

The ring-substituted amphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA) is a popular recreational drug best known by its street name ecstasy. MDMA and some analogues are mostly used by young people aged 18 to 30 and are particularly popular among visitors of raves and disco clubs (Green *et al.*, 2003). MDMA binds to all presynaptic monoamine transporters, most strongly to the serotonin transporter (SERT), and induces rapid and powerful release of serotonin (5-HT) and dopamine (DA) from presynaptic terminals. Animal studies evidence clearly that MDMA is neurotoxic upon central serotonergic systems (Ricaurte *et al.*, 2000). High and/or repeated doses of MDMA lead to widespread degeneration of presynaptic serotonergic axon terminals, loss of SERT and 5-HT depletion in brain tissue. The mechanism of MDMA neurotoxicity is not entirely understood. However, data from animal studies strongly suggest that the formation of free radicals is a key factor, that hyperthermia enhances both the formation of free radicals and the neurotoxic effects of MDMA, and, finally, that a metabolite, and not MDMA itself, is responsible for the neurotoxic effects on the serotonergic systems (Green *et al.*, 2003). The neurotoxic effects of MDMA can be very long-lasting or even permanent in animal studies (Hatzidimitriou *et al.*, 1999).

Current evidence suggests that MDMA may be also neurotoxic in humans and may be associated with alterations in psychological functions, cognition or other brain functions (e.g. McCann *et al.*, 1998a, 2000; Reneman *et al.*, 2001). Cerebrospinal fluid (CSF), positron emission tomography and single photon emission computed tomography studies (PET and SPECT) have yielded some evidence for long-term reductions of 5-HT and SERT availability with recent data pointing to partial recovery after prolonged abstinence (Reneman *et al.*, 2001; Thomasius *et al.*, 2003). To date, the most consistent functional finding in ecstasy users is that of subtle deficits in episodic memory and learning abilities, particularly in users with heavy patterns of MDMA use (Green *et al.*, 2003; Gouzoulis-Mayfrank and Daumann, in press).

However, many studies in this field of research have significant

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methodological limitations and for some of these methodological problems we can expect no perfect solutions. One of the most important confounds in research with recreational ecstasy/MDMA users is the widespread pattern of polysubstance use. The overwhelming majority of ecstasy users also take a range of other psychoactive compounds, most commonly alcohol, cannabis and stimulants (Fox *et al.*, 2001; Winstock *et al.*, 2001; Scholey *et al.*, 2004). Therefore, it is difficult to draw conclusions on the effects of MDMA from studies involving non-users as controls. Interestingly, in recent studies with relatively large samples of up to 234 polydrug ecstasy users and polydrug controls who did not use ecstasy, elevated psychopathology appeared to be associated with polydrug use in general and not specifically with ecstasy use (Parrott *et al.*, 2001; Thomasius *et al.*, 2003; Roiser and Sahakian, 2004). However, even studies with control groups of polydrug users who do not use ecstasy are difficult to interpret, because these users mostly display a more moderate pattern of drug use compared to polydrug ecstasy users (Bolla *et al.*, 1998; Morgan, 1998, 1999; McCann *et al.*, 1999, 2000; Gamma *et al.*, 2000; Parrott *et al.*, 2000; Reneman *et al.*, 2000; Wareing *et al.*, 2000). Theoretically, the parallel use of stimulants (amphetamines and cocaine) which are also neurotoxic may act synergistically and enhance the long-term adverse effects of MDMA, while the interactions between MDMA and cannabis use may be more complex. In this paper, we will provide a brief overview on this topic and will outline future research perspectives.

Stimulant amphetamines are neurotoxic for central dopaminergic and serotonergic systems

Stimulant amphetamines bind to presynaptic monoamine transporters and induce acute release and reuptake inhibition of DA and 5-HT. Similar to MDMA, stimulant amphetamines were shown to be neurotoxic in animal studies (Seiden and Sabol, 1996). Moreover, stimulant-related neurotoxicity is not restricted to the serotonergic system. High and/or repeated doses of amphetamine (AMPH) or methamphetamine (METH) induce widespread degeneration of presynaptic serotonergic *and* dopaminergic axon terminals, which, in turn, leads to 5-HT *and* DA depletion and to lower 5-HT *and* DA transporter densities (SERT and DAT) in brain tissue (Seiden and Sabol, 1996; Hanson *et al.*, 2004; McCann and Ricaurte, 2004). The long-term effects on the DA system tend to be more pronounced than the effects on the 5-HT system.

Recent studies with PET (DAT concentration, cerebral glucose metabolism) and MR-spectroscopy suggest that stimulants may be neurotoxic in humans and that alterations in the brain of users may persist over prolonged periods of time (McCann *et al.*, 1998b; Ernst *et al.*, 2000; Volkow *et al.*, 2001a, 2001b; Renemann *et al.*, 2002; Wang *et al.*, 2004). Theoretically, neurotoxic dopaminergic lesions could be associated with motor, cognitive and psychopathological failures. To date, the literature on long-term psychopathological sequelae of stimulant use is inconclusive (e.g. Riehman *et al.*, 2002). Similarly, recent cross-sectional studies in chronic stimulant users demonstrated deficits in short-term memory, frontal executive control and planning abilities (Ornstein *et al.*, 2000; Simon *et al.*, 2000, 2002; Salo *et al.*, 2002; Lawton-Craddock *et al.*, 2003; Woods *et al.*, 2005). However, it is not clear whether these deficits are a consequence of the use of stimulants or whether they reflect pre-existing low cognitive abilities in people who become drug users later in their lives. Nevertheless, Volkow *et al.* (2001b) demonstrated associations of reduced DAT densities with longer duration of amphetamine use as well as poorer performance in both fine motor and memory tasks in 15 currently abstinent amphetamine users.

In summary, the co-use of stimulants may enhance MDMA-related neurotoxicity upon serotonergic neurons and may add neurotoxic effects to the dopaminergic system

Cannabis: psychopathological sequelae and cognitive deficits, but neuroprotection at the cellular level

Cannabis is the most widespread illegal drug among young people. Accordingly, the co-use of cannabis is an important confound when studying the long-term effects of ecstasy use. Most MDMA users have used cannabis more or less regularly before they start taking ecstasy and they continue smoking cannabis parallel to the use of MDMA. A recent survey showed that every novice ecstasy user (cumulative dose: 1–9 pills) had smoked cannabis at least once during the preceding month and 32% had smoked cannabis on five or more occasions during the preceding month. In addition, the more pills these novice users had taken, the more frequently they had smoked cannabis before (Scholey *et al.*, 2004). Previous studies yielded similar results with rates of 90–100% for co-use of cannabis in MDMA users (Schuster *et al.*, 1998; Rodgers, 2000; Winstock *et al.*, 2001).

The main psychoactive ingredient of cannabis, Δ9-Tetrahydrocannabinol (THC), is a direct agonist at endogenous cannabinoid CB1 receptors. The cannabinoid system interacts with other neurotransmitters and is involved in various functions such as appetite, pain regulation, vegetative and motor functions. Regular use of cannabis is a well-recognized risk factor for psychiatric disorders such as depression, psychosis and amotivation (Patton *et al.*, 2002; Degenhardt *et al.*, 2003; Hall *et al.*, 2004; Macleod *et al.*, 2004). Moreover, regular cannabis users suffer from deficits of attention and memory, which persist after resolution of the acute drug effects (e.g. Solowij *et al.*, 2002). However, cognitive failures may normalize after weeks of abstinence (e.g. Pope *et al.*, 2001), and, at least to some extent, this also holds true for the psychological sequelae of cannabis. There has been some debate on possible long-term neurotoxic effects of THC, particularly in heavy users. This discussion has been originally stimulated by *in vitro* studies which demonstrated neurotoxicity of large THC doses at the cellular level (e.g. Chan *et al.*, 1998). However, the evidence for cannabis related neurotoxicity in humans has never been convincing. On the contrary, numerous studies showed antioxidant, anti-excitotoxic and anti-inflamatory properties of cannabinoids at the cellular level as well as neuroprotection in a variety of models of neuronal injury, both *in vitro* and *in vivo* (e.g.

Hampson *et al.*, 1998; Hampson and Grimaldi, 2001; Grundy *et al.*, 2001; Mechoulam *et al.*, 2002; van der Stelt *et al.*, 2002; van der Stelt, 2005). Moreover, a recent *in vivo* study demonstrated neuroprotection from binge ethanol-induced neurotoxicity by the nonpsychotropic cannabinoid cannabidiol (CBD) in rodents (Hamelink *et al.*, 2005). Finally, and most importantly, both THC and a synthetic cannabinoid receptor agonist were shown to ameliorate MDMA-induced long-term 5-HT depletion in various brain regions in the rat (Morley *et al.*, 2004). In this latter study wistar rats were treated with a neurotoxic MDMA regimen alone or in combination with THC, a synthetic CB1 receptor agonist, a CB1 receptor antagonist or an agonist/antagonist combination. Two or 7 weeks after the treatment the animals were sacrificed and neurochemical analyses of 5-HT and its major metabolite 5-HIAA were performed in homogenates of various brain regions. Both THC and the CB1 agonist prevented the acute hyperthermia and partially prevented the long-term 5-HT depletion induced by MDMA. The CB1 antagonist prevented the hypothermic response to the agonist, but did not alter the protective effect of the agonist on the MDMA-induced 5-HT depletion. The authors concluded that a CB1-independent mechanism of neuroprotection possibly through counteracting oxidative stress might be responsible for the attenuation of the long-term effects of MDMA upon serotonergic systems (Morley *et al.*, 2004).

These data along with the high prevalence of co-use of cannabis and MDMA mean that we have to consider complex interactions between the two drugs in combined users: the subacute or middle-term effects of cannabis on psychological well-being and cognition may well be negative. However, beneficial long-term effects are also conceivable due to the neuroprotective cellular properties of cannabinoids which may protect from ecstasy and amphetamine related neurotoxicity.

Indeed, the literature on the contribution of cannabis to the long-term effects of MDMA use is inconsistent. In a cross-sectional study with 28 combined ecstasy and cannabis users, 28 pure cannabis users and 28 non-users self-reported subclinical psychopathology was mainly associated with the extent of cannabis use (Daumann *et al.*, 2001). Morgan *et al.* (2002) reported similar findings. The most recent study of our group combined a cross-sectional with a longitudinal approach (Daumann *et al.*, 2004). At baseline, we assessed 60 currently abstinent polydrug ecstasy users and 30 matched controls. From this initial sample of ecstasy users we re-examined 38 subjects 18 months later. Again, self-reported psychopathology such as obsessive-compulsive behaviour, interpersonal sensitivity, depression, anxiety, phobic anxiety and paranoid ideation was mainly associated with the extent of cannabis rather than MDMA use. Interestingly, at follow-up, subjects who stopped using ecstasy after the baseline examination did not differ from those reporting prolonged consumption. In contrast, subjects with regular cannabis use during the follow-up period reported more psychological problems than subjects who had stopped smoking cannabis after the baseline examination (Daumann *et al.*, 2004). These findings suggest that self-reported psychopathology in ecstasy users may be largely attributable to the concomitant use of cannabis. However, other groups reported clearer associations between psychopathology and the extent of ecstasy, but not cannabis use, or even less psychological complaints in MDMA users with cannabis co-use compared to purer MDMA users (Milani *et al.*, 2002; Parrott *et al.*, 2002).

A number of studies which assessed cognitive performance in ecstasy users reported a more or less close relationship between the extent of MDMA use and relative cognitive deficits, with little indication for an effect of other drugs (e.g. Bolla *et al.*, 1998; Morgan *et al.*, 2002; Gouzoulis-Mayfrank *et al.*, 2003). However, some studies reported an additional impact of the co-use of cannabis on short- and medium-term memory and learning performance (e.g. Gouzoulis-Mayfrank *et al.*, 2000; Rodgers *et al.*, 2001; Montgomery *et al.*, 2005). Moreover, a minority of studies found that cognitive deficits were even more closely associated with the extent of cannabis compared to MDMA use in combined users (Croft *et al.*, 2001; Simon and Mattick, 2002; Dafters *et al.*, 2004). Interestingly, a recent study with amphetamine users reported less cognitive impairments in subjects with cannabis co-use compared to subjects who did not smoke cannabis on a regular basis (Gonzalez *et al.*, 2004). In this study the two user groups were similar in terms of demographic data and the extent of previous amphetamine as well as other drug use except for cocaine, for which the combined group (amphetamine and cannabis) displayed a higher prevalence of dependence. Theoretically, these findings might reflect neuroprotection from amphetamine related neurotoxicity by cannabinoids (Gonzalez *et al.*, 2004).

The results from a small pilot study of our group with the functional magnetic resonance technique (fMRI) and a working memory (WM) task (Daumann *et al.*, 2003) could be interpreted as pointing to the same direction as the study by Gonzalez *et al.* (2004). Here, we used an n-back task and fMRI to investigate WM performance and related cerebral activation in eight, currently abstinent pure MDMA users and two matched groups of non-users and polyvalent MDMA users with concomitant use of cannabis and amphetamines. Pure MDMA users presented lower activations than controls and/or combined users, most notably in inferior temporal regions, the angular gyrus and the striate cortex, whereas the combined users did not differ from non-users. We concluded that altered brain activation patterns during cognitive processing in combined users may be mainly associated with prior MDMA use and that concomitant use of cannabis might ameliorate the MDMA-related alterations even when subjects use additional neurotoxic drugs such as stimulant amphetamines (Daumann *et al.*, 2003). However, it should be noted that the literature on the effects of cannabis and combinations of cannabis and other drugs on brain activation patterns is far from being conclusive: e.g. two recent fMRI WM studies in cannabis users reported greater activation in typical WM brain regions such as the prefrontal cortex and anterior cingulate and recruitment of additional regions such as in the basal ganglia suggesting compensation of subtle deficits by 'working harder' (Kanayama *et al.*, 2004), and deficient deactivation of the hippocampus compared to controls (Jacobsen *et al.*, 2004). Finally, a recent PET study demonstrated lower regional glucose metabolism in amphetamine users with, compared to amphetamine users without concomitant cannabis use (Voytek *et al.*, 2005).

In summary, there are important interactions between MDMA and cannabis use upon brain activity, psychopathology and

cognition. However, the interactions are probably very complex and they cannot be described adequately by simple synergistic or antagonistic effects.

Summary and perspectives for future research

All in all, the reports on residual neuropsychiatric effects of ecstasy in humans are alarming, although the evidence cannot be considered definite. A large number of cross-sectional studies on psychological functioning, neurocognition, neuroendocrine regulation and vegetative functions reported subtle abnormalities in MDMA users that may reflect functional sequelae of long-lasting, neurotoxic alterations in serotonergic systems (Green *et al.*, 2003). However, at least to some part, these findings may also reflect pre-existing traits of people being prone to drug use or sequelae of drug use in general and/or of the associated lifestyle, as most MDMA users exhibit a polydrug use pattern and associated behaviours. Indeed, polydrug use is one of the most important confounds in this field of research: some of the earlier investigations have not captured data on the parallel use of other drugs and many studies have used poorly matched control groups consisting of non-users or polydrug users with overall more moderate use patterns than the polydrug ecstasy users.

Among all functional domains examined so far, the most extensive and consistent finding is a subtle cognitive dysfunction in MDMA users. Several studies support a relative weakening of memory functions compared to control groups with a meaningful correlation between the degree of impairment and the extent of ecstasy use (Green *et al.*, 2003; Gouzoulis-Mayfrank and Daumann, in press). However, the role of other drugs, particularly stimulant amphetamines and cannabis, is not entirely clear with some studies favouring an important impact of the co-use of cannabis on cognitive impairments. The polydrug problem and other methodological shortcomings are inherent in this field of research. Hence, research designs in cross-sectional open field studies will never be perfect. Longitudinal studies may be advantageous, but it is questionable whether they will be sufficient to address the important issue of polydrug use. Therefore, in our view, it will be important for research strategies to evolve gradually towards prospective designs. Ideally, we should start with large cohorts of young people who are not or not yet users but may belong to specific risk groups, follow up on and re-examine these people over years, record their drug histories and test them for psychological functions and cognitive performance. Such studies would be arduous, but they should hopefully lead to a better understanding of the relation between drug use and subclinical psychological symptoms or neurocognitive failures and, also, of questions around interactions between the various substances of abuse. In addition, animal studies should be most ideal to further address the issues of drug interactions and, particularly, the potential of cannabinoids to protect from MDMA related neurotoxicity.

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