Psychopharmacology (2002) 159:335–340
DOI 10.1007/s00213-001-0930-0

ORIGINAL INVESTIGATION

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Use of amphetamine by recreational users of ecstasy (MDMA) is associated with reduced striatal dopamine transporter densities: a [^{123}I]β-CIT SPECT study – preliminary report

Received: 2 July 2001 / Accepted: 25 September 2001 / Published online: 20 November 2001

Abstract *Rationale:* Tablets sold as ecstasy often contain not only 3,4-methylenedioxymethamphetamine (MDMA) but other compounds well known to cause dopaminergic neurotoxicity, such as (meth)amphetamine. Furthermore, the use of ecstasy in the Netherlands is often combined with the use of amphetamine. However, little is known about the effects of ecstasy use or the combination of ecstasy and amphetamine use on dopamine (DA) neurones in the human brain. *Objectives:* This study was designed to investigate the effects of ecstasy as well as the combined use of ecstasy and amphetamine on the density of nigrostriatal DA neurones. *Methods:* [^{123}I]β-CIT SPECT was used to quantify striatal DA transporters. Striatal [^{123}I]β-CIT binding ratios of control subjects (n=15) were compared with binding ratios of ecstasy users (n=29) and individuals with a history of combined ecstasy and amphetamine use (n=9) after adjustment for age. *Results:* Striatal [^{123}I]β-CIT binding ratios were significantly lower in combined ecstasy and amphetamine users compared to sole ecstasy users (6.75 versus 8.46, respectively: –20.2%, P=0.007). Binding ratios were significantly higher in ecstasy users when compared to controls (8.46 versus 7.47, respectively: +13.2%, P=0.045). *Conclusions:* These initial observations suggest that the sole use of ecstasy is not related to dopaminergic neurotoxicity in humans. In contrast, the reported use of amphetamine by regular users of ecstasy seems to be associated with a reduction in nigrostriatal DA neurones.

Keywords Ecstasy · Amphetamine · Neurotoxicity · DA transporter · [^{123}I]β-CIT SPECT

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Introduction

Amphetamine and some of its analogues have been shown to be neurotoxic to dopamine (DA) and/or serotonin (5-HT) neurones in animals. For instance, after administration of methamphetamine, animals develop long-lasting decreases in brain DA and 5-HT axonal markers, including the neurotransmitters themselves (i.e. DA and 5-HT), and their transporter sites. Administration of amphetamine to animals, including non-human primates, results in decreases in DA levels and DA transporter densities. Furthermore, the popular recreational drug 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") has been shown to be neurotoxic to brain 5-HT neurones in animals and possibly humans (McCann et al. 1998a; Semple et al. 1999; Ricaurte et al. 2000; Reneman et al. 2001a, 2001b). Brain levels of DA and its metabolite homovanillic acid (HVA) are not reduced by low doses of MDMA but they are after higher doses, suggesting that while MDMA is more toxic to 5-HT than DA systems, it can also damage DA neurones (Commins et al. 1987; Taffe et al. 2001).

While the potential neurotoxic effects of MDMA on DA neurones have been extensively studied in animals, little is known about the dopaminergic effects of MDMA in the human brain. Only two studies have investigated the effects of MDMA on DA neurones by evaluating ce-

rebrospinal fluid HVA (McCann et al. 1994) and DA transporter densities using SPECT (Semple et al. 2000). HVA and DA transporter densities in MDMA users were comparable with control subjects. Furthermore, since tablets sold as ecstasy often contain not only MDMA, but also other compounds well known to cause DA neurotoxicity, such as amphetamine and methamphetamine, it is important to study its effects in the human brain directly. The Drugs Information and Monitoring System (DIMS), a unique project in The Netherlands to chemically monitor the ecstasy market, reported that in 1997 a substantial proportion (32%) of the street substances being marketed as ecstasy contained amphetamine or methamphetamine (Spruit et al. 1999), ranging from a low of 7 to 23% (on average 32 mg) per tablet (Konijn et al. 1997). Furthermore, a recent survey in the Netherlands investigated the prevalence of the combined use of ecstasy and amphetamine (the use of methamphetamine is uncommon in The Netherlands). It was found that in 26% of the 847 cases ecstasy was often or always combined with the use of amphetamine (Van de Wijngaart et al. 1997).

These observations press for further investigation of the effects of ecstasy, as well as the combined use of ecstasy and amphetamine, on brain DA neurones in human beings. The development of ^{123}iodine-2β-carbomethoxy-3β-(4-iodophenyl) tropane (β-CIT) has made it possible to image concomitantly DA and 5-HT transporters in the human brain using single photon emission computed tomography (SPECT) (Brücke et al. 1993). The DA transporter is a structural element of the DA neuron that is substantially decreased in animals given DA neurotoxins, such as methamphetamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Booij et al. 1997a; Villemagne et al. 1998).

This study compared the density of striatal [^{123}I]β-CIT labelled DA transporters in ecstasy users. Furthermore, the effects of combined ecstasy and amphetamine use on [^{123}I]β-CIT labelled DA transporters were analysed. Previous studies in rodents have demonstrated that drugs that bind to the 5-HT transporter enhance binding of [^{123}I]β-CIT to the DA transporter (Scheffel et al. 1994; Fujita et al. 1997), although this was not observed with other DA transporter ligands (Booij et al. 1998; Lavalaye et al. 2000). Therefore, striatal [^{123}I]β-CIT binding ratios in a group of combined ecstasy and amphetamine users were compared both with ecstasy users and healthy controls. This study was part of a larger [^{123}I]β-CIT investigation, in which the effects of ecstasy on the 5-HT system were studied in more detail (Reneman et al. 2001a, 2001b).

Materials and methods

Participants

Ecstasy users were compared with ecstasy-naive but drug using controls. Subjects were recruited with flyers distributed at venues associated with the "rave scene" in Amsterdam with the help of UNITY, an agency which provides harm reduction information and advice. Experimental and control groups were thus recruited from the same community sources. Subjects selected were matched for gender and age, between 18 and 45 years, otherwise healthy, and with no psychiatric history. Thirty-eight ecstasy users and 15 ecstasy-naive subjects were recruited. The 15 ecstasy-naive subjects ("controls") were healthy subjects with no self-reported prior use of ecstasy. Of the 38 ecstasy users, nine reported that they intentionally used amphetamine in the 3 months prior to this study ("Ecstasy+amphetamine users"; Table 1). Participants agreed to abstain from use of all psychoactive drugs for at least 3 weeks before the study, and were asked to undergo urine drug screening (with an enzyme-multiplied immunoassay for amphetamines, barbiturates, benzodiazepine metabolites, cocaine metabolite, opiates, and marijuana) before enrolment. After testing urine samples, exclusion criteria were: a positive drug screen; pregnancy; a severe medical or neuropsychiatric illness that precluded informed consent, and a lifetime psychiatric disorder. Subjects were interviewed with a structured computer assisted diagnostic psychiatric interview (Composite International Diagnostic Interview: CIDI, version 2.1) to screen for current axis I psychiatric diagnoses. The institutional Medical Ethics Committee approved the study. After complete description of the study to the subjects, written informed consent was obtained from all participants.

Imaging

For SPECT scanning the Strichmann Medical Equipment 810X tomographic system was used. This 12-detector single-slice scanner has a full-width at half-maximum (FWHM) resolution of approximately 7.5 mm. Each acquisition consisted of at least 15 slices (acquired in a 64×64 matrix), 3 min per slice, and with a slice distance of 5 mm. The energy window was set at 135–190 keV. Subjects lay in the supine position with the head aligned in parallel to the orbitomeatal line, and were positioned such that the scanning volume initially included the cerebellum. Acquisition was commenced 20 h after IV injection of approximately 140 MBq [^{123}I]β-CIT (radiolabelling as described by Neumeyer et al. 1991), a time when specific binding to the striatum is maximal and stable for up to 24 h following injection (Brücke et al. 1993; Laruelle et al. 1994). For analysis of [^{123}I]β-CIT binding, a standard template with regions of interest (ROIs) was constructed manually from MR images. For positioning we used these MR images as a guide. The template with a ROI for the left and right striatum, a brain region rich in DA transporters, was placed on three consecutive SPECT slices, demonstrating best visualisation of the striatum (Booij et al. 1997b). An additional template was constructed with a ROI for the cerebellum. An investigator unaware of the participant's history performed ROI analysis. The uptake in the cerebellum, presumed free from DA transporters, was used as a reference for background radioactivity (non-specific binding+free ligand). Striatal [^{123}I]β-CIT binding was calculated by dividing total binding in the striatum by binding in the cerebellum.

Statistics

Differences between the three groups with regard to demographic variables and other drug exposure were analysed using *ANOVA* (log transformed if necessary).

The difference in mean [^{123}I]β-CIT labelled DA transporters was analyzed using a general linear regression model. The starting model included group (three levels), gender (two levels), age (linear) and extent of previous cannabis use (linear; log transformed).

Pearson correlation analyses was performed between striatal [^{123}I]β-CIT binding ratios, and extent of previous MDMA and amphetamine use. Results were considered significant at $P<0.05$. Data were analysed using SPSS (SPSS Software Inc, Chicago, Ill., USA version 9.0).

Table 1 Demographics and comparison of striatal [^{123}I]β-CIT binding ratios between controls, ecstasy and ecstasy+amphetamine users[a]

	Controls	Ecstasy users	Ecstasy+amphetamine users
n	15	29	9
Age	26.1 (5.5)	26.1 (5.6)	22.1 (2.8)
Men/women	7/8	15/14	6/3
Ecstasy			
Duration of use (years)	–	5.1 (2.9)	4.4 (1.9)
Usual dose (tablets)	–	1.7 (0.7)	2.3 (0.7)
Lifetime dose (tablets)	–	324 (527)	358 (610)
Time since last tablet (months)	–	3.4 (4.6)	1.0 (0.3)
Amphetamine			
Amphetamine (no. times used past year)	–	–	47.5 (45.0)
Mean amphetamine dose (g)	–	–	0.41 (0.31)
Alcohol and other drugs			
Alcohol (units/week)	10.6 (9.8)	10.3 (8.6)	12.8 (13.9)
Tobacco (cigarettes/day)	10.0 (5.0)	8.5 (8.0)	12.7 (13.2)
Cannabis (no. joints last 3 months)	1.7 (3.1)	54.1 (107.0)	87.0 (102.8)[b]
SPECT[c]			
Estimated striatal [^{123}I]β-CIT binding ratios	7.47 (SE 0.39)	8.46 (SE 0.28)[d]	6.75 (SE 0.52)[e]

[a] Data are expressed in mean±SD values except for estimated [^{123}I]β-CIT binding ratios

[b] Significantly different from controls (log transformed: ANOVA F=5.7, df=35, P<0.01; post hoc comparison P<0.01)

[c] Estimated marginal means after correction for the difference in age distribution (evaluated at 25.6 years of age)

[d] Significantly different from controls (overall ANOVA F=4.9, df=2, P<0.01; post hoc comparison P=0.045)

[e] Significantly different from ecstasy users (overall ANOVA F=4.9, df=2, P<0.01; post hoc comparison P<0.01)

Results

Participants

Ecstasy+amphetamine users were younger than controls and sole ecstasy users, though this did not reach statistical significance (P=0.10). The groups were similar for gender distribution (Table 1).

The two ecstasy using groups were similar with regard to use of ecstasy, alcohol and other drugs, except for the use of amphetamine (Table 1). Ecstasy+amphetamine users indicated using more cannabis than controls (Table 1). Similar and only occasional use of LSD (lysergic acid diethylamide), "magic mushrooms" and cocaine was reported in both groups (data not shown).

SPECT imaging

Gender and extent of previous cannabis use were dropped from the starting model as they had no significant contribution (P=0.75 and 0.62, respectively). Age had a highly significant effect (P=0.000) on mean [^{123}I]β-CIT binding ratios and was therefore kept in the model. Comparisons of groups revealed that binding ratios were significantly higher in ecstasy users compared to controls (P=0.045). [^{123}I]β-CIT binding ratios were significantly lower in ecstasy+amphetamine users compared to sole ecstasy users (P=0.007), but not when compared to controls (P=0.275) (Table 1 and Fig. 1).

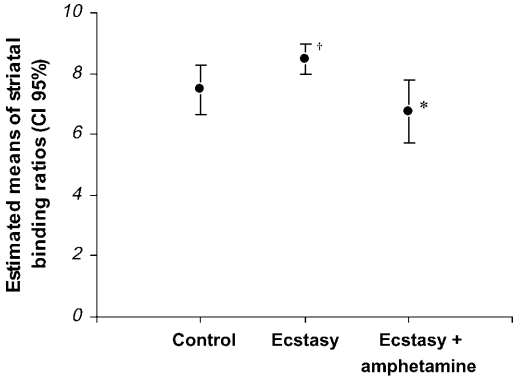

Fig. 1 Estimated marginal means of [^{123}I]β-CIT binding ratios with 95% CI after correction for the difference in age distribution (evaluated at 25.6 years of age) in each group. *Significantly different from ecstasy users. †Significantly different from controls

There was no correlation between the extent of previous ecstasy use and striatal [^{123}I]β-CIT binding (r=0.05, P=0.718). In addition, the association between striatal [^{123}I]β-CIT binding ratios and extent of previous amphetamine use did not reach statistical significance (n=9, r=–0.204, P=0.092).

Discussion

The results of this preliminary study suggest that while sole ecstasy use does not decrease striatal DA transporter

densities in human beings, the combined use of amphetamine and ecstasy may be associated with reduced striatal DA transporter densities.

To our knowledge, this is the first study reporting on the effects of amphetamine on striatal dopamine transporter densities in human brain. PET studies in amphetamine treated monkeys have shown reductions in striatal [^{18}F]fluoro-L-dopa uptake in vervet monkeys (Melega et al. 1996, 1997). Furthermore, studies on rat striatal DA system have established that chronic amphetamine exposure results in neurotoxicity characterised by decreases in dopamine levels and DA transporter densities, swollen nerve terminals and degenerated axons. Given the large body of evidence directly documenting the DA neurotoxic potential of amphetamine in rodents and non-human primates, our data provide preliminary evidence that recreational use of combined amphetamine and ecstasy use might be neurotoxic to DA neurones.

While few studies have investigated the effects of amphetamine in humans, recently a number of studies have reported on the effects of methamphetamine in the human brain. Like amphetamine, methamphetamine is an amphetamine derivative known to cause damage to DA neurones in animals treated with this drug. The present findings are in good agreement with these studies in methamphetamine users. For instance, using PET, re-ductions in DA terminal markers have been demonstrated in methamphetamine-treated monkeys and human methamphetamine users using the DA transporter ligands [^{11}C]WIN-35,248 and [^{11}C]d-threo-methylphenidate (McCann et al. 1998b; Villemagne et al. 1998). Reductions in DA transporter densities in methamphetamine users have been associated with motor and cognitive impairments (Volkow et al. 2001) and the severity of persistent psychiatric symptoms (Sekine et al. 2001).

The presently observed absence of neurotoxic effects of ecstasy on human DA neurones is in good agreement with previous animal studies which failed to find any damage to DA neurones following MDMA treatment (Steele et al. 1994; Green et al. 1995). It is also in agreement with a recent [^{123}I]β-CIT SPECT study (Semple et al. 2000), in which no reductions in striatal binding ratios were observed between ecstasy users and control subjects. McCann and colleagues (1994) also found no evidence of neurotoxic effects of MDMA on DA neurones in the human brain, since HVA levels in the cerebral spinal fluid of ecstasy users did not differ from controls.

The present finding of absence of neurotoxic effects of ecstasy on human DA is of interest for a number of reasons. First, our findings may indicate that the effects of drugs with known DA neurotoxic effects (such as amphetamine) in tablets sold as “ecstasy” in the Netherlands, may be too small to be neurotoxic. It cannot be excluded that the ecstasy tablets taken by our subjects did not contain amphetamine or methamphetamine. However, there is substantial support that a considerable proportion of the ecstasy users in this study must have, unintentionally, been exposed to amphetamine or methamphetamine, since 83% of the ecstasy users indicated having used ecstasy in 1997. In that particular year, 32% of all ecstasy drug samples (n=7009) tested by DIMS contained amphetamine or methamphetamine (on average 32 mg per tablet; Spruit et al. 1999). Second, interestingly, it has been suggested that a recent case of parkinsonism in a chronic human ecstasy user may have resulted from a neurotoxic effect of MDMA on the nigrostriatal dopaminergic neurones. It was suggested by Mintzer and co-workers (1999) that the parkinsonism may have resulted from amphetamine or methamphetamine present in ecstasy tablets taken by the patient. However, in the present study we did not observe evidence indicating loss of DA neurones in sole ecstasy users, whereas in the group of combined ecstasy and amphetamine users [^{123}I]β-CIT binding ratios were only approximately 12% lower when compared to ecstasy users. It is well known that parkinsonian signs do not occur before more than 50% of DA terminals are degenerated (Fearnley and Lees 1991). Therefore, we can now say that the parkinsonian signs were most probably not caused by use of ecstasy or the combined use of ecstasy with amphetamine or methamphetamine. Third, the present findings stress the importance to perform studies like these in well-matched groups, not only with respect to age and gender, but the use of other drugs as well. Ideally, two groups under study will differ only on one variable that is the focus of the study. In the present study, combined ecstasy and amphetamine users differed only on the use of ecstasy, suggesting that it is the use amphetamine, and not ecstasy, that may lead to loss of nigrostriatal neurones.

Previous studies in rodents have demonstrated increased binding of [^{123}I]β-CIT to the DA transporter short after administration of 5-HT reuptake inhibitors (Scheffel et al. 1994; Fujita et al. 1997). In line with this, we presently observed increased striatal binding of [^{123}I]β-CIT in ecstasy users when compared to controls. One possible explanation for this enhancement of binding is regulation of the DA transporter through inhibition of 5-HT uptake. It has been suggested that (rapid) regulation, such as post-translational regulation, is evoked by the inhibition of 5-HT uptake, for instance by MDMA. However, since ecstasy users were scanned at least 3 weeks after the last MDMA tablet taken, future experimental studies will have to find out what the long-term effects of 5-HT reuptake inhibitors (or MDMA) are on DA transporter densities. Whatever the underlying mechanism, the present findings clearly demonstrate the need for careful matching of study groups. To investigate the effects of amphetamine use on DA neurones in ecstasy users it is of crucial importance to compare DA transporter densities between ecstasy using subjects that only differ on the intentional use of amphetamine, rather than to control subjects, such as performed in the present study.

Displacement studies in animals and humans have shown that striatal uptake of β-CIT is associated with DA transporters (Laruelle et al. 1993, 1994). Moreover,

it has been shown that striatal [^{123}I]β-CIT binding, measured 24 h after injection, adequately reflects the density of DA transporters (Laruelle et al. 1994). When considered with results of previous SPECT studies directly documenting the validity of SPECT with [^{123}I]β-CIT for detecting MPTP-induced DA neurotoxicity, the present findings of reduced DA transporter densities in combined ecstasy and amphetamine users may be related to damage to striatal DA axons and axon terminals. It should be kept in mind, however, that it is an assumption that a decrease in DA transporter density directly reflects axonal loss. The presently observed decreases in DA transporter densities could also be related to a neuroadaptive process, not associated with actual DA nerve terminal degeneration.

Several potential limitations of the current study should be mentioned. The absence of effects of ecstasy use on human DA neurones may be related to the fact that we had to rely upon participant's report of drug abuse. As with all retrospective studies, it is impossible to determine exactly what drug at what dose was taken, and to ensure abstention from MDMA. Urine screening was performed to detect concealed recent MDMA use. In future studies, hair-sample analysis would be a useful way to assess more appropriately what drug was taken at what time and to ascertain previous use of MDMA. However, of particular relevance to this study is that we were able to get a fairly good impression on what an ecstasy tablet is likely to have contained in The Netherlands, because of the DIMS project. Second, there is a possibility that pre-existing differences between amphetamine users and amphetamine non-users underlie differences in DA transporter densities. People with low DA transporter densities may be predisposed to use amphetamine and to have low DA transporter densities. Future studies taking the recently described functional polymorphism in the promoter for the DA transporter gene into account, could be of interest (Heinz and Goldman 2000; Heinz et al. 2000). However, the two groups of amphetamine users were both regular users of ecstasy and differed only on the point that one subgroup had a history of amphetamine use. It is therefore unlikely that pre-existing differences or the use of other drugs than amphetamine should account for changes in striatal DA transporter densities. Considering the small sample size of the amphetamine group, the results of the present study should be interpreted as preliminary.

We conclude that the use of ecstasy seems not to be associated with dopaminergic neurotoxicity in humans. In contrast, the reported use of amphetamine in regular ecstasy users seems to be associated with toxic damage to dopaminergic neurones, in line with previous studies in animals. These initial observations suggest potential harmful effects of amphetamine on DA system.

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