

# Plasma concentrations of 5-HT, 5-HIAA, norepinephrine, epinephrine and dopamine in ecstasy users

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## Abstract

Recreational use of the synthetic methamphetamine derivative MDMA (3,4-methylenedioxymethamphetamine), the main constituent of the illegal drug "ecstasy", has increased dramatically in recent years. The reasons for ecstasy-associated cardiovascular complications like tachycardia, arrhythmias and hypertensive crises and psychiatric symptoms like psychotic episodes are not well understood. We have measured the plasma concentrations of 5-HIAA, 5-HT, norepinephrine, epinephrine and dopamine in 159 ecstasy users and controls. Ecstasy users showed elevated resting sympathetic activity, reflected in increased norepinephrine, epinephrine and dopamine levels. The levels of these catecholamines correlated positively with the cumulative dose and also with consumption during the last 30 days and 12 months. Although it is known that significant changes in 5-HT and 5-HIAA appear in the cerebrospinal fluid in ecstasy users, we could not detect alterations in serotonergic neurotransmitters in plasma in this large sample of subjects. Thus, in the drug-free interval, ecstasy users show lowered central serotonergic activity (lowered 5-HT and 5-HIAA concentrations in CSF) along with unchanged central noradrenergic and dopaminergic activity (HVA and MHPG unchanged in CSF) and elevated peripheral noradrenergic, dopaminergic and adrenergic activity along with unchanged peripheral serotonergic activity (plasma levels). We conclude, that the data presented here could argue for a noradrenergic hyperreactivity in the drug-free interval in ecstasy users resulting from previous ecstasy consumption. Also for an association with psychotic episodes and cardiovascular complications like tachycardia, arrhythmias.

## Introduction

Recreational use of the synthetic methamphetamine derivative MDMA, the main constituent of the illegal drug "ecstasy", has increased dramatically in recent years. It is primarily used by adolescents and young adults. Neurochemical studies on the degradation products of the serotonergic neurotransmitters in the cerebrospinal fluid (CSF) of ecstasy users have revealed a significant reduction of 5-hydroxyindoleacetic acid (5-HIAA) concentrations in the CSF (Ricaurte et al. 1988, McCann et al. 1994). The radioligand [<sup>11</sup>C]McN5652, which binds specifically to the serotonin transporter, showed reduced serotonin transporter binding in ecstasy users (Bolla et al. 1998). As part of a comprehensive study (Thomasius et al. 1998) we also measured 5-HT, 5-HIAA, norepinephrine, epinephrine and dopamine in plasma (using HPLC with electrochemical detection) in these subjects.

## Patients, Materials and Methods

Blood samples were taken after the subject had been lying down for 30 minutes, and all subjects had been ecstasy-free (verified by toxicological analysis of the urine) for at least 3 days. In addition, information given by the subjects about their ecstasy intake and toxicological analysis of the hair ecstasy content were compared. A concordance of 91.3% was found between the self-reported data and levels detected in hair. We investigated 159 subjects (68 female, 91 male). 107 of them were ecstasy users, and they were grouped according to cumulative dose:

- group **E1**, <100 tablets (n = 34);
- group **E2**, 100–499 tablets (n=42);
- group **E3**, 500–2500 tablets (n = 30).

The ecstasy users in our random sample had taken ecstasy for four days up to eight years (on average, 5.3 months). In 49% of the users, the time that had elapsed since the last use of ecstasy was one month or less. We also investigated

- 11 abstinent subjects (group **A**), and
- 41 subjects who used other drugs, but not ecstasy (group **P**).

## Results

The 5-HT concentration in plasma was not significantly different between the individual groups (using one-way analysis of variance; results are given here as mean ± S.D., pg/ml):

- group **E1** 8.56 ± 8.6 ;
- group **E2** 8.85 ± 9.01;
- group **E3** 10.93 ± 13.55;
- group **A** 7.57 ± 4.32;
- group **P** 7.46 ± 3.89.

Similarly, the 5-HIAA concentration in plasma did not differ significantly between the individual groups:

- group **E1** 22.09 ± 22.1;
- group **E2** 33.15 ± 25.45;
- group **E3** 25.39 ± 20.12;
- group **A** 20.34 ± 17.82;
- group **P** 25.4 ± 20.12.

There was no significant correlation between 5-HT or 5-HIAA and either the cumulative dose, the consumption in the last 30 days, or the consumption in the last 12 months (Spearman rank correlation test).

In contrast, epinephrine differed significantly between groups **E1** (59.1 ± 52.8) and **P** (33.21 ± 23.2; *p* < .05) and between groups **E1** and **A** (23.8 ± 12.7; *p* < .05).

There was no significant correlation between the epinephrine concentration and either the cumulative dose, the consumption in the last 30 days, or the consumption in the last 12 months. Norepinephrine in plasma differed significantly between groups

- E1** (346.7 ± 168) and **A** (189.8 ± 66.3; *p* < .05),
- between groups **E1** and **P** (201.8 ± 117.3; *p* < .05),
- between groups **E2** (349.3 ± 202) and **A** (*p* < .05) or
- between groups **E2** and **P** (*p* < .05).

Norepinephrine in plasma was correlated significantly with the cumulative dose (*r* = .26, *p* < .01), the consumption in the last 30 days (*r* = .30, *p* < .001) and the consumption in the last 12 months (*r* = .48, *p* < .001).

Dopamine in plasma differed significantly between groups **E2** (45.3 ± 42.9) and **P** (22.7 ± 37.7; *p* < .05), and plasma dopamine was correlated significantly with consumption in the last 12 months (*r* = .26, *p* < .01).

Norepinephrine correlated significantly with epinephrine (*r* = .51, *p* < .0001) and dopamine (*r* = .49, *p* < .001), but there was no correlation of norepinephrine with 5-HT (*r* = .09, *p* = .29) or 5-HIAA (*r* = .11, *p* < .17).

## Discussion

We have measured the plasma concentrations of 5-HIAA, 5-HT, norepinephrine, epinephrine and dopamine in 159 ecstasy users and controls. Although it is known that significant changes in 5-HT and 5-HIAA appear in the cerebrospinal fluid in ecstasy users, we could not detect alterations in serotonergic neurotransmitters in plasma in this large sample of subjects. In conclusion, plasma concentrations of 5-HT and 5-HIAA might not be used as a parameter of ecstasy consumption, in contrast to the CSF concentrations, and do not reflect the fall in 5-HT and 5-HIAA in the CSF. However, ecstasy users showed elevated resting sympathetic activity, reflected in increased norepinephrine, epinephrine and dopamine levels. The positive correlation of the levels of these catecholamines with the cumulative dose and also with consumption during the last 30 days and 12 months validates these results. Measurements of blood glucose and hema-

tocrit excluded the possibility that these differences could have been caused by hypoglycemia or hypovolemia. Previous investigations of the CSF concentrations of the dopamine and the norepinephrine metabolites HVA and MHPG in primates showed no changes due to MDMA intake (Ricaurte et al. 1988). Thus, in the drug-free interval, ecstasy users show lowered central serotonergic activity (lowered 5-HT and 5-HIAA concentrations in CSF) along with unchanged central noradrenergic and dopaminergic activity (HVA and MHPG unchanged in CSF) and elevated peripheral noradrenergic, dopaminergic and adrenergic activity along with unchanged peripheral serotonergic activity (plasma levels). Acute peripheral noradrenergic effects of ecstasy have already been described in animal models (Fitzgerald and Reid, 1994), with tachycardia, arrhythmias and facilitated vasoconstrictor responses to norepinephrine. This suggests that the peripheral sympathetic activation in the drug-free interval, which we have shown here, could also be a risk factor for ecstasy – associated cardiovascular complications like tachycardia, arrhythmias and hypertensive crises. The significance of increased sensitivity to stress associated with noradrenergic hyperactivity involving dopaminergic alterations in spontaneous recurrences of methamphetamine psychosis (flashbacks) was examined by Yui et al. (2000). Plasma monoamine metabolite levels were assayed in subjects with flashbacks who had been exposed to stressful events plus methamphetamine – induced frightening psychotic symptoms or frightening psychotic symptoms alone. The numbers of stressful events (mostly threatening events) and frightening psychotic symptoms were significantly higher in the flashbackers than in the nonflashbackers. Plasma norepinephrine levels were increased, implying that threatening stressful events, together with methamphetamine use, may induce noradrenergic hyperreactivity to subsequent mild stressors. Consequently, the data presented here could argue for a noradrenergic hyperreactivity in the drug-free interval resulting from previous ecstasy consumption, perhaps also for an association with psychotic episodes.

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