

Striatal serotonin is depleted in brain of a human MDMA (Ecstasy) user

Article abstract—The authors found that striatal levels of serotonin and those of its metabolite 5-hydroxyindoleacetic acid were severely depleted by 50 to 80% in brain of a chronic user of methylenedioxyamphetamine (MDMA) whereas concentrations of dopamine were within the normal control range. Our data suggest that MDMA exposure in the human can cause decreased tissue stores of serotonin and therefore some of the behavioral effects of this drug of abuse could be caused by massive release and depletion of brain serotonin.

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Recreational use of the amphetamine derivative methylenedioxyamphetamine (MDMA; “Ecstasy”) has become a major health issue. Animal data suggest that the mechanism of the acute behavioral action of this abused amphetamine derivative is probably related to the ability of MDMA to cause a massive and rapid release in brain of the neurotransmitter serotonin, whereas the dysphoric syndrome following drug withdrawal might be explained by a serotonin depletion.¹ To our knowledge, there are no data on the status of serotonin measured directly in autopsied brain of a confirmed MDMA user. We report that striatal (caudate, putamen, nucleus accumbens) levels of serotonin and those of its major metabolite 5-hydroxyindoleacetic acid are markedly decreased in brain of an MDMA user, proven by forensic hair analysis to have used the drug chronically.

Subjects and methods. *Brain material.* Autopsied brain was obtained from 11 neurologically normal subjects (30 ± 3 years, mean ± SE) and from one user of MDMA (male, age 26 years). At autopsy, one half-brain was placed into formalin fixative whereas the other half-brain was frozen at –80 °C for neurochemical analysis. The interval between death and freezing of the brain was 14 ± 2 hours for the controls and 21 hours for the MDMA user. Histopathologic analysis disclosed no abnormalities in brain (including substantia nigra) of the MDMA user or of the

control subjects. This study was approved by the University of Toronto Institutional Review Board.

MDMA user characteristics. The subject began use of MDMA, his primary drug of abuse, at age 17. The frequency of MDMA use was initially once a month and increased to 2 to 3 times a month. From age 23 to 26 he would use the drug 4 to 5 nights a week at rave clubs. This usually included a 3-day weekend binge at which 6 to 8 tablets of MDMA would be ingested. The day after the binge he would appear to his friends to be depressed and to have slow speech, movement, and reaction time. At age 26, during the last few months of life, he began to coabuse cocaine and heroin. He was considered to have at least normal intelligence and was not reported by his family or friends to have any movement disorder. At age 20 he sought psychiatric help for reactive depression but did not continue treatment. The suspected cause of death at age 26 was drug intoxication.

Forensic drug analyses. As shown in table 1, forensic drug analysis revealed the presence of MDMA in blood, brain (occipital cortex), and in the four available one-half inch sequential hair segments (representative of approximately the last 4 months of life). This indicates that the subject had used MDMA both acutely and chronically. A lower concentration of methylenedioxyamphetamine (MDA), considered to be a metabolite of MDMA,² was also observed in all samples with the exception of hair segment 1 (closest to the root ball). Drug analyses also disclosed the presence of cocaine or its metabolite benzoylecgonine in blood, brain, and hair samples, and morphine in blood and brain, indicating that the subject had used cocaine both chronically and acutely, and opiates acutely. Methamphetamine and amphetamine were not detected in any samples.

Neurochemical methods. Levels of monoamine neurotransmitters and metabolites were determined by high pressure liquid chromatography with electrochemical detection.³ No statistically significant correlations (Pearson) were observed between postmortem times and levels of the monoamine neurotransmitters or metabolites in the control subjects.

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Table 1 Concentrations of drugs of abuse or metabolites in blood, brain, and sequential hair segments of a human methylenedioxymethamphetamine (MDMA) user

Drug	Femoral blood ($\mu\text{g/mL}$)	Occipital cortex (ng/g tissue)	Sequential one-half inch hair segments (ng/mg)			
			Segment 1	Segment 2	Segment 3	Segment 4
MDMA	4.40	986	11.7	20.3	23.7	40.6
MDA	0.08	194	ND	3.3	3.0	4.1
Cocaine	0.28	350	11.7	18.9	18	15.6
BZE	2.54	1864	ND	ND	ND	ND
Morphine	0.36	232	ND	ND	ND	ND

No methamphetamine, amphetamine, or 6-acetylmorphine was detected in any specimen.

MDA = methylenedioxyamphetamine; BZE = benzoylecgonine (cocaine metabolite); ND = not detected.

Results. As shown in table 2, striatal concentrations of serotonin and of its metabolite 5-hydroxyindoleacetic acid were decreased by 50 to 80% in brain of the MDMA user as compared with those of the control subjects. Levels of dopamine and those of its major metabolites 3-methoxytyramine and homovanillic acid were within the range of the control values with the exception of increased (by 45%) homovanillic acid in the putamen of the MDMA user.

Discussion. Our major finding is that striatal concentrations of serotonin and those of its major metabolite are severely decreased in brain of a human user of MDMA. These data are consistent with previous reports of decreased levels of 5-hydroxyindoleacetic acid in CSF of some chronic MDMA users.⁴

The MDMA user in our study used the drug both chronically (over a 9-year period) and, as indicated by the presence of the drug in blood and brain, acutely. As animal studies indicate that MDMA can cause release of serotonin from its nerve endings and, in high doses, produce a long-lasting decrement in serotonin nerve terminal markers,¹ the striatal serotonin depletion could have been due to toxic damage to striatal serotonin nerve terminals or acute, reversible depletion of neurotransmitter stores. Further study will be required to assess whether decreased serotonin in brain of the MDMA

user was accompanied by actual loss of serotonergic nerve terminals. Irrespective of the cause of the reduction, our data provide the first demonstration that doses of MDMA taken by humans are in fact sufficient to cause actual depletion of tissue stores of serotonin and suggest that some of the behavioral effects during drug taking and withdrawal could be due to massive release and depletion of the neurotransmitter. Animal data indicate that MDMA causes release of both serotonin and dopamine in the striatum, but with the magnitude of serotonin release being more marked at lower doses of the drug.⁵ In this respect, our data suggest that recreational doses of MDMA, unlike those of methamphetamine,⁶ might not cause sufficient release of dopamine to cause depletion of stores of the neurotransmitter in the striatal subdivisions of the caudate and putamen; however, the observation of a moderate dopamine reduction (by 47%) in the nucleus accumbens allows for the possibility that this limbic striatal subdivision might be more sensitive to the dopamine-releasing action of the drug.

A potential confound of our investigation is that although the subject of our study had used MDMA as the primary drug of abuse for 9 years, he had also used other drugs of abuse—namely, cocaine and heroin—which might have direct effects on serotonin

Table 2 Striatal concentrations of dopamine, serotonin, and metabolites in a human methylenedioxymethamphetamine (MDMA) user

Substance	Caudate		Putamen		Nucleus accumbens	
	Controls	MDMA user	Controls	MDMA user	Controls	MDMA user
Dopamine	6.60 \pm 0.47	6.63	6.95 \pm 0.51	6.04	2.22 \pm 0.27	1.18
HVA	6.46 \pm 0.54	12.1	9.71 \pm 0.83	14.1*	5.53 \pm 0.48	5.34
3-MT	2.05 \pm 0.14	3.35	2.57 \pm 0.22	2.97	1.70 \pm 0.13	1.55
Serotonin	0.30 \pm 0.07	0.07*	0.31 \pm 0.06	0.07*	0.40 \pm 0.05	0.20
5-HIAA	0.63 \pm 0.11	0.18*	0.90 \pm 0.09	0.19*	0.90 \pm 0.13	0.36

Values (ng/mg tissue) represent \pm SE of 11 subjects.

* Value outside of control range.

5-HIAA = 5-hydroxyindoleacetic acid; 3-MT = 3-methoxytyramine; HVA = homovanillic acid.

neurons or influence the action of MDMA on monoaminergic neurons (e.g., cocaine blockade of MDMA uptake). Although this possibility cannot be ruled out, it should be noted that the subject's use of these drugs had been reported to have occurred only during the last few months (cocaine) or at most weeks (heroin) before death. Furthermore, striatal serotonin concentrations are normal in brain of users of cocaine⁷ and of users of heroin (Kish, unpublished observations) who had taken the drug chronically and had died shortly after taking the drug.

We recognize that conclusions based on a single case can only be tentative. However, our limited data, which must be confirmed in a representative number of subjects, suggest that depletion of serotonin might occur in brain of some users of the drug and therefore therapeutic efforts to normalize levels of the neurotransmitter might address some of the behavioral problems occurring during drug withdrawal.

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Disease progression in sporadic inclusion body myositis: Observations in 78 patients

Article abstract—Functional decline for each decade at symptom onset and need for cane, walker, or wheelchair were assessed in 78 biopsy-proved patients with sporadic inclusion body myositis. Patients with disease onset between 40 and 59 years used a walker after 10.2 ± 5.8 years, whereas those with disease onset between 60 and 79 years used a walker after 5.7 ± 5.0 years ($p = 0.05$). Because patients progress faster to disability when symptoms begin after the age of 60, age at disease onset may define patient subsets for stratification in clinical trials.

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Sporadic inclusion body myositis (s-IBM) is a common inflammatory myopathy, contracted at or older than the age of 50 years, that causes proximal and distal muscle weakness.^{1–4} The disease is slowly but relentlessly progressive, leading eventually to wheelchair confinement. Although some immunomodulating therapies may exert transient and mild benefits, there is no effective treatment for s-IBM. The natural history of the disease and the expected rate of functional decline over time remain unknown. This information is needed not only to advise patients but also to design experimental therapeutic drug trials. In this study we assessed disease progression in 78 patients by examining their functional decline according to the age of symptom onset.

Methods. *Patients.* Questionnaires were mailed to 92 patients with clinical and histologic confirmation of definite s-IBM⁴ who were studied at the neuromuscular diseases section of the NIH during the past 10 years and who did not have a known preexisting cognitive impairment. The survey requests the age at which symptoms appeared and the age at which the patient began using a cane, walker, or wheelchair. These discrete landmarks were used to assess the stages of functional decline and disease progression.

Functional decline. The data extracted from the surveys were recorded in a database set up in FileMaker Pro (Santa Clara, CA), which is designed to calculate the elapsed time period that patients progressed from the use of one assistive device to the next. The profile curve of a modified survival analysis was plotted according to the decade of disease onset and first presentation. The following four decades of symptom onset were used as artificial age divisions: 40s, covering age of symptom onset between 40 and 49 years; 50s, for onset between 50 and 59 years; 60s, for onset between 60 and 69 years; and 70s, for onset between 70 and 79 years. Two patients with disease onset younger than age 40 were grouped within the 40s age group.

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