Psychopharmacology (1998) 136 : 390–393

ORIGINAL INVESTIGATION

Stuart Brody · Clemens Krause
Ralf Veit · Harald Rau

Cardiovascular autonomic dysregulation in users of MDMA ("Ecstasy")

Received: 1 August 1997/Final version: 16 October 1997

Abstract The present study examined resting heart rate variability (HRV; an index of parasympathetic tone) and heart rate response to the Valsalva maneuver (Valsalva ratio; an index of overall autonomic responsiveness) in 12 repeat users of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"), and a matched comparison group of presumed nonusers. HRV and Valsalva ratio were smaller in users than in controls. Three out of 12 MDMA users but no controls had Valsalva ratios below 1.50, the cut-off for autonomic dysfunction. In several users, there was a total absence of post-Valsalva release bradycardia. All MDMA users were polydrug users. Parasympathetic cardiovascular tone appears impaired in repeat MDMA users, although the ubiquitous problems in such epidemiologic designs (including lack of testing before the first use of the drug and confounding with use of other drugs) preclude definitive causal interpretations.

Key words 3,4-Methylenedioxymethamphetamine (MDMA) · Heart rate variability · Valsalva maneuver · Parasympathetic nervous system

Introduction

In recent years, 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") has become popular as a recreational drug. MDMA is chemically related to amphetamine and psychedelics such as mescaline, but with effects which are different from those two categories of substances (Gouzoulis et al. 1993). A review of the pharmacology of MDMA (Green et al. 1995) cited case reports of toxicity and death associated with MDMA use, but noted that in many cases polydrug use was involved, as well as dehydration and other factors which likely exacerbated any pharmacological effects. MDMA has also been associated with hyperthermia, hyperactivity, hepatotoxicity, hypertension, and arrhythmias, and concerns have been raised about the drug causing damage to central serotonergic neurons (Ricuarte et al. 1985). Green et al. (1995) noted the commonality of impurity in illegal drugs and also noted that reports of psychiatric complications following MDMA use may be attributable to the use of MDMA by persons already at high risk for such complications.

MDMA induced dysrhythmias in seven of 11 rat isolated perfused heart preparations. The tachycardia induced by MDMA was blocked by both the beta-blocker propranolol and the neuronal uptake inhibitor desipramine (Fitzgerald and Reid 1994). In rats, MDMA in conjunction with elevated ambient temperatures produced increased metabolic rate and vasoconstriction (as well as dysrhythmias; Gordon et al. 1991).

In the course of conducting a study on the effects of psychological and autonomic stress on intraocular pressure (Brody et al., submitted), we obtained unusual results of autonomic tests (lack of bradycardia during the release phase of the Valsalva maneuver) in two seemingly healthy young people. Careful questioning based on clinical suspicion led to the subjects reporting repeated use of MDMA (although not within 3 days of testing). This led to our recruiting subjects who were admitted ecstasy users, for a separate comparison with the presumed nonusers in the rest of the original study sample.

The Valsalva maneuver is one of the most common autonomic tests, and stimulates both sympathetic and

S. Brody (✉)
1223 Wilshire Blvd, Suite 677,
Santa Monica, CA 90403, USA
e-mail: stuart.brody@uni-tuebingen.de

S. Brody · C. Krause · R. Veit · H. Rau
Institute of Medical Psychology and Behavioral Neurobiology,
Eberhard-Karls University of Tübingen,
Tübingen, Germany

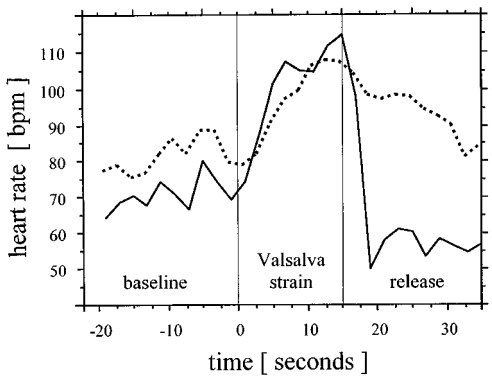

Fig. 1 Heart rate response to the Valsalva maneuver in one MDMA user (*dotted line*) and one control subject (*solid line*)

parasympathetic branches of the autonomic nervous system and also has mechanical effects on blood pressure and indirectly heart rate (Ravits et al. 1996). The reduced cardiac output and hypotension during the strain phase of Valsalva produces reflex-mediated tachycardia and peripheral vasoconstriction. After release, the increased cardiac output encounters the constricted vasculature, raising blood pressure and decreasing heart rate. In Fig. 1, the solid line depicts the heart rate response to the Valsalva maneuver for one of the control subjects (presumed nonuser of MDMA). The heart rate responses, particularly the overshoot portion of the release phase, are mediated by the baroreceptors (Piha 1993) and their vagal connections.

Heart rate variability (HRV) is a measure of vagal parasympathetic activity, and is usually assessed by the standard deviation of heart rate (or interbeat interval) at rest. HRV is inversely associated with several risk factors for coronary artery disease (Kristal-Boneh et al. 1995), and has been shown to be predictive (inversely) of mortality following cardiac arrest as well as in controls (Dougherty and Burr 1992).

Materials and methods

Subjects

Twelve MDMA users [eight female, mean age 25.3 (range 18–31), weekly alcohol consumption mean 227 g, 11 cigarette smokers, body mass index (kg/m^2) mean 22.3] were recruited through word of mouth (snowballing) among adherents of the local "techno scene", and were paid for participation. The 12 controls were presumed nonusers matched for sex distribution (eight female), age (mean 25.3; range 22–38), weekly alcohol use, cigarette smoking status, minutes of exercise per week, and body mass index. The controls were also paid for participation.

Questionnaires

The 12 MDMA users completed the German version of the Eysenck Personality Questionnaire (EPQ; Eysenck 1974) and our own questionnaires on drug use. The drug use questionnaire covered duration and frequency of MDMA use, and ever use of LSD, botanical hallucinogens, amphetamines, heroin, cocaine, barbiturates, phencyclidine, ether, nitrous oxide, ketamine, amyl nitrite, chlorpromazine or fluoxetine. The questionnaire also inquired about ever use of "KLZ" (an imaginary drug included as a check for false endorsement) and questions on whether there had ever been an experience of cardiovascular symptoms following MDMA use. The controls also completed the EPQ but their supplementary questionnaire, which included items on alcohol and cigarette use, lacked items on drug use. BMI was calculated from self-reported height and laboratory measured weight. For all subjects, substance use history was by self-report only. Although biochemical verification would have been desirable, none of the users scored above four on the Lie (social desirability) scale of the EPQ, and the pool of potential controls had already excluded subjects scoring above that cutoff for that form of biased self-report (Eysenck 1974).

Cardiovascular measures

Resting blood pressure was measured thrice with an automated Riva-Rocci brachial cuff (BOSO Digimat), and the median was used for analysis. Ag/AgCl electrodes were attached to positions on the thorax and the electrocardiogram signal was filtered (high frequency cut-off of 30 Hz, time constant of 0.3 s) digitized at 1000 Hz, and delivered to a computer for off-line calculation of HR (from R-R intervals with an accuracy of 1 ms) and for statistical analysis. The first beat's heart rate value from each series was dropped. The standard deviation of heart rate over 5 min was the HRV measure.

In the Valsalva maneuver, subjects blew into a tube with a slight leak to require continuous blowing, to produce a pressure in an autonomic manometer of 40 mmHg for 20 s, and the Valsalva ratio was calculated as the maximum interval between R-waves divided by the minimum R-R interval during the blowing or strain phase and the 20 s afterward (Levin 1966). Two Valsalva maneuvers (separated by a 5-min rest period) were performed, with the greater value used for analyses.

Procedure

The subjects were examined in a quiet laboratory in the Institute of Medical Psychology at the University of Tübingen. All subjects gave informed consent prior to participation, and the experiment was conducted in accordance with the Declaration of Helsinki, and approved by the University human subjects committee. Subjects were not required to abstain from food before testing, but no MDMA was taken for 6 days before testing, and no smoking was allowed during the laboratory session. Subjects sat in a comfortable chair (at 2 or 4 p.m.) and after electrocardiographic electrodes were attached, blood pressure was measured, and a 5-min rest period followed. The Valsalva maneuver was performed twice, and for technical reasons, the subjects upper torsos were rotated during the maneuver. After a 5-min break, resting HRV was measured for 5 min, and subjects completed questionnaires in private and sealed them in an envelope.

Results

Among users, the mean frequency of ecstasy use over the preceding 6 months was slightly less than once weekly (range once per 8 months to 20 times monthly), and the mean time since first use was 4 years (range 1.5–7 years). All users had also used marijuana and

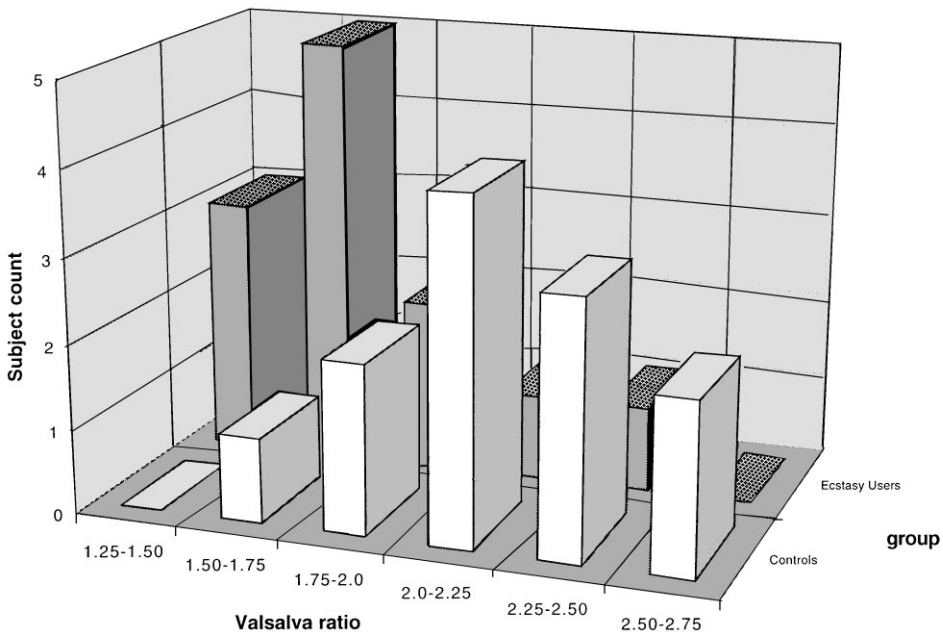

Fig. 2 Frequency distribution of subjects Valsalva ratios as a function of MDMA use status. □ Controls, ■ ecstasy users

LSD and botanical hallucinogens and amphetamines, all but one of the users had used cocaine, half had used amyl nitrite, and eight tried heroin (none reported use of fluoxetine, chlorpromazine, barbiturates, phencyclidine, ether, ketamine, or the imaginary "KLZ"). Eight reported having experienced both tachycardia and circulatory problems while using MDMA.

The Valsalva ratio was also significantly ($t = 4.5$, $P = 0.0002$) smaller in users than in controls (mean 1.7 versus 2.2). Three users but no controls had Valsalva ratios of less than 1.50 (chi-square = 3.4, $P = 0.06$; likelihood ratio 4.6, $P = 0.03$), the cut-off for autonomic dysfunction (Levin 1966). In addition, five out of 12 users and no controls had Valsalva ratios between 1.50 and 1.70, making for a total of eight users and no controls having defective or marginal Valsalva ratios (chi-square = 12.0, $P = 0.0005$; likelihood ratio = 15.3, $P = 0.00009$). The dotted line in Fig. 1 depicts the heart rate response of a representative ecstasy user to the Valsalva maneuver. Note (in contrast to the representative control's normal Valsalva with the solid line) the failure to exhibit post-release bradycardia and smaller overall range. Figure 2 displays the distribution of Valsalva ratios as a function of ecstasy use status.

HRV was significantly ($t = 3.06$, $P = 0.006$) smaller in users than in controls (mean 4.15 versus 6.0). Only three users, compared to nine controls, had HRV of at least 5.0 bpm (chi-square = 6.0, $P = 0.014$; likelihood ratio 6.3, $P = 0.014$).

The two dependent variables are related: HRV and Valsalva ratio were correlated ($r = 0.55$, $P = 0.005$). Resting heart rate (mean 81 versus 68; $t = 3.8$, $P < 0.001$) and resting systolic blood pressure (114 versus 106; $t = 2.09$, $P = 0.05$), but not resting diastolic blood pressure, were greater in users than in controls. The trend toward users having higher EPQ extraversion and lower EPQ neuroticism scores narrowly failed to achieve significance.

Discussion

Compared to matched controls, seemingly healthy users of MDMA (ecstasy) exhibited cardiovascular signs of autonomic dysregulation. They had lower HRV (a vagal index of parasympathetic tone), smaller Valsalva ratios (three of 12 below the 1.50 level suggested as the cut-off for autonomic dysfunction (Levin 1966), and an additional five out of 12 users but no controls evidencing marginal autonomic function as indexed by Valsalva ratios between 1.50 and 1.70), and often an absence of post-release bradycardia (another sign of parasympathetic dysfunction). The smaller Valsalva ratios obtained in users were comparable to those found in diabetics (Hartwig et al. 1994).

The controls were presumed nonusers, and it is possible that some of them had indeed used ecstasy. However, none of them showed impaired Valsalva ratios, and any users in the control group would likely result in an underestimate of the effect of ecstasy use in the present study. As with any "epidemiologic" style study (nonrandom assignment to groups, no pre-test), it cannot be safely inferred that ecstasy caused the autonomic dysregulation. It is important to note that the ecstasy users were experienced with many other recreational drugs, including cocaine and amphetamines, so it may have been these other substances or polypharmacy that contributed to autonomic dysregulation. In addition, it is possible that the autonomic dysregulation preceded ecstasy and other drug use, and may have been related to sensation seeking. Indeed, certain

behavior patterns in 6-year-olds predict the development of substance use in early adolescence and preadolescence (Masse and Tremblay 1997), and autonomic responsiveness in infancy and early childhood is related to emotional responsiveness to the environment (Fox 1989).

However, the present results are intriguing, and potentially of clinical importance given the recent reports of cardiac damage and pulmonary hypertension in users of fenfluramine (Connolly et al. 1997). Like MDMA (albeit far less intensively), fenfluramine is also an amphetamine derivative which increases serotonin levels through enhanced release and blocked reuptake. The reports of Connolly and colleagues were based on persons presenting with cardiovascular symptoms (and a likely history of obesity, given the indication for fenfluramine) who were a mean of 20 years older than our seemingly asymptomatic subjects.

Acknowledgement This study was supported by the German Research Society (DFG Ra 481/9-1).

References

Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, Schaff HV (1997) Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 337:581–588

Dougherty CM, Burr RL (1992) Comparison of heart rate variability in survivors and nonsurvivors of sudden cardiac arrest. Am J Cardiol 70:441–448

Eysenck HJ (1974) Eysenck Persönlichkeits Inventar. Verlag für Psychologie, Göttingen

Fitzgerald JL, Reid JJ (1994) Sympathomimetic actions of methylenedioxymethamphetamine in rat and rabbit isolated cardiovascular tissues. J Pharm Pharmacol 46:826–832

Fox NA (1989) Psychophysiological correlates of emotional reactivity during the first year of life. Dev Psychol 25:364–372

Gordon CJ, Watkinson WP, O'Callaghan JP, Miller DB (1991) Effects of 3,4-methylenedioxyethamphetamine on autonomic thermoregulatory responses of the rat. Pharmacol Biochem Behav 38:339–344

Gouzoulis E, von Bardeleben U, Rupp A, Kovar K-A, Hermle L (1993) Neuroendocrine and cardiovascular effects of MDE in healthy volunteers. Neuropsychopharmacology 8:187–193

Green AR, Cross AJ, Goodwin GM (1995) Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy"). Psychopharmacology 119:247–260

Hartwig MS, Hathaway DK, Cardoso SS, Gaber AO (1994) Reliability and validity of cardiovascular and vasomotor autonomic function tests. Diabetes Care 17:1433–1440

Kristal-Boneh E, Raifel M, Frrom P, Ribak J (1995) Heart rate variability in health and disease. Scand J Work Environ Health 21:85–95

Levin AB (1966) A simple test of cardiac function based upon the heart rate changes induced by the Valsalva maneuver. Am J Cardiol 18:90–99

Masse LC, Tremblay RE (1997) Behavior of boys in kindergarten and the onset of substance abuse during adolescence. Arch Gen Psychiatry 54:62–68

Piha SJ (1993) Cardiovascular responses to various autonomic tests in males and females. Clin Auton Res 3:15–20

Ravits J, Hallett M, Nilsson J, Polinsky R, Dambrosia J (1996) Electrophysiological tests of autonomic function in patients with idiopathic autonomic failure syndromes. Muscle Nerve 19:758–763

Ricaurte G, Bryan G, Strauss L, Seiden L, Schuster C (1985) Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. Science 229:986–988