RESEARCH UPDATE

national institutes of health **mdma** research controlled study of mdma's neurotoxic potential in humans

DR. GEORGE RICAURTE
AND DR. UNA MCCANN

IN ANIMALS, MDMA is known to damage brain serotonin (5-HT) neurons, and in non-human primates (monkeys), neurotoxic changes persist for greater than 12 months after the last dose of MDMA. Whether or not MDMA is also neurotoxic in humans has not been established. Since direct measurement of brain serotonin levels is not currently possible in living humans, "indirect" measures, thought to reflect brain serotonin activity, must be utilized to answer this question. One such indirect "biological" measure is the concentration of the major serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF). Alternatively, since serotonin is thought to be involved in the regulation of a number of normal behavioral functions, such as mood, anxiety, sleep, appetite, personality, pain, sexual behavior, and neuroendocrine regulation, measurements of these "behavioral" functions can also be used to determine whether brain serotonin systems are intact.

Two preliminary studies used measures of CSF 5-HIAA to test possible MDMA-induced serotonin injury in MDMA users[1,2]. One study found no changes in CSF 5-HIAA[1], while the second found an approximate 30% decrease of CSF 5-HIAA concentrations in MDMA users compared to control subjects[2]. Since a number of factors are know to influence CSF 5-HIAA (e.g., activity, diet, age, sex), and since neither of the two preliminary studies controlled these factors, it is perhaps not surprising that results from the two studies conflict.

In an effort to better define the potential neurotoxicity of MDMA to humans, the first controlled study to test for alterations in serotonin function on human MDMA users was conducted. Thirty MDMA users who had used MDMA in at least 25 separate occasions (Mean number of times used = 94.4 + 90.6; range 25-300) and 28 age- and sex-matched control subjects who had never used MDMA participated in the study. Both groups of subjects were allowed to have used other recreational drugs in the distant past, but agreed to refrain from all recreational drugs for at least two weeks prior to study participation. Exclusion criteria included any known neuropsychiatric or medical condition which might influence serotonin measurements. All subjects were admitted to a controlled inpatient setting over a five day period for measurement of biological and behavioral indices of brain function. These included: 1) concentrations of 5-HIAA in the CSF (as well as concentrations of other neurotransmitter metabolites); 2) neuroendocrine responses to L-tryptophan, the precursor to serotonin; 3) self-ratings of ischemic pain; 4) personality characteristics in which serotonin has been implicated (i.e., impulsivity and aggression); 5) sleep, using all-night polysomnograms.

MDMA subjects, as a group, were found to have lower levels of CSF 5-HIAA than controls (32% less). Female MDMA users, who, as a group had used more MDMA than their male counterparts (115 times versus 85 times), and who weighed less, yet generally took the same dose as males (100 to 150 mg), had greater reductions in CSF 5-HIAA than males. In addition, female MDMA users had reductions in CSF HVA, the major metabolite of the neurotransmitter, dopamine. Although not different from controls in their prolactin response to L-tryptophan or their response to ischemic pain, MDMA users had lower scores on personality measures of impulsivity and hostility (i.e., were less impulsive and hostile). MDMA users were also found to have less total sleep, with decreases due primarily to reductions in Stage 2 sleep [the most abundant sleep stage that occurs during the transition from "light" sleep (stage 1) to slow wave sleep (stages 3 and 4)]. (For further details, refer to the published manuscript in *Neuropsychopharmacology* 1994, 10(2):129-138).

The CSF findings suggest that 5-HT neurotoxicity may be a potential complication of recreational MDMA use, although converging lines of evidence and additional studies in greater numbers of MDMA users are needed before definitive conclusions can be reached. Differences in personality also support the notion that MDMA leads to long term alterations in brain serotonin function, although the direction of the personality changes (i.e., decreased impulsivity and hostility) are in the opposite direction than what would have been predicted from studies in impulsive and hostile patient populations. The absence of differences in pain and neuroendocrine measures could indicate that no differences exist, or could be an indication that the type of testing used was not specific or sensitive enough. Alternatively, it is possible that serotonin neurons involved in pain and neuroendocrine function are less susceptible to MDMA injury, or are capable of recovery. Additional controlled studies of MDMA-exposed individuals are planned to confirm and extend the present findings.

Individuals who have taken MDMA on 25 or more occasions and who are in general good health are being recruited. Studies will take place at the Johns Hopkins Bayview Medical Center in Baltimore, Maryland during a 5-day inpatient admission. Travel fees will be provided, and participants will receive financial compensation for time spent in the study. If you are interested in participating or learning more details about these studies, please contact Dr. George Ricaurte at (410) 550-0993 or Dr. Una D. McCann at (301) 402-2947, or e-mail gricaurt@welchlink.welch.jhu.edu. Some individuals who do not meet the criteria for study participation, but who have experienced neuropsychiatric changes following MDMA use will also be studied. Please contact the same investigators if you are interested in this option. •

1 Peroutka SJ, Pascoe N, Faull KF (1987): Monoamine metabolite in the cerebrospinal fluid of recreational users of 3,4-methelenedioxymethamphetamine (MDMA; "Ecstasy"). Res Commun Substance Abuse 8:125-138.

2 Ricaurte GA, Finnegan KT, Irwin I, Langston JW (1990): Aminergic metabolites in cerebrospinal fluid of humans previously exposed to MDMA: Preliminary observations. Ann NY Acad Sci 600:699-710.

Dr. George Ricaurte, Department of Neurology, Johns Hopkins School of Medicine, FSK Medical Center, 4940 Eastern Avenue, Building B, Room 122, Baltimore, MD 21224, e-mail address gricaurt@welchlink.welch.jhu.edu, and Dr. Una McCann, National Institutes of Health, National Institute of Mental Health, Building 10, Room 3N-212, 9000 Rockville Pike, Bethesda, MD 20892

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