commentary on article by ricaurte and colleagues

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THE RECENTLY PUBLISHED ARTICLE by Ricaurte and colleagues (J. Neurosci. 15: 5476-5485, 1995) describes the effects of MDMA ("Ecstasy") on various indices thought to reflect the integrity of serotonergic innervation in the brain. Both the rat and squirrel monkey were examined in this study. The conclusions reached by the authors are that the long term effects of MDMA cause a reorganization of serotonin innervation of the brain, effects which are repeatedly referred to as evidence of "serotonin neurotoxicity." While the actions of MDMA in the rat and primate brain at the high dosages employed in the study (at least 25 times the human dosage) may in fact reflect a toxic effect of this drug on serotonin pathways, other interpretations of the data are possible. For example, what Ricaurte and others have shown is, at high dosages, MDMA causes prolonged decreases in brain serotonin. This effect, per se, cannot be equated to destruction of serotonergin axons (i.e. bonafide serotonin neurotoxicity) because assessments of serotonin are only indicative of the presence of this transmitter in neurons, not the actual neuronal structures themselves. In other words, MDMA can decrease the level of serotonin without necessarily destroying serotonergic axons. An analogy would be draining water from a pipe without destroying the plumbing. The prolonged decreases in serotonin seen after high dosages of MDMA have not been associated with the classic evidence of neuronal destruction such as astrogliosis (O'Callaghan and Miller, 1993) or silver degeneration staining (Commins et al., 1987; Jensen et al., 1993). Moreover, retrograde transport studies, which could be used to assess whether serotonergic axons are still functional even when depleted of serotonin, have yet to be performed following exposure of rats or primates to MDMA.

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Despite the interpretive drawbacks associated with the present and previous papers on MDMA "neurotoxicity," the Ricaurte paper makes an important addition to the literature. In contrast to many previous studies, Ricaurte and colleagues have combined a qualitative examination of serotonin innervation with a quantitative analysis of serotonin content in the brain regions affected by MDMA. This serves to distinguish subjective impressions of serotonin innervation from actual quantitative changes on serotonin concentration. For example, while the pictures (published in the article) of serotonin innervation of the rat brain cortex appear to show a less than normal amount of serotonin staining one year after dosing, analysis of the serotonin content of this brain region shows that serotonin levels have returned to control. This is not unexpected given the qualitative (i.e. subjective) nature of serotonin immunohistochemistry as compared to quantitative analysis of serotonin levels. Thus, in the rat, no data is shown that indicates that there is decreased serotonin innervation one year after exposure to MDMA. No quantitative studies were conducted with the primate.

Future studies of the potential neurotoxic effects of MDMA and other substituted amphetamines would benefit from an analysis of indices known to reflect damage to central nervous system neurons in combination with an examination of traditional markers of serotonergic neurons. Such data would be highly useful in setting margins of safety for the therapeutic usage of these compounds. •

Fisher, C., Hatzidimitriou, G., Wios, J., Katz, J., and Ricaurte, G.: Reorganization of Ascending 5-HT Axon Projections in Animals Previously Exposed to the Recreational Drug 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy"). J. Neurosci. 15: 5476-5485, 1995.

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Jensen, K.F., Haykal-Coates, N., Olin, J.K., O'Callaghan, J.P., Miller, D.B., and de Olmos, J.: Mapping toxicant-induced nervous system damage with a cupric silver stain. A quantitative analysis of neural degeneration induced by 3,4-methylenedioxymethamphetamine (MDMA). In: Assessing Neurotoxicity of Drugs of Abuse. Erinoff L, Ed., National Institute on Drug Abuse Monograph 136, pp 133-154, Washington, D.C., US Government Printing Office, 1993.

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The opinions expressed in this commentary are solely those of the author and not of the U.S. Environmental Protection Agency.