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LETTER TO THE EDITOR

Response☆

In their letter (see pg. 333), McCann and Ricaurte (2001) raise objections to a Neuropsychopharmacology editorial (Lieberman and Aghajanian, 1999) pertaining to the article by Vollenweider et al. (1998) and a subsequent letter-to-the-editor by Gijsman et al. (1999). Our editorial stated, ". . . the data do not support the view that single oral doses at 1.7 mg/kg of MDMA are likely to produce damage to serotonin terminals in humans" (Lieberman and Aghajanian, 1999). McCann and Ricaurte argue that if interspecies dose scaling is applied to the human dose that was used by Vollenweider et al. (1999) (i.e., 1.7 mg/kg), this would be within the range of the "known" single oral neurotoxic dose of MDMA in the monkey (5.0 mg/kg). It should be noted, however, that our editorial was aimed at the issue, of whether it had actually been demonstrated that a single 5.0 mg dose of MDMA was in fact neurotoxic in the monkey.

The salient passage from our editorial was as follows: "The key study that the authors [i.e., Gijsman et al., 1999] cite to support their point is that of Ricaurte et al. 1988), who reported that a single 5 mg/kg dose of MDMA produced long-term damage (assessed at two weeks) to the serotonin system in non-human primates. An examination of these data, however, indicate that while multiple oral doses of 5 mg/kg MDMA produced a large depletion of serotonin in all regions examined, a single oral dose produced no change in the frontal cortex, hippocampus, putamen, or caudate, and only a small change in the thalamus and hypothalamus. The absence of depletion in the frontal cortex and caudate by a single dose is particularly important because these regions receive the type of fine fiber afferents from the dorsal raphe nucleus that have been shown to be most sensitive to MDMA neurotoxicity (O'Hearn et al. 1988; Wilson et al. 1989)". Given these equivocal results, which were obtained with an "n" of three, it remains unclear as to whether a single dose of 5 mg/kg of MDMA is in fact neurotoxic in the monkey. One would wish for more extensive dose-response data to determine the threshold for clear-cut neurotoxicity of single oral doses of MDMA in the monkey, especially in regions that are known to be vulnerable after chronic administration (e.g., frontal cortex and striatum). However, in the absence of such data, it would seem premature to conclude that a single oral dose of 1.7 mg/kg is likely to be neurotoxic in humans.

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REFERENCES

Gijsman HJ, Verkes RJ, van Gervan JMA, Cohen AF (1999): MDMA study. Neuropsychopharmacology 21:597

Lieberman JA and Aghajanian GK (1999): Caveat Emptor: Researcher Beware. Neuropsychopharmacology 21: 471–473

McCann UD, Ricaurte GA (2001): Caveat Emptor: Editors Beware. Neuropsychopharmacology 24:333–334

O'Hearn E, Battaglia G, De Souza EB, Kuhar MJ, Molliver ME (1988): Methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA) cause selective ablation of serotonergic axon terminals in forebrain: Immunocytochemical evidence for neurotoxicity. J Neurosci 8:2788–2803

Ricaurte GA, DeLanney LE, Irwin I, Langston JW (1988): Toxic effects of 3,4-methylenedioxymethamphetamine

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on central serotonergic neurons in the primate: Importance of route and frequency of drug administration. Brain Res 446:165–168

Vollenweider FX, Gamma A, Liechti M, Huber T (1999): Is a single dose of MDMA harmless? Neuropsychopharmacology 21:598–600

Vollenweider FX, Gamma A, Liechti M, Huber T (1998): Psychological and cardiovascular effects and short-term sequelae of MDMA ("Ecstasy") in MDMA-naïve healthy volunteers. Neuropsychopharmacology 19:241–251

Wilson MA, Ricaurte GA, Molliver ME (1989): Distinct morphologic classes of serotonergic axons in primates exhibit differential vulnerability to the psychotropic drug 3,4 methenedioxymethamphetamine. Neuroscience 28:121–137

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