Published in final edited form as:
Biol Psychiatry. 2010 December 15; 68(12): 1082–1083. doi:10.1016/j.biopsych.2010.10.020.

Is ecstasy an empathogen?

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Bedi et al., (1) conducted an acute, double-blind challenge study with two doses of MDMA (1.5 mg/kg and 0.75 mg/kg), methamphetamine and placebo in 21 adults using a crossover design. All subjects had reported a prior history of taking MDMA as a recreational drug. The study adds to the longstanding effort to evaluate the potential "empathogenic" effects of MDMA. Outcomes included subjective reports on visual analog scales on feeling *sociable*, *playful*, *loving* and *lonely*. Change in self-reported friendliness on the Profile of Mood States (POMS) was also measured. In addition, subjects were asked to evaluate complex emotions such as fear, anger, happiness, sadness in response to video presentations of changing facial expressions – either full face or just the eye region. Finally, the study included presentation of brief vocal clips; subjects were asked to judge whether the voice communicated emotional tones such as happiness, sadness, anger or fearfulness.

Although no specific outcome was nominated as *primary*, the authors were careful to correct for multiple comparisons. Compared to placebo, the 1.5 mg/kg dose of MDMA showed a significantly higher score on the *friendliness* scale of the POMS and on the *playful* and *loving* visual analog scales. The 1.5 mg/kg MDMA condition also showed decreased accuracy on the identification of fearful facial expressions. Contrary to the authors' expectation, methamphetamine produced significantly higher scores on the *sociable* and *playful* visual analog scales. We note that these observations are not inconsistent with the stimulant and euphoriant properties of methamphetamine.

The neuropharmacology of MDMA should be considered in the context of other serotonergic enhancers including the precursor tryptophan, selective serotonin reuptake inhibitors (SSRIs), and the serotonin releasing agent, fenfluramine. Although these agents act through a variety of mechanisms, all increase extracellular serotonin, resulting in increased stimulation across a broad range of serotonin receptor subtypes. At typical doses for each of these compounds, neurochemical studies suggest a continuum of serotonergic enhancement from tryptophan through the SSRIs, fenfluramine and MDMA having the largest effect. Pharmacodynamically, the picture is more complex as the relative importance of the stimulatory effects on any specific receptor subtype in a particular neuroanatomic region changes as serotonin levels rise throughout the brain. Effects at 5-HT2A and 5-HT1A receptors appear to be of particular importance in the pharmacology of MDMA. Moreover,

Dr. Scahill has served as a consultant to NeuroSearch, Pfizer, Shire, Boehringer-Ingelheim, and received research funding from Seaside Therapeutics and Shire. Dr. Anderson reports no biomedical financial interests or potential conflicts of interest.

compared to methamphetamine, MDMA produces far less dopaminergic receptor stimulation (2).

Human and animal studies show that serotonin enhancers can have pro-social effects. In humans, for example, tryptophan is reported to decrease quarrelsome behaviors, increase agreeable behaviors and perceived affability in roommates (3). Acute and chronic exposure to SRRIs have been reported to improve processing of social cues, increase cooperation and affiliation, and decrease hostility (4). As noted by Bedi and colleagues (1), several studies have consistently observed self-reported prosocial effects of MDMA on the related qualities of friendliness, extroversion, closeness and amicability. By studying the effects of MDMA on self-reported sociability, and friendliness as well as performance on emotion recognition tasks, the investigators hoped to characterize the potential benefits of MDMA on social cognition and empathy.

As suggested in the title of the paper, MDMA has been labeled an “empathogen.” To be sure, empathy is a critical concept when considering the action of MDMA and when interpreting the findings of Bedi et al. (1). The simplest definition of empathy is the ability to share emotions with another person. However, the current discourse on empathy suggests that it incorporates two interacting elements: the recognition of emotions in others (cognitive component) as well as the actual experience of sharing emotion (5;6). Bedi et al (1) cite recent studies reporting benefit of MDMA-assisted psychotherapy in PTSD as evidence of the “empathogenic” effects of MDMA. On balance, the findings presented in the Bedi et al. (1) study indicate that although MDMA might enhance the emotional component of empathy, it appears to cause impairment in cognitve component.

The potential relevance of these findings to autism, a disorder characterized by profound delay in social relatedness is intriguing – but unlikely. First, even if additional study shows that MDMA has positive effects on the emotional component of empathy, accumulating evidence suggests that it is the cognitive aspects of empathy that are deficient in autism. By contrast, the emotional component appears less impaired (7;8). This insight concerning the ability of individuals with autism to feel the emotions of others is relatively recent. It parallels the emerging evidence that individuals with autism do not display a reduced sensitivity to painful stimulation, but rather have an altered expression of the sensation of pain (9) – suggesting that the obvious may not be true. Second, serotonin enhancing drugs such as fenfluramine and citalopram do not appear effective in autism (10). Third, although concern about the neurotoxicity of MDMA has declined based on accumulated evidence over the past decade, the potential for adverse effects should not be dismissed (11). This concern may be heightened in vulnerable populations such as individuals with autism. Finally, given that autism is characterized by decreased sensitivity to reading social cues, the finding that MDMA reduced the ability to detect fearful facial expression seems potentially counterproductive in this population. Thus, even setting aside possible safety concerns, MDMA (and perhaps other serotonin enhancing drugs) appear unlikely to be useful in autism.

Nonetheless, the challenge paradigm used in the study could be adapted and applied to subjects with high functioning autism to investigate effects of other promising compounds. The study model could be enhanced through the application of computer technology to present facial expression and eye tracking technology to evaluate facial scanning techniques. Future studies could combine promising compounds with cognitive training focused on improving reading faces and emotion recognition.

Acknowledgments

This work was supported in part by NIMH grant R01MH081148, L. Scahill PI and R01 MH083707, L. Scahill PI.

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