



HOT TOPICS

Better living through chemistry: MDMA's prosocial mechanism as a starting point for improved therapeutics

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MDMA, the once-demonized party drug still known as “ecstasy”, is racing toward FDA approval as a potentially powerful adjunct to psychotherapy for the treatment of PTSD. However, MDMA has abuse potential, and long term use is associated with a host of neurological, psychiatric and cardiovascular complications [1, 2]. Improving on MDMA to develop a safe, scalable treatment for millions of patients requires an understanding of the pharmacology and neural dynamics underlying MDMA's various effects. MDMA releases supraphysiological levels of serotonin (5-HT), dopamine (DA) and norepinephrine (NE) via actions on their respective reuptake transporters (SERT, DAT, and NET) [1, 2]. MDMA also stimulates release of hormones including oxytocin, vasopressin and cortisol [3]. Which among these neuromodulators, and where in the brain they might act to produce MDMA's hallmark feelings of openness, trust and social connection was unclear. Based on recent work in our lab [4], we hypothesized that 5-HT released by MDMA, specifically into the nucleus accumbens (NAc), could account for MDMA's prosocial effect but not its potential addictive properties.

We modeled the prosocial and acutely reinforcing effects of MDMA in mice and investigated the mechanism of these processes using brain-region specific pharmacology, transgenic manipulations, electrophysiology, and *in vivo* calcium imaging [2]. We found convergent evidence demonstrating that MDMA acts at SERT-containing 5-HT terminals within the NAc. This interaction was both necessary and sufficient to explain MDMA's prosocial effect, but not its nonsocial drug reward, which was instead mediated by DA signaling in the NAc. Electrophysiology experiments in acutely dissected brain slices showed that a brief application of MDMA could induce a long-term depression (LTD) of excitatory synaptic strength, suggesting a possible synaptic analog of MDMA's lasting therapeutic effect. This LTD required activation of the 5-HT1b receptor, was mimicked by d-fenfluramine, a selective 5-HT-releasing drug, and did not require oxytocin receptor activation. These electrophysiological findings directly matched results from our behavioral experiments. We predict that perhaps a 5-HTR1b agonist or even d-fenfluramine, in the context of psychotherapy, could produce beneficial subjective effects similar to MDMA while minimizing the addictive potential.

Recent preclinical work from other groups offers alternative hypotheses on the therapeutic mechanism of MDMA-assisted psychotherapy. First, MDMA disrupts fear memories in a widely used rodent model for PTSD, a paradigm that does not involve any particular social context [5]. Second, although available data from rodents and humans suggest that oxytocin and MDMA have distinct effects on social behavior [3], and oxytocin receptor

signaling is not required for MDMA's acute prosocial effects [2], oxytocin may be involved in longer term plasticity processes initiated by MDMA [6]. Finally, each study implicates different 5-HT receptor subtypes [2, 3, 5, 6], although it is unclear if any one subtype's activity can alone reproduce MDMA's therapeutic effect. Nevertheless, these preclinical findings on MDMA's mechanism of action are useful for making mechanistic predictions about novel approaches for human therapy and should inform mechanism-focused human trials.

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AUTHOR CONTRIBUTIONS

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ADDITIONAL INFORMATION

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