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How could MDMA (ecstasy) help anxiety disorders? A neurobiological rationale

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Abstract

Exposure therapy is known to be an effective treatment for anxiety disorders. Nevertheless, exposure is not used as much as it should be, and instead patients are often given supportive medications such as serotonin reuptake inhibitors (SSRIs) and benzodiazepines, which may even interfere with the extinction learning that is the aim of treatment. Given that randomized controlled trials are now investigating a few doses of ±3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') in combination with psychotherapy for treatment-resistant anxiety disorders, we would like to suggest the following three mechanisms for this potentially important new approach: 1) MDMA increases oxytocin levels, which may strengthen the therapeutic alliance; 2) MDMA increases ventromedial prefrontal activity and decreases amygdala activity, which may improve emotional regulation and decrease avoidance and 3) MDMA increases norepinephrine release and circulating cortisol levels, which may facilitate emotional engagement and enhance extinction of learned fear associations. Thus, MDMA has a combination of pharmacological effects that, in a therapeutic setting, could provide a balance of activating emotions while feeling safe and in control, as described in case reports of MDMA-augmented psychotherapy. Further clinical and preclinical studies of the therapeutic value of MDMA are indicated.

Key words

emotional enhancer; empathy; pharmaceutical; posttraumatic stress disorder (PTSD); psychiatry; translational neuroscience

Increased understanding of anxiety disorders suggests common principles and strategies of effective treatment (McNally, 2007). Here, we will focus on posttraumatic stress disorder (PTSD), a serious public health problem that has been extensively studied. PTSD is an anxiety disorder characterized by intrusive re-experiencing of the trauma coupled with efforts to avoid triggers or reminders and excessive arousal. PTSD symptoms occur routinely following major traumatic events, and through natural recovery the intensity and frequency of the stress response declines within a few months in most people. Rates of chronic PTSD are especially high (over 20%) in survivors of intrapersonal traumas such as rape, torture and combat (Charuvastra, *et al*., 2008), resulting in life-restricting anxiety that can persist for years.

Fear conditioning and extinction has provided a successful model for the development and treatment of anxiety disorders (McNally, 2007; Myers, *et al*., 2007). Extinction is not the same as erasure of fear memories; rather, extinction is also an essential form of emotional learning elicited by repeated exposure to safe but fear evoking triggers in the absence of harmful consequences (Myers, *et al*., 2007). Inhibition of fear responses and improved emotional regulation is demonstrated in a range of anxiety disorders following extinction-based exposure therapy (McNally, 2007).

Most PTSD patients receiving 10 weekly sessions of extinction-based exposure therapy have long-lasting and clinically meaningful responses, yet over 40% continue to meet diagnostic criteria (Bradley, *et al*., 2005; Schnurr, *et al*., 2007). Combining daily medications such as SSRIs together with exposure therapy has not shown much additive effect on the therapeutic outcome (Simon, *et al*., 2008), and anxiety-reducing treatments may actually interfere with extinction learning, which leads to long-term recovery. Based on the neurobiology of extinction learning, new augmenting treatments are being developed that could make exposure easier, faster or more effective (McNally, 2007; Myers, *et al*., 2007; Quirk and Mueller, 2008). It is in this context that we consider ±3,4-methylenedioxymethamphetamine (MDMA) as a therapeutic option.

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MDMA is a substituted phenethylamine with profound subjective effects including increased empathy and affiliation. A typical clinical dose of MDMA is 125 mg, and the pronounced effects last from 3 to 6 h. MDMA binds and reverses monoanime transporters, resulting serotonin release seems to mediate most of the subjective effects, as human trials show that SSRIs attenuate most of the subjective effects of MDMA, but MDMA produces a complex profile of direct and indirect effects (Green, *et al*., 2003). Open-label trials of MDMA-augmented psychotherapy (Greer and Tolbert, 1986) and controlled human studies (Dumont and Verkes, 2006; Kolbrich, *et al*., 2008) suggest that MDMA strengthens the therapeutic alliance, decreases avoidance behaviour and improves tolerance for recall and processing of painful memories. It is important to distinguish between controlled clinical use of MDMA and illicit use of 'ecstasy' of unknown purity and dosage.

Following over two decades of research on the effects and potential risks of MDMA, including clinical studies in hundreds of healthy volunteers, three randomized placebo-controlled clinical trials are now testing MDMA as an augment to psychotherapy for chronic, treatment-resistant PTSD or for anxiety associated with advanced-stage cancer (clinicaltrials.gov: NCT00402298, NCT00353938 and NCT00252174). All of these trials have a similar design: MDMA (or placebo) is administered during a few therapy sessions, within a course of short-term psychological treatment. Recent preliminary results from two randomized controlled trials for PTSD show initial promise (Bouso, *et al*., 2008; Mithoefer, *et al*., 2008). Here we suggest three mechanisms for this potentially important new approach.

The first mechanism concerns the hormone oxytocin, which is involved in trust and empathy and mediates the anxiety-regulating effect of social closeness. Social support is a key factor in preventing development of PTSD following trauma, and the therapeutic alliance is recognized as an important factor in the treatment of psychiatric disorders, and research has established an especially strong link between therapeutic alliance and outcome for PTSD (Charuvastra, *et al*., 2008). People with PTSD often report feeling emotionally disconnected and unable to benefit from the supportive presence of family and friends or therapists (Charuvastra, *et al*., 2008), likely contributing to the development and maintenance of the disorder. MDMA increases oxytocin release (Baggott, *et al*., 2008; Thompson, *et al*., 2008) this may strengthen the alliance between the therapist and patient. Oxytocin has been shown to enhance the encoding of positive social memories (Guastella, *et al*., 2008) and increase the social support benefit of having a close-friend present during a psychosocial stress test (Heinrichs, *et al*., 2003). Consistent with increased oxytocin release, increased closeness to others is regularly described following MDMA administration (Dumont and Verkes, 2006; Iversen, 2006). Furthermore, MDMA increases cuddling behaviour in rats, and this prosocial effect is attenuated by blocking oxytocin receptors (Thompson, *et al*., 2007). By increasing oxytocin levels, MDMA may strengthen engagement in the therapeutic alliance and facilitate beneficial exposure to interpersonal closeness and mutual trust.

Secondly, two mutually connected brain areas, the ventromedial prefrontal cortex (vmPFC) and the amygdala, form an emotional regulation circuit that has been identified as central to the maintenance and recovery of PTSD. In particular, extinction of conditioned fear requires strengthening of vmPFC inhibition of the amygdala-mediated fear response, and people with PTSD show dysfunctional activity in both of these brain areas (Shin, *et al*., 2005). An imaging study in healthy volunteers found that MDMA increased activity in the vmPFC and decreased activity in the amygdala (Gamma, *et al*., 2000), and this may reduce emotional avoidance and permit bearable revisiting of traumatic memories.

Thirdly, stress-related release of norepinephrine and cortisol is essential to trigger emotional learning, including fear extinction (Quirk and Mueller, 2008). MDMA increases norepinephrine and cortisol release (Green, *et al*., 2003) and this may induce emotional engagement that could help with eliciting emotional recall of traumatic experiences and enhance the rate of extinction learning. Administration of cortisol before exposure therapy has been shown to enhance extinction learning in some anxiety disorders (Myers, *et al*., 2007; Quirk and Mueller, 2008). Pharmaceutical compounds that acutely increase norepinephrine may increase emotional activation (Southwick, *et al*., 1999) and also enhance extinction learning (Mueller, *et al*., 2008), but such compounds may also temporarily increase anxiety in people with PTSD (Southwick, *et al*., 1999). Conversely, anxiety-reducing treatments, which decrease activation in response to stress, can actually interfere with extinction learning (McNally, 2007; Myers, *et al*., 2007). A goal during exposure therapy for PTSD is to recall distressing experiences while at the same time remaining grounded in the present (Foa, 2006). Emotional avoidance is the most common obstacle in exposure therapy for PTSD (Foa and Kozak, 1986), and high within session emotional engagement predicts better outcome (Jaycox, *et al*., 1998).

Reduction of avoidance behaviour linked to emotions is a common treatment target for all anxiety disorders. MDMA has a combination of pharmacological effects that, in a therapeutic setting, could provide a balance of activating emotions while feeling safe and in control, as has been described in case reports of MDMA-augmented psychotherapy. Basic research studies in animals and humans could more closely examine the acute effects of MDMA on behavioural, endocrine and brain activation responses to social and emotional stimuli, particularly during fear extinction. Future clinical trials could combine MDMA with evidence-based treatment programs for disorders of emotional regulation, such as prolonged exposure therapy for PTSD.

Declaration of conflict of interest

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