

Oxytocin Enhancement of Fear Extinction: A New Target for Facilitating Exposure-Based Treatments?

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It has been more than a decade since Ressler *et al.* published the first demonstration of facilitation of exposure-based therapy with the *N*-methyl-D-aspartate co-agonist D-cycloserine (1). Since that pivotal study, there has been a surge of research to identify additional targets that enhance fear extinction for adjunctive treatment strategies. Potential pathways include catecholamines, endocannabinoids, and various neuropeptide systems and epigenetic pathways (1). Among the neuropeptide candidates, oxytocin (OT) has gained attention as a modulator of conditioned fear processes including fear extinction. OT receptors are located on neural circuits mediating fear learning and extinction, and there is substantial preclinical literature supporting modulatory effects of OT receptor signaling on conditioned fear learning, recall, and extinction (2). Furthermore, the putative prosocial effects of OT make it attractive as an adjunctive treatment for behavioral therapies, as it may facilitate patient-therapist alliance and acceptability of treatment. Initial support for the hypothesis that OT may enhance fear extinction in humans came from a study from our laboratory, which found that OT administration before extinction training significantly increased 24-hour extinction recall. However, the mechanism by which OT affects extinction in humans is unknown.

In this issue of *Biological Psychiatry*, Eckstein *et al.* (3) address the question of neural mechanisms of OT effects on extinction in important ways. They studied 62 healthy men who were randomly assigned to receive either intranasal OT or placebo spray after a fear conditioning procedure. Participants then received fear extinction training 30 min after OT treatment. Compared with men given placebo, participants given OT exhibited increased conditioned fear responses in the early phase of extinction, but by the last training phase they showed significantly lower conditioned fear responses than the placebo group. Despite initial increases in fear responding, the OT-treated group had significantly enhanced extinction learning by the end of training. The authors showed that OT affected activity in neural circuits associated with fear processing, including the prefrontal cortex (PFC) and the amygdala.

The findings of Eckstein *et al.* are intriguing in that they did not implicate OT engagement of the well-known PFC region implicated in extinction, the ventromedial PFC, but instead a dorsal region of the mid-medial PFC. The mid-medial PFC was activated only during initial fear extinction training, when fear responding was significantly higher than in the placebo group, but not during the second phase corresponding to lower fear responses. The dorsolateral PFC is associated with deliberate regulation of responses to conditioned cues, whereas the dorsomedial PFC is more commonly associated with fear

expression. One possible interpretation is that OT is modulating effortful fear regulation during implicit learning of the new contingency as opposed to automatic mechanisms, which could be a unique feature of this treatment compared with other “pro-extinction” molecules such as D-cycloserine. However, it cannot be determined if the PFC activation observed is associated simply with increased physiologic responses during this learning phase (i.e., increased fear expression), or if it is important for initiation of the improved learning observed in the second phase (i.e., increased fear extinction). The authors also found that amygdala activity was reduced throughout the extinction session in the OT-treated group, supporting the growing literature on OT-induced suppression of amygdala activity in response to social and nonsocial aversive stimuli (4). Taken together, OT enhancement of within-session extinction (3) as well as recall (5) supports further research of OT effects on fear extinction and how to translate this effect to enhance exposure-based psychotherapies. This is an exciting prospect for increasing treatment effectiveness for patients with anxiety and fear-related disorders.

Despite this promise, two preliminary studies foreshadow a greater complexity of OT effects on fear memory and extinction related to potential for adjunctive treatment strategies with exposure therapy. In a study of 25 patients with social anxiety disorder, OT treatment before undergoing public speaking exposure improved self-appraisal of speaking skills across treatment. However, OT did not improve overall social anxiety disorder symptoms compared with placebo (6). This same group using similar methodology did detect effects of D-cycloserine to enhance exposure-induced reductions of social anxiety disorder symptoms. These findings suggest that OT treatment does enhance extinction of fears specific to the exposure target, but that it may not enhance generalization to related fears outside the clinic. We recently tested OT efficacy to enhance exposure therapy in 24 individuals with arachnophobia (7). Contrary to the results predicted by laboratory tests, OT delivered before a single-session exposure-based treatment had no effects on therapy-induced reductions in avoidance and tended to decrease therapeutic alliance and response to treatment at follow-up. Compared with the laboratory studies of OT on extinction ($N \approx 60$), these were very small studies ($N \approx 25$), and the results should be considered with caution. However, both extant clinical studies suggest that we need to know much more about exactly how OT acts on fear learning and anxiety before it may be effectively implemented as a treatment. For example, OT is administered within 1 hour after fear conditioning in the studies of OT effects on extinction in healthy controls. It is

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possible that the effects on extinction may be due to modulation of memory consolidation, an effect that has been reported in animal studies after OT (8). As Eckstein *et al.* point out, studies are needed to test OT effects on extinction of fully consolidated memories to model the fear memory process most accurately in clinical populations.

As seen in the present study, under certain circumstances OT administration can produce anxiogenic effects and can bias memory toward negative aspects of events, challenging a simple anxiolytic model of OT treatment effects. OT administration increases in-group/out-group perceptions and reduces prosocial behavior toward strangers, which has led to a much more nuanced contemporary view of OT effects on emotional and social behavior (9). Eckstein *et al.* found increased galvanic skin responses to fear cues in the early stage of extinction training after OT treatment, similar to other studies showing increased potentiated startle to fear cues (5). It was not known what the neural substrate might be for this initial increase in fear expression, and the findings of Eckstein *et al.* rule out that this effect is associated with amygdala activity and may instead be related to PFC activation. These findings support the notion that for OT to be put into effective clinical use, the specific parameters under which it might be effectively delivered must be identified to prevent deleterious outcomes due to anxiogenic effects, negative memory bias, or interference with prosocial processes.

A further challenge for understanding intranasal OT effects on emotional behavior and its potential clinical application is that we do not understand the mechanism by which OT treatment is influencing these behaviors. Are the effects on extinction via engagement of OT receptor at fear circuits (10)? Given the relatively low levels of OT measured in brain after large peripheral administration, it is still heavily debated whether the effects of OT are via direct action in the brain or via downstream mechanisms triggered by peripheral signaling. A further complication is that OT is a close relative of vasopressin, from which it differs by only two amino acids. At high levels, OT can bind to vasopressin receptors, which could also mediate either potential peripheral or central effects of OT at the fear circuit. These issues can be resolved only when a positron emission tomography ligand for OT receptor has been developed. Finally, understanding of how OT dosing affects regional OT receptor activation will be critical for our understanding of OT treatment mechanisms, as selective OT receptor activation in the PFC versus the amygdala may have opposing effects on fear extinction (8).

The impact of OT on fear extinction learning and memory has also yet to be tested in patient samples with known disruption in extinction, such as posttraumatic stress disorder. Given that impaired fear extinction performance may be considered an etiological or maintaining factor in anxiety and fear-related psychopathology, it is possible that OT may act differentially on these processes in clinically anxious individuals relative to healthy control individuals. Thus, it will be informative to conduct laboratory demonstrations of OT effects on extinction with clinical samples. An additional avenue for future research is potential sex differences in the response to OT effects on fear extinction: Growing evidence supports substantial differences between sexes in how OT

impacts emotional processes. Because most clinical anxiety disorders are more prevalent among women, sex differences in OT effects on fear extinction must be explored.

In conclusion, the work of Eckstein *et al.* represents an exciting step forward in understanding the potential for OT to facilitate positive outcomes for individuals with anxiety and fear-related disorders and provides a window to the potential key circuits mediating these effects. However, much work remains to be done to fully understand the potential and limitations of OT as a therapeutic agent for fear-related disorders.

Acknowledgments and Disclosures

This work was supported by the Brain & Behavior Research Foundation (DTA), U.S. Navy Bureau of Medicine and Surgery (DTA, VBR), Department of Veterans Affairs Center of Excellence for Stress and Mental Health (VBR, DTA), National Institute of Mental Health (VBR), and Department of Veterans Affairs Laboratory Research and Development Service (VBR).

In the last 3 years, VBR has received research funding from Johnson & Johnson and Sunovion, Inc. DTA reports no biomedical financial interests or potential conflicts of interest.

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Received Jun 1, 2015; accepted Jun 2, 2015.

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