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Commentary

Toward Comprehensive Understanding of the Effects of Intranasal Oxytocin on the Human Amygdala

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Over recent years, evidence has accumulated for the critical role of the neuromodulator oxytocin (OXT) in the regulation of emotions. In animal models, the effects of OXT on emotional and social processes are easily assessed by introducing OXT through intrabrain microinjection or systemic routes. In humans, a seminal study showed that OXT introduced through an intranasal route increases trust (1). This study opened wide avenues for research using OXT in human subjects and demonstrated that OXT can be safely and effectively administered to human subjects intranasally, bypassing the gastrointestinal tract and the blood-brain barrier, where it is thought to accumulate in cerebrospinal fluids. The translational value of this result is not only in research that aims to understand the effects of OXT on cognitive and emotional processes in humans, but also as a potential treatment of human psychopathologies. This is particularly significant in light of an abundance of data that show the beneficial effects of OXT in treatment of a wide range of social behaviors and coping with stress. However, research determining how and where intranasally administered OXT affects humans, and whether optimal temporal constrains exist, is still in its infancy.

In this issue of *Biological Psychiatry*, Spengler *et al.* (2) present a study aiming to pinpoint the optimal intranasal OXT dosage and administration time for manipulating amygdala activity in response to the facial emotion recognition test in healthy adult subjects. The study's focus on the amygdala stems from continuous efforts and progress made in elucidating the role of the amygdala in emotional regulation, social interaction, and the perception of emotional faces. In humans, the amygdala has a central role in recognition of emotional faces and is strongly activated when the subject is presented with images of angry or fearful faces (3).

Spengler *et al.* used functional magnetic resonance imaging (fMRI) to examine amygdala reactivity to a facial emotion recognition task in 116 healthy subjects following self-administered intranasal synthetic OXT. The effects of three different doses of OXT (12, 24, and 48 international units [IU]) or placebo were examined at dose-test latencies of 15, 45, or 75 minutes. The rationale for the doses stemmed from previous reports on the effects of OXT in humans. Striepens *et al.* (4) detected an increased OXT signal in human cerebrospinal fluid 75 minutes after intranasal delivery of 24 IU, and Cardoso *et al.* (5) reported that a 24-IU dose is more effective than a 48-IU dose. Thus, the underlying hypothesis was that dampened amygdala activation will be observed after the administration of the 24-IU OXT.

Spengler *et al.* presented subjects with stimuli that included morphed face pictures displaying a neutral mood, happiness, and high- and low-intensity fear while inside the fMRI. The subjects were asked to identify the emotion depicted by each face presented during the test and categorize it as neutral mood, happiness, or fear as quickly and accurately as possible by pressing one of three response buttons. Analysis of the fMRI data indicated that 24-IU OXT administration 45 minutes prior to the test significantly reduced the response to fearful faces in the left amygdala. This was distinct from the outcome of higher and lower dosages, which either generated the opposite effect or had no effect at all. The attenuation of amygdala response was associated with increased occurrences of rating low-intensity fearful faces as having a neutral mood by the subjects who received the 24-IU dose 45 minutes before the test. This suggests a correlation between dampened amygdala activity and the behavioral readouts/output.

Administration of synthetic OXT at the three doses resulted in an elevating effect on plasma and saliva OXT levels. These findings correspond with preclinical data that addressed for the first time the levels of OXT in the brain following intranasal application of synthetic OXT and reported increased extracellular OXT levels in brain regions that are targeted by oxytocinergic projections (amygdala) or are free of them (dorsal hippocampus). The peak occurred during the 30- to 60-minute sampling interval after administration. Notably, this local rise positively correlated with the rise in plasma levels (6).

Interestingly in Spengler *et al.*'s study, 48 IU did not elevate plasma and saliva levels of OXT beyond those of the 24-IU group. Authors speculate that this is due to a ceiling effect, with 24 IU generating the maximum possible effect of nasal administration on plasma and saliva levels.

Spengler *et al.* report that the higher dose of OXT (48 IU) resulted in an increase in the amygdala response to fearful faces. This finding is in line with preclinical data that show the negative influence of the OXT in regulating fear responses. Specifically, local microinjection of OXT agonists into the basolateral amygdala resulted in enhanced fear responses (7). These negative effects may be mediated via interaction of OXT with vasopressin receptors that have opposite effects. Conversely, it may support several studies that suggest that OXT can have a dark side, leading to unwanted and maladaptive effects on fear and social memory (8).

The effect of OXT on social interaction is believed to be relevant to autism spectrum disorder. Consequently, many

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studies have attempted to alleviate autism spectrum disorder symptoms with OXT treatment. The results of this have been mixed (9). Spengler *et al.* addressed the issue by assessing the autistic-like traits of the subjects using the autism spectrum quotient (AQ). As the study was conducted only on healthy individuals the average AQ was low and all subjects were below the clinical cutoff. Interestingly, the subjects exhibiting a relatively higher AQ (higher than the group median AQ score) were more sensitive to the 24-IU 45-minute latency OXT treatment. In these subjects both the behavioral and neural effects of OXT were more pronounced. Interestingly, a whole-brain regression analysis of the higher-AQ subjects revealed a greater left amygdala response to high-intensity fearful faces in the placebo group, suggesting an association between autism spectrum disorder–like traits and amygdala reactivity.

In conclusion, intranasal OXT is a powerful and highly relevant tool for researching behaviors and pathologies associated with amygdala dysfunction. This study brings the first evidence on dose-response effect while determining the optimal latency and opening an avenue for further optimization of OXT applications to humans to promote more translational studies and the development of treatments for human pathologies such as autism spectrum disorder, anxiety disorder, and posttraumatic stress disorder. The possible application in posttraumatic stress disorder is particularly relevant in light of recent data suggesting that OXT can impair fear memory reconsolidation, and thus suggesting that OXT can be used outside the time window of the exact occurrence of the trauma (10). The results of Spengler *et al.* present an exciting potential to extend preclinical findings on the role of OXT within the amygdala to clinical studies and emphasize the necessity for cooperation between preclinical and clinical studies.

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Article Information

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