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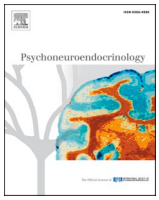

Oxytocin release in stressful times

The COVID-19 pandemic has altered our social lives in ways few could have imagined. In the early phases of the pandemic, the loss of rewarding interactions with family and friends is thought to have contributed to increases in mental health and substance abuse disorders. Yet for some, working or studying from home had important benefits, allowing them to avoid stressful social situations. There is growing evidence that oxytocin plays a key role in amplifying both positive and negative emotional responses to social experiences. This suggests that rather than promoting social approach behaviors, oxytocin enhances the salience of social contexts (Shamay-Tsoory and Abu-Akel, 2016). This idea stems in part from research on human participants demonstrating that intranasal oxytocin can either reduce (Domes et al., 2007) or increase (Eckstein et al., 2014) anxiety in social contexts.

How oxytocin can generate diverse behavioral effects is an essential problem to solve, as there is strong interest in oxytocin-based therapeutics (Ford and Young, 2022). Versatility in oxytocin function can occur through activation of distinct but overlapping brain circuits in positive or negative contexts (Steinman et al., 2019). Also important is how is oxytocin released in response to social contexts. These dynamics are poorly described, in part because quantifying oxytocin is not a trivial task. Oxytocin levels in both brain and plasma are at about 1000 times lower than other hormones such as cortisol (Leng and Sabatier, 2016). In the current issue, Tabak and colleagues use rigorous methods to set a high bar for quantifying oxytocin reactivity in human subjects (Tabak et al., 2022).

The authors quantified changes in oxytocin levels before, during, and after the Trier Social Stress test-a standardized tool to induce social stress in human participants. They achieved an unusual level of temporal precision for a human subjects study by using small intravenous catheters to collect blood samples at five different time points over the one hour period. This collection method also allowed for a more direct measure of oxytocin than indirect methods such as saliva. Furthermore, the authors extracted baseline plasma samples and assayed oxytocin using gold-standard radioimmunoassays. This reduces the impact of the plasma matrix, known to interfere with antibody binding. Just as critical as these biochemical methods were the pre-registered study design and analyses. The sample included both men and women who completed questionnaires that rate state anxiety, social anxiety, and depression. This allowed the authors to determine the extent to which individual differences in oxytocin levels tracked anxiety.

Tabak and colleagues showed that the Trier Social Stress test induced an almost 2-fold increase in plasma oxytocin in women, whereas no changes in oxytocin were seen in men. An increase in oxytocin can be interpreted in several ways. One possibility is that oxytocin might represent a coping response to facilitate seeking of social support. However, the authors' behavioral data suggest that an alternate explanation is more likely. The sex-specific increase in oxytocin was driven primarily by women with higher anxiety scores (who had lower baseline oxytocin levels), which suggest the possibility that oxytocin release during stressful social contexts could contribute to the exaggerated anxiety. This mechanism is supported by work from rodent stress models. Social defeat stress exposure induces social avoidance and an enduring increase in the reactivity of oxytocin neurons in female but not male California mice. Further, social avoidance can be prevented or induced with blockade or stimulation, respectively, of a population of oxytocin receptors located in the bed nucleus of the stria terminalis (BNST) (Duque-Wilckens et al., 2020, 2018). Humans with higher social anxiety ratings have stronger BOLD responses within the BNST in response to unpredictable threats compared to individuals with lower anxiety scores (Clauss et al., 2019). Together, these suggest that in stressful contexts enhanced reactivity of oxytocin neurons in females may facilitate social-anxiety related behaviors. This has important implications for the use of oxytocin-based therapeutics, including the possibility that in some cases, blocking oxytocin receptors could reduce anxiety.

Comprehensive, high-quality quantification of oxytocin in realistic social contexts will be essential for the refinement of current theories of how oxytocin modulates social behavior. Previous studies attempting to link baseline plasma oxytocin levels with social anxiety have yielded inconsistent results. This inconsistency is reminiscent of previous studies attempting to link baseline testosterone levels with survey-based measures of aggression, which also reported weak or inconsistent associations (Archer, 2006). However, when testosterone levels are measured during a competitive task, hormone-behavior relationships are stronger (Fuxjager et al., 2017). Despite recent breakthroughs showing circuit- and dose-specific effects of oxytocin on social behaviors, we have comparatively little data on the dynamic changes in oxytocin levels in the brain or plasma during social contexts. Tabak and colleagues provide a strong example of how to collect these samples in human subjects, and the reward that can come from collecting these data. New tools for measuring dynamic changes in oxytocin release in rodents will be an important complement for these methods (Qian et al., 2022).

An intriguing question is why oxytocin reactivity was more prominent in women versus men during the Trier Social Stress test. State anxiety levels increased in both men and women during the Trier test, suggesting that sex differences could be driven by the affective or neuroendocrine responses rather than differences in anxiety induction. Estrogens can enhance oxytocin transcription in the brain, but it is unclear whether this mechanism can explain such a rapid change in hormone release. Alternatively, recent data suggest there may be sex differences in oxytocin dose-response curves in social contexts. For example, a dose of oxytocin that generated a social reward response in male hamsters generated a social aversion response in female hamsters (Borland et al., 2019). The mechanism for this response is unknown, but

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could be important for understanding the function of sex differences in oxytocin release.

In summary, the data from Tabak and colleagues highlight how rigorous experimental design and methods can generate data that provide key insights into how oxytocin is released in realistic social contexts. Continued quantification of oxytocin release in more diverse populations of participants along with further refinements in preclinical rodent models will help guide continued rational development of oxytocin-based therapeutics to improve mental health.

Conflict of interest

The authors have no conflicts of interest to disclose

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