Oxytocin and the salience of social cues

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The neuropeptide oxytocin (OT) is rapidly moving from a molecule with interesting effects in model systems to an important mediator of a range of human social behaviors. In this issue of PNAS, Gamer et al. (1) report on a study in which they show that subjects given OT, relative to subjects given placebo, are more likely to make eye movements toward the eye region when viewing images of human faces, which replicates and extends previous work (2, 3). Gamer et al. (1) also use functional brain imaging to show that the amygdala is an important brain area mediating this effect. These findings have broad implications for understanding the role of OT in normal social behavior as well as the possible therapeutic impact of OT in brain disorders characterized by social dysfunction.

OT is a neuropeptide produced in the hypothalamus, a brain structure important for regulating physiological homeostasis including effects on the autonomic nervous system. OT is released into the circulatory system where it acts as a hormone mediating contractions of the uterus during parturition as well as milk production during breast feeding (4). However, OT is also released directly into the brain where it functions as a neurotransmitter, and it is the effects of OT on the central nervous system that are currently eliciting much interest.

Effects of Oxytocin on Social Behavior in Rodents

Early studies on the behavioral effects of OT focused on rodent models of social behaviors including pair bonding and maternal nurturing (5). Simplified model systems allow for clear tests of hypotheses and detailed exploration of mechanism. When OT is released from the axons of hypothalamic neurons, it binds to OT receptors (OTRs). These receptors mediate the effects of OT on the target or postsynaptic neurons in the brain. This makes a number of experimental manipulations possible. First, OT can be injected directly into the brain to mimic the release of OT from hypothalamic neurons. When this is done, virgin female rats that normally find rat pups aversive begin to show maternal behaviors including nest building and grooming and licking pups (6). Second, injection of OT antagonists that block the effects of OT at OTRs delays the onset of maternal behavior in rats after parturition (7). The effects of OT on pair bonding have also been studied extensively in the monogamous prairie vole. In this species, similar experimental approaches have shown that injection of OT directly into the brain facilitates pair bonding in the absence of mating (8), and the injection of OT antagonists blocks the formation of pair bonds even after extended mating bouts (9).

Effects of Oxytocin on Social Behavior in Human Subjects

Recent work, building on the animal experiments, has shown that OT also plays an important role in human social behavior. Experiments in humans are necessarily more limited than experiments in animal models.

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However, it has been shown that neuropeptides delivered intranasally lead to elevations in their concentrations in the cerebral–spinal fluid (10). Thus, OT levels can be experimentally elevated in the brain over periods of time sufficient to carry out behavioral testing and functional imaging. Using this approach, a rapidly growing list of studies has examined performance in tasks that ask participants to identify emotions from images of the face under various manipulations. For example, in the reading the mind from the eyes task (RMET), images of the eye region of faces are presented, and the participant is asked to infer the emotion from just this information (11). It has been shown that OT increases performance in this task, particularly on difficult classifications (12). In related work, it has been shown that OT increased gaze to the eye region of the human face (2), an effect that might underlie increased performance in the RMET task, because the information necessary for solving the task is only available in the eye region. Recently, the improvement in RMET performance with OT administration has also been shown in individuals with autism spectrum disorders (ASD) (13). Functional MRI has been used to locate the anatomical substrates of these changes in face processing. These studies have shown that amygdala activation to angry faces is decreased on OT relative to placebo (14) and that OT can also decrease activation to angry, fearful, and happy expressions (15).

Complementing the work on face perception, a few studies have examined the effects of OT in the context of social decision making. One of the earliest studies of OT on social behavior examined its effects in a trust game (16). In the trust game, investors choose how much of an endowment (e.g., $10) to transfer to a trustee. The value transferred is then increased by tripling the amount transferred so that the trustee ends up with a larger sum than was transferred. The trustee can decide how much to return to the investor. If the trustee shares a large portion of the transfer, the investor can end up with more money. However, the trustee can choose to betray the investor and keep all of the money. Thus, the investor risks their investment, and they transfer money based on trust and an assumed social norm that the trustee will return a fair portion of the investment (17). In the study by Kosfeld et al. (16), investors on OT transferred significantly more money than investors on placebo. This increased generosity has also been seen in the ultimatum game (18).

In a follow-up study to the original trust study, this group examined how investments in the trust game would change after the revelation that many of the trustees did not reciprocate in the first 6 of 12 rounds (19). In this study, it was shown that after the lack of reciprocation in 50% of the initial investment trials, participants on OT increased their investment, whereas participants on placebo decreased their investment, an effect mediated by the bilateral amygdala. This suggests that the aversive outcomes associated with the lack of reciprocation by trustees had a decreased effect on the OT group. Thus, OT may not lead to the wisest investment decisions, but it may lead to forgiving colleagues in social interactions. In an important control in both trust studies, participants also engaged in a risk game where the outcomes of investments were probabilistically matched to the outcomes in the trust game. However, participants knew that a computer was deciding the outcome, not another player. It was found that OT did not affect performance in the risk game. Consistent with the

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hypothesis that OT decreases the aversive aspects of negative social interactions, work has also shown that OT can decrease affective evaluations of faces that have been negatively conditioned with shock (20). This study also found that the decreased affective evaluations were mediated by the amygdala.

The above described results are beginning to provide evidence for an important role for OT in a broad range of human social interactions. Many studies have also begun considering a possible role of disrupted or pathological OT signaling in psychiatric disorders including ASD and schizophrenia. We already considered one study that has shown that OT can improve the identification of emotions in the RMET task in individuals with ASD (13). Other work has shown that when patients with ASD played a game in which they could choose to throw a ball to one of three players who would throw the ball back to the patients different amounts of times, treatment with OT increased the number of times patients threw the ball to the player most likely to return the ball (3). OT treatment also increased ratings of trust and preference for the most interactive player. In additional results reported in the same study, OT treatment also increased the number of saccades to the eye region when patients with ASD viewed pictures of faces.

The emotion-recognition tasks suggest that OT improves emotion recognition in the RMET task, an effect that might be mediated by increased eye movements to the informative eye region. The decision-making tasks suggest that OT may decrease the aversive aspects of negative social stimuli. How might these effects be linked together into a coherent hypothesis of the role of OT in behavior? The study by Gamer et al. provides additional insight. They show that OT increases responses in the superior colliculus (SC), a brainstem area critically important for eye movements and attention, when fixations were initially centered on the mouth. In this condition, participants also made increased saccades to the eye region. Furthermore, the functional connectivity between the amygdala and the SC was increased on OT. Thus, OT may increase the salience of the eye region by giving it increased positive affective valence through facilitated amygdala activity and connectivity with the SC. It is possible that patients with ASD or schizophrenia find the eye region aversive, and therefore, they avoid fixations on the eye region, foregoing the valuable emotion information contained in the eyes. Treatment with OT may reduce the aversive valence of the eye region for these patients, increasing saccades to this region and facilitating emotion identification.

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