【総説】

A Review of the Effect of Oxytocin on Prosocial Behavior

Qiulu Shou[1], Haruto Takagishi[2]

[1]Graduate School of Brain Sciences, Tamagawa University

[2]Brain Science Institute, Tamagawa University

Oxytocin

Oxytocin (OXT) is a neuromodulator and a hormone consisting of nine amino acids. OXT is synthesized in neurons in the paraventricular and supraoptic nuclei of the hypothalamus. It is released by the neurohypophysis into the peripheral circulation (and from there into saliva and urine) and is one of the hormones involved in parturition and lactation (Forsling et al., 1979). However, some of the OXT is transported in axons and released in target brain areas (e.g., hippocampus, amygdala, striatum, hypothalamus, nucleus accumbens, and midbrain). Moreover, OXT released from the cell bodies of neurons also diffuses to the central nervous system (CNS), functioning as a neuromodulator. Biologists and neuroscientists initially discovered that OXT in the CNS can regulate maternal, sexual, and attachment behaviors (Nelson & Panksepp, 1998). Because OXT receptors accumulate in the amygdala (Insel & Shapiro, 1992), which is a CNS region associated with human social behaviors, the effect of OXT on human sociality has attracted the interest of researchers. Specifically, in this paper, we will review studies on the effect of OXT on prosocial behavior, including trust and cooperation.

Oxytocin and Prosocial Behavior

Two main methods, using either exogenously or endogenously administered OXT, are used to study the influence of OXT on prosocial behavior. The exogenous OXT study administers OXT through the nasal cavity and then examines its influence on cognition, behavior, and brain function and structure in order to understand the function of OXT in the CNS. Previous studies have demonstrated that OXT can cross the blood-brain barrier as a neuropeptide after intranasal administration (Born et al., 2002) and can influence the brain limbic system, such as the amygdala (Baumgartner et al., 2008) and hippocampus (Owen et al., 2013). Exogenous OXT experiments usually use a double-blind method, with participants administered either OXT (the OXT group) or saline (the placebo group) intranasally. After administration, the participants complete the experiment and the researchers compare the results between the two groups. The advantage of this method is that it can manipulate the OXT content in the CNS and, thus, directly demonstrate a causality relationship of OXT. However, because intranasal administration of OXT could result in far higher OXT levels than what would occur naturally, even in the peripheral circulation (Striepens et al., 2013), it is difficult to determine the real role of OXT in social behavior and to explain OXT function in human society.

The endogenous OXT study measures endogenous OXT levels and examines the association of OXT with cognition, behavior, and brain function and structure. Endogenous OXT levels can be assessed in the peripheral circulation as well as in urine and saliva. Some studies have examined the relationship between social behaviors and baseline endogenous OXT levels, which can be measured from samples collected before the experiment. Other studies have focused on stimuli-

induced endogenous OXT levels or changes in OXT levels from baseline. As an endogenous OXT study is necessarily a correlation study, it is impossible for researchers to determine a causal relationship between OXT and behavior. However, endogenous OXT studies can investigate the role of OXT in natural situations, which is important for researchers to understand the true function of OXT in real life and human society.

Effect of Exogenous OXT on Prosocial Behaviors

Exogenous OXT has been demonstrated to affect various aspects of human sociality, such as theory of mind (Domes et al., 2007) and social cognition (Kirsch et al., 2005). Research focusing on the effects of exogenous OXT on prosocial behavior was initiated by Kosfeld et al. (2005), who administered intranasal OXT or placebo to 128 healthy male subjects who then played the trust game (TG). The TG is a two-person economic game that is commonly used to measure trust behavior and reciprocity in various studies. The first player, called a trustor, is initially endowed with a certain amount of money and is asked to transfer any amount to the second player. The amount of transferred money is tripled and given to the second player, called a trustee. The trustee then decides how much of the received money to return to the trustor or to keep all of it. The transferred amount implies a trustor's trust level, and the returned amount implies the trustee's reciprocity level. Kosfeld et al. (2005) showed that people who had been administered OXT exhibit more trust than those given placebo. This experiment demonstrated that exogenous OXT could promote human trust behavior. Subsequently, Baumgartner et al. (2008) conducted a pharmaco-imaging study and found that exogenous OXT can reduce activity in the amygdala and then increase one's trust even after a low return rate from the trustee. Based on these findings, researchers proposed an "anxiety reduction hypothesis" to explain the effect of OXT on trust; OXT increases trust behavior by reducing fear and anxiety towards betrayal (Bartz et al., 2011). Recently, Declerck et al. (2020) failed to replicate the findings of the study by Kosfeld et al. (2005) and found that the effect of OXT on trust is modulated by one's general trust level. In their study, a positive effect of OXT on trust behavior in the TG was observed only among participants with a low level of general trust, which was measured by Yamagishi's trust scale (Yamagishi & Yamagishi, 1994). It is possible that individual differences in general trust levels play an important role in OXT's effect on trust.

Zak et al. (2007) first examined the effect of OXT on prosocial behavior related to equity. In this study, participants played the dictator game (DG) and the ultimatum game (UG). The first player in both games is initially endowed with a certain amount of money and is asked to distribute the money between themself and a second player. The second player has to accept the allocation. Unlike the DG, the second player in the UG is able to reject the allocation proposed by the first player. This means that the first player in the UG must consider the minimum amount acceptable to the second player. The results showed that exogenous OXT promotes the generosity of the first player in the UG, but it does not affect the allocation proposed by the first player in the DG. Hu et al. (2016) conducted a functional magnetic resonance imaging (fMRI) study to examine the effect of exogenous OXT on brain function during observations of others playing the DG. The participants acted as a third person and observed others playing the UG and DG. The study found that exogenous OXT could enhance the activity of the left temporo-parietal junction (TPJ) while observing others being treated unfairly in the DG, in which the second player cannot reject the proposal. Based on the findings that the TPJ was associated with perspective taking (e.g., Wang et al., 2016), it is possible that exogenous OXT promotes consideration for others and then promotes the equity of allocation in the UG to avoid rejection.

A number of studies have examined the effect of exogenous OXT on cooperation and found that whether OXT promotes prosocial behavior is constrained by situational features. Declerck et al. (2010) examined how social contact before an

experiment influences the effect of OXT on cooperation behavior. Declerck et al. (2010) manipulated two factors of a situation: cooperative motivation and whether there was social contact with the partner before the game. The study manipulated cooperative motivation by the prisoner's dilemma game (PDG; with low incentives to cooperate) and the coordination game (CG; with high incentives to cooperate). The PDG is a well-studied paradigm in social dilemma research. The PDG is a two-person economic game that is commonly used to measure cooperative behavior. Two players make the decision to cooperate or not to cooperate simultaneously. If both players choose to cooperate, the players will obtain a certain amount of money. However, if one of players chooses not to cooperate while the other chooses to cooperate, the player who has chosen not to cooperate will obtain a larger amount of money than that received when choosing to cooperate. The other player who has chosen to cooperate will obtain less money than what one would have gotten when both players choose to cooperate. However, if both players choose not to cooperate, the players will obtain less money than that given to both players choosing to cooperate, but more than that given to the player who chooses to cooperate and then is betrayed by the other player. In other words, in the situation where one player chooses to cooperate and the other chooses not to cooperate, the player who chooses to cooperate will obtain the least money among all situations. Therefore, fear and greed motivates people toward non-cooperation to obtain more money. Compared to the PDG, the motive of non-cooperation is removed in the CG, and the CG becomes about coordinating with each other's decision. In the CG, both players will obtain the largest amount of money when they choose to cooperate compared to the money given in other situations, including when one player chooses to cooperate and the other player chooses not to cooperate. Therefore, the CG provides players with high incentives for cooperation. The results showed that OXT promoted cooperative behavior only when there was social contact with the partner for the game before the experiment, especially in the CG, which has a high incentive for cooperation. When social contact was lacking, OXT, surprisingly, decreased cooperation. According to a series of studies conducted by De Dreu et al. (2012), exogenous OXT can promote cooperation and trust only towards in-group members. Shamay-Tsoory et al. (2009) proposed the social salience hypothesis, wherein the social effects of OXT are that it alters the perceptual salience and/or processing of social cues. Based on this hypothesis, researchers speculate that OXT can promote cooperative behavior only when social cues implying promotion of cooperation are highlighted.

Moreover, individual differences also influence the effect of exogenous OXT on prosocial behavior. For example, social value orientation (SVO) is commonly used to identify differences in one's social disposition in pro-social and pro-self preferences, independent of actual behavioral choices in economic games (Yamagishi et al., 2016). In previous studies, SVO was found to correlate with human prosocial behaviors (Yamagishi et al., 2016). The effect of exogenous OXT on human prosocial behavior was modulated by SVO (Declerck et al., 2013, Liu et al., 2018). Declerck et al. (2013) found that after a brief moment of social contact with the game partner in the PDG, intranasal administration of OXT enhanced cooperative behavior measured during the PDG only in pro-self individuals, which did not hold for pro-social individuals. Recently, an event-related fMRI study (Liu et al. 2018) found that exogenous OXT can enhance amygdala activity in response to unfair allocations and improve prosocial behavior; this effect was observed only in pro-self individuals. Based on these findings, exogenous OXT can modulate the activity of the amygdala in response to unfair allocations and then modulate prosocial behavior. Future studies on the relationship between OXT, prosocial behavior, and SVO are needed.

In summary, exogenous OXT can promote various prosocial behaviors such as trust, monetary allocation, and cooperation. However, the effect of exogenous OXT is moderated by situational features and individual differences. Various theories have been proposed to explain the effect of exogenous OXT on

social behavior, for example, the anxiety reduction hypothesis and social salience hypothesis. However, the mechanism underlying the effect of OXT on prosocial behavior remains unclear.

Effect of Endogenous OXT on Prosocial Behaviors

Endogenous OXT levels are associated with various social behaviors such as parenting behavior (Feldman, 2015) and social bonding (Feldman, 2012). Zak et al. (2005) first examined the effect of endogenous OXT on prosocial behavior. In this study, participants played a one-shot TG as the trustee with other persons or a computer. Researchers collected blood before and after the TG and then measured the plasma OXT level. OXT levels were higher in subjects who received a monetary transfer from a person relative to that when an unintentional monetary transfer of the same amount from the computer was received. In addition, higher OXT levels are associated with the reciprocation of trust (transferred amount from trustee). Subsequently, Barraza and Zak (2009) examined the relationship between endogenous OXT level and prosocial behavior and found that empathy could induce an increase in OXT levels and is associated with subsequent generosity. Morhenn et al. (2008) found that the change in plasma OXT levels due to physical contact, only after being trusted in the TG, is associated with reciprocity behavior in the TG. The study also found that women were more susceptible than men to OXT release and monetary sacrifice after touch. Based on these findings, OXT can be induced by empathy and prosocial cues, for example, being trusted in the TG. In these studies, elevated OXT levels were associated with prosocial behavior. Considering real life, it is possible that various social cues (e.g., in-group signal) could induce OXT release and promote prosocial behavior. However, it is possible that individual differences, such as gender differences, could influence endogenous OXT release (Morhenn et al., 2008). Future studies are needed to determine which type of social cue could induce OXT release and how endogenous OXT influences prosocial behavior.

Some recent studies provide evidence that endogenous OXT is associated with in-group prosocial behavior. Fujii et al. (2012) conducted an experiment with preschool participants. Endogenous OXT levels were measured in saliva, and the prosocial behavior toward in-group or out-group members was measured by an allocation task. Endogenous OXT levels were negatively associated with prosocial behavior regardless of in-group or out-group status in boys, whereas OXT levels were positively associated with allocations made to in-group girls. McClung et al. (2018) conducted an experiment with adults and found that endogenous OXT levels are positively associated with in-group cooperation and not associated with out-group cooperation. The different findings might result from the differences in the age of the participants, and future studies are needed to determine the relationship between endogenous OXT and prosocial behavior.

The relationship between endogenous OXT levels and trust has also been examined in other studies (Christensen et al., 2014; Zhong et al., 2012). Although one study found a significant U-shaped relationship between baseline plasma OXT level and behavioral trust in male participants playing the TG (Zhong et al., 2012), another study found no such association between these plasma levels after playing the game and behavioral trust in this task (Christensen et al., 2014). The inconsistent findings might result from the possibility that OXT is associated with only one part of trust. According to Yamagishi's emancipation theory of trust (Yamagishi, 2011), trust consists of two independent factors: an expectation of the trustworthiness of others, referred to as general trust, and a degree of caution with others referred to as caution. However, no study has examined which part of trust is associated with OXT. We examined the relationship between OXT level and attitudinal trust level in adults (unpublished observation). Attitudinal trust reflects the tendency of beliefs toward people's trustworthiness in general (Yamagishi, 2011). Individual differences exist in trust attitudes, which influence behavioral trust measured during the TG (Mifune & Li, 2018). A study measuring attitudinal trust using the

General Trust and Caution Scale (Yamagishi & Yamagishi, 1994) concluded that trust consists of two independent factors: general trust based on a general expectation of the trustworthiness of others and caution based on a belief in the necessity of caution while dealing with others. We measured OXT levels in saliva and found that endogenous OXT level was associated with caution but not with general trust. Our study implies that endogenous OXT is associated with a degree of caution when dealing with people but not an expectation of the trustworthiness of others, which is consistent with the anxiety reduction hypothesis that OXT increases trust by reducing fear of betrayal.

There are few studies on the relationship between endogenous OXT and prosocial behavior. Based on the findings of a series of studies conducted by Zak and colleagues (Barraza & Zak, 2009; Morhenn et al., 2008; Zak et al., 2005), OXT levels that are elevated due to social stimuli are positively associated with prosocial behavior. However, the relationship between endogenous OXT baseline levels and prosocial behavior remains unclear.

Criticism of OXT Studies

Exogenous OXT studies have been criticized because of small sample size, low statistical power, and publication bias (Walum et al., 2016). Walum et al. (2016) pointed out that because of the small sample size and low statistical power, it is possible that published findings of studies using intranasal OXT do not represent true effects. Regarding endogenous OXT studies, criticisms mainly arise from inconsistent OXT measurement procedures, measurement validity, and lack of evidence for a relationship between peripheral OXT levels and central OXT levels (McCullough et al., 2013). For example, the OXT level differs depending on the measurement method used, such as radioimmunoassay and enzyme-linked immunosorbent assay, or the different measuring protocols used (Szeto et al., 2011; McCullough et al., 2013). Other critics have pointed out that there is no overarching theory to explain the diverse findings that result from exogenous and endogenous OXT studies of prosocial behavior. For example, the anxiety-reduction hypothesis which states that OXT reduces anxiety, especially social anxiety, could explain the promotion effect of OXT on trust, as OXT increases prosocial behavior by reducing anxiety in response to betrayal (Bartz et al., 2011). However, this hypothesis could not explain other effects of OXT on prosocial behavior (e.g., cooperation). Similarly, although the social salience hypothesis can explain some of the effect of OXT on prosocial behavior (e.g., Liu et al., 2019), it is difficult to explain the effect of OXT on trust. Moreover, there are some inconsistent findings between exogenous OXT studies and endogenous OXT studies. For example, exogenous OXT has been found to promote trust, especially in people with low general trust levels, whereas no such result has been found in endogenous OXT studies.

Future directions

First, for exogenous OXT studies, a direct replication study using the same procedure and a relatively large sample size is necessary. For example, Nave et al. (2015) raised doubts about the robustness of the effect of exogenous OXT on trust, pointing out that six studies failed to replicate the initial findings reported by Kosfeld et al. (2005). However, these studies were not direct replications because they did not use the same methods and procedures as the original study. Declerck et al. (2020) conducted a direct replication study with a sample size of over 600 and obtained robust results. A direct replication study on the relationship between exogenous OXT and other prosocial behaviors is also needed.

Second, regarding endogenous OXT studies, the assessed OXT level is influenced by the measurement method used (McCullough et al., 2013). Therefore, taking multiple endogenous OXT measurements using different methods could help replicate previous study findings as well as increase the robustness of findings. Additionally, because of conflicts in the measurement of endogenous OXT levels (McCullough et al., 2013), it is necessary to unify the measurement method in the future, which could make it easier to compare studies.

Finally, there is a lack of an overarching theory to

explain the effect of OXT on prosocial behavior. Pharmaco-imaging can be a good method to determine the mechanism of the effect of OXT. For example, Liu et al. (2018) conducted an event fMRI experiment and found an important role of the amygdala in the effect of exogenous OXT on human prosocial behavior, which is moderated by individual differences in SVO. In future studies, especially endogenous OXT studies, it is necessary to examine the relationship between OXT level, brain structure and function, and prosocial behavior.

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