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Intranasal administration of oxytocin increases human aggressive behavior

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ABSTRACT

Considering its role in prosocial behaviors, oxytocin (OT) has been suggested to diminish levels of aggression. Nevertheless, recent findings indicate that oxytocin may have a broader influence on increasing the salience of social stimuli and may therefore, under certain circumstances, increase antisocial behaviors such as aggression. This controversy led to the following speculations: If indeed oxytocin promotes primarily prosocial behavior, administration of OT is expected to diminish levels of aggression. However, if oxytocin mainly acts to increase the salience of social stimuli, it is expected to elevate levels of aggression following provocation. In order to test this assumption we used the Social Orientation Paradigm (SOP), a monetary game played against a fictitious partner that allows measuring three types of responses in the context of provocation: an aggressive response – reducing a point from the fictitious partner, an individualistic response – adding a point to oneself, and a collaborative response – adding half a point to the partner and half a point to oneself. In the current double-blind, placebo-controlled, within-subject study design, 45 participants completed the SOP task following the administration of oxytocin or placebo. The results indicated that among subjects naïve to the procedure oxytocin increased aggressive responses in comparison with placebo. These results support the saliency hypothesis of oxytocin and suggest that oxytocin plays a complex role in the modulation of human behavior.

Introduction

Aggression is defined as any behavior intended to harm another individual, who is motivated to avoid being harmed (Baron and Richardson, 2004). From an evolutionary perspective, aggression has an adaptive value, ensuring survival when used for obtaining food or mates. Aggression encompasses vast and diverse forms of behavior and therefore has been described by numerous classifications. One accepted classification distinguishes between *reactive aggression*, also known as affective aggression, and *proactive aggression*, also known as instrumental or predatory aggression (McEllistrem, 2004). Reactive aggression is usually triggered by perceived threat or provocation, and is considered to be a product of frustration. Proactive aggression, on the other hand, is thought to occur without provocation. It is considered to be planned, goal-oriented (Wahlund and Kristiansson, 2009) and an acquired instrumental behavior which is controlled by its reinforcements or vicarious learning (Dodge et al., 1997). Reactive and proactive aggressions are closely related behaviors, yet can be distinguished clearly according to their function (Polman et al., 2007).

A variety of hormones and neurochemical compounds have been shown to participate in the formation and modulation of aggressive behavior (Chichinadze et al., 2011). The role of testosterone, serotonin and norepinephrine in aggression is well documented and consistently linked to aggressive behavior (Siegel, 2005). Interestingly, although some literature connects vasopressin to aggression (Albers, 2012), and despite the well-documented role of oxytocin in social behavior, knowledge about the role of this hormone in aggressive behavior is limited.

Oxytocin is a nonapeptide well known for its peripheral role as a hormone that facilitates uterine contractions during labor and lactation in nursing females. In addition to this role in the reproductive system, oxytocin also plays a central role as a neurotransmitter in the central nervous system. It initiates sexual and parental behavior (Insel et al., 1997) and is known for its effects on human social cognition and behavior (Bartz et al., 2011b). Oxytocin was found to reduce physiological and psychological correlates of stress (Heinrichs et al., 2003) and increase trust in humans (Kosfeld et al., 2005). It has been suggested that oxytocin increases the benefits of social interaction and promotes social approach and affiliation (Heinrichs and Domes, 2008).

Given the role of oxytocin in trust, pair bonding and emotion recognition, a recent study (Striepens et al., 2011) suggested that oxytocin mediates behaviors that are mainly prosocial. Nonetheless, other studies from animal research challenged this view, by showing, for

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example, that oxytocin can enhance anxiety (Guzmán et al., 2013). Other studies supported the importance of social context in determining the nature of oxytocin's modulation of behavior (Bredewold et al., 2014). Similarly, among humans, recent studies demonstrated conflicting effects that extend beyond the traditional function of promoting positive prosocial behavior. In fact, several studies have reported antisocial effects of intranasal administration of oxytocin. For example, oxytocin was found to increase envy and gloating (Shamay-Tsoory et al., 2009), decrease trust and the tendency to cooperate in individuals with borderline personality disorder (Bartz et al., 2011a), and facilitate out-group derogation (De Dreu et al., 2011). Thus, although oxytocin is widely viewed as a prosocial compound, it may also promote antisocial responses, thus suggesting a context-dependent effect (Goodson and Thompson, 2010).

Considering the conflicting evidence regarding the role of oxytocin in social behavior, some researchers have suggested that oxytocin may play a broader role in modulating social behavior by means of increasing the salience of social stimuli (Shamay-Tsoory et al., 2009; Shamay-Tsoory and Abu-Akel, 2015). According to this theoretical framework, oxytocin is expected to enhance a wide range of emotions and behaviors, not solely positive ones. Therefore, if indeed oxytocin increases the salience of social agents, a plausible assumption is that oxytocin will increase aggressive reactions in competitive situations involving aggressive provocations.

Only a handful of studies have directly examined the role of oxytocin in aggressive behavior. These studies were all based on different procedures, various types of aggressive behavior and various environmental conditions, and accordingly yielded inconsistent findings. Mutant mice with targeted disruption of the gene encoding oxytocin showed a significant decrease in aggressive behavior towards an intruder (DeVries et al., 1997). Lubin et al. (2003) found that the infusion of oxytocin antagonist into the central nucleus of the amygdale of rat dams increased aggression towards intruders, whereas the results of Bosch et al. (2005) indicated that oxytocin antagonist infusion into the paraventricular nucleus or central nucleus of the amygdale reduced maternal aggression among high anxiety dams. It has been reported that oxytocin has an important influence on the formation and maintenance of dominant-subordinate relationships through inhibiting the expression of offensive aggression (Harmon et al., 2002). In addition, neonatal female prairie voles treated with oxytocin showed enhanced intra-sexual aggression after exposure to a male (Bales and Carter, 2003). Two recent studies supported the prosocial effects of oxytocin, showing that oxytocin can reduce offensive aggression among rodents when induced through intranasal administration (Calcagnoli, Kreutzmann, de Boer, Althaus, & Koolhaas, 2015), as well as when infused directly to the central amygdale and the dorsal raphe (Calcagnoli, Stubbendorff, Meyer, de Boer, Althaus, & Koolhaas, 2015).

Yet, very little is known about the effect of oxytocin on human aggression. Lee et al. (2009) reported an inverse correlation between cerebral spinal fluid (CSF) oxytocin levels and life history of aggression, indicating that oxytocin plays a mechanistic role in human aggression. Furthermore, a recent study suggested that oxytocin administration reduced reactive aggression among state anxious women under conditions of provocation (Campbell and Hausmann, 2013).

Considering these diverse findings, the following question remains: How does oxytocin modulate aggression? To address this question, we designed the Social Orientation Paradigm (SOP) based on the Point Subtraction Aggression Paradigm (PSAP) (Cherek, 1981), a behavioral measure of aggressive responding under laboratory conditions, which was found to be directly related to aggressive behavior occurring outside the laboratory (Cherek et al., 1997). Similarly to the PSAP, it has been shown that subtracting points from other participants in the SOP predicts violent behavior, but unlike the original PSAP, the SOP offers the subject a cooperative behavioral choice while being provoked (Perach-Barzilay et al., 2013). According to the prosocial hypothesis of oxytocin, the administration of oxytocin should diminish levels of aggressive responses and elevate cooperative responses regardless of the context, whereas according to the social salience hypothesis, administration of oxytocin should increase levels of aggressive responses in situations that provoke aggression. Furthermore, it was speculated that since reactive aggression is usually triggered by perceived threat or provocation in the social environment, the effects of oxytocin should be more evident in reactive aggression than in proactive aggression.

Method and materials

Participants

Forty-eight adults (28 men, 20 women) were recruited to participate in the study. All responded to advertisements posted either in the local community or at the University of Haifa. The size of the sample was based on power analysis of previous studies with similar procedures (Arueti et al., 2013). Participants ranged in age from 19 to 46 (mean: 27, S.D.: 6.0). All participants were native Hebrew speakers and underwent the Mini International Neuropsychiatric Interview (Lecrubier et al., 1997) prior to the two experimental sessions in order to rule out major psychiatric disorders. Data concerning the menstrual cycle phase of women participants were available for 17 women. Of those, 7 were in the luteal phase and 10 were in the follicular phase.

Exclusion criteria included: mental retardation; systemic disease that required routine medical care or chronic medications; diagnosis of either axis I or II mental disorder (according to the Mini International Neuropsychiatric Interview, Lecrubier et al., 1997); substance dependency or suicidal risk. In addition, women who reported that they were pregnant or taking contraceptive pills were excluded. All participants signed an informed consent form in the presence of a physician who also administered the drug. Participants were requested to abstain from caffeine and nicotine on the day of the experiment. Ethical approval was provided by the Helsinki Ethics Committee of the Shalvata Mental Health Center.

Task and stimuli

The Social Orientation Paradigm (SOP) (Perach-Barzilay et al., 2013) is a modified version of the Point Subtraction Aggression Paradigm (PSAP). It measures real-time aggressive behavior in response to provocation, rather than self-reported aggressive behaviors or tendencies. The duration of the modified version is 8 min, and it provides a measure of cooperative behavior in addition to the measure of individualistic tendency and aggressive behavior provided by the PSAP. The task was controlled via the E-prime 2.1 software package (Schneider et al., 2002) to manage the timing and presentation of the stimuli, as well as to record the responses.

Before introducing the task instructions, participants were told they were about to take part in a decision-making game with a same-sex participant. In fact, all participants played against a fictitious partner, and all trials were pre-programmed. The experimenter was instructed to read aloud to the participant the following instructions for the task out of a document placed in front of the participant:

> *Today you will participate in a task of decision making. Another individual will take part in this task at the same time, using a similar response panel.*
>
> *At the center of the screen there are three numbers 1, 2, 3, and at the bottom of the screen a counter will show the amount of points you earn throughout the task. At the beginning of each trial you will be able to choose one out of three options. Pressing "1" will cause options "2" and "3" disappear from the screen. After pressing the "1" key 30 times the number "1" will also disappear from the screen, and one point will be added to your counter. Approximately one second later the three*