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Intranasal oxytocin effects on social cognition: a critique

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Abstract

The last decade has seen a large number of published findings supporting the hypothesis that intranasally delivered oxytocin (OT) can enhance the processing of social stimuli and regulate social emotion-related behaviors such as trust, memory, fidelity, and anxiety. The use of nasal spray for administering OT in behavioral research has become a standard method, but many questions still exist regarding its action. OT is a peptide that cannot cross the blood-brain barrier, and it has yet to be shown that it does indeed reach the brain when delivered intranasally. Given the evidence, it seems highly likely that OT does affect behavior when delivered as a nasal spray. These effects may be driven by at least three possible mechanisms. First, the intranasally delivered OT may diffuse directly into the CNS where it directly engages OT receptors. Second, the intranasally delivered OT may trigger increased central release via an indirect peripheral mechanism. And third, the indirect peripheral effects may directly lead to behavioral effects via some mechanism other than increased central release. Although intranasally delivered OT likely affects behavior, there are conflicting reports as to the exact nature of those behavioral changes: some studies suggest that OT effects are not always “pro-social” and others suggest effects on social behaviors are due to a more general anxiolytic effect. In this critique, we draw from work in healthy human populations and the animal literature to review the mechanistic aspects of intranasal OT delivery, and to discuss intranasal OT effects on social cognition and behavior. We conclude that future work should control carefully for anxiolytic and gender effects, which could underlie inconsistencies in the existing literature.

Keywords

Oxytocin; Intranasal administration; CSF; Social Stimuli; pro-social neuropeptide; anxiety; Social Cognition

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Introduction

Oxytocin (OT) is a peptide that has numerous functions in the body, both peripherally as a hormone and centrally as a neurotransmitter, and OT-like peptides can be found in nearly all vertebrate species (Gimpl and Fahrenholtz, 2001). Peripheral functions are wide ranging. OT has a well-established role in reproductive function (Corona et al., 2012; Courtois et al., 2013) and in parturition and lactation in females (Carson et al., 2013; Gimpl and Fahrenholtz, 2001). Synthetic OT has been used to assist in childbirth for decades. In addition, OT receptors are located in visceral organs such as kidneys and pancreas, as well as in the heart, fat cells, and adrenal glands (Gimpl and Fahrenholtz, 2001), and OT has been found to be involved in the regulation of water balance, bone density, and appetite (Carson et al., 2013).

In contrast, it has been suggested that OT effects in the central nervous system (CNS) might be more specific, with OT playing an important role in modulating social behaviors and the processing of social stimuli. Whether these behavioral changes are modulated by OT in system-specific ways or due to more general effects are, however, unknown. The study of central effects of OT has been carried out in animal models and humans using different delivery methods: in animals both central and peripheral administration has been used, while in humans studies investigating the effects of exogenous OT typically use intranasal spray for delivery, with few exceptions (Hollander et al., 2003). How or if the OT enters the brain using this method is, however, still unknown. The purpose of this critique is twofold. We firstly discuss the potential mechanisms by which OT could enter the brain, and weigh the evidence from work in animals. Implications for human studies using intranasal OT are discussed. We then provide an overview of intranasal OT effects on social cognition in healthy humans, and explore whether OT is genuinely a neuropeptide with specifically “pro-social” effects. We incorporate findings published since other recent reviews on this topic (Bartz et al., 2011; Guastella et al., 2013; MacDonald et al., 2011), identify potential confounds that could underlie current inconsistencies in the literature, and provide suggestions as to how these could be resolved. In tying together both the mechanistic and behavioral aspects of intranasal OT delivery, we provide a summary several issues as a guide for future research.

Intranasal delivery: mechanisms

The OT peptide is comprised of nine amino acids and is produced in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus in mammals. OT is released peripherally primarily from the neurohypophysis by exocytosis (Carson et al., 2013; Viero et al., 2010). Since OT is a relatively large, hydrophilic molecule, blood-brain penetration is too poor to cause any measurable effects on central systems (McEwen, 2004), so peripheral OT likely re-enters the brain in negligible amounts. Instead, OT is released directly in the CNS by OT neurons that project to numerous brain regions from the PVN, separate from those that go to the pituitary (Ross and Young, 2009; Veening et al., 2010).

OT receptors are widely distributed through many brain areas in rat, including the spinal cord, brainstem, hypothalamus, amygdala, and nucleus accumbens (Ross and Young, 2009).

While localization of OT receptors have yet to be definitively mapped in primates and humans (Toloczko et al., 1997), efforts are being made to develop a radioligand that will bind with high specificity to human OT receptors (Smith et al., 2012). Distribution patterns of OT receptors across brain areas are highly species dependent (Insel and Shapiro, 1992; Young et al., 1996), and binding sites are up-regulated in specific areas in response to peripheral (such as pregnancy) or environmental (such as social cooperation) cues (Viero et al., 2010). Many OT neuron axonal projections run close to the ventricles, which may allow for release of OT into the ventricles for communication across numerous OT-receptive brain areas via the cerebrospinal fluid (CSF) (Veening et al., 2010). It has been proposed that this global communication process through CSF within the CNS is what may allow for the necessary simultaneous changes in the numerous neural mechanisms involved in rapid behavioral adaptation to environmental stimuli (Veening et al., 2010).

CSF versus plasma

The relationship between peripheral (plasma) and central (CSF) OT levels is complex. Studies in humans are typically restricted to peripheral OT assessments due to the risks associated with invasive CSF collection procedures (Carter, 2007; Challinor et al., 1994; Domes et al., 2010; Modahl et al., 1998; Parker et al., 2010). Studies that use measures in plasma to track changes in OT levels after nasal administration in humans have found significant increases in OT levels from baseline at 30 minutes (Gossen et al., 2012), 45 minutes (Domes et al., 2010), and over the course of one hour (Burri et al., 2008). Furthermore, a number of human studies have reported correlations between peripheral levels of endogenous OT and behavior. High levels of plasma OT have been associated with trust and trustworthiness (Zak et al., 2005; Zak et al., 2007), positive physical contact with a partner (Grewen et al., 2005), and lower levels of anxiety in patients with depression (Scantamburlo et al., 2007). By contrast, low peripheral levels of OT have been found in patients with depression (Cyranowski et al., 2008), schizophrenia, (Goldman et al., 2008; Keri et al., 2009) and autism spectrum disorders (Green et al., 2001).

However, there are numerous animal studies that show no correlation between plasma and CSF levels of OT in response to a variety of manipulations, ranging from hormone administration to environmental cues (Amico et al., 1990; Rosenblum et al., 2002; Seckl and Lightman, 1987; Veening et al., 2010; Winslow et al., 2003). Winslow et al., (2003) reported significant differences in endogenous CSF OT levels between nursery and mother reared rhesus monkeys over a period of development, but no difference in plasma OT between the groups, and no correlation between CSF and plasma OT. Because OT cannot cross the blood-brain barrier (BBB), central and peripheral OT systems may be independently regulated, thus peripheral and central effects of OT are thought to be coordinated through its common release as a result of collateral axons in the pituitary and nucleus accumbens (Ross and Young, 2009). It may be that correlations cannot be detected due to temporal differences in responses between peripheral and central systems (Neumann et al., 2013). Bioavailability differs significantly in plasma versus CSF; OT is broken down within two minutes in plasma, while it lasts for up to a half an hour in CSF due to a lack of hydrolyzing enzymes (Jones and Robinson, 1982; Mens et al., 1983; Robinson et al., 1982; Robinson and Coombes, 1993; Veening et al., 2010; Viero et al., 2010).

Importantly, whether peripheral OT levels are indicative of central OT levels remains an open question. It is interesting that both CSF and plasma OT levels can be correlated with behavioral changes, but do not have a detectable correlation with each other. More work needs to be done to further investigate the nature of the relationship between peripheral and central levels.

Intranasal delivery

There is considerable uncertainty as to how intranasal OT might exert behavioral effects. Animal studies suggest that intranasal delivery can bypass the BBB via extracellular pathways in the epithelium, though more than one route is possible. Two potential pathways have been identified: a peripheral olfactory route connecting the nasal passages with the olfactory bulbs and rostral brain regions (e.g. anterior olfactory nucleus and frontal cortex), and a peripheral trigeminal system connecting the nasal passages with brainstem and spinal cord regions. Both routes provide rapid entry to the CNS (Thorne et al., 2004). Given that the behavioral effects of intranasal OT can appear shortly after delivery, these routes are likely candidates for a transport mechanism by which OT could enter the brain. Recent rodent work supports this suggestion (Neumann et al., 2013). After nasal administration of OT in rats and mice, it has been shown using microdialysis that OT levels increase in the dorsal hippocampus and amygdala of rats and mice, with peak levels occurring 30–60 min after administration. Corresponding changes were also observed in plasma. OT was found to be quite uniformly distributed within the brain extra cellular fluid (ECF) suggesting that effects were not due to locally released endogenous OT, particularly because there are no OT receptors in the dorsal hippocampus and no local OT pathways terminate in that area (Neumann et al., 2013). This is of note, since it has been speculated that very small volumes of the intranasally delivered drug might be sufficient to trigger release of endogenous OT as exogenous OT has been shown to have a positive-feedback effect on endogenous release in a dose-dependent fashion (Falke, 1989; Moos et al., 1984). However, the lowest dose of OT applied in this study was about 400 pg/ml. Estimates of the CSF level of OT in rats and monkeys following intranasal delivery is about 50 pg/ml (Neumann et al., 2013; Chang et al., 2012). Thus, estimates of CSF levels achieved by intranasal delivery are lower than the levels (400 pg/ml) that have been shown to lead to endogenous release and therefore it is not clear if the intranasally delivered OT can drive this mechanism.

Work with other peptides shows consistent findings. Neuropeptide S (NPS), another large, hydrophilic molecule, is detectable in the rat brain using fluorophore-conjugation techniques at 15min after its intranasal delivery. It was also found that the neuronal populations targeted by intranasal administration were identical to those targeted by intracerebroventricular injection of NPS into the right lateral ventricle (Ionescu et al., 2012), suggesting that either delivery method would lead to similar results. Also, intranasal administration of radiolabeled 60-amino acid galanin-like peptide has been shown to cause transport of the peptide into the rat olfactory bulb, as well as other selected brain regions when combined with cyclodextrins for specific targeting (Nonaka et al., 2008).

Corresponding human data does not exist for OT, as clinical studies are limited to assessing only plasma levels after intranasal delivery (but see Born et al., 2002, for vasopressin

assessment in CSF), though these studies consistently find correlations with increased plasma OT levels and changes in behavior (Challinor et al., 1994; Domes et al., 2010). OT behavioral studies often cite work showing that vasopressin, which is closely related to OT, reaches peak levels in CSF in 30–50 minutes when administered intranasally (Born et al., 2002). Limited data has shown increased levels of central OT after nasal administration, in two rhesus macaques (Chang et al., 2012). Future studies with a larger group of subjects are planned to determine whether intranasal administration of OT leads to reliable elevation of OT in the CSF and plasma compared to placebo.

While there is some suggestion that intranasal administration of OT increases CSF OT levels, the route of action is still unknown. It is not clear whether behavioral effects that follow peripheral administration of OT are driven by increased central concentrations of OT due to the OT entering the CNS, or to an indirect peripheral effect driving central production and release of OT. A third possibility is that peripheral effects of OT may drive indirect behavioral effects through unknown mechanisms. Further studies will be needed to determine the route and distribution of OT following intranasal delivery. There are at least two possible experimental approaches to track the intranasal route into the CNS. First, using a peripheral OT antagonist that does not cross the BBB in conjunction with intranasal OT administration would eliminate any peripheral actions (blocking peripheral OT receptors) that might confound interpretation of central effects. Second, radiolabelling or fluorophore-conjugated OT delivered in nonhuman primates would reveal the pattern of uptake and distribution, and show whether it is the exogenous OT that is acting directly in central locations, or whether it is triggering endogenous production and release without uptake into central areas.

Finally, it should be noted that individual differences in anatomy likely introduce variation in intranasal OT uptake. Nasal anatomy influences airflow, which influences the degree to which OT accesses the epithelium following nasal spray. Whether other constituents are included in the manufacture of the spray (e.g. uptake enhancers) is important, and dosage has also varied considerably between studies. The confounding effects of these factors could explain some of the inconsistencies in findings that are discussed in the next section. To minimize these effects, a protocol, which standardizes intranasal OT administration, has been proposed by Guastella et al (2013).

Intranasal oxytocin: effects on social cognition

A possible “pro-social” role for OT was first suggested by work showing that OT could induce maternal behaviors in virgin female rats (Pedersen and Prange, 1979). Subsequent work showed that pulsatile release of OT influences pair bonding in the monogamous female prairie vole, in combination with olfactory signals (Williams et al., 1994). These findings, along with the availability of OT nasal sprays, inspired researchers to search for corresponding effects in humans. The last decade or so has seen a large number of published findings demonstrating that OT can enhance the processing of social stimuli and regulate various social behaviors.

Facial expressions

OT has been shown to influence the recognition of emotional facial expressions in static (Di Simplicio et al., 2009; Guastella et al., 2010; Marsh et al., 2010) and dynamic (Fischer-Shofty et al., 2010; Lischke et al., 2012a) images of faces. In addition, studies have shown that OT affects probabilistic learning when participants have to learn to associate reward with happy, sad or angry faces: OT appears to counteract the natural aversion to selecting angry face stimuli while having no effects on other expressions (Evans et al., 2010). Other work has shown that OT can introduce a general positive bias in face judgment. OT administration increases ratings of trustworthiness and attractiveness of male and female targets in raters of both sexes (Theodoridou et al., 2009), and some researchers have found that OT enhances emotion recognition only for positive expressions (Marsh et al., 2010) and slows recognition of fearful ones (Di Simplicio et al., 2009), although conflicting results have been reported, with some studies reporting effects for fearful expressions only (Fischer-Shofty et al., 2010). Work by Lischke et al., (2012b) found that OT reduced the intensity at which all emotions could be recognized, with some evidence that this effect favors angry and fearful expressions. Several of these results are inconsistent with respect to which emotions are differentially processed following OT administration. This may be due to the small number of participants often used, and differences in the experimental approaches.

Studies of covert attention have shown that OT creates an attentional bias towards happy over angry faces, indicating that OT might shift early attentional processes towards positive social stimuli (Domes et al., 2013). Eye-tracking studies with male participants have shown that OT increases gaze time spent exploring the eye region compared with other parts of a face (Andari et al., 2010; Gamer et al., 2010; Guastella et al., 2008a), suggesting that improvements in facial emotion recognition might be due to an enhanced processing of the information-rich eye region. Three other studies, however, have not replicated this finding in female participants (Domes et al., 2010; Lischke et al., 2012a; Lischke et al., 2012b).

In males, OT enhances the ability to infer the mental states of another person when only the eye regions are presented as a cue (Domes et al., 2007; Guastella et al., 2010). OT has been shown to decrease amygdala activation to fearful, angry and happy faces even when presented implicitly (Domes et al., 2007), suggesting that an OT-mediated reduction in amygdala activation might encourage the perception of social cues by making participants feel more at ease while viewing faces, since perception of any face stimulus activates the amygdala, particularly if its unfamiliar (Haxby et al., 2000) or involves direct eye contact (Kawashima et al., 1999). After intranasal OT, decreased activity in amygdala sub-regions associated with face processing seems to be associated with increases in sub-regions associated with gaze, supporting this suggestion; there is also evidence that OT can enhance amygdala activity for happy expressions, possibly reflecting a shift of processing toward positive social stimuli (Gamer et al., 2010). Whether these effects generalize to females is unclear; the issue of gender effects is discussed further below.

Trust

One of the most highly publicized effects of OT is its role in trust. Kosfeld et al. (2005) used a trust game involving real monetary stakes, where participants were asked to play the role of either investor or trustee. Investors who had been treated with OT made significantly more investments compared to investors treated with placebo. Importantly, no difference was seen in an identical ‘risk’ task where participants were playing against a computer rather than another human. OT has also been shown to affect trust adaptation: OT-treated individuals have been shown to persist in trusting behaviors even after repeated betrayal, and this has been linked to a modulation of amygdala activity (Baumgartner et al., 2008). Conscious and implicit distrust of faces is associated with amygdala activation (Winston et al., 2002) while amygdala lesions increase trust (Adolphs et al., 1998). Thus amygdala deactivation could explain why OT enhances stimulus processing and promotes trust behavior.

However, other findings contradict the notion that OT reliably promotes “pro-social” behavior (Bosch et al., 2005; Shamay-Tsoory et al., 2009). For example, findings by Shamay-Tsoory et al. (2009) seem to suggest that OT effects are not always positive in a trust context. Using a game of chance with financial stakes, it was found that OT increased self-report ratings of envy when another (fake) participant won more money, and increased ratings of gloating when the other participant lost more money. These results are presented as evidence for OT effects on a wide range of (not necessarily positive) social emotion-related behaviors. However, an alternative view is that OT reduces social inhibition, thus making participants more likely to admit to socially unacceptable emotions such as gloating.

Memory

OT also seems to promote recognition memory for social stimuli. OT administered before encoding of face stimuli improves the accuracy of familiarity made a day later, by lowering the false alarm rate and thereby improving the signal-to-noise ratio for discriminating new faces from old (Rimmele et al., 2009). Other studies have shown similar results, although Savaskan et al. (2008) found that OT improved recognition memory for neutral and angry, but not happy faces, whereas Guastella et al. (2008b) found that the effect was only present for happy faces. Despite this inconsistency, Rimmele et al. showed that OT does not improve recognition for non-social stimuli. It has been argued that this result parallels similar findings in mice, since OT-knockout mice seem to be impaired at detecting whether an intruder is novel or familiar, while non-social memory and olfactory function appear intact (Ferguson et al., 2002), and OT injected into the amygdala can reinstate normal performance (Ferguson et al., 2001). However, as noted by Insel and Fernald (2004), mouse social recognition paradigms differ from person recognition in humans in that pheromonal recognition is a major factor.

Relationship Status

There is intriguing evidence that OT might promote fidelity within monogamous human relationships and thus carry out a function similar to that observed in prairie voles. OT administration causes men in a monogamous relationship, but not single ones, to distance themselves from an attractive female experimenter, and to approach pictures of attractive

women more slowly (Scheele et al., 2012). The early stages of romantic attachment have been linked to enhanced OT levels in plasma, the levels of which can predict whether the relationship is sustained 6 months later (Schneiderman et al., 2012). Physical intimacy and greater spousal support in a relationship has been linked to higher plasma OT levels (Grewen et al., 2005; Light et al., 2005), and it has been shown that a dose of intranasal OT delivered prior to a couple conflict discussion can increase positive communication and reduce conflict-related rises in salivary cortisol levels (Ditzen et al., 2009). Thus higher basal OT levels, and intranasal OT, seem to promote attachment to a partner and the resolution of conflicts, and OT causes males in a monogamous relationship to behave cautiously in the presence of another female, promoting monogamy. Interestingly, other studies have shown that plasma OT also increases with relationship distress in women (Taylor et al., 2006; Taylor et al., 2010), and this is supported by work in prairie voles showing that long-term social isolation causes elevated plasma OT in females (Grippe et al., 2007). Elevated OT in this context has been interpreted as a signal to affiliate with others because the pair-bond relationship is threatened (Taylor et al., 2010). This issue requires further exploration, as does the gender-specificity. It would also be interesting to investigate whether relationship status affects response to OT within other social settings, such as trust.

Inconsistent gender effects

As discussed briefly above, both animal and human studies have reported inconsistent responses to OT between male and female subjects. Animal studies have suggested that the effects of OT might be modified by interactions with estrogen (McCarthy et al., 1996), and many human studies have opted to include male participants to simplify interpretation of results. Significant sex specific effects have been found for vasopressin (AVP). In men, intranasally administered AVP stimulates agonistic facial expressions and decreases perception of trust in response to pictures of same-sex strangers. In women, administration of the same peptide results in affiliative facial expressions and increased perception of friendliness (Thompson et al., 2006). Although limited data is available, studies point to powerful gender differences in OT effects as well. A recent study has investigated the role of exogenous OT in reaction to social stress in both genders (Kubzansky et al., 2012). Males given OT reported less distress to stress exposure, while females reported more distress and more anger. Moreover, neuroimaging work suggests divergent effects on amygdala activation. In males, OT tends to elicit decreased amygdala activity in response to emotional faces (Domes et al., 2007); in females, OT enhances reactivity to social and non-social threat, an effect which could be mediated by estrogen (Domes et al., 2010; Lischke et al., 2012b). More work is needed to investigate these gender differences; this is particularly relevant when considering OT in a therapeutic context.

Effects in clinical populations

Despite considerable interest in the “pro-social” effects of OT as a potential treatment option for schizophrenia and autism, it is important to note that OT does not always produce positive social effects in clinical populations. It has been shown that the “typical” responses to acute intranasal administration can be altered by individual variation in psychological profile or endocrine systems, and dose levels. OT can actually hinder trust and cooperation in participants with Borderline Personality Disorder (Bartz et al., 2010). A dose-dependent

result in identifying emotional expressions in schizophrenic patients was found by Goldman et al. (2011), showing that emotion recognition actually decreased from baseline at a low dose of 10 IU, but then improved above baseline at 20 IU. Bales and colleagues (2013) also found dose-dependent effects on the development of pair-bonding in male voles; the direction of OT effects differed according to whether it was delivered acutely or chronically, demonstrating further that dosing regimen might be critical. The “pro-social” effects outlined above might not generalize to a chronic administration schedule.

Specificity of OT effects

A criticism of the work outlined above concerns the issue of specificity. The animal literature argues convincingly for OT effects to be specifically social in nature. Studies in humans have tended to work from the assumption that this is also the case, to the exclusion of considering alternative explanations for their findings. Churchland and Winkielman (2012) argue that OT effects might be better characterized in terms of more general mechanisms such as anxiety reduction, affiliative motivation, or social saliency. Indeed, it would be unusual for a hormone and neurotransmitter such as OT to affect processing and responses under very particular circumstances, especially when such circumstances are those which require the relatively abstract, ‘higher order’ operations of the social brain. Churchland and Winkielman instead suggest that the anxiolytic effects of OT can explain the majority of findings. These anxiolytic effects have been well demonstrated in mice (Mantella et al., 2003; Ring et al., 2006) and there is some evidence for similar effects in humans. Nursing mothers with higher OT plasma levels are more likely to describe positive mood states and reduced anxiety (Carter et al., 2001; Heinrichs et al., 2001) whereas abuse in childhood has been linked to lower OT concentrations in CSF and higher anxiety scores (Heim et al., 2009). Intranasal OT has been shown to decrease anxiety in a simulated public speaking test (de Oliveira et al., 2012; Heinrichs et al., 2003). The findings described above, which show that OT acts to promote affiliative social behaviors, could be due to a general reduction in anxiety. However, studies that have attempted to assess mood and anxiety changes using brief self-report questionnaires after intranasal OT tend not to find any changes (Guastella et al., 2008b). This is confirmed by a systematic review of 38 randomised controlled trials of intranasal OT, which concluded that OT produces no detectable subjective changes in recipients (MacDonald et al., 2011).

Nevertheless, the notion that anxiolytic effects must be present to some degree is supported by the OT neuroimaging data, the majority of which concerns the amygdala, a key site in anxiety regulation. A study by Singer et al. (2008) investigated OT effects on empathy (using a paradigm where participants observe, and receive, painful stimulation of the hand), and “pro-social” behavior (using an economic exchange paradigm). The only observed effects were a reduction in amygdala activation in response to painful stimulation of self; “pro-social” behavior and empathy were unaffected, as was activity in brain regions implicated in empathy tasks of this type, such as insula.

In contrast, there are some lines of evidence suggesting that OT effects are indeed specific to social contexts and not anxiety-dependent. The use of non-social controls demonstrates specificity of effects, although it could be argued that some other variable (e.g. perceived

complexity or importance) is not identical across conditions and thus responsible for the lack of effects (Kosfeld et al., 2005). It is hard to level such criticism at a study by Unkelbach et al. (2008), who found that OT speeds detection of positive words specifically associated with sexuality, bonding, and social relationships while having no effects on other positive and negative stimuli. Pupillometry studies have shown greater cognitive resource allocation to social stimuli under OT (Prehn et al., 2013). Hurlemann et al. (2010) used social (happy/angry faces) and non-social (colored dots) reinforcements in an associative learning task to show that OT improves learning in the social condition only. OT also improved self-reported emotional empathy intensity ratings for both positively and negatively valence pictures.

Perhaps the evolutionary importance of our social world justifies an argument for the effect of OT being socially specific. It is possible that a more general mechanism could explain the findings, but since the literature is so heavily biased towards social processing there is at present insufficient data. However, it is important to note that the anxiolytic effects of OT, which have been put forward as a possible explanatory mechanism (Churchland and Winkielman, 2012), are poorly specified in humans. Evidence of anxiolytic effects has been inferred from studies measuring basal levels of plasma OT (and thus offers no proof of a direct relationship, as well as being subject to the criticisms outlined above), and work showing an anxiolytic effect in a social context. Could it be that anxiolytic effects only emerge in a social setting, with anxiolysis actually resulting from a positive processing bias for social stimuli, generating an enhanced sense of social approval? In line with this suggestion, OT has been shown to potentiate the anxiolytic effect of social support during a stressful public speaking test (Heinrichs et al., 2003). It is clear that the anxiolytic effects of intranasal OT need to be better characterized, and all future studies should take more care in excluding anxiolytic effects as a confound. The literature would also benefit from a wider use of non-social control conditions, to assert specificity of effects with more confidence.

It is interesting to note that OT effects on the processing of social stimuli seem to be more robust than effects on social behaviors. In contrast to the work by Kosfeld et al. described above, some studies have shown that OT can actually decrease trust behaviors if the other party is portrayed as untrustworthy (Mikolajczak et al., 2010), is unknown (Declerck et al., 2010) or is a member of a social out-group (De Dreu et al., 2010). It could be that OT reliably increases the salience of social stimuli, but “pro-social” behaviors only emerge in the presence of context-dependent anxiolytic effects, or be dependent on other factors. Researchers should therefore be wary of assuming that OT enhances all aspects of social function. This is demonstrated by Hurlemann et al. (2010), who found that while OT increased self-reported emotional empathy in the Multifaceted Empathy Test, OT did not improve a participant’s accuracy for inferring mental states. This finding supports the notion that OT makes social stimuli more salient, presumably at the level of the amygdala, but this enhancement does not necessarily translate to improved theory of mind. OT effects on higher-order social function seem to be complex and more work is certainly needed to determine the circumstances under which intranasal OT is “pro-social”.

Conclusion

In conclusion, there are still many questions regarding the mechanisms by which intranasal delivery of OT enters the brain and the inconsistent behavioral effects reported in literature. Future studies with larger subject groups should investigate whether intranasal administration of OT leads to reliable elevation of OT in the CSF and plasma and if peripheral and central OT levels are correlated. Furthermore, more studies will be needed to determine the route and distribution of OT following intranasal delivery. Despite the multitude of studies investigating the effects of OT on human behavior and social cognition, the inconsistent results leave open the debate between the notion that OT reliably promotes “pro-social” behavior or has anxiolytic effects. Moreover, some studies have pointed out powerful gender differences in OT effects, but most studies were conducted in males only, discounting gender effects. It seems that the small numbers of male participants typically employed, combined with differences in methods, tasks, and the stimulus sets used, could underlie these inconsistent findings. Future studies should investigate OT effects across genders and be designed to determine the degree to which possible general anxiolytic effects contribute to changes in response in socially specific challenges.

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