Oxytocin and Aggression

Trynke R. de Jong and Inga D. Neumann

Abstract The neuropeptide oxytocin (OT) has a solid reputation as a facilitator of social interactions such as parental and pair bonding, trust, and empathy. The many results supporting a pro-social role of OT have generated the hypothesis that impairments in the endogenous OT system may lead to *antisocial* behavior, most notably social withdrawal or pathological aggression. If this is indeed the case, administration of exogenous OT could be the "serenic" treatment that psychiatrists have for decades been searching for.

In the present review, we list and discuss the evidence for an endogenous "hypo-oxytocinergic state" underlying aggressive and antisocial behavior, derived from both animal and human studies. We furthermore examine the reported effects of synthetic OT administration on aggression in rodents and humans.

Although the scientific findings listed in this review support, in broad lines, the link between a down-regulated or impaired OT system activity and increased aggression, the anti-aggressive effects of synthetic OT are less straightforward and require further research. The rather complex picture that emerges adds to the ongoing debate questioning the unidirectional pro-social role of OT, as well as the strength of the effects of intranasal OT administration in humans.

Keywords Aggression • Conduct disorder • CU traits • Oxytocin • Resident-intruder test

Contents

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1 Introduction

Oxytocin (OT) has a solid reputation as a pro-social neuropeptide, promoting af-filiation and bonding in various species ranging from fish and birds to rodents and primates (Donaldson and Young 2008). This raises an important question: if OT indeed promotes bonding, care-giving, trust, empathy, sharing, and affiliation, does this mean that impairment of OT neurotransmission leads to antisocial and ego-centric behaviors, in particular social rule-breaking and aggression? And, if this is so, is it feasible to treat pathologically aggressive individuals with drugs targeting the OT system?

   In the present review, we first describe the various methods used to quantify ag-gression and antisocial behavior in rodents, primates, and humans. We point out some inconsistencies and translational gaps that still exist. Then, we provide an overview of studies exploring associations between variability in the endogenous OT system (at the genetic, epigenetic, or protein level of OT and/or its receptor) and aggressive behavior in rodents and humans. Next, we discuss if and how various pharmacological manipulations altering OT neurotransmission affect aggression-related behaviors. Finally, we integrate these findings to describe a working model of how the OT system may modulate aggression and we list the most urgent re-search questions that need to be answered.

2 Categorizing and Quantifying Aggression

Translational animal models have proven to be highly useful in the identification of biomarkers predicting high aggression and the detection of "serenic" effects of drug treatments (Blanchard and Blanchard 2003). However, the translation of data ob-tained in animal models of aggression to violent human individuals is not without caveats (Blanchard et al. 2003). In this context, major methods of quantifying and categorizing aggression in both animal models and humans need to be discussed in order to define potential translational gaps.

   In behavioral neuroscience, psychology, and psychiatry, the term "aggression" is typically used to describe behaviors aimed at another individual with the goal to

subordinate or to cause physical or psychological harm. These behaviors generally include threatening postures, actions that limit the movements of the other individual (such as pinning them down or pushing them against a wall), and actions that physically injure the other individual (biting, clawing, punching, kicking, etc.). These behaviors are similar in animals and humans, although humans have added verbal aggression (shouting, cussing, insulting) and indirect aggression (gossiping, social exclusion) to their repertoire (Krahé 2013), as well as the use of highly efficient firearms and weapons of mass destruction. The term "violence" is often used interchangeably with human aggression; however, in the present review, we will use it to signify extreme human aggression resulting in considerable physical injury of the victim.

In laboratory animals, especially rats and mice, the resident-intruder test (RIT) is most often used to quantify inter-male aggressive behavior (Koolhaas et al. 2013; Neumann et al. 2010), and this has recently been extended to inter-female aggression using the female intruder test (FIT) (De Jong et al. 2014). In this standardized behavioral test, the experimental animal (the resident) is first allowed to establish its home cage territory and is then confronted with a smaller same-sex conspecific intruder in that territory for a brief, defined period (typically 10 min). Trained observers score the latency time until the resident first attacks, the frequency or duration in which aggressive behaviors occur, as well as qualitative aspects such as ferociousness of attacks, attacks of vulnerable body parts, or the presence/absence of warning signals prior to attack. In sum, these behavioral data are interpreted as the aggressive state of the resident animal, which can be associated with endogenous markers or manipulated pharmacologically.

Of course, such a paradigm is not feasible in human subjects for obvious ethical reasons. Therefore, the acute quantification of human aggression is realized using competitive computer games. Popular options are (versions of) the point subtraction aggression paradigm (PSAP) and the response choice aggression paradigm (RCAP) (Giancola and Chermack 1998). In the PSAP, subjects can both earn and steal points by rapidly pushing buttons, but so can their "opponent" (who is virtual, unknown to the subject). Aggressive behavior is quantified in terms of proactive or retaliatory point stealing. In the RCAP, subjects are playing a competitive reaction time test and are being punished by the (again, virtual) opponent when losing, for example by a loud aversive sound or a painful electric shock. Test subjects are then allowed to punish the opponent as well and their level of aggression is quantified as the frequency and severity of punishment they deliver. These and other comparative paradigms have been under considerable debate with respect to their validity as a reflection of true aggression (Ferguson and Rueda 2009). Nevertheless, the major factors influencing acute aggression in real life (sex, trait aggression, alcohol, and many others) influence aggression in these laboratory paradigms in the same direction (Anderson and Bushman 1997), supporting the external validity of these measures.

A second approach in both animal and human aggression research is the categorization of individuals in high- or low-aggressive subgroups. In animals, this may be achieved via elaborate behavioral screening of large cohorts in order to select individuals displaying stable high or low aggressive traits. Subsequently, these individuals

can be compared with respect to selected neurobiological or neuroendocrine markers of interest, or their response to pharmacological manipulations. This approach has been proven particularly fruitful in Wildtype Groningen (WTG) rats, a feral rat strain of which the males display a marked individual variability in aggression (De Boer et al. 2003). Furthermore, animals with contrasting aggressive traits may be selected for parallel breeding lines resulting in offspring with predictable levels of aggression (Natarajan et al. 2009). Such contrasting traits have also been found in rats selectively bred for high and low anxiety behavior (HAB and LAB rats, respectively), in which especially male LAB rats display excessive aggression (Neumann et al. 2010; Beiderbeck et al. 2012). Additional approaches include the knocking-out of potential aggression-related genes to generate high- or low-aggressive strains (Takahashi and Miczek 2014) or manipulating the early-life social environment resulting in alterations in trait aggression in juvenile and adult male rats (Veenema and Neumann 2009; Veenema et al. 2006).

In humans, the categorization into high- and low-aggressive subtypes can be done by assessing an individual's life history of aggression or tendency to be aggressive using convictions for violent crimes or, more commonly, questionnaires. It is of note here that a multitude of questionnaires exist for this purpose and that rarely the same questionnaire was used more than once throughout the publications cited in the present review. A third method of categorization is the diagnosis of an aggression-related psychiatric disorder such as conduct disorder (CD), antisocial personality disorder (ASPD), intermittent explosive disorder (IED), or borderline personality disorder (BPD). The selection of human subjects with high or low levels of trait aggression is then most often used to associate their behavior with certain biomarkers, such as hormone levels or single nucleotide polymorphisms (SNPs). In this context, an additional topic deserving some attention is the increasing scientific interest in "callous and unemotional traits" (CU traits) as a quantifiable correlate of aggression, at least in humans. CU traits are defined by a lack of feelings of guilt, a lack of empathy, and callous use of others for egoistic reasons (Frick and White 2008). These traits are associated with instrumental aggression used for personal gain (as opposed to reactive and defensive aggression used to prevent or retaliate a personal loss) and, together with stealing, lying, and vandalism, form the main antisocial symptoms of CD and ASPD. Importantly, the recent interest in CU traits in humans is not yet complemented with translational animal models. The investigation of endogenous variability in, or pharmacological manipulation of, empathy and altruism in laboratory rodents is therefore a promising future research topic (Bartal et al. 2011; Hernandez-Lallement et al. 2014; Sato et al. 2015).

3 Associations Between the Endogenous OT System and Aggressive Phenotypes

Aggression is a highly variable trait. It can vary across species, across individuals, and even within individuals over time. How much of this behavioral variability can be explained by a relative up- or down-regulation of the endogenous OT system? We will look at the evidence from studies in rodents as well as in humans.

3.1 Markers of the Endogenous OT System in the Periphery and the Brain

The mammalian OT system is mainly constituted of magnocellular neurons in the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei that project to the neurohypophysis and secrete OT into the blood stream in response to various physiological stimuli. Thus, an important marker of the OT system, accessible both in animals and humans, is the concentration of OT in plasma or saliva under basal conditions or in response to a relevant challenge such as emotional stress or physical exercise (Crockford et al. 2014; De Jong et al. 2015; Neumann and Landgraf 2012). Whereas basal concentrations assessed in the laboratory may vary depending on previous (uncontrolled) activities of the individual, controlled stimulation of the OT system (for example by physical exercise, emotional challenge, or sex) allows to directly assess the responsiveness of the system. Especially the quantification of OT in saliva, which can be collected under completely stress-free conditions even at home, could be an excellent option to assess OT levels in children, adolescents, or patients (De Jong et al. 2015). Importantly, we have to keep in mind that plasma or saliva OT does not reflect the activity of the brain OT system, although most physiological stimuli which trigger OT secretion into blood also stimulate OT release in selected brain regions (Neumann and Landgraf 2012). Another possible peripheral marker of the OT system is OTR binding in different tissues (e.g., skin, heart), although this has, to our knowledge, never been performed in the context of behavioral studies in animals or humans. However, genetic (SNPs) or epigenetic (e.g., methylation patterns) variability in the gene coding for OTR can be easily assessed in human blood cells and may serve as biomarkers of aggression (see Sect. 3.3).

Reliable and relevant biomarkers of extreme aggression (or other types of pathological or abnormal social behavior) are far more likely to be found in the *central* OT system. Due to its limited access in humans, the brain OT system is rather a target for rodent studies. Here, the local expression of the genes for OT (*OT*) or OTR (*OTr*) can be studied under basal conditions or, for example, in response to behavioral challenges such as the RIT. Moreover, the amount of OT-immunoreactive (OT-IR) neurons or the strength of local OTR binding may provide associative indicators in the context of aggressive behavior. Also, the expression of immediate early genes at mRNA or protein level in hypothalamic OT neurons provides at least a punctual picture of stimulus-

dependent activation of hypothalamic OT neurons, e.g., in response to an intruder. Finally, OT content in the cerebrospinal fluid (CSF) has been used in both humans and animals to provide information about the global activity of the central OT system. In animals, a considerably higher temporal and spatial resolution can be reached using intracerebral microdialysis, i.e., the collection of extracellular fluid samples under basal conditions and during and after a challenge followed by quantification of OT content using highly sensitive radioimmunoassays (Neumann et al. 2013).

3.2 Endogenous OT and Aggression in Animals

Most studies in rodents have shown that high aggression is associated with reduced expression of OT or lower activation of OT neurons, as well as altered OTR binding. Thus, excessively aggressive male WTG rats express less OT mRNA in the PVN compared to low-aggressive individuals (Calcagnoli et al. 2014a). Consistently, adult male mice that underwent daily 3-h bouts of maternal separation in the first 2 postnatal weeks showed a marked reduction in aggression, which coincided with an increased number of OT-IR neurons in the PVN in one study (Tsuda et al. 2011), though not in another (Veenema et al. 2007). Using exposure to a female intruder as a social challenge in the FIT, virgin female Wistar residents that attacked the intruder showed less activation of OT neurons (using pERK as a marker) compared with females that tolerated the intruder (De Jong et al. 2014). Likewise, exposure to an intruder increased the activation of OT neurons in the PVN in non-aggressive worker males, but not in aggressive soldier males, in the eusocially organized naked mole rat (*Heterocephalus glaber*) (Hathaway et al. 2016). The higher activation of the OT system in friendly compared with aggressive encounters was not or very modestly reflected in increased plasma levels of OT (Ebner et al. 2005; Trainor et al. 2010).

Thus far, no reports have been published about the central release of OT during aggressive behavior, except in the context of maternal aggression (see below). Preliminary data from our lab indicate that OT is robustly released in the PVN of male Wistar residents during aggressive encounters with an intruder as revealed by intracerebral microdialysis. In contrast, in female rats, both the release of OT within the PVN and the duration of aggression displayed during the FIT were lower in virgin female residents (Fig. 1a). Although this may at first sight suggest that high OT release is linked to high aggression, when looking more closely, it appears that among virgin females (but not males), the relative increase in OT in the PVN correlated negatively with the duration of aggression (Fig. 1b). These preliminary results form a starting point for further microdialysis studies encompassing additional target areas, which may each display a unique pattern of aggression-related OT release (as shown for AVP release; Veenema et al. 2010). These data indicate a clear sex difference in the role of OT in the regulation of aggressive behavior that requires follow-up research.

A few studies have quantified OTR binding associated with aggression. Specific emphasis has been placed on a number of OTR-positive brain areas that are known
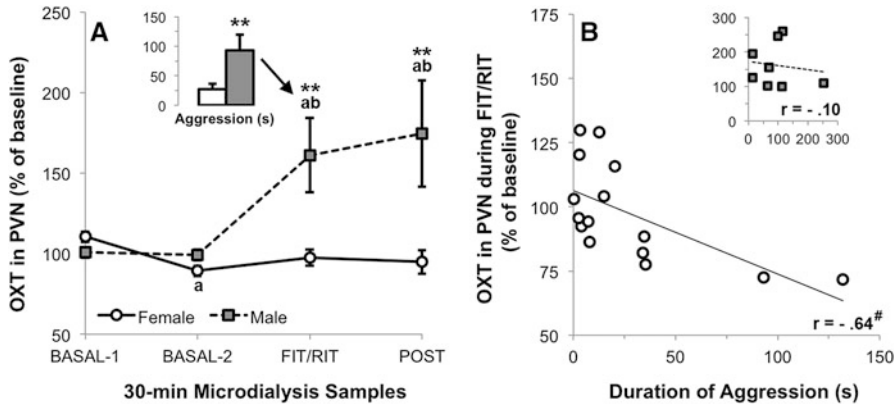
Fig. 1 Relative OXT content in microdialysates sampled from the PVN of adult male ($n = 8$) and virgin female ($n = 15$) Wistar rats during (**a**) four consecutive 30-min microdialysis samples collected before (BASAL-1/2), during (FIT/RIT), and after (POST) a 10-min interaction with an intruder, with insert depicting the average duration of aggression toward the intruder, and (**b**) the FIT/RIT sample correlated with the duration of aggression toward the intruder in females, with insert depicting the same correlation in males. Microdialysis procedures were followed as described earlier (Waldherr and Neumann 2007). Until surgery, male residents were co-housed with one female for at least 12 days and female residents were group-housed with 2–3 females since weaning (females). All residents underwent one RIT/FIT ("pre-test"), 4–7 days prior to surgery. A two-way mixed model ANOVA revealed a main effect of time (within-subjects factor, $F[1.72] = 7.43$, $P = 0.003$), a main effect of sex ($F[1] = 11.97$, $P = 0.002$), and a significant interaction of time $\times$ sex ($F[1.72] = 9.16$, $P = 0.001$). [a/b]Sample differs from corresponding [a]BASAL-1 or [b]BASAL-2 sample ($P < 0.05$). **Sample differs from corresponding female sample ($P < 0.01$). [#]Significant Pearson's correlation coefficient ($P < 0.05$)

to be involved in aggressive behavior in rodents, such as the central and medial amygdala (CEA/MEA), bed nucleus of the stria terminalis (BNST), lateral septum (LS), medial preoptic area (MPOA), lateral hypothalamic area, ventromedial hypothalamus, and the PVN (Nelson and Trainor 2007). Thus, high-aggressive WTG rats show elevated OTR binding in the CEA and BNST, but not the LS, compared with low-aggressive males (Calcagnoli et al. 2014a). Reduced OTR binding in the caudate putamen and LS and elevated OTR binding in the MPOA were found in male Wistar rats that had become highly aggressive in response to daily 3-h bouts of maternal separation in the first 2 postnatal weeks (Lukas et al. 2010). Although it is not quite clear whether locally increased OTR binding indeed reflects increased or even reduced (due to reduced availability of the ligand) OT neurotransmission in that brain area, these associative binding studies are particularly useful for the selection of target areas for future local manipulations or measurements.

Although the results described above have linked variability in endogenous OT expression and activation, as well as OTR binding, with aggressive traits and/or acute aggression, they have not revealed whether variability in the OT system is the cause or the effect. To tackle the problem of causality, knockout mouse strains missing the gene for either OT ($OT^{-/-}$) or its receptor ($OTr^{-/-}$) were generated and their aggressive

tendencies compared. The first wave of studies was performed in $OT^{-/-}$ mice, but results were inconsistent and both increases and decreases in aggression were reported (DeVries et al. 1997; Lazzari et al. 2013; Ragnauth et al. 2005; Winslow et al. 2000). The contrasting results were later explained by the fact that, in some studies, $OT^{-/-}$ mice were born to $OT^{-/-}$ mothers, whereas in others they were born to $OT^{+/-}$ mothers, the latter condition leading to transient exposure to maternal OT during gestation and lactation and, as a result, reduced aggression in adulthood (Dhakar et al. 2012; Takayanagi et al. 2005). A second problem in $OT^{-/-}$ mouse strains is the ability of AVP to bind to OTR, which may result in considerable compensatory mechanisms that are difficult to unravel in terms of behavioral outcome (Ragnauth et al. 2004). The generation of $OTr^{-/-}$ mice resulted in a second wave of studies that equivocally reported increased levels of aggression in the absence of OTR (Dhakar et al. 2012; Takayanagi et al. 2005; Hattori et al. 2015; Sala et al. 2011, 2013). If, however, the OTr knockout was induced after weaning, rather than at fertilization, and was limited to forebrain areas rather than the entire body, the effect on aggression disappeared (Dhakar et al. 2012). Limiting the ablation of OTr to serotonergic neurons in the dorsal and median raphe nucleus, on the other hand, reduced aggression in males (Pagani et al. 2015).

Clearly, the majority of studies rather point towards an anti-aggressive effect of an up-regulated endogenous OT system, at least in male and non-lactating virgin female rodents. Maternal aggression, which is the violent response of dams in late pregnancy, and early lactation, towards intruders threatening their offspring, is part of the complex patterns of maternal behavior only seen in the peripartum period and appears to be regulated in a different manner (Bosch 2013; Lonstein and Gammie 2002). Thus, as part of their specific behavioral profile initiated by a variety of neuroendocrine changes, including an up-regulated activity of the brain OT system (Russell et al. 2003; Slattery and Neumann 2008), lactating mammals generally display heightened levels of aggression in order to protect their offspring. Interestingly, a peak in OTR binding in the LS occurs simultaneously with the peak in maternal aggression (Caughey et al. 2011). Furthermore, OT is released within the PVN and CEA during the display of maternal aggression (Bosch et al. 2004, 2005). This local OT release is particularly pronounced in high-aggressive and highly maternal HAB dams as compared with low-aggressive LAB dams (Bosch et al. 2005). Consistently, lesion of the PVN (including the majority of magnocellular and parvocellular OT neurons in the brain) inhibits maternal aggression (Consiglio and Lucion 1996). Although these results point to a positive link between the endogenous OT and maternal aggression, some studies have found the opposite. Thus, selective lesion of parvocellular brainstem-projecting OT neurons facilitated maternal aggression and this effect could be mimicked with the selective down-regulation of OT synthesis in the PVN via antisense administration (Giovenardi et al. 1998). Furthermore, high-aggressive rat dams (as a result of social stress during pregnancy) had lower levels of OT mRNA in the MEA (Murgatroyd et al. 2015) and high-aggressive mouse dams (as a result of early life stress) had lower levels of OT-IR in the PVN (Veenema et al. 2007).

3.3 Endogenous OT and Aggression in Humans

Based on the results obtained in rodent models, it can be hypothesized that high-aggressive humans differ from the normal population with respect to their OT system. As mentioned above, the available methods to assess the activity of the endogenous OT system in humans in order to verify this hypothesis are relatively limited and large-ly comprise of (1) the measurement of OT levels in blood, saliva, or cerebrospinal fluid and (2) the assessment of SNPs in, or methylation patterns of, *OTr*.

The first study, using plasma OT levels as a readout parameter for the OT system in humans, surprisingly showed a positive correlation with indirect aggression and irritability, as quantified with the *Karolinska Scales of Personality questionnaire* (Uvnäs-Moberg et al. 1991). Since then, all other studies have reported a negative relationship. Thus, basal plasma OT levels correlated negatively with aggression (measured using the *Buss-Perry Aggression questionnaire*) and positively with empathy (measured using the *Bryant's Empathy Index*) in boys with attention deficit and hyperactivity disorder (Demirci et al. 2016). In young adult women with BPD, basal plasma OT levels were lower compared with healthy controls and correlated negatively with trait aggression, as assessed by the *Buss-Durkee Hostility Inventory* (Bertsch et al. 2013a). Basal salivary OT levels correlated negatively with CU traits within a cohort of boys with conduct problems (Levy et al. 2015). Similarly, OT-reactive immunoglobulin G and M autoantibodies were increased in the plasma of adult men diagnosed with conduct disorder or convicted for a violent crime, compared to healthy, normal males (Fetissov et al. 2006); however, it is not known whether this reflects a general up- or down-regulation of OT system activity. Similar to the negative correlations between aggression and *peripheral* OT levels, increased aggression as measured with *Life History of Aggression* interviews correlated negatively with basal levels of OT in the CSF of men and women (including both healthy subjects and patients with various diagnosed psychiatric disorders) (Lee et al. 2009). A somewhat weaker trend in the same direction was found among women, but not men, in a cohort of suicide attempters and healthy controls, using the *Karolinska Interpersonal Violence Scale* to assess aggression (Jokinen et al. 2012).

Together, these results from both animal and human studies support the hypothesis that reduced peripheral and central basal OT levels (potentially reflecting a "hypo-oxytocinergic state" (Malik et al. 2012)) seem to predict aggression in some contexts, although the data is in dire need of both replication and extension. Aside from a decreased availability of OT itself, a hypo-oxytocinergic state could also be the result of alterations in the expression pattern, sensitivity, or intracellular signaling pathways of OTR, possibly caused by genetic or epigenetic modifications of *OTr*. Indeed, using a broad approach with rigorous statistical procedures, it could be demonstrated that variability in *OTr* in general (without defining specific SNPs) strongly predicts aggressive behavior in the RCAP (LoParo et al. 2016). In addition, another study showed that the level of methylation of *OTr* was positively correlated with CU traits in boys with conduct problems and negatively correlated with circulating plasma OT levels, supporting the "hypo-oxytocinergic state" hypothesis (Dadds et al. 2014a). Various

other investigations have searched for specific SNPs underlying aggression or anti-social behavior, but the emerging picture is inconsistent. Importantly, the functional consequences of the reported SNPs, with respect to *OTr* expression and OTR binding as determinants of OT neurotransmission, need to be demonstrated. Nevertheless, such results generally support the search for OT-related treatment options. Thus, one research group genotyped multiple cohorts of high-aggressive children and healthy controls and reported an association between SNP rs237885AA and high CU-traits within high-aggressive subjects (Beitchman et al. 2012), as well as a sex-specific link between high aggression and SNP rs677032T (in girls) and SNP rs1042778C (in boys) (Malik et al. 2012). However, in a later study they could only confirm their finding in girls, as well as a direct link between high aggression and SNPs rs237898A and rs237902C in boys (Malik et al. 2014). Interestingly, SNP rs1042778TT (not C!) was found to be associated with high CU traits in boys and girls with conduct problems (Dadds et al. 2014b), as well as with increased amygdala activation upon exposure to angry faces in adult men, which is considered a consistent neuropsychological marker of antisocial behavior (Waller et al. 2017). SNP rs7632287AA was strongly associated with *Life History of Aggression* interview scores and *Self-Reported Delinquency* scores in two cohorts of children representing the normal Swedish population (Hovey et al. 2016).

Two additional lines of research deserve to be mentioned here. In the first line, two independent studies could demonstrate that SNP rs53576GG predicts aggression or antisocial behavior under circumstances of high social stress in females (Buffone and Poulin 2014; Smearman et al. 2015). In the second line, it could be shown that SNPs rs4564790C and rs1488467C were predictive of higher levels of aggression, as measured in the RCAP and various questionnaires, but only in adult males that were under the influence of alcohol (Johansson et al. 2012a, b). These studies clearly emphasize the importance of the context in which aggression is measured and confirm that further research is needed to establish how the genetic or epigenetic variability in *OTr* can be utilized as a marker of abnormal aggressive or antisocial behavior.

4 Effects of Exogenous OT on Aggressive Behavior

The correlational studies described above clearly point towards a modulatory role for the endogenous OT system in aggressive and antisocial behavior. If this is indeed the case, then the administration of synthetic OT could be an effective treatment for highly aggressive individuals, in particular for those characterized by a hypo-OT state. Numerous animal and a few human studies have explored this promising possibility. In this context, a clear methodological limitation, especially in human studies, is the inability of OT to cross the blood–brain barrier under physiological circumstances. In rodents and primates, this problem can be solved by the administration of OT directly into the ventricles (intracerebroventricular [ICV] infusion) or into target brain areas. Treatment of human subjects with synthetic OT is mainly performed using intranasal

administration and this has been reported to affect various (social) behaviors. Although the uptake of intranasally applied OT into the brain compartment is likely (Neumann and Landgraf 2012; Neumann et al. 2013; Modi et al. 2014; Striepens et al. 2013), the scientific strength of many of the reported findings and the underlying mechanisms is critically debated (Leng and Ludwig 2016; Walum et al. 2016).

4.1 Effects of Exogenous OT on Animal Aggression

In general, acute central infusion of OT inhibits aggression, independent of the route of administration and sex of the individual. So, ICV infusion of OT inhibits inter-male aggression in male WTG rats both after acute (1,000 ng) and chronic (10 ng/h for 7 days) infusion (Calcagnoli et al. 2013, 2014b). Acute ICV infusion of OT also reduced inter-female aggression in virgin Wistar rats (at 100 ng) (De Jong et al. 2014). In steroid-primed female prairie voles, ICV OT also lowered female-to-male aggression (at 1 and 1,000 ng) (Witt et al. 1990), whereas it did not affect male-to-female aggression in male prairie voles (Witt et al. 1990; Mahalati et al. 1991). Also, in male C57bl/6 mice, acute ICV infusion of OT (100 ng) reduced aggression after co-housing with unfamiliar male conspecifics, whereas an OTR antagonist (OTRA, 500 ng) had the opposite effect (Arakawa et al. 2015). Acute and repeated (once daily over 7 days) intranasal application of 20 μg OT reduced aggression in high-aggressive WTG rats (Calcagnoli et al. 2015a) and a similar acute effect was found in socially isolated and high aggressive C57Bl/6 mice, in response to 200 ng intranasal OT (Karpova et al. 2016). Some neutral or pro-aggressive effects of OT have also been reported: 24 h of chronic ICV infusion with OT (0.5 ng/h) did not affect mating-induced aggression of male prairie voles against male intruders (Winslow et al. 1993), whereas acute ICV OT (100–1,000 ng) increased aggressive behavior in dominant male squirrel monkeys without affecting aggression in subordinate individuals (Winslow and Insel 1991).

Only a handful of studies have attempted to localize the predominantly anti-aggressive effects of OT via infusion of OT or an OTR antagonist (OTRA) into target brain areas. In male WTG rats displaying normal to high aggression, bilateral infusion of 30 ng OT into the CEA inhibited aggression, whereas bilateral infusion of a selective OTRA into the CEA had only a modest pro-aggressive effect (Calcagnoli et al. 2015b). In virgin female Syrian hamsters, bilateral infusion of OT (at 9 ng/200 nL) into the MPOA and anterior hypothalamus reduced aggression (Harmon et al. 2002), whereas bilateral infusion of an OTRA had a robust effect in the opposite direction.

Keeping in mind that maternal defense is part of the suite of maternal behaviors emerging strictly in the context of complex peripartum adaptations, including those of the OT system, reports of pharmacological OT manipulations affecting maternal aggression should be mentioned in this review. These reports describe somewhat inconsistent results that appear to depend on the experimental conditions. On the one hand, modest anti-aggressive effects of OT were found in Wistar and Sprague-Dawley rat dams. Local infusion of 10–20 ng OT into the CEA (and BNST) reduced

maternal aggression, whereas a higher dose of 200 ng OT was not effective (Consiglio et al. 2005). ICV infusion of a selective OTRA did not affect maternal aggression in Wistar rats (Neumann et al. 2001), but infusion of OTRA into the CEA or infralimbic prefrontal cortex enhanced maternal aggression (Lubin et al. 2003; Sabihi et al. 2014). On the other hand, a pro-aggressive effect of OT has been found in HAB and LAB dams: chronic 5-day ICV infusion of OT enhanced the low levels of maternal aggression in LAB dams, whereas acute ICV infusion of a selective OTRA reduced the high levels of maternal aggression in HAB dams (Bosch and Neumann 2012). In support, bilateral application of a selective OTRA into the CEA via retrodialysis during ongoing behavioral testing decreased maternal aggression only in highly aggressive HAB dams (Bosch et al. 2005). Effects in the same direction were found in lactating golden hamsters, where 2 ng of OT infused into the CEA increased maternal aggression (Ferris et al. 1992).

4.2 Effects of Exogenous OT on Human Aggression

Following initial reports of shifts in social decision-making following intranasal OT treatment in humans (Kosfeld et al. 2005), an avalanche of papers claiming pro-social effects of intranasal OT has followed. Relatively few of these papers have measured the hypothetical anti-aggressive effects of OT and the handful of reported results has been far from encouraging.

The effects of intranasal OT treatment on aggressive behavior were mainly assessed in versions of the PSAP. No acute behavioral effects were detected in either aggressive adult males with ASPD or healthy adult males (Alcorn et al. 2015a, b), whereas a modest increase in both reactive and proactive aggression was found in healthy adult men and women using a modified PSAP, the *Social Orientation Paradigm* (Ne'eman et al. 2016). Acute intranasal OT modestly decreased aggression in the PSAP in (otherwise healthy) women with higher state anxiety while not affecting non-anxious women (Campbell and Hausmann 2013). De Dreu et al. found that intranasal OT shifted behavior of healthy males towards sharing with in-group members combined with punishment of out-group members (De Dreu et al. 2010). In follow-up studies, intranasal OT facilitated in-group conformity and cooperation while increasing aggressive and anti-social tendencies towards out-group individuals (De Dreu and Kret 2016). Finally, Bertsch et al. found that, in young adult female BPD patients with high trait aggression, intranasal OT could reverse their disorder-induced increased threat sensitivity, as reflected by the higher level of eye-fixation changes and increased amygdala reactivity (measured with fMRI) in response to angry faces (Bertsch et al. 2013b).

Taken together, these results do not equivocally support the theory that intranasal OT treatment is capable of inhibiting aggression, at least in healthy subjects. In patients with a confirmed impaired endogenous OT system (such as BPD patients with lowered basal plasma OT levels (Bertsch et al. 2013a)), intranasal OT administration may be beneficial. In future research, the possible anti-aggressive effects

of intranasal OT will need to be tested in selected cohorts of high-aggressive patient groups (for example, suffering from CD with high CU traits) that are positive for one or more biomarkers indicating altered/reduced OT neurotransmission. Currently, the EU-funded research consortium FemNAT-CD is collecting data towards this goal in girls and boys with CD (Freitag 2014).

5 Integration and Future Research

There is no doubt that both endogenous and exogenous OT are capable of modulating antisocial and aggressive behavior, but the strength of the effects and, in some cases, even the direction, depends on the context. Variability within the endogenous OT system as a result of genetic variations, early life stress, reproductive state, seasonal cues, or unknown other parameters is likely to shift an individual's tendency to respond aggressively towards an encountered conspecific. According to the hypo-OT state hypothesis, a down-regulated OT system will rather be associated with the facilitation of aggression, whereas an up-regulated OT system will inhibit aggression. This hypothesis clearly fits with the known pro-social effects of OT, which include an increase in social preference, an improvement in social memory, and a reduction in social fear (Neumann and Landgraf 2012; Maroun and Wagner 2016; Neumann and Slattery 2016). A more complex association can be expected with the anxiolytic properties of OT, since the links between aggression and anxiety are not straightforward (Neumann et al. 2010).

In general, we have to critically scrutinize the current knowledge and presume that our work in this field is far from complete. Especially, investigations with a higher spatial resolution (i.e., focusing on variability in OT neurotransmission in specific brain areas associated with aggression and social behavior mentioned above) and in contexts beyond inter-male territorial defense (i.e., females, adolescents, non-territorial instrumental aggression, and CU traits) are needed. Such (animal) studies will help to interpret the low-resolution findings in humans and to define novel hypotheses to be tested in humans. Furthermore, although treatment with synthetic OT is still a promising possibility to inhibit aggression and violent behavior in subgroups of patients with a verified impairment in their endogenous OT system, these effects are not expected to be consistent across subjects in different contexts. In fact, when designing future pharmacological experiments, it needs to be taken into account that selection of subjects (in terms of animal species, age, sex, reproductive state, or patient subgroup) and context may yield vastly different outcomes and results need to be interpreted with this information in mind.

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