Review

Biological Psychiatry

Oxytocin in General Anxiety and Social Fear: A Translational Approach

Inga D. Neumann and David A. Slattery

ABSTRACT

The neuropeptide oxytocin (OXT) has been revealed as a profound anxiolytic and antistress factor of the brain, besides its many prosocial and reproductive effects. Therefore, there is substantial scientific and medical interest in its potential therapeutic use for the treatment of psychopathologies associated with anxiety, fear, and social dysfunctions, such as generalized anxiety disorder, posttraumatic stress disorder, and social anxiety disorder, as well as autism and schizophrenia, among others. Focusing on preclinical studies, we review the existing evidence for the regulatory capacity of OXT to fine-tune general and social anxiety-related behaviors, as well as cued and social fear conditioning from a translational perspective. The available evidence from animal and human studies substantiates the hypothesis of an imbalance of the endogenous brain OXT system in the etiology of anxiety disorders, particularly those with a social component such as social anxiety disorder. In addition, such an imbalance of the OXT system is also likely to be the consequence of chronic OXT treatment resulting in a dose-dependent reduction in OXT receptor availability and increased anxiety.

Keywords: Amygdala, Anxiety, Fear, Human, Rodent, Social anxiety

http://dx.doi.org/10.1016/j.biopsych.2015.06.004

Anxiety disorders, such as generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), and social anxiety disorder (SAD), are among the most common psychiatric illnesses with a lifetime prevalence of approximately 30% (1). GAD is defined as a persistent and unnecessary anxiety of everyday life and/or events for a period of at least 6 months. The main treatment options for GAD are benzodiazepines and beta blockers or drugs originally used for major depressive disorder. SAD and PTSD, the second and third most prevalent anxiety disorders, respectively, are largely characterized by fear of a previously encountered situation (2,3). PTSD occurs in a subset of people who have witnessed, or experienced, a traumatic event, such as war or personal assault, and is manifest as flashbacks of the event or, in more serious cases, generalization of the event to similar contexts. In contrast, SAD, also often referred to as social phobia, is characterized by the persistent fear and avoidance of social situations (4). There are two main forms of SAD: specific SAD, which is described as fear and avoidance of particular social situations and interactions (e.g., fear of public speaking) (5), and generalized SAD, characterized by the avoidance of all social situations (6–8). Treatment for PTSD and SAD is rather unspecific and involves cognitive psychotherapy in combination with pharmacotherapies originally designed for depression or GAD.

These anxiety disorders are highly comorbid with other affective disorders, including major depressive disorder, autism, or Prader-Willi-syndrome (9,10). Interestingly, symptoms of SAD often emerge first, indicating that SAD may be a major risk factor for other psychiatric disorders. Therefore, early specific intervention of social fear might reduce the risk of comorbidities. However, treatment of anxiety disorders generally achieves only partial remission of symptoms or shows a high rate of relapse (11), highlighting the necessity for more specific treatment options. Recently, neuropeptides have emerged as viable candidates, such as oxytocin (OXT), arginine vasopressin (AVP) (12) [for reviews, see (13,14)], neuropeptide Y (15), and neuropeptide S (16–18).

BRIEF OVERVIEW OF THE BRAIN OXT SYSTEM AS A POTENTIAL THERAPEUTIC TARGET

The first reported behavioral effects of the two closely related neurohypophysial nonapeptides OXT and AVP date back to the 1960s and 1970s, when effects on maternal behavior (19) and on memory functions (20), respectively, were described. From a translational view, AVP first predominated scientific interest due to its anxiogenic and depressive-like effects [for review, see (13,21)]. However, despite the development of various nonpeptidergic AVP receptor antagonists, research in this direction has almost halted due to a lack of clinical efficacy. In contrast, the discovery of anxiolytic, antistress, and prosocial effects of OXT in rodents in the 1990s has promoted a switch to this nonapeptide. This has further been facilitated by the discovery of a plethora of OXT effects after intranasal application in humans [see below and (22,23)].

ISSN: 0006-3223

Table 1. Summary of Rodent Studies Assessing the Effect of Acute, Repeated, or Chronic Application of Synthetic OXT on Anxiety-Related Behavior Including General Anxiety and Conditioned Fear Cited in Text

	Sex and Species	Finding	Reference
Acute Studies			
General anxiety-related behavior			
OXT 1 μg; central amygdala	Female Sprague Dawley rats	Anxiolytic; OF (trend on EPM)	(53)
OXT 1 μg; icv	Male and female HAB rats	No effect on LDB	(65)
OXT 1 μg; icv	Female Wistar rats	No effect on EPM	(65)
OXT .1–.5 μg; icv	Male CD1 mice	No effect on EPM	(102)
OXT .1–10 μg; icv	Male Swiss-Webster and BABL/c mice	Anxiolytic (3 and 10 ug, FPT; 1 ug, EZM)	(55)
Carbetocin 10–100 μg; icv	Male Sprague Dawley rats	Anxiolytic (32 and 100 μg; EPM)	(56)
Atosiban 1 mg/kg; iv	Male Sprague Dawley rats	Anxiolytic; EPM	(56)
Carbetocin 2.5–5 mg/kg; iv	Male Sprague Dawley rats	No effect on the EPM	(56)
OXT 1–30 mg/kg; ip	Male C57BL/6N and Swiss-Webster mice	Anxiolytic (1–10 mg/kg; SIH [C57BL/6N]; 10 mg/kg; FPT [Swiss])	(55)
OXT .01 nmol; PVN	Male and female Wistar rats	Anxiolytic; EPM (male) and LDB (male and female)	(54,57)
OXT 5 ng; dorsolateral septum	Male CD1 mice	No effect on EPM	(102)
OXT .1–1 μg; prelimbic cortex	Male and female Sprague Dawley rats	Anxiolytic (1 ug, EPM)	(58)
OXT-R antagonist .75 μg; icv	Virgin, pregnant, and lactating Wistar rats	Anxiogenic; EPM (pregnant and lactating rats)	(51)
OXT-R antagonist .75 μg; icv	Male Wistar rats	No effect on LDB	(101)
OXT-R antagonist .75 μg; icv	Male and female LAB rats	No effect on EPM or LDB	(65)
OXT-R antagonist .75 μg; icv	Male CD1 mice	No effect on EPM	(101)
OXT-R antagonist .75 μg; icv	Male and Female Wistar rats	Attenuation of mating-induced anxiolysis	(60,62)
Fear conditioning			
OXT 1 μg; icv	Male Wistar rats	Before cued-fear acquisition: decreased fear expression; before extinction training: impaired extinction	(94)
OXT .1 μg; icv	Male CD1 mice	Before extinction training: impaired extinction	(94)
OXT .1 μg; icv	Male CD1 mice	Before social fear extinction: abolished social fear expression	(102)
OXT .01 μg; basolateral amygdala	Male Sprague Dawley rats	Before contextual fear conditioning: enhanced fear expression and impaired extinction	(95)
WAY-267464 3 μg; TGOT 7 ng; central amygdala	Male Sprague Dawley rats	Before contextual fear conditioning: reduced fear expression	(95)
OXT optogenetically evoked release; central amygdala	Female Wistar rats	Before retrieval: attenuated contextual fear expression	(39)
TGOT 7 ng; central amygdala		Before retrieval: attenuated contextual fear expression	(97)
OXT .01 μg; infralimbic cortex	Male Sprague Dawley rats	Following contextual fear retrieval: facilitated subsequent extinction	(95)
TGOT 7 ng; central amygdala	Male Sprague Dawley rats	Attenuated contextual fear expression	(97)
OXT .01 μg; infralimbic cortex	Male Sprague Dawley rats	Following contextual fear retrieval: facilitated subsequent extinction	(95)
OXT .01 μg; infralimbic cortex	Male Sprague Dawley rats	Following contextual fear retrieval: facilitated subsequent extinction	(95)
OXT; dorsolateral septum	Male CD1 mice	Before social fear extinction: abolished social fear expression	(102)
OXT-R overexpression; lateral septum	Male C57/BL6N mice	Enhanced social defeat-induced contextual fear expression	(107)
OXT-R antagonist .75 μg; icv	Male Wistar rats	Before cued-fear acquisition: impaired fear extinction; no effect before extinction training	(94)
Chronic/Repeated Studies			
OXT .08–8 IU/kg, 21 days; in	Male prairie voles	No effect in EPM	(70)
OXT .8 IU/kg, 8 days; in	Male and female C57BL/6J and BTBR mice	No effect in OF	(71)
OXT 20 ng/hour, 7 days; icv	Male Wistar rats	No effect in OF or EPM	(69)
OXT 10–100 ng/hour, 5 days; icv	Female Sprague Dawley rats	Anxiolytic; EPM	(72)
OXT 1 and 10 ng/hour, 15 days; icv	Male C57BL/6 mice	Anxiogenic; 10 ng/hour on LDB and EPM	(67)
OXT 1 ng/hour, 19 days; icv	Male C57BL/6	Prevention of chronic stress-induced anxiogenesis; no effect in nonstressed mice	(67)
OXT 10 ng/hour, 6 days; icv	Male and female HAB rats	Anxiolytic; LDB in female rats	(65)
Carbetocin 10–100 μg, 10 days; icv	Male Sprague Dawley rats	Anxiolytic; 32 and 100 μg on EPM	(56)
OXT-R antagonist 7.5 ng/hour, 6 days; icv	Male and female LAB rats	Anxiogenic effect; LDB in female rats	(65)
Oxytocin knockout mice	Female 129 Mice	Higher anxiety in knockouts; EPM	(63)

EPM, elevated plus maze; EZM, elevated zero maze; FPT, four plate test; HAB, high anxiety-related behavior; icv, intracerebroventricular; in, intranasal; ip, intraperitoneal; LAB, low anxiety-related behavior; LDB, light-dark box; OF, open-field; OXT, oxytocin; OXT-R, oxytocin receptor; PVN, paraventricular; SIH, stress-induced hyperthermia.

The physiology of the hypothalamic-neurohypophysial system and its main neuropeptides OXT and AVP has become a textbook example. Briefly, the synthesis of OXT and AVP in magnocellular neurons located within the supraoptic (SON), paraventricular (PVN), and accessory nuclei of the hypothalamus (24); the electrophysiological properties of such neurons; stimuli triggering their peripheral secretion into blood; and subsequent physiological functions are well defined. Moreover, although our knowledge regarding other sites of neuronal synthesis, neuropeptidergic circuitries (25,26) and region- and stimulus-dependent central release patterns (14,26,27) is continuously rising, many aspects are still a matter of intense research interest. For example, the subcellular location of OXT receptors (OXT-R) at either axosynaptic, dendritic or somatic fractions; the dynamics of local receptor expression and binding; and associated intracellular signaling cascades that determine—possibly sex-dependent—OXT actions are largely unknown (28,29). Such details are essentially needed before OXT can be considered a routine treatment option for anxiety-related diseases or social dysfunctions.

OXT INVOLVEMENT IN ANXIETY-RELATED BEHAVIOR

Responsiveness of the OXT System to Anxiety and Stress

Anxiogenic and stressful stimuli significantly activate the body's OXT system, as reflected by increased electrophysiological activity of OXT neurons, increased OXT gene expression within the SON and PVN, and stimulated peripheral and intracerebral OXT release (30–35) [for review, see (14,27,36)]. For example, exposure of male rats to novelty, forced swimming, or social defeat rapidly increases OXT release into blood but also within the PVN and/or SON and in other limbic brain regions, such as the central amygdala or septum (27,36). Similarly, increased OXT release into blood (37) and within the PVN and central amygdala (38) has also been found in female rats exposed to psychosocial stress (maternal defeat by an aggressive lactating resident dam). Magnocellular OXT neurons within the PVN (or SON) themselves may provide the neuroanatomical basis for these observations: in addition to their projections to the neurohypophysis, they can also release OXT locally within the PVN (or SON) from dendrites and perikarya, as well as from axon collaterals that project to distinct brain regions, for example, the central amygdala (39,40). Thus, it is tempting to conclude that fearful and stressful events activate the OXT system and, consequently, both peripheral and central OXT release (27,36) [but see (41)]. This is an important observation with implications for human studies, as it speaks in favor of peripheral OXT measures being a global biomarker for the general activity of the endogenous OXT system also, at least partly, reflecting the central (re)activity of an individual's OXT system to stress. However, we have to be aware of the fact that plasma OXT may, at best, only roughly reflect the temporal dynamics of central release patterns, which was shown to substantially differ from peripheral release patterns of OXT (14,27,41–43). Further, plasma OXT necessarily ignores brain region-dependent events, which play an important role in the behavioral effects of OXT (see below).

Whereas these OXT-related events are well-characterized in rodents, there are only a few human reports of stress- or anxiety-induced changes in plasma OXT, such as in response to physical exercise (running), psychosocial stress (e.g., separation), or fear (44–47). This is surprising given that plasma (or saliva) OXT is the only easily accessible biomarker of the human OXT system. However, reliable assays are an important prerequisite [for details, see (48,49) and Leng and Ludwig (50), this issue]. In several published studies, the validity of OXT data obtained with enzyme-linked immunosorbent assay from plasma samples without prior extraction procedure is questionable; corresponding studies are, therefore, not listed here.

Acute Anxiolytic Effects of OXT

Once released within the brain, OXT acts as a key modulator of anxiety-related behaviors and hypothalamic-pituitary-adrenal axis activity (51,52). Relatively simple pharmacologic approaches using intracerebroventricular (icv) or local (PVN, central amygdala, prefrontal cortex) administration of an OXT-R agonist or antagonist have consistently shown an anxiolytic effect of synthetic or endogenous OXT in male and female rodents (53–58). Particularly intriguing is the anxiolytic effect of endogenous brain OXT during periods of robust activation and increased central release, including lactation (51,57,59) and sexual activity in both male and female rodents (60–62). In contrast, under nonreproductive and stress-free conditions (and thus low OXT system activity), we have never been able to reveal an anxiolytic effect of brain OXT using an OXT-R antagonist. Thus, endogenous OXT does not seem to play a major role in the maintenance of a basal level of anxiety, but rather comes into play during psychosocial or physiological activation of the system. Behavioral data from transgenic mice lacking OXT provide further support for the anxiolytic importance of brain OXT in anxiety regulation, as female knockout mice show greater anxiety-related behavior than their wild-type counterparts on the elevated plus maze (63) (for a summary of these findings including doses and tests employed, please see Table 1).

We have also shown that the robust anxiolytic activity of OXT in the PVN depends on the sequential activation of several OXT-R-mediated intraneuronal signaling pathways. Specifically, local infusion of OXT results in activation of the mitogen-activated protein kinase pathway (54,57), and blockade of this pathway prevents the local anxiolytic effects of OXT. Interestingly, in the peripartum period, both the OXT system and the OXT-R-driven mitogen-activated protein kinase pathway are highly activated within the PVN, even in the absence of synthetic OXT (57). Blockade of the signaling pathway also prevents the anxiolytic state of lactating rats. Additionally, we could recently identify that increased intracellular calcium levels via insertion of transient receptor potential vanilloid (TRPV) channels into the membrane also mediates the acute anxiolytic effect of OXT in the PVN (64).

Chronic Effects of Synthetic OXT on Anxiety

When considering OXT as an anxiolytic treatment option for humans, chronic neuropeptide effects should be of major

interest. However, relevant basic studies are rare, and those performed reveal that chronic OXT effects strongly depend on the dose and duration of application, are likely to vary between male and female subjects (65–72), and are dependent upon the innate level of anxiety (65). For example, in male mice, chronic icv infusion of OXT (10 ng/hour) over 2 weeks induced a robust increase in anxiety-related behavior in two independent behavioral tests, whereas a tenfold lower dose did not alter anxiety (67). In contrast, in ovariectomized, steroid-treated female rats, 5 days of icv OXT (10 ng/hour) reduced anxiety levels and stress-induced c-Fos activation in relevant brain regions (66,72). In support of such sex differences, 7 days icv OXT (20 ng/hour) in male rats did not affect anxiety-related behavior (69).

To further test for the potential therapeutic value of OXT in the context of anxiety disorders, we proved its efficacy in rats selectively bred for high anxiety-related behavior (HAB) versus low anxiety-related behavior (LAB) (13,73). Interestingly, we only found an anxiolytic effect of OXT in female, but not male, HAB rats after chronic, but not acute, icv application. In contrast, LAB females administered chronic OXT-R antagonist showed increased anxiety-related behavior, which provides further indication for a role of the endogenous OXT system in the anxiety phenotype of HAB and LAB female rats (65). The relatively low effectiveness of OXT to modulate extreme anxiety levels in these animals is likely due to their rigid genetic predisposition toward the selected behavioral trait, namely anxiety.

Importantly, chronic icv infusion as well as repeated (twice daily) nasal application of synthetic OXT were found to affect the endogenous OXT system by reducing OXT-R binding in several brain regions relevant for anxiety regulation (septum, amygdala, median raphe nucleus, nucleus accumbens, hippocampus) (67,68). These findings follow a general principle in neuropharmacology in that persistent agonist stimulation by chronic exposure to the receptor ligand, OXT in this case, results in downregulation and desensitization of receptors (74). Interestingly, after chronic OXT treatment, AVP receptor binding was found to be increased in the lateral septum (68), where AVP exerts robust anxiogenic effects (12). In this context, it is worth mentioning that OXT can bind to AVP receptors (and vice versa) (75), but to what extent chronic alterations in OXT or OXT-R availability directly affect AVP receptor expression remains unknown at present.

Taken together, these studies highlight potential species and sex differences in the response to chronic OXT (for summary see Table 1). Without any doubt, we have to expect similar undesired counterregulatory consequences after chronic or repeated intranasal OXT application in humans, and more detailed basic studies are essentially needed.

OXT AND GENERAL ANXIETY: HUMAN RESEARCH

Human researchers have suggested a possible relationship between peripheral OXT levels, OXT-R gene polymorphisms, and GAD. In detail, basal plasma OXT concentrations were found to depend upon the mental health state and gender of the test person. For example, a positive relationship between (basal) plasma OXT and state anxiety has been reported in women (47,76), whereas plasma (and cerebrospinal fluid) OXT concentrations negatively predicted trait anxiety scores in a mixed-gender cohort (11 male and 16 female subjects) of child and adult patients (46) and in male, but not female, subjects in another study (77). Moreover, associations between OXT-R polymorphisms and anxiety were described with two single nucleotide polymorphisms (SNPs), rs53576 and rs2254298, found to be associated with separation anxiety in depressed patients (78) and to interact with the level of anxiety symptoms in adolescent girls (79). Similarly, in a large study assessing multiple OXT-R polymorphisms, an interaction between retrospectively assessed early-life stress exposure and OXT-R genotype on self-reported anxiety symptoms was found (80). However, the functional implications of these SNPs on the OXT system remain to be shown.

There have been surprisingly few attempts to investigate whether intranasal OXT has anxiolytic properties in GAD patients (81) [see (22) for review]. This one study supports a beneficial effect of daily OXT administration in GAD patients over 3 weeks, especially in male subjects (80). In the context of human anxiety, the majority of studies have been performed in volunteers in variants of the Trier Social Stress Test, which, on the whole, revealed that acute intranasal OXT reduces anxiety symptoms (82–86). However, it is clear that further studies assessing the effect of chronic or repeated OXT administration, and in GAD patients, are warranted.

THE BALANCED ACTIVITY OF THE BRAIN OXT SYSTEM IN GENERAL ANXIETY REGULATION

Regarding the role of OXT in animal and human anxiety regulation, we have previously hypothesized that the balanced activity of brain OXT (and AVP) systems importantly impacts on emotional (and social) behaviors along a continuum reaching from mental health up to psychopathology (21) (Figure 1). For example, low brain OXT activity, hypothesized to be associated with high anxiety levels, can be reflected by 1) low hypothalamic OXT gene expression, 2) low levels of central OXT release and OXT availability in the local extracellular fluid under basal and/or stimulated conditions, and/or 3) low OXT-R expression and binding in brain regions relevant for emotional and social behaviors. These parameters can be shifted towards the right (Figure 1) by physiological (e.g., lactation, sexual activity) and environmental (e.g., positive social interactions) stimuli and are likely determined by genetic and epigenetic factors. Moreover, increasing the availability of OXT in the brain extracellular fluid, possibly in combination with psychopharmacotherapy, may also result in a shift of OXT activity toward the right (Figure 1). Indeed, factors that acutely increase the activity of the OXT system have been shown to reduce state anxiety and to promote prosocial behaviors (see below). However, an adaptive shift of the brain OXT system toward the left, for example, in chronic adverse life environments, might be important to ensure evolutionary beneficial anxiety levels.

OXT AND CUED FEAR CONDITIONING AS A RODENT MODEL OF POSTTRAUMATIC STRESS DISORDER

Inability to extinguish fear memories is a core symptom in several psychiatric disorders, such as PTSD, SAD, and panic

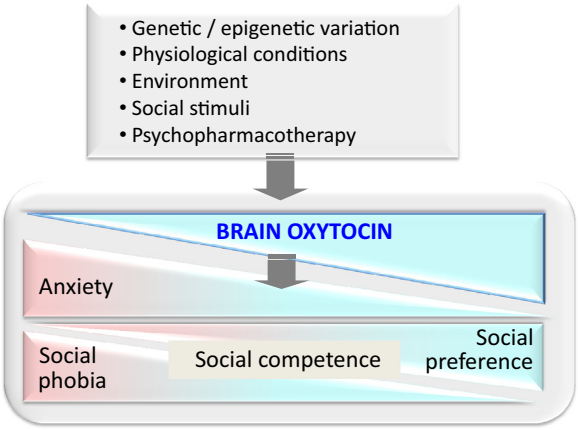

Figure 1. The activity of the brain oxytocin (OXT) system is mainly reflected by the level of expression of OXT or its receptor, by local OXT release into and local OXT availability within the extracellular fluid, and by the OXT receptor binding capacity. Genetic and epigenetic factors, physiological conditions, such as reproduction or stress, as well as environmental and social stimuli significantly contribute to the individual expression and modulation of these parameters. Further, combined psychopharmacotherapy with the aim to increase central oxytocin availability may shift the activity of the oxytocin system toward the right, which is likely to be accompanied by reduced anxiety and improved social competence. For details, see text. [Adapted from Neumann and Landgraf (21)].

disorder, and has been linked to hyperactivity of the amygdala (87,88). Cued fear conditioning has been used in laboratory animals as a model of PTSD and involves pairing a neutral stimulus (tone or light as conditioned stimulus) with an aversive, unconditioned stimulus, such as a mild foot shock, thereby eliciting a freezing response to the previously neutral stimulus (89,90). During fear extinction performed 24 hours later and repeated exposure to the conditioned stimulus only, the conditioned response should be attenuated via processes of relearning (91,92).

Initial studies revealing distinct and differential c-Fos activation of OXT neurons following various phases of fear conditioning supported a role for the endogenous OXT system in fear acquisition and extinction (93). Thereafter, studies revealed that, as with other systems that affect fear learning, the timing and location of OXT administration critically determine its outcome. Thus, we could demonstrate in male rats that icv OXT before acquisition of cued fear conditioning did not affect cued fear acquisition, as OXT-infused rats learned the association between the conditioned and unconditioned stimulus to the same degree as control rats. In contrast, the same treatment decreased fear expression 24 hours later. In confirmation of a substantial role of brain OXT in fear consolidation, icv administration of an OXT-R antagonist at the same time impaired fear extinction. Surprisingly, when applied 10 minutes before fear extinction training, icv OXT impaired, whereas the OXT-R antagonist facilitated, cued fear extinction (94). Moreover, the effects of OXT on fear expression and extinction appear to be region specific. Infusion of OXT into the basolateral amygdala of male rats before contextual fear conditioning led to enhanced fear expression and impaired extinction, whereas infusion of either WAY-267464 or TGOT (both OXT agonists) into the central amygdala before fear conditioning reduced fear expression (95). In an elegant study, optogenetically stimulated local release of OXT as well as synthetic OXT infusion in the central amygdala of rats before contextual fear extinction reduced fear expression by reducing the output of the centromedial amygdala in response to the conditioned stimulus (39,96,97).

Taken together, these studies support a role of the endogenous OXT system in the acquisition and extinction of fear, and this appears to be time- and region-dependent (for summary see Table 1). Moreover, these temporally- and spatially-dependent effects of OXT on fear extinction clearly extend our model of the balanced brain OXT system (Figure 1) and indicate an adaptive role of OXT in fear conditioning. A generally high OXT activity at the time of acquisition, due to either endogenous factors or pharmacologic manipulation, is likely to be associated with lower fear expression. However, once cued fear has consolidated, an acute high OXT may rather impair fear extinction.

Also, these findings have to be carefully considered and extended before using OXT for the treatment of PTSD caused by nonsocial traumatic events. However, as we will see further in the text, OXT seems to be particularly effective only in a social context.

OXT EFFECTS ON SOCIAL BEHAVIOR: FROM SOCIAL PREFERENCE TO SOCIAL FEAR

The prosocial effects of OXT are extensively summarized elsewhere (23,85,98–100), but in this context, it is worth mentioning that brain OXT is essential for naturally occurring social preference behavior in rats and mice as analyzed in the social preference-avoidance test (4,101). In detail, OXT was found to be released within the lateral septum during social interaction and investigation of conspecifics (102). Blockade of central receptor-mediated OXT actions by icv infusion of an OXT-R antagonist prevented social preference behavior in rodents (101). Moreover, exposure to 30 minutes of social defeat by a slightly larger male resident rat before the social preference test induced an avoidance of the conspecific, which could be acutely reversed by icv infusion of OXT. These observations together with the findings that OXT knockout mice display impaired social behaviors (103) support the hypothesis that high levels of brain OXT activity generally promote naturally-occurring social preference and social competence (Figure 1). Although further, and especially more long-lasting, studies are needed, the possibility emerged of OXT being a treatment option for social dysfunctions and, specifically, for social fear (101).

However, social defeat can result in a variety of other symptoms that may influence social anxiety. Therefore, to more specifically study the role of OXT in social fear, we have recently established an operant social fear conditioning paradigm in mice, where conditioned mice receive a footshock when actively investigating a conspecific (4,104,105). As a result, social fear conditioning specifically induces social fear toward unknown conspecifics, which is expressed as decreased social investigation and aversive responses toward conspecifics in the experimental animal's home cage. Moreover, as occurs in SAD (and PTSD), this fear sensitizes over

time and lasts for at least 2 weeks. During fear extinction training, repeated exposure to social stimuli without punishment gradually reinstates social preference behavior, i.e., loss of social fear (4,104,105).

Social fear could be associated with profound changes in the brain OXT system, as it specifically resulted in elevated OXT-R binding in regions associated with the fear circuitry, including the dorsolateral septum, central amygdala, hippocampus, and the median raphe nucleus (102). The alterations in OXT-R binding were found to be reversed after social fear extinction. In support of our findings of elevated OXT-R binding in socially fearful mice are the observations that 1) OXT-R expression is locally elevated in chronically defeated mice, which also showed signs of social avoidance (106); and 2) virus-induced overexpression of the OXT-R within the septum increased contextual fear expression (107). It is likely that these observed changes in OXT-R binding are directly due to reduced local OXT release and availability, as OXT release within the dorsolateral septum during exploration of a conspecific—strongly increased in unconditioned mice—was indeed blunted in social fear conditioning mice. In support, both icv and intraseptal OXT infusion before extinction training abolished fear expression (102). The findings that OXT strongly facilitates extinction of social fear, in contrast to the differential effects on cued fear extinction, suggest that either the circuitry involved in social fear differs from that of cued fear (see above) or that the combined prosocial and anxiolytic properties of OXT are sufficient to overcome social fear. Thus, increasing brain OXT activity toward the right, for example, by intracerebral infusion of synthetic OXT, and consequently increasing OXT availability in the local extracellular fluid (Figure 1) is associated with the attenuation or even reversal of social fear. To what extent stimulation of the endogenous OXT system may also be beneficial in this context needs to be shown.

OXT IN PTSD AND SOCIAL ANXIETY DISORDER: HUMAN RESEARCH

Numerous human studies have reported on the OXT system in relation to both PTSD and SAD. In one of the first reports assessing intranasal OXT in Vietnam veterans with PTSD, no beneficial effects on physiological responses to combat imagery were observed (108). However, more recent studies support a beneficial role for intranasal OXT in healthy volunteers exposed to a conditioning/extinction paradigm with respect to the bodily response and reduction of amygdala activity throughout extinction (109,110). In contrast, intranasal OXT increased the startle response to unpredictable shocks (111). Thus, in addition to the temporal and spatial differences of OXT on fear extinction reported above, the nature of the threat (social vs. nonsocial, predictable vs. unpredictable traumatic events) also appears to play an important role in the effectiveness of synthetic OXT in humans.

Various studies performed in SAD patients have assessed plasma OXT levels, OXT-R gene methylation and SNPs, and the effect of intranasal OXT on SAD symptoms. The reports relating to plasma OXT and SAD have been inconsistent and need to be interpreted with caution due, partly, to invalid assay methods (see above). Moreover, reduced OXT-R methylation in SAD patients was associated with symptom severity, elevated stress-induced cortisol responses, and increased amygdala activity (112). Since decreased methylation is likely to result in increased OXT-R expression, these findings support our results in socially fearful mice (102). Thus, increased OXT-R expression possibly due to low local OXT release may represent a conserved mechanism whereby the memory of adverse social events is maintained leading to social anxiety.

Intranasal OXT given either alone or in combination with exposure therapy has generally led to positive results in SAD in terms of positive self-evaluation of public performance (113) and regional neuronal activity patterns and amygdala-prefrontal connectivity in response to emotional faces (114–116). Also, in fragile X patients, who also display symptoms of social anxiety, intranasal OXT improved eye gazing and reduced cortisol response to a social challenge (117).

SUMMARY

In summary, there is profound evidence for an important role of the OXT system in general anxiety and social fear, in addition to its many prosocial effects. Differing activities of the brain OXT system, including gene expression patterns and local release, which are determined by genetic and epigenetic factors, are likely to underlie differences in emotional and social behaviors. High central OXT availability, for example, seems to be associated with an anxiolytic and prosocial, socially competent phenotype. In contrast, a gradual shift of the activity scale toward the left, e.g., by diminished OXT–OXT-R interactions, is associated with elevated nonsocial anxiety, lack of social preference, and social fear. However, before the OXT system can be considered a safe treatment target, various molecular, neuronal, and brain network variables need to be studied in more detail after acute, repeated, or chronic OXT application in animal and human studies. Moreover, biological markers of the activity and responsiveness of the endogenous OXT system (Figure 1) need to be validated and employed to distinguish potential OXT responders and nonresponders to avoid disadvantageous effects in the latter.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the European Research Council, Bundesministerium für Bildung und Forschung, Elitenetwork of Bavaria (IDN), and the Deutsche Forschungsgemeinschaft (IDN, DAS).

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Behavioral and Molecular Neurobiology, University of Regensburg, Regensburg, Germany.

Address correspondence to Inga D. Neumann, University of Regensburg, Department of Behavioral and Molecular Neurobiology, Universitaetsstr. 31, Regensburg, 93040, Germany; E-mail: inga.neumann@ur.de.

Received Feb 19, 2015; revised Jun 1, 2015; accepted Jun 3, 2015.

REFERENCES

1. Kessler RC, Wang PS (2008): The descriptive epidemiology of commonly occurring mental disorders in the United States. Annu Rev Public Health 29:115–129.
2. Alonso J, Petukhova M, Vilagut G, Chatterji S, Heeringa S, Ustun TB, *et al*. (2011): Days out of role due to common physical and mental

conditions: Results from the WHO World Mental Health surveys. Mol Psychiatry 16:1234–1246.
3. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU (2012): Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res 21:169–184.
4. Toth I, Neumann ID (2013): Animal models of social avoidance and social fear. Cell Tissue Res 354:107–118.
5. Bogels SM, Alden L, Beidel DC, Clark LA, Pine DS, Stein MB, Voncken M (2010): Social anxiety disorder: Questions and answers for the DSM-V. Depress Anxiety 27:168–189.
6. den Boer JA (1997): Social phobia: Epidemiology, recognition, and treatment. BMJ 315:796–800.
7. Kessler RC, Stein MB, Berglund P (1998): Social phobia subtypes in the National Comorbidity Survey. Am J Psychiatry 155:613–619.
8. Ruipérez MA, Garcia-Palacios A, Botella C (2002): Clinical features and treatment response in social phobia: Axis II comorbidity and social phobia subtypes. Psicothema 14:426–433.
9. Chartier MJ, Walker JR, Stein MB (2003): Considering comorbidity in social phobia. Soc Psychiatry Psychiatr Epidemiol 38:728–734.
10. Schneier FR, Foose TE, Hasin DS, Heimberg RG, Liu SM, Grant BF, Blanco C (2010): Social anxiety disorder and alcohol use disorder co-morbidity in the National Epidemiologic Survey on Alcohol and Related Conditions. Psychol Med 40:977–988.
11. Blanco C, Bragdon LB, Schneier FR, Liebowitz MR (2013): The evidence-based pharmacotherapy of social anxiety disorder. Int J Neuropsychopharmacol 16:235–249.
12. Landgraf R, Gerstberger R, Montkowski A, Probst JC, Wotjak CT, Holsboer F, Engelmann M (1995): V1 vasopressin receptor antisense oligodeoxynucleotide into septum reduces vasopressin binding, social discrimination abilities, and anxiety-related behavior in rats. J Neurosci 15:4250–4258.
13. Frank E, Landgraf R (2008): The vasopressin system–from antidiuresis to psychopathology. Eur J Pharmacol 583:226–242.
14. Landgraf R, Neumann ID (2004): Vasopressin and oxytocin release within the brain: A dynamic concept of multiple and variable modes of neuropeptide communication. Front Neuroendocrinol 25:150–176.
15. Wu G, Feder A, Wegener G, Bailey C, Saxena S, Charney D, Mathé AA (2011): Central functions of neuropeptide Y in mood and anxiety disorders. Expert Opin Ther Targets 15:1317–1331.
16. Slattery DA, Naik RR, Grund T, Yen Y-C, Sartori SB, Füchsl A, *et al*. (2015): Selective breeding for high anxiety introduces a synonymous SNP that increases neuropeptide S receptor activity. J Neurosci 35: 4599–4613.
17. Meis S, Bergado-Acosta JR, Yanagawa Y, Obata K, Stork O, Munsch T (2008): Identification of a neuropeptide S responsive circuitry shaping amygdala activity via the endopiriform nucleus. PLoS One 3:e2695.
18. Lukas M, Neumann ID (2012): Nasal application of neuropeptide S reduces anxiety and prolongs memory in rats: Social versus non-social effects. Neuropharmacology 62:398–405.
19. Pedersen CA, Prange AJ Jr (1979): Induction of maternal behavior in virgin rats after intracerebroventricular administration of oxytocin. Proc Natl Acad Sci U S A 76:6661–6665.
20. De Wied D (1965): The influence of the posterior and intermediate lobe of the pituitary and pituitary peptides on the maintenance of a conditioned avoidance response in rats. Int J Neuropharmacol 4:157–167.
21. Neumann ID, Landgraf R (2012): Balance of brain oxytocin and vasopressin: Implications for anxiety, depression, and social behaviors. Trends Neurosci 35:649–659.
22. MacDonald K, Feifel D (2014): Oxytocin's role in anxiety: A critical appraisal. Brain Res 1580:22–56.
23. Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M (2011): Oxytocin and vasopressin in the human brain: Social neuropeptides for translational medicine. Nat Rev Neurosci 12:524–538.
24. Rhodes CH, Morrell JI, Pfaff DW (1981): Immunohistochemical analysis of magnocellular elements in rat hypothalamus: Distribution and numbers of cells containing neurophysin, oxytocin, and vasopressin. J Comp Neurol 198:45–64.
25. De Vries GJ, Buijs RM (1983): The origin of the vasopressinergic and oxytocinergic innervation of the rat brain with special reference to the lateral septum. Brain Res 273:307–317.
26. Knobloch HS, Grinevich V (2014): Evolution of oxytocin pathways in the brain of vertebrates. Front Behav Neurosci 8:31.
27. Neumann ID (2007): Stimuli and consequences of dendritic release of oxytocin within the brain. Biochem Soc Trans 35:1252–1257.
28. Gimpl G, Fahrenholz F (2001): The oxytocin receptor system: Structure, function, and regulation. Physiol Rev 81:629–683.
29. van den Burg EH, Neumann ID (2011): Bridging the gap between GPCR activation and behaviour: Oxytocin and prolactin signalling in the hypothalamus. J Mol Neurosci 43:200–208.
30. Gibbs DM (1984): Dissociation of oxytocin, vasopressin and corticotropin secretion during different types of stress. Life Sci 35:487–491.
31. Williams TD, Carter DA, Lightman SL (1985): Sexual dimorphism in the posterior pituitary response to stress in the rat. Endocrinology 116:738–740.
32. Lang RE, Heil JW, Ganten D, Hermann K, Unger T, Rascher W (1983): Oxytocin unlike vasopressin is a stress hormone in the rat. Neuroendocrinology 37:314–316.
33. Onaka T, Yagi K (1993): Effects of novelty stress on vasopressin and oxytocin secretion by the pituitary in the rat. J Neuroendocrinol 5: 365–369.
34. Jezova D, Skultetyova I, Tokarev DI, Bakos P, Vigas M (1995): Vasopressin and oxytocin in stress. Ann N Y Acad Sci 771:192–203.
35. Wotjak CT, Ganster J, Kohl G, Holsboer F, Landgraf R, Engelmann M (1998): Dissociated central and peripheral release of vasopressin, but not oxytocin, in response to repeated swim stress: New insights into the secretory capacities of peptidergic neurons. Neuroscience 85:1209–1222.
36. Engelmann M, Landgraf R, Wotjak CT (2004): The hypothalamic-neurohypophysial system regulates the hypothalamic-pituitary-adrenal axis under stress: An old concept revisited. Front Neuroendocrinol 25:132–149.
37. Neumann ID, Toschi N, Ohl F, Torner L, Kromer SA (2001): Maternal defence as an emotional stressor in female rats: Correlation of neuroendocrine and behavioural parameters and involvement of brain oxytocin. Eur J Neurosci 13:1016–1024.
38. Bosch OJ, Kromer SA, Brunton PJ, Neumann ID (2004): Release of oxytocin in the hypothalamic paraventricular nucleus, but not central amygdala or lateral septum in lactating residents and virgin intruders during maternal defence. Neuroscience 124:439–448.
39. Knobloch HS, Charlet A, Hoffmann LC, Eliava M, Khrulev S, Cetin AH, *et al*. (2012): Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron 73:553–566.
40. Ludwig M, Leng G (2006): Dendritic peptide release and peptide-dependent behaviours. Nat Rev Neurosci 7:126–136.
41. Engelmann M, Ebner K, Landgraf R, Holsboer F, Wotjak CT (1999): Emotional stress triggers intrahypothalamic but not peripheral release of oxytocin in male rats. J Neuroendocrinol 11:867–872.
42. Ludwig M, Callahan MF, Neumann I, Landgraf R, Morris M (1994): Systemic osmotic stimulation increases vasopressin and oxytocin release within the supraoptic nucleus. J Neuroendocrinol 6:369–373.
43. Neumann I, Landgraf R, Bauce L, Pittman QJ (1995): Osmotic responsiveness and cross talk involving oxytocin, but not vasopressin or amino acids, between the supraoptic nuclei in virgin and lactating rats. J Neurosci 15:3408–3417.
44. Landgraf R, Hacker R, Buhl H (1982): Plasma vasopressin and oxytocin in response to exercise and during a day-night cycle in man. Endokrinologie 79:281–291.
45. Pierrehumbert B, Torrisi R, Ansermet F, Borghini A, Halfon O (2012): Adult attachment representations predict cortisol and oxytocin responses to stress. Attach Hum Dev 14:453–476.
46. Carson DS, Berquist SW, Trujillo TH, Garner JP, Hannah SL, Hyde SA, *et al*. (2015): Cerebrospinal fluid and plasma oxytocin concentrations are positively correlated and negatively predict anxiety in children. Mol Psychiatry 20:1085–1090.
47. Holt-Lunstad J, Birmingham W, Light KC (2011): The influence of depressive symptomatology and perceived stress on plasma and

salivary oxytocin before, during and after a support enhancement intervention. Psychoneuroendocrinology 36:1249–1256.
48. Suraev AS, Bowen MT, Ali SO, Hicks C, Ramos L, McGregor IS (2014): Adolescent exposure to oxytocin, but not the selective oxytocin receptor agonist TGOT, increases social behavior and plasma oxytocin in adulthood. Horm Behav 65:488–496.
49. Robinson KJ, Hazon N, Lonergan M, Pomeroy PP (2014): Validation of an enzyme-linked immunoassay (ELISA) for plasma oxytocin in a novel mammal species reveals potential errors induced by sampling procedure. J Neurosci Methods 226:73–79.
50. Leng G, Ludwig M (2016): Intranasal oxytocin: Myths and delusions. Biol Psychiatry 79:243–250.
51. Neumann ID, Torner L, Wigger A (2000): Brain oxytocin: Differential inhibition of neuroendocrine stress responses and anxiety-related behaviour in virgin, pregnant and lactating rats. Neuroscience 95: 567–575.
52. Neumann ID, Wigger A, Torner L, Holsboer F, Landgraf R (2000): Brain oxytocin inhibits basal and stress-induced activity of the hypothalamo-pituitary-adrenal axis in male and female rats: Partial action within the paraventricular nucleus. J Neuroendocrinol 12: 235–243.
53. Bale TL, Davis AM, Auger AP, Dorsa DM, McCarthy MM (2001): CNS region-specific oxytocin receptor expression: Importance in regulation of anxiety and sex behavior. J Neurosci 21:2546–2552.
54. Blume A, Bosch OJ, Miklos S, Torner L, Wales L, Waldherr M, Neumann ID (2008): Oxytocin reduces anxiety via ERK1/2 activation: Local effect within the rat hypothalamic paraventricular nucleus. Eur J Neurosci 27:1947–1956.
55. Ring RH, Malberg JE, Potestio L, Ping J, Boikess S, Luo B, *et al*. (2006): Anxiolytic-like activity of oxytocin in male mice: Behavioral and autonomic evidence, therapeutic implications. Psychopharmacology (Berl) 185:218–225.
56. Mak P, Broussard C, Vacy K, Broadbear JH (2012): Modulation of anxiety behavior in the elevated plus maze using peptidic oxytocin and vasopressin receptor ligands in the rat. J Psychopharmacol 26: 532–542.
57. Jurek B, Slattery DA, Maloumby R, Hillerer K, Koszinowski S, Neumann ID, van den Burg EH (2012): Differential contribution of hypothalamic MAPK activity to anxiety-like behaviour in virgin and lactating rats. PLoS One 7:e37060.
58. Sabihi S, Durosko NE, Dong SM, Leuner B (2014): Oxytocin in the prelimbic medial prefrontal cortex reduces anxiety-like behavior in female and male rats. Psychoneuroendocrinology 45:31–42.
59. Neumann I, Russell JA, Landgraf R (1993): Oxytocin and vasopressin release within the supraoptic and paraventricular nuclei of pregnant, parturient and lactating rats: A microdialysis study. Neuroscience 53: 65–75.
60. Waldherr M, Neumann ID (2007): Centrally released oxytocin mediates mating-induced anxiolysis in male rats. Proc Natl Acad Sci U S A 104:16681–16684.
61. Waldherr M, Nyuyki K, Maloumby R, Bosch OJ, Neumann ID (2010): Attenuation of the neuronal stress responsiveness and corticotrophin releasing hormone synthesis after sexual activity in male rats. Horm Behav 57:222–229.
62. Nyuyki KD, Waldherr M, Baeuml S, Neumann ID (2011): Yes, I am ready now: Differential effects of paced versus unpaced mating on anxiety and central oxytocin release in female rats. PLoS One 6: e23599.
63. Amico JA, Mantella RC, Vollmer RR, Li X (2004): Anxiety and stress responses in female oxytocin deficient mice. J Neuroendocrinol 16: 319–324.
64. van den Burg EH, Stindl J, Grund T, Neumann ID, Strauss O (2015): Oxytocin stimulates extracellular Ca2+ influx through TRPV2 channels in hypothalamic neurons to exert its anxiolytic effects. Neuropsychopharmacology 40:2938–2947.
65. Slattery DA, Neumann ID (2010): Chronic icv oxytocin attenuates the pathological high anxiety state of selectively bred Wistar rats. Neuropharmacology 58:56–61.
66. Windle RJ, Kershaw YM, Shanks N, Wood SA, Lightman SL, Ingram CD (2004): Oxytocin attenuates stress-induced c-fos mRNA expression in specific forebrain regions associated with modulation of hypothalamo-pituitary-adrenal activity. J Neurosci 24:2974–2982.
67. Peters S, Slattery DA, Uschold-Schmidt N, Reber SO, Neumann ID (2014): Dose-dependent effects of chronic central infusion of oxytocin on anxiety, oxytocin receptor binding and stress-related parameters in mice. Psychoneuroendocrinology 42:225–236.
68. Huang H, Michetti C, Busnelli M, Manago F, Sannino S, Scheggia D, *et al*. (2014): Chronic and acute intranasal oxytocin produce divergent social effects in mice. Neuropsychopharmacology 39: 1102–1114.
69. Havranek T, Zatkova M, Lestanova Z, Bacova Z, Mravec B, Hodosy J, *et al*. (2015): Intracerebroventricular oxytocin administration in rats enhances object recognition and increases expression of neurotrophins, microtubule-associated protein 2, and synapsin I. J. Neurosci Res 93:893–901.
70. Bales KL, Perkeybile AM, Conley OG, Lee MH, Guoynes CD, Downing GM, *et al*. (2013): Chronic intranasal oxytocin causes long-term impairments in partner preference formation in male prairie voles. Biol Psychiatry 74:180–188.
71. Bales KL, Solomon M, Jacob S, Crawley JN, Silverman JL, Larke RH, *et al*. (2014): Long-term exposure to intranasal oxytocin in a mouse autism model. Transl Psychiatry 4:e480.
72. Windle RJ, Shanks N, Lightman SL, Ingram CD (1997): Central oxytocin administration reduces stress-induced corticosterone release and anxiety behavior in rats. Endocrinology 138:2829–2834.
73. Landgraf R, Wigger A (2003): Born to be anxious: Neuroendocrine and genetic correlates of trait anxiety in HAB rats. Stress 6:111–119.
74. Conti F, Sertic S, Reversi A, Chini B (2009): Intracellular trafficking of the human oxytocin receptor: Evidence of receptor recycling via a Rab4/Rab5 "short cycle". Am J Physiol Endocrinol Metab 296: E532–E542.
75. Chini B, Manning M (2007): Agonist selectivity in the oxytocin/vasopressin receptor family: New insights and challenges. Biochem Soc Trans 35:737–741.
76. Tops M, van Peer JM, Korf J, Wijers AA, Tucker DM (2007): Anxiety, cortisol, and attachment predict plasma oxytocin. Psychophysiology 44:444–449.
77. Weisman O, Zagoory-Sharon O, Schneiderman I, Gordon I, Feldman R (2013): Plasma oxytocin distributions in a large cohort of women and men and their gender-specific associations with anxiety. Psychoneuroendocrinology 38:694–701.
78. Costa B, Pini S, Gabelloni P, Abelli M, Lari L, Cardini A, *et al*. (2009): Oxytocin receptor polymorphisms and adult attachment style in patients with depression. Psychoneuroendocrinology 34:1506–1514.
79. Thompson RJ, Parker KJ, Hallmayer JF, Waugh CE, Gotlib IH (2011): Oxytocin receptor gene polymorphism (rs2254298) interacts with familial risk for psychopathology to predict symptoms of depression and anxiety in adolescent girls. Psychoneuroendocrinology 36: 144–147.
80. Myers AJ, Williams L, Gatt JM, McAuley-Clark EZ, Dobson-Stone C, Schofield PR, Nemeroff CB (2014): Variation in the oxytocin receptor gene is associated with increased risk for anxiety, stress and depression in individuals with a history of exposure to early life stress. J Psychiatr Res 59:93–100.
81. Feifel D, MacDonald K, McKinney R, Heisserer N, Serrano V (2011): A randomized, placebo-controlled investigation of intranasal oxytocin in patients with anxiety. Neuropsychopharmacology 36: S324–S449.
82. Alvares GA, Chen NT, Balleine BW, Hickie IB, Guastella AJ (2012): Oxytocin selectively moderates negative cognitive appraisals in high trait anxious males. Psychoneuroendocrinology 37:2022–2031.
83. de Oliveira DC, Zuardi AW, Graeff FG, Queiroz RH, Crippa JA (2012): Anxiolytic-like effect of oxytocin in the simulated public speaking test. J Psychopharmacol 26:497–504.
84. Goodin BR, Anderson AJ, Freeman EL, Bulls HW, Robbins MT, Ness TJ (2014): Intranasal oxytocin administration is associated with

enhanced endogenous pain inhibition and reduced negative mood states [published online ahead of print November 3]. Clin J Pain.
85. Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U (2003): Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol Psychiatry 54:1389–1398.
86. Pierrehumbert B, Torrisi R, Laufer D, Halfon O, Ansermet F, Beck Popovic M (2010): Oxytocin response to an experimental psychosocial challenge in adults exposed to traumatic experiences during childhood or adolescence. Neuroscience 166:168–177.
87. Shin LM, Orr SP, Carson MA, Rauch SL, Macklin ML, Lasko NB, *et al*. (2004): Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. Arch Gen Psychiatry 61:168–176.
88. Williams LM, Kemp AH, Felmingham K, Barton M, Olivieri G, Peduto A, *et al*. (2006): Trauma modulates amygdala and medial prefrontal responses to consciously attended fear. Neuroimage 29:347–357.
89. Orsini CA, Maren S (2012): Neural and cellular mechanisms of fear and extinction memory formation. Neurosci Biobehav Rev 36:1773–1802.
90. Singewald N, Schmuckermair C, Whittle N, Holmes A, Ressler KJ (2015): Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. Pharmacol Ther 149:150–190.
91. Cammarota M, Bevilaqua LR, Vianna MR, Medina JH, Izquierdo I (2007): The extinction of conditioned fear: Structural and molecular basis and therapeutic use. Rev Bras Psiquiatr 29:80–85.
92. Quirk GJ, Pare D, Richardson R, Herry C, Monfils MH, Schiller D, Vicentic A (2010): Erasing fear memories with extinction training. J Neurosci 30:14993–14997.
93. Zhu L, Onaka T (2002): Involvement of medullary A2 noradrenergic neurons in the activation of oxytocin neurons after conditioned fear stimuli. Eur J Neurosci 16:2186–2198.
94. Toth I, Neumann ID, Slattery DA (2012): Central administration of oxytocin receptor ligands affects cued fear extinction in rats and mice in a timepoint-dependent manner. Psychopharmacology (Berl) 223:149–158.
95. Lahoud N, Maroun M (2013): Oxytocinergic manipulations in corticolimbic circuit differentially affect fear acquisition and extinction. Psychoneuroendocrinology 38:2184–2195.
96. Huber D, Veinante P, Stoop R (2005): Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. Science 308:245–248.
97. Viviani D, Charlet A, van den Burg E, Robinet C, Hurni N, Abatis M, *et al*. (2011): Oxytocin selectively gates fear responses through distinct outputs from the central amygdala. Science 333:104–107.
98. Neumann ID (2009): The advantage of social living: Brain neuropeptides mediate the beneficial consequences of sex and motherhood. Front Neuroendocrinol 30:483–496.
99. Donaldson ZR, Young LJ (2008): Oxytocin, vasopressin, and the neurogenetics of sociality. Science 322:900–904.
100. Lukas M, Neumann ID (2013): Oxytocin and vasopressin in rodent behaviors related to social dysfunctions in autism spectrum disorders. Behav Brain Res 251:85–94.
101. Lukas M, Toth I, Reber SO, Slattery DA, Veenema AH, Neumann ID (2011): The neuropeptide oxytocin facilitates pro-social behavior and prevents social avoidance in rats and mice. Neuropsychopharmacology 36:2159–2168.
102. Zoicas I, Slattery DA, Neumann ID (2014): Brain oxytocin in social fear conditioning and its extinction: Involvement of the lateral septum. Neuropsychopharmacology 39:3027–3035.
103. Crawley JN, Chen T, Puri A, Washburn R, Sullivan TL, Hill JM, *et al*. (2007): Social approach behaviors in oxytocin knockout mice: Comparison of two independent lines tested in different laboratory environments. Neuropeptides 41:145–163.
104. Toth I, Neumann ID, Slattery DA (2013): Social fear conditioning as an animal model of social anxiety disorder. Curr Protoc Neurosci Chapter 9:Unit9.42.
105. Toth I, Neumann ID, Slattery DA (2012): Social fear conditioning: A novel and specific animal model to study social anxiety disorder. Neuropsychopharmacology 37:1433–1443.
106. Litvin Y, Murakami G, Pfaff DW (2011): Effects of chronic social defeat on behavioral and neural correlates of sociality: Vasopressin, oxytocin and the vasopressinergic V1b receptor. Physiol Behav 103:393–403.
107. Guzman YF, Tronson NC, Jovasevic V, Sato K, Guedea AL, Mizukami H, *et al*. (2013): Fear-enhancing effects of septal oxytocin receptors. Nat Neurosci 16:1185–1187.
108. Pitman RK, Orr SP, Lasko NB (1993): Effects of intranasal vasopressin and oxytocin on physiologic responding during personal combat imagery in Vietnam veterans with posttraumatic stress disorder. Psychiatry Res 48:107–117.
109. Eckstein M, Becker B, Scheele D, Scholz C, Preckel K, Schlaepfer TE, *et al*. (2015): Oxytocin facilitates the extinction of conditioned fear in humans. Biol Psychiatry 78:194–202.
110. Acheson D, Feifel D, de Wilde S, McKinney R, Lohr J, Risbrough V (2013): The effect of intranasal oxytocin treatment on conditioned fear extinction and recall in a healthy human sample. Psychopharmacology (Berl) 229:199–208.
111. Grillon C, Krimsky M, Charney DR, Vytal K, Ernst M, Cornwell B (2013): Oxytocin increases anxiety to unpredictable threat. Mol Psychiatry 18:958–960.
112. Ziegler C, Dannlowski U, Brauer D, Stevens S, Laeger I, Wittmann H, *et al*. (2015): Oxytocin receptor gene methylation: Converging multilevel evidence for a role in social anxiety. Neuropsychopharmacology 40:1528–1538.
113. Guastella AJ, Howard AL, Dadds MR, Mitchell P, Carson DS (2009): A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. Psychoneuroendocrinology 34:917–923.
114. Dodhia S, Hosanagar A, Fitzgerald DA, Labuschagne I, Wood AG, Nathan PJ, Phan KL (2014): Modulation of resting-state amygdala-frontal functional connectivity by oxytocin in generalized social anxiety disorder. Neuropsychopharmacology 39:2061–2069.
115. Gorka SM, Fitzgerald DA, Labuschagne I, Hosanagar A, Wood AG, Nathan PJ, Phan KL (2015): Oxytocin modulation of amygdala functional connectivity to fearful faces in generalized social anxiety disorder. Neuropsychopharmacology 40:278–286.
116. Labuschagne I, Phan KL, Wood A, Angstadt M, Chua P, Heinrichs M, *et al*. (2010): Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder. Neuropsychopharmacology 35:2403–2413.
117. Hall SS, Lightbody AA, McCarthy BE, Parker KJ, Reiss AL (2012): Effects of intranasal oxytocin on social anxiety in males with fragile X syndrome. Psychoneuroendocrinology 37:509–518.