Opinion

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Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors

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Oxytocin and vasopressin are regulators of anxiety, stress-coping, and sociality. They are released within hypothalamic and limbic areas from dendrites, axons, and perikarya independently of, or coordinated with, secretion from neurohypophysial terminals. Central oxytocin exerts anxiolytic and antidepressive effects, whereas vasopressin tends to show anxiogenic and depressive actions. Evidence from pharmacological and genetic association studies confirms their involvement in individual variation of emotional traits extending to psychopathology. Based on their opposing effects on emotional behaviors, we propose that a balanced activity of both brain neuropeptide systems is important for appropriate emotional behaviors. Shifting the balance between the neuropeptide systems towards oxytocin, by positive social stimuli and/or psychopharmacotherapy, may help to improve emotional behaviors and reinstate mental health.

Introduction

Over the past years, substantial progress has been achieved with respect to our neurobiological understanding of the link between anxiety and stress-coping, on the one hand, and social behaviors on the other. A dynamic interplay of genetic, epigenetic, and environmental factors orchestrates both individual behavioral variations and the etiology of anxiety- and depression-related disorders. Despite this progress, available treatment options are far from being mechanism-based, which explains the need for innovative therapeutic interventions. One focus of modern psychiatric research for future therapies has been on neuropeptide systems, with oxytocin (OXT) and arginine vasopressin (AVP) featuring prominently in such endeavors [1–5]. The synthesis and release of OXT and AVP within the brain are driven by anxiogenic, stressful, and notably social (both positive and negative) stimuli [1,6]. In turn, once released, both neuropeptides are key regulators of anxiety-related behavior, passive versus active stress-coping as an indicator of depression-like behavior, and multiple aspects of social behavior [1–4,7].

We here discuss experimental evidence, primarily from rodents, but with complementary data from human studies ([5] for review of human data), for opposing effects of OXT and AVP on the fine-tuned regulation of emotional behavior. Specifically, OXT exerts anxiolytic and antidepressive effects, whereas AVP predominantly increases anxiety- and depression-related behaviors. We will therefore put forward the hypothesis that a dynamic balance between the activities of brain OXT and AVP systems impacts upon hypothalamic and limbic circuitries involved in a broad spectrum of emotional behaviors extending to psychopathology.

Central release patterns of OXT and AVP: coordinated and independent secretion into blood

Following their neuronal synthesis in the hypothalamic supraoptic (SON) and paraventricular (PVN) nuclei (OXT, AVP), or in regions of the limbic system (AVP), both neuropeptides are centrally released to regulate neuronal processes in a spatially and temporally fine-tuned manner. As neurotransmitters, following release from axon terminals they contribute to the synaptic mode of rapid information processing via hard-wired neuronal connections [1,8]. A complementary mode of OXT and AVP release is non-synaptically from dendritic, somatic, and non-terminal axonal regions of the neuronal membrane [1,9] (Figure 1). Upon diffusion to nearby or remote receptors via the extracellular fluid (ECF) and ligand binding, the association of the OXT receptor (OXTR) and the AVP receptor (AVPR) subtypes AVPR1A and AVPR1B with specific intraneuronal signaling cascades determines their acute or long-term effects [10–12]. Whereas the quality of neuropeptide-induced effects is primarily determined by localization of their receptors in distinct, particularly hypothalamic and limbic, brain areas [10], local concentration of the neuropeptide ligand in the ECF and receptor density are the major determinants of the intensity and duration of such actions. Importantly, OXT and AVP actions may partly overlap, due to >85% homology between their receptors, and this has both physiological and pharmacological implications [13,14].

Simultaneous microdialysis and blood sampling has provided evidence for both coordinated and independent release of OXT and AVP within the brain, and from neurohypophysial terminals into blood (Figure 1), and these seem to be both stimulus-dependent and peptide-specific [1,15]. Providing evidence for coordinated release, numerous

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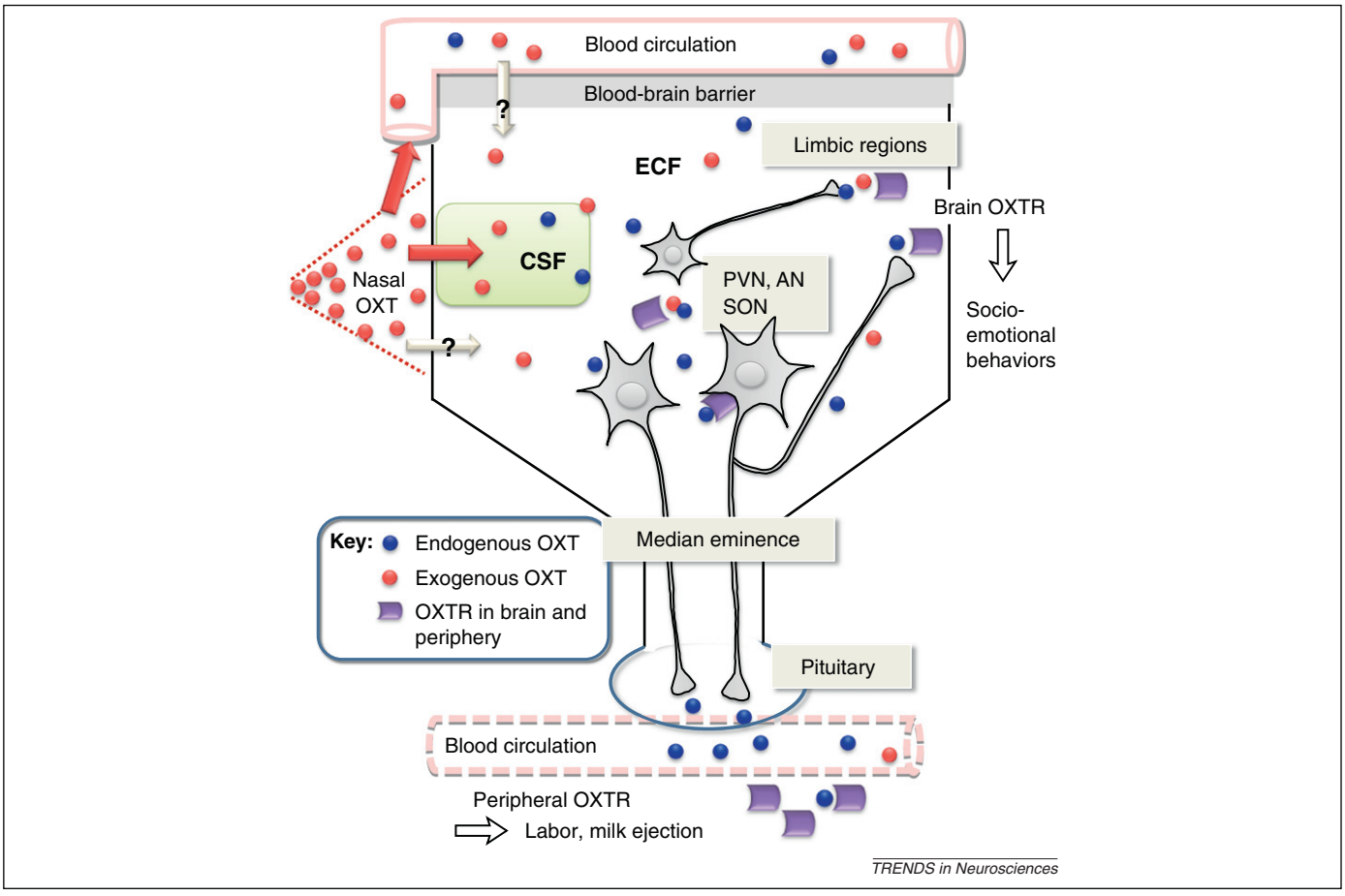

Figure 1. The brain oxytocin (OXT) system: neuronal projections, release, receptor-mediated effects, and external application. Physiologically, OXT is secreted as a neurohormone into the bloodstream from axon terminals of magnocellular hypothalamic OXT neurons via neurohemal contacts within the posterior pituitary upon stimulation (e.g., birth, suckling, stress). These neurons may also target brain (e.g., limbic) regions via axon collaterals [8]. In addition to release from axon terminals as a neurotransmitter, central release of OXT as a neuromodulator was shown to occur from dendrites and perikarya [1,9], explaining basal and stimulated levels in the extracellular fluid (ECF) of distinct brain regions, as well as spatially and temporally precise point-to-point signaling. Central release can occur both independently of, and simultaneously with, peripheral secretion. Together with the regional distribution and density of OXT receptor (OXTR), the amount of locally released OXT largely determines the activity of the brain OXT system, thus contributing to the regulation of emotional and social behaviors [7]. Brain OXT availability can be further raised by intranasal administration of OXT; exogenous OXT reaches both the cerebrospinal fluid (CSF) of brain ventricles and the systemic circulation [110,111]. From CSF, synthetic neuropeptides may readily diffuse through the ventricular ependyma into the ECF according to the concentration gradient; blood–brain barrier (BBB) transport (Box 1) may, to some extent, augment brain neuropeptide levels in a concentration-dependent manner [1]. Although exemplified for the brain OXT system in this cartoon, there is substantial evidence for a comparable neurobiology of the brain arginine vasopressin (AVP) system with respect to neuronal synthesis, central release, peripheral secretion, and external application [1]. Abbreviation: AN, accessory magnocellular nuclei.

physiological stimuli trigger both central and peripheral OXT release, including birth, suckling, sexual activity, and various forms of stress, with essentially synergistic behavioral and physiological actions of centrally (maternal behavior, sexual behavior, anxiolysis, social preference, and recognition) and peripherally (labor, milk ejection, orgasm) released OXT, respectively [15,16]. Magnocellular OXT neurons projecting to the posterior pituitary, but also targeting limbic regions via axon collaterals [8], may explain such coordinated release.

Although these findings speak in favor of plasma OXT as being a global biomarker of central OXT system activity, the temporal dynamics of central and peripheral release may substantially differ in a stimulus-dependent way. Moreover, various stressors have been shown to trigger OXT (and AVP) release within hypothalamic and limbic regions, whereas neuropeptide secretion into blood remains virtually unchanged [1,15,16].

Accordingly, changes in neuropeptide concentrations in human plasma, saliva, or urine in a behavioral context need to be interpreted with caution. Uncertainties as to the site and dynamics of central release, and whether altered levels reflect causes or consequences of behavioral alterations, limit their plausibility. In contrast to the separation of central from peripheral compartments by the blood–brain barrier (BBB) (Box 1), these neuropeptides may readily diffuse between brain ECF and ventricular cerebrospinal fluid (CSF) (Figure 1). Therefore, quantification in the CSF provides at least a global measure of neuropeptide activity in the brain, and affords a more accurate reflection of central release patterns [1]. Importantly, in any body fluid, questions about the reliability of neuropeptide measurements must be raised. Until assays are strictly validated and standardized to detect bioavailable neuropeptide, interpretation of data (particularly from commercial assays without extraction) remains vague at best.

Box 1. OXT, AVP, and the blood–brain barrier (BBB)

The BBB prevents endogenous neuropeptides, such as OXT and AVP, from crossing in physiologically relevant amounts. OXT/AVP plasma levels are generally lower than those in the ECF, further restricting diffusion from blood to brain. The separation of central and peripheral compartments under physiological conditions coevolved with the functional divergence of neuropeptide effects in blood and brain. Indeed, there are primarily independent physiological functions at peripheral (e.g., antidiuresis) and central (socio-emotional behaviors) levels. In addition, coordinated and possibly synergistic actions of peripheral and central neuropeptides may occur following simultaneous release into both compartments (e.g., during birth). Thus, instead of being merely a protective structure, the BBB contributes to both independent and fine-tuned coordinated neuropeptide regulation. However, it should be noted that exogenous neuropeptides may reach the brain parenchyma through the BBB in minute, but functionally significant, amounts (as indicated in Figure 1).

OXT and AVP: anxiety and social phobia

Brain OXT and AVP are important regulators of anxiety, although usually in opposing directions. Once released in brain regions involved in stress and anxiety regulation, for example in response to anxiogenic stimuli [1,15,16], OXT exerts anxiolytic effects and modulates neuronal functions related to physiological stress responses, mainly at the levels of the PVN and amygdala [8,17–21]. Particularly intriguing is the reduction in emotional responsiveness during periods of high activity of the endogenous OXT system, such as during lactation [22] and sexual activity [23,24]. Acute or chronic central administration of synthetic OXT in rodents, thereby increasing neuropeptide availability in the ECF (Figure 1), confirmed the anxiolytic and stress-protective effects in various experimental settings both in females and males [25–28]. Moreover, the brain OXT system seems to be important for fear expression and extinction, as shown in a rodent model of cued fear conditioning [8,29]. Behavioral data from transgenic mice lacking either OXT or the OXTR provide further support for involvement of the brain OXT system in anxiety regulation [14,30]. The OXTR-mediated acute anxiolytic effect of OXT within the PVN requires the intracellular activation of signaling cascades, such as the mitogen-activated protein kinase cascade, which may contribute to long-term behavioral adaptations via gene regulation [12,20].

It is worth emphasizing that OXT exerts various prosocial effects [7,31] which may, in particular, contribute to its anxiolytic effects in a social context. Naturally occurring social approach and social preference behavior was shown to be strictly dependent on brain OXT in rats and mice, and social anxiety prevents such behavior [32,33]. In a rodent model of social defeat-induced social phobia, central administration of OXT reversed social avoidance and rescued social preference [33] (Figure 2). Thus, according to our hypothesis, activation of the brain OXT system, for example, by positive social stimuli or pharmacotherapy, results in increased central OXT availability and a (local or global) shift of the OXT–AVP balance towards the former, thus resulting in reduced levels of general and social anxiety (Figure 3).

In contrast to OXT, the brain AVP system mediates anxiogenic effects, as shown by a variety of gain- and loss-of-function studies on AVP and its AVPR1A and AVPR1B subtypes. Specifically, central or peripheral administration of AVPR antagonists, local antisense targeting of AVPR1A, AVPR knockout mice, and adenoviral vector-induced AVPR1A upregulation [28,34–38] have confirmed the anxiogenic effects of endogenous AVP. In a rat model of high (HAB) versus low (LAB) anxiety-related behavior, representing natural extremes of trait anxiety, the AVP gene was identified as a candidate gene for inborn anxiety [39]. As exemplified in this model, as well as in early-life stress approaches [40,41], hyperactivity of the AVP system severely disturbs the neuropeptide balance, thus shifting behavior along a continuum towards hyperanxiety and passive coping (Figure 3). Consequently, reinstatement of the OXT–AVP balance, and of emotional behavior, could be achieved by either loss-of-function approaches targeting the AVP system [36] or, alternatively, by chronic OXT treatment, as shown in HAB rats [4].

With respect to social anxiety, the AVPR1A of the mouse medial amygdala was suggested to mediate prosocial behaviors, with an opposite, antisocial role for AVPR1B, emphasizing the potential utility of the AVPR1B antagonist SSR149415 in patients with social anxiety or social phobia [42]. However, an involvement of the OXT system cannot entirely be excluded because SSR149415 has also been shown to weakly bind to OXTR [13].

There is also general support for an anxiolytic effect of OXT in humans. For example, nursing mothers with higher OXT levels are more likely to describe positive mood states and reduced anxiety [43,44]. By contrast, women who were abused in childhood have lower OXT concentrations in CSF and higher anxiety scores [45].

In a plethora of human studies, intranasal administration of synthetic OXT is currently used to increase the availability of OXT in the brain ECF and, consequently, brain OXT system activity (Figure 1). Despite individual variations in OXT effectiveness [46], these studies support the capacity of the neuropeptide to modulate anxiety circuitries, including reduced [47] and enhanced [48] amygdala reactivity to fearful faces in men and women, respectively, indicating gender-specific modulation of perceptual salience and the processing of social cues. Whereas there appears to be little effect of nasal OXT on trait anxiety in healthy men [49], OXT was shown to attenuate anxiety and fear responses in social contexts [50] ([5,51,52] for review). Moreover, in patients suffering from social anxiety disorder or autism, intranasal OXT reduced several symptoms of social impairment [53–56].

Supporting rodent studies, emotional effects of synthetic AVP in humans also include increased anxiety and fear responses. For example, autonomic and behavioral responses to threatening faces were elevated upon intranasal AVP [57]. Further, amygdala responses to similar socio-emotional stimulation were found to be associated with genetic variations of AVPR1A [58] (Table 1). Although intranasal administration of AVP did not affect anxiety in healthy men [59], AVPR1B antagonists were shown to attenuate indices of anxiety and depression in animal models and depressed individuals [37,60].

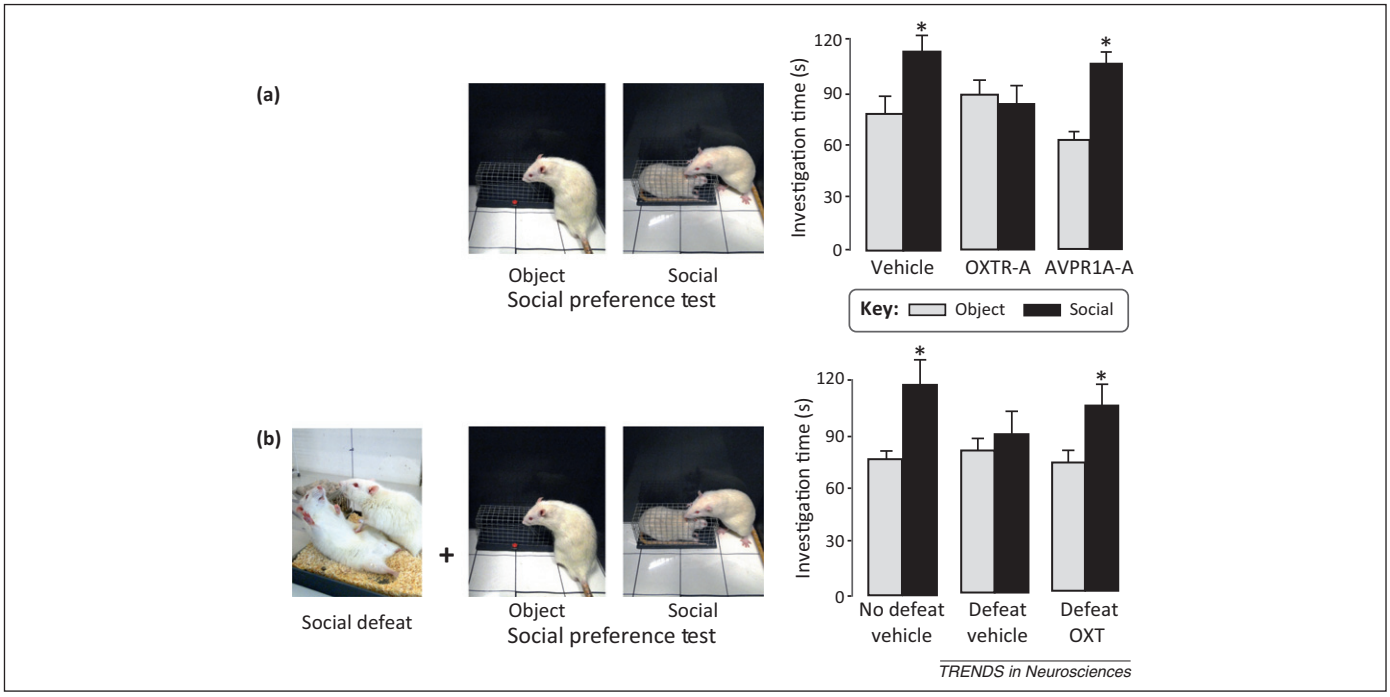

Figure 2. Brain oxytocin (OXT) promotes social preference and reverses defeat-induced social phobia in rodents. **(a)** In the social preference test, social preference is reflected by longer exploration of the small cage containing a conspecific (social stimulus) than an empty small cage (object stimulus). The naturally occurring social preference is prevented by central administration of an OXT receptor (OXTR) antagonist (OXTR-A), but not of an arginine vasopressin receptor (AVPR) antagonist (AVPR1A-A). **(b)** 30 min exposure to social defeat (20 min before social preference testing) prevents social preference and results in social avoidance in vehicle-treated rats. Social phobia can be reversed by intracerebroventricular infusion of OXT 20 min before behavioral testing. $*P < 0.01$. Adapted, with permission, from [33].

OXT, AVP, and depression-like behavior

Due to the high degree of comorbidity between anxiety and depression disorders, common mediators are likely to underlie both conditions. Indeed, in addition to its anxiolytic effect, synthetic OXT was shown to shift stress-coping in rodents towards a more active coping style, after either central or peripheral administration, indicating antidepressive-like effects ([4,61,62] for review). Further, there is preclinical and clinical evidence that OXT may also contribute to the improvement of other depression-related symptoms, including sexual dysfunctions [63,64], sleep disturbances [65], and anhedonia ([4] for review).

Another phenomenon possibly related to both depression and central OXT is hippocampal neurogenesis, which seems to be important for stress-coping and the buffering of depressive behavior [66]. OXT, but not AVP, was recently shown to stimulate neuronal growth and to rescue glucocorticoid- or stress-induced suppression of neurogenesis in the hippocampus of adult rats [67].

In depressed patients, evidence for an altered OXT system, as deduced from plasma and CSF levels, is limited and inconsistent [4,68]. Although increased OXT mRNA expression and OXT immunoreactivity were found in postmortem hypothalamic tissue from depressed patients [69], several questions remain – for example, whether such alterations represent causes or consequence of the disorder, and whether antidepressant treatment can normalize such changes.

Similarly to anxiety, brain AVP appears to modulate depression-like behavior in an opposite manner to OXT, in other words, shifting it towards passive stress-coping. Indeed, in the above-mentioned HAB rats, AVP overexpression in the PVN not only contributed to hyperanxiety but also to a depression-like phenotype, which could be normalized by long-term treatment with the antidepressant paroxetine [70]. Analogously, both AVP and AVPR1A mRNAs were found to be overexpressed, and the number of AVP-expressing neurons increased in the PVN of depressed patients [71,72]. Thus, shifting the neuropeptide balance towards OXT by inhibition of brain AVP might be beneficial also in depression (Figure 3). Accordingly, modulators of AVPR activity are potential therapeutic tools, such as the AVPR1B antagonist SSR149415 with anxiolytic, antidepressant, and stress-buffering effects [37,42,73]. However, to date none of these drugs has reached the market [38].

Mechanisms of effects of OXT and AVP related to anxiety and depression

Multiple brain neurotransmitter and neuromodulator systems are presumed to interact at various brain levels to shape individual variations in emotionality. The mechanisms underlying anxiolytic and antidepressive effects of OXT are likely to include interactions with monoaminergic, in particular the serotonergic, and corticotropin-releasing factor (CRF) systems, both of which have been implicated in anxiety disorders and depression [2,72,74]. A subpopulation of OXTR-expressing serotonergic neurons exists within the raphe nucleus [75]; in turn, stimulation of serotonin release activates hypothalamic OXT neurons [76]. Moreover, in female rhesus monkeys, both serotonin and OXT are potential targets of estradiol, and as such are likely to mediate its prosocial and anxiolytic effects [77,78]. Thus, OXT-based therapy might be an additional option to reverse the postulated deficits in serotonergic (and possibly noradrenergic) neurotransmission in depressed individuals, the more

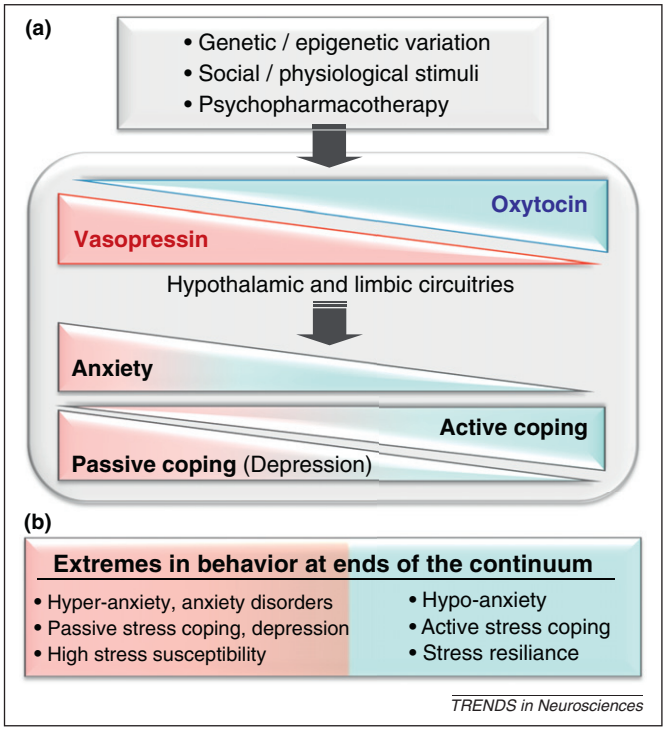

Figure 3. Hypothetical model depicting the balance in brain oxytocin (OXT) and arginine vasopressin (AVP) systems activity and its implications for behavioral regulation from mental health to psychopathology. **(a)** Although brain OXT acts as an endogenous anxiolytic and antidepressive neuropeptide, AVP exerts anxiogenic and depression-like effects. Consequently, the balanced activities of the brain OXT and AVP systems may impact upon individual variations in anxiety and stress-coping style, indicative of depression-related behavior, along a continuum. The brain OXT/AVP systems activity in hypothalamic and limbic regions and, thus, neuropeptide balance is determined by genetic, epigenetic, physiological, social, and other environmental (risk) factors and can be further modulated by psychopharmacotherapy (e.g., by administration of selective receptor agonists or antagonists). Shifting the OXT–AVP balance to the left, for example, by genetic risk factors (Table 1) and/or by negative social cues early in life, resulting in reduced OXT system activity, is probably associated with increased anxiety-related behavior and passive stress-coping, thus increasing the risk of psychopathology. A neuropeptide imbalance can be reflected by reduced OXT and elevated AVP system activity, respectively, or both. Thus, shifting the OXT–AVP balance does not necessarily mean reciprocal changes of both neuropeptide systems. Pharmacologically, the neuropeptide balance may be shifted towards the right by intranasal application of synthetic OXT and increased brain OXT availability (Figure 1), thus promoting the anxiolytic, anti-depressive, stress-protective, and prosocial effects of the brain OXT system. **(b)** Examples from animal and human studies for extremes in behavioral phenotypes at the ends of the anxiety/stress-coping continuum; the middle range represents species-specific phenotypic variation.

because some effects of selective serotonin reuptake inhibitors (SSRI) are thought to be mediated by OXT [77]. Supporting this view, polymorphisms in the serotonin transporter and OXTR genes have recently been shown to interact in healthy men and women, thereby influencing their vulnerability for psychopathology [79].

In addition to AVP, hyperactivity of the brain CRF system has been linked to both passive stress-coping in rodents, and stress-related disorders such as depression [2,60,80]. In support, CRF and CRF receptor 1 genes are overexpressed in the PVN of both HAB rats [39,70] and depressed patients [71,72]. OXT actions may partly be mediated via effects on hypothalamic CRF neurons [25], which express OXTR [81]. Thus, following its activation by social or rewarding stimuli, endogenous OXT may contribute to the attenuation of anxiogenic, depressive, and stress effects of CRF.

Studies on neuropeptide mechanisms have recently been complemented by the demonstration that OXT and AVP modulate anxiety responses and fear extinction in the central amygdala of rats in opposite manners, and target distinct neuronal populations. Following local release, OXT attenuated fear by acting on two major populations of neurons of an inhibitory network, one inhibited by OXT, but excited by AVP (via AVPR1A), the other being excited by OXT but unresponsive to AVP [19,21]. These findings suggest important functional implications of neuropeptide balance not only at the behavioral but also neuronal network levels.

Similar mechanisms of OXT action are expected to underlie the emotional and anti-stress effects seen in a continuously rising number of human neuroimaging studies after intranasal administration (Figures 1 and 3). For example, in OXTR risk allele carriers (rs53576A; Table 1) who display deficits in socio-behavioral domains, alterations in hypothalamic-amygdala coupling were found [82]. Along the same lines, intranasal OXT has been shown to potently alter activation of the amygdala and its coupling to brainstem regions in response to social and threatening stimuli [48,49]. Intranasal administration of AVP has been found to modulate the activity and connectivity patterns within prefrontal cortex-amygdala regions, circuitries that are implicated in threat perception, the processing of anxiety/fear, and in social behaviors [59].

OXT, AVP, and social behaviors

According to the social brain hypothesis, the need to adapt behaviorally to increasing social complexity has substantially contributed to the development of brain mass, cognitive abilities, emotions, and language [83]. Brain OXT and AVP, as well as their evolutionary ancestors, are major players in the complex orchestra shaping sociality, and this impacts upon both anxiety and stress-coping [3,7,31]. Following their central release, both OXT and AVP promote important aspects of social behavior, including social preference (OXT) [33], maternal care, and aggression (OXT and AVP) [84,85], sexual behavior (OXT) [63], pair-bonding in monogamous species (OXT and AVP) [31,86,87], social cognition (OXT and AVP) [88–90], and inter-male aggression (AVP) [91,92]. It is of note in this context that the high levels of sociability observed in rats after 3,4 methylenedioxymethamphetamine (ecstasy) administration were shown to be OXT-mediated [93].

In contrast to mostly opposite effects of OXT and AVP on anxiety and depression-related behavior, as discussed above, social behaviors are often regulated in the same direction, as seen, for example, in the context of pair-bonding in monogamous voles (although in a sex- and region-dependent manner) [31], maternal behavior [85], and social memory [88,90]. However, only the brain OXT system appears to be essential for social preference and for the avoidance of social anxiety as a prerequisite for social interaction, because AVP lacks such effects [33] (Figure 2). Also, the facilitation of social fear extinction by OXT seems to be a neuropeptide-specific effect [94].

Human studies confirm multiple prosocial effects of both OXT and AVP after intranasal administration in healthy subjects, as well as in patients with emotional or social

Table 1. Examples of genetic polymorphisms in genes encoding OXTR, AVPR1A, and AVP that are associated with emotional and social phenotypes[a]

Gene/polymorphism	Species	Associated phenotypes	Refs
Oxytocin receptor			
rs53576 (SNP in the 3rd intron of the *OXTR* gene) or haplotype including rs53576	Humans	Optimism, self-esteem, depression	[124]
		Social support seeking	[117]
		Empathy, stress reactivity	[125]
		Sensitive parenting	[126]
		Prosocial temperament; variations in hypothalamic, amygdala/cingulate structure and function	[82]
		Emotional loneliness	[127]
		Behavioral manifestations of prosociality	[128]
		Autism	[129]
rs2254298 (SNP in the 3rd intron of the *OXTR* gene)	Humans	Volume, function, and connectivity of hypothalamus and limbic brain regions; ethnically and sex-dependent effects	[113,130]
		Susceptibility to anxiety, depression, autism	[131,132]
Vasopressin receptor 1A			
Length variation in tandem repeats in promoter region	Voles	Monogamy, partner preference; modified receptor expression and distribution; phenotypic confirmation in transgenic mice and rats	[31]
RS1, RS3 (polymorphic microsatellite repeats near the promoter)	Humans	Autism, personality traits; differential activation of amygdala	[58]
		Altruism, trust; levels of AVPR1A mRNA in post-mortem hippocampi	[133]
		Partner bonding	[134]
Haplotypes consisting of RS1, RS3, and an intronic microsatellite	Humans	Autism	[135]
Vasopressin			
Deletion in LAB promoter	Mice (F2 panel from HAB × LAB crosses)	Anxiety-related behavior	[136]

[a]Examples were selected based on reproducibility and functional confirmation.

dysfunctions [5,57,95,96]. In this context, OXT is particularly prominent in the processing of positive social stimuli [49,52,97,98]. Opposing effects of OXT and AVP on social recognition and socio-emotional perception have been described, with intranasal OXT elevating [48] and AVP impairing [99] mind-reading, respectively. Moreover, neuropeptide effects are nuanced, with a sizeable minority of human studies showing that OXT can even produce antisocial effects under particular conditions [46].

Influence of the social environment on brain OXT and AVP activity

Positive and rewarding social stimuli (such as mother–offspring or socio-sexual interactions, and social support), and negative social experiences (such as defeat, subordination, or interruption of maternal care early in life), differentially affect both neuropeptide systems. This is reflected by alterations in the expression, release, and receptor binding of OXT/AVP within limbic regions and, partly, in plasma OXT or AVP concentrations [15,41,42,100–102]. We propose that in this way the social environment may contribute to the modulation of the activity of the brain OXT and AVP systems, with positive stimuli being likely to shift the balance towards OXT (Figure 3). Indeed, rodent and human studies suggest that reinforcing positive social interactions is generally beneficial for mental health, and improves emotional stability and concomitantly protects against psychopathologies [7]. Many other positive health effects of social support were described in animal and human studies, for example on immunological and cardiovascular functions [7,103,104]. It is noteworthy that even intense social interaction of humans with their pets leads to elevated plasma OXT [105], and this may give rise to some of the beneficial effects described above.

Conversely, interrupted or lack of social interactions – anticipated as psychosocial stress – have been associated with increased anxiety, especially social anxiety, or depression-like behavior in rodents [33,101,106]. Indeed, psychosocial stressors including adverse social experiences early in life cause alterations in the OXT and AVP systems [40,42,101,107–109]. Similarly, in humans, emotional neglect or child maltreatment increase the risk for mental disorders and, under particular conditions, have also been shown to be accompanied by lower OXT concentrations in CSF in adulthood [45].

Overall, whereas activation of the OXT system with simultaneous inhibition of the AVP system might be a promising therapeutic option to treat anxiety disorders and depression due to mostly opposite emotional effects [4,54,55] (Figure 3), the impact of neuropeptide balance for social behavior is less clear. Particularly in the case of unidirectional neuropeptide effects (e.g., on social cognition), the situation is further complicated by potential OXT/AVP (including antagonist [13]) cross-reactivity,

particularly at high dosages, due to the high extent of receptor homology [14]. Whether this is relevant for human studies remains to be shown, given the low neuropeptide dose that is likely to reach the brain compartment after intranasal administration [110,111]. In any case, the functional and structural overlap of the OXT and AVP systems emphasizes the complexity of the pharmacology involved in developing neuropeptide-based selective psychopharmacotherapies.

Gender-dependent effects of OXT and AVP

An important aspect of neuropeptide functions that balance emotional behavior is the sexual dimorphism of OXT/AVP systems, and this may underlie the higher incidence of anxiety disorders and depression in women, and antisocial behavior and autism in males [112]. Estrogens upregulate OXT synthesis within the PVN and regulate OXTR expression in the amygdala via estrogen α- and β-receptor actions, respectively. Sexually dimorphic amygdala reactivity to intranasal OXT [48], and gender-dependent impact of genetic variations in the OXTR upon hypothalamic and amygdala volume and functional coupling [82,113,114], further support the hypothesis of sex-dependent activity of the brain OXT system.

In contrast to OXT, AVP is mainly influenced by testosterone via androgen, but also estrogen, receptor-mediated mechanisms [115]. It remains to be shown, to which extent such mechanisms contribute to sexually dimorphic effects of intranasal AVP on human social communication and strategies in stressful contexts [57].

Genes of the OXT and AVP systems in association studies

The data described so far, suggesting reliable OXT and AVP effects on socio-emotional behaviors, stand in contrast to how little is currently known about candidate genes underlying such behaviors and psychiatric disorders [116]. One approach that can shed light on the genes involved is to associate polymorphic variations, particularly single nucleotide polymorphisms (SNPs), with variations in emotional and social behaviors. However, genetic associations generally raise issues related to replicability and the functional effects of SNPs. It is, for instance, generally unknown how polymorphic variations translate into differential expression and availability of brain neuropeptides and their receptors. Therefore, the selected examples presented in Table 1 include only polymorphisms (i) that have repeatedly been confirmed to impact upon socio-emotional phenotypes, or (ii) with functional/structural correlates based on expression and neuroimaging genetics approaches.

The neuropeptide variants that have been most extensively studied in their relation to behavioral traits are located in the *OXTR* and *AVPR* genes (Table 1). For example, the A allele of rs53576 of the human *OXTR* gene (AA, AG genotypes relative to G/G homozygotes) and haplotypes including this SNP confer particular risks for deficits in socio-emotional domains. Compared with their receptors, however, less is known about behavioral implications of genetic variations in neuropeptide genes (Table 1).

Generally, single-gene associations are ultimately limited in their ability to explain large portions of variability in socio-emotional behaviors [3]. Their complexity is further enhanced by gene–gene [79] and gene–environment [117] interactions, including epigenetic modifications shown to modify AVP expression by early-life stress in mice [41], and OXTR deficiency in autism [118]. Such modifications are particularly capable of complementing association studies, linking them to an environmental context [119].

Thus, both genetic and epigenetic variations are likely to contribute to the activity of the brain OXT and AVP systems shaping individual anxiety- and depression-related behaviors and, consequently, the risk for psychopathology (Figure 3).

Neuropeptide balance in the regulation of emotional behaviors

The opposing effects of brain OXT and AVP systems on anxiety and depression-related neuronal functions and behaviors, as discussed above, support our hypothesis that a dynamic balance of the activities of the brain OXT and AVP systems impacts upon emotional behaviors along a continuum from mental health to psychopathology (Figure 3). Accordingly, psychiatric disorders can be considered as extremes of quantitative dimensions at the negative end of a given continuum [120], explaining why, for example, pathological anxiety may evolve from normal anxiety [121]. We hypothesize that this shift towards psychopathology is, at least in part, due to an OXT–AVP imbalance determined by negative environmental, in particular negative social, stimuli, in concert with genetic and epigenetic (risk) factors. Conversely, based on findings that the brain OXT system can be activated by social stimuli, we further extend this model and hypothesize that positive social interactions have the potential to shift the neuropeptide balance towards OXT, thereby attenuating anxiety- and depression-related behaviors (Figure 3).

Importantly, our hypothesis of an OXT–AVP balance primarily linked to emotional behaviors does not mean that increased signaling of one neuropeptide is necessarily linked to reduced signaling of the other (although such regulatory capacity has recently been shown, both at neuropeptide ligand [122] and receptor [123] levels). Instead, it suggests that hypoactivity of OXT and hyperactivity of AVP, alone or together, may underlie a shift to the left along the behavioral continuum (Figure 3). In this case, we speculate that, in addition to appropriate stimulation of the endogenous system, combined psychopharmacotherapy of both an OXTR agonist and AVPR antagonists may have the potential to synergistically improve psychopathological behavior.

Social dysfunctions are key symptoms not only of social anxiety disorders, but also of several psychopathologies, including major depression, post-traumatic stress disorders, schizophrenia, and autism. Because OXT and AVP modulate multiple aspects of both emotionality and sociality, we further propose that a neuropeptide imbalance is also likely to contribute to social deficits accompanying psychopathologies.

Concluding remarks

Individual variations in anxiety- and depression-related behaviors are determined by the dynamic interplay of

Box 2. Outstanding questions

Despite accumulating knowledge about the neurobiology of brain OXT and AVP systems from preclinical and clinical studies, several questions remain. For example:

- How do axonally versus dendritically released neuropeptides locally interact to specifically regulate socio-emotional behaviors?
- Which social stimuli and epigenetic mechanisms, especially early in life, modulate regional OXT/AVP gene expression and release and, consequently, shift the OXT–AVP balance?
- Which neuropeptide receptor-mediated intracellular signaling cascades determine rapid and long-term OXT and AVP neuronal and behavioral effects?
- How do individual variations in neuropeptide receptor genes contribute to the endogenous OXT–AVP balance, and to the response of an individual to social stimuli and intranasal OXT?
- Which reliable biomarkers can be used, in addition to plasma/CSF neuropeptide levels and genetic risk factors, to assess central neuropeptide activities, to diagnose an OXT–AVP imbalance, and to select patients for psychopharmacotherapy?
- Despite encouraging effects of intranasal administration of synthetic OXT, transport routes to the brain, the extent and duration of behavioral effects, and acute or long-lasting interactions with the endogenous system are unknown. For example, does the rise in exogenous OXT trigger or instead inhibit endogenous neuropeptide activity?

theoretically unlimited combinations of underlying genetic, epigenetic, environmental, and social (risk) factors. Based on preclinical and clinical evidence, we propose that each of these factors, alone or in concert, also contributes to individual differences in central OXT/AVP release patterns or receptor binding, thereby modulating their balance and thus, in turn, emotionality. Accordingly, neuropeptide imbalance and a shift of emotional behaviors towards psychopathology (Figure 3) may be corrected by stimuli that facilitate and inhibit central release and actions of OXT and AVP, respectively, in a locally and temporally adequate manner. Although future studies are required to reveal the characteristics of appropriate stimuli in more detail (Box 2), present knowledge suggests that positive social stimuli may contribute to activation of the OXT system, thus rebalancing aberrant neuropeptide signaling. Such therapeutic options, in combination with psychopharmacotherapy, seem to be a particularly promising approach for risk-allele carriers (Table 1) living in an adverse social environment. However, to further qualify the selection of potentially responsive patients for treatment, reliable biomarkers reflecting the dynamics of the endogenous OXT–AVP balance need to be identified. Only then can a combination of specific stimuli and intranasal application of OXT agonists and/or AVPR antagonists potentially improve emotional behaviors and overall mental health.

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