Symposium-Mini-Symposium

Limbic Neuropeptidergic Modulators of Emotion and Their Therapeutic Potential for Anxiety and Post-Traumatic Stress Disorder

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Post-traumatic stress disorder (PTSD) is characterized by hypervigilance, increased reactivity to unpredictable versus predictable threat signals, deficits in fear extinction, and an inability to discriminate between threat and safety. First-line pharmacotherapies for psychiatric disorders have limited therapeutic efficacy in PTSD. However, recent studies have advanced our understanding of the roles of several limbic neuropeptides in the regulation of defensive behaviors and in the neural processes that are disrupted in PTSD. For example, preclinical studies have shown that blockers of tachykinin pathways, such as the Tac2 pathway, attenuate fear memory consolidation in mice and thus might have unique potential as early post-trauma interventions to prevent PTSD development. Targeting this pathway might also be beneficial in regulating other symptoms of PTSD, including trauma-induced aggressive behavior. In addition, preclinical and clinical studies have shown the important role of angiotensin receptors in fear extinction and the promise of using angiotensin II receptor blockade to reduce PTSD symptom severity. Additional preclinical studies have demonstrated that the oxytocin receptors foster accurate fear discrimination by facilitating fear responses to predictable versus unpredictable threats. Complementary human imaging studies demonstrate unique neural targets of intranasal oxytocin and compare its efficacy with well-established anxiolytic treatments. Finally, promising data from human subjects have demonstrated that a selective vasopressin 1A receptor antagonist reduces anxiety induced by unpredictable threats. This review highlights these novel promising targets for the treatment of unique core elements of PTSD pathophysiology.

Key words: **anxiety; angiotensin II; oxytocin; PTSD; tachykinin; vasopressin**

Introduction

Animals respond to impending threats or signals predicting threats through a combination of behavioral and physiological responses related to fear and anxiety. Fear is an adaptive defensive behavior and is necessary for survival (Paré et al., 2004; Gross and Canteras, 2012; Fanselow, 2018). However, maladaptive processing of fear memories can contribute to stress-related psychiatric disorders, such as post-traumatic stress disorder (PTSD). PTSD is characterized by hypervigilance, inability to properly discriminate between threat and safety, disproportionately higher fear reactivity to unpredictable versus predictable threats, and an inability to extinguish learned fear (Craske et al., 2008; Grillon et al., 2009; Jovanovic et al., 2010). First-line pharmacotherapies for psychiatric disorders have limited therapeutic efficacy in PTSD, and the need for new pharmacotherapies remains largely unmet, as clinical trials of many potential

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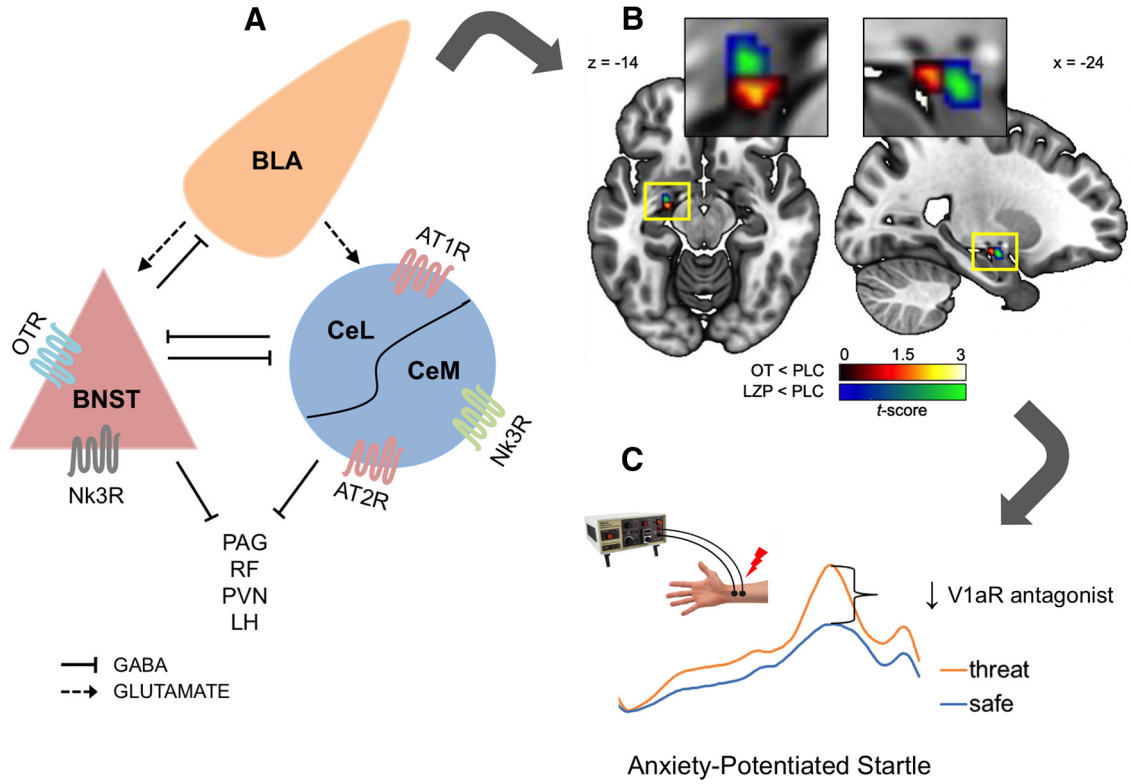

Figure 1. Limbic neuropeptides and their receptors are promising targets for PTSD prevention and treatment. Translational potential of the limbic neuropeptides is illustrated by gray arrows from preclinical studies using animals models of fear and anxiety (***A***), to neuroimaging studies on the effects of the neuropeptides (e.g., oxytocin) on the amygdala activity in humans (***B***), to behavioral studies (anxiety-potentiated startle) testing the effects of compounds targeting neuropeptidergic receptors (e.g., vasopressin receptor antagonist) on anxiety measured in humans (***C***). ***A***, Neuropeptidergic GPCRs in the extended amygdala modulate unique phases of fear learning and thereby can moderate core features of PTSD pathophysiology. OTRs in rat BNST facilitate fear discrimination by strengthening fear responses to predictable, signaled threats. Nk3R-expressing cells in the BNST mediate trauma-induced aggression in mice, whereas in mouse CeM, the Nk3R antagonist osanetant prevents fear memory consolidation. In the CeL and CeM, AT_1R antagonist accelerates fear memory extinction in mice. LH, Lateral hypothalamus; PAG, periaqueductal gray; RF, reticular formation. Solid lines indicate inhibitory (GABAergic) projections. Dashed arrows indicate excitatory (glutamatergic) projections. ***B***, Using 7T fMRI in healthy human subjects, it was shown that, compared with placebo (PLC), oxytocin (OT, 24 IU) dampened the left centromedial amygdala response to fearful relative to neutral faces in a manner similar to lorazepam (LZP, 1 mg) (red-yellow cluster represents OT vs PLC; blue-green cluster represents LZP vs PLC). ***C***, A novel V1aR antagonist, SRX246, decreases startle amplitude during presentation of an unpredictable threat (mild electrical shock) in a translational paradigm of anxiety in humans. Traces represent processed EMG recordings of eye blink startle after administration of a loud white noise. In the safe condition, participants are not at risk of shock. In the unpredictable threat condition, participants can receive a mild electric shock (red lightning bolt) at any time. Anxiety-potentiated startle is quantified as the change in startle amplitude from safe to threat.

agents, including initially promising corticotropin-releasing factor antagonists, have delivered inconclusive results (Spierling and Zorrilla, 2017). In this review article, we first introduce the brain regions, particularly the extended amygdala, that are critical for the modulation of defensive behaviors and learned fear and describe the basic neurobiology of neuropeptides. We then discuss how basic research on the role of limbic neuropeptides in the regulation of fear and anxiety in animal models is being directly translated into potential treatments for PTSD in humans. The content of the review has an important translational validity with regard to psychiatric disorders in humans because we present data on the effects of the same neuropeptides using clinically relevant measures (e.g., fear-potentiated startle [FPS] and fear conditioning) in both animal and human studies. We also address sex-specific effects in both rodents and humans and the importance of sex-specific pharmacotherapies for PTSD.

The neurocircuitry of fear and anxiety

The extended amygdala is composed of the central amygdala (CeA) and the bed nucleus of the stria terminalis (BNST) (Sun and Cassell, 1993; Alheid, 2003). Neurons of the extended amygdala are primarily GABAergic and they also produce a vast diversity of neuropeptides, thus forming multiplex neural populations with a wide range of functions (for review, see Beyeler and Dabrowska, 2020). Both the CeA and the BNST receive afferent glutamatergic information from the BLA among many other regions (Jennings et al., 2013; Torrisi et al., 2018) (Fig. 1*A*). During fear conditioning (fear memory acquisition), a sensory cue (conditioned stimulus [CS^+]) coterminates with an aversive somatosensory stimulus (unconditioned stimulus [US]), usually a foot shock. When tested for fear recall, animals display fear-like behaviors when presented with the CS^+ alone and/or in the conditioning context. In the neurocircuitry of fear conditioning, the lateral amygdala (LA) is the main point of entry of sensory inputs (about CS, US, and context) from the thalamus; LA conveys this sensory information to the lateral nucleus of the CeA (CeL) (but see Paré et al., 2004). The CeL projects to the medial CeA (CeM), which is the major output structure of the amygdala (Duvarci and Paré, 2014). Neuronal activity of the LA and CeL is required for fear memory acquisition, whereas activity in the CeM is required for the expression of conditioned fear responses (Pascoe and Kapp, 1985; Fanselow and LeDoux, 1999; Phelps and LeDoux, 2005; Wilensky et al., 2006; Ciocchi et al., 2010).

The BNST also receives direct projections from the CeA and the BLA (Roberts et al., 1982; McDonald et al., 1999). Both the CeM and the BNST project to many overlapping brainstem effector structures, including the periaqueductal gray (which mediates freezing behavior), reticular formation (which

produces startle response), lateral hypothalamus (which regulates cardiovascular and respiratory tone), and paraventricular nucleus (PVN) (which secretes various hormones) (Gungor and Paré, 2016; Shackman and Fox, 2016). The CeA and BNST also heavily innervate each other and can modulate each other's activity (Gungor et al., 2015; Pomrenze et al., 2018; Yamauchi et al., 2018) (Fig. 1*A*).

According to the classic theory formulated by Michael Davis and colleagues (Walker and Davis, 2008; Davis et al., 2010), after a threat stimulus, the CeA is required for fear memory of a short, discrete stimulus (phasic or cued fear), whereas the BNST is necessary for long-duration fear responses (sustained or contextual fear) that resemble anxiety-like behavior. Recently, it has become apparent that the BNST also mediates fear responses to unpredictable, diffuse, or unsignaled threats (Gungor and Paré, 2016; Goode and Maren, 2017; Goode et al., 2019), but it might also inhibit cued fear responses (Meloni et al., 2006; Moaddab and Dabrowska, 2017). Similarly, although the CeA primarily promotes cued fear, it also modulates anxiety-like behavior (Asok et al., 2018; Pomrenze et al., 2018).

Neuropeptidergic modulators versus classic neurotransmitters

Although neuropeptides were once viewed as having mild neuromodulatory effects, we now know they control a variety of behaviors. In contrast to classic neurotransmitters that are synthesized at the nerve terminal, neuropeptides are synthesized at the cell body and then transported to release sites. They can be released not only from the axonal terminal (axonal release), but also from boutons along the axons, as well as from the soma and dendrites (somatodendritic release). At the release sites, neuropeptides are stored in large dense core vesicles, as opposed to small vesicles, such as those storing classic neurotransmitters (van den Pol, 2012). However, there are some exceptions, as in case of angiotensin II: a network of different brain cells (rather than one cellular phenotype) may contribute to the synthesis and storage of this peptide (for review, see de Kloet et al., 2015). Because large dense core vesicles are stored further back in the terminal than synaptic vesicles, they typically require a prolonged stimulus and a large influx of calcium to be released. Hence, a rapid train of action potentials, rather than a single action potential, is needed to trigger the release of neuropeptides (Bondy et al., 1987). In some cases, however, neuropeptides can be secreted via activity-independent mechanisms, for example, in hypothalamic magnocellular neurons (which produce oxytocin and/or vasopressin), some neurosecretory responses are directly coupled to voltage but independent of internal or external calcium concentrations (for review, see Tasker et al., 2020).

In contrast to classic neurotransmitters, neuropeptides do not possess a reuptake system and are not taken back up into the presynaptic neuron or metabolized in the synapse. As a result, they can diffuse and act at a distance from the release site on a longer time scale than synaptic signaling, in a process called volume transmission (Fuxe et al., 2005). Eventually, neuropeptides are lysed by catabolic peptidases (van den Pol, 2012). Neuropeptide effects are linked to G-protein coupled receptors (GPCRs); therefore, they require more time to have a biological effect, compared with some neurotransmitters acting directly on ion channels and causing an immediate change in neuronal activity. Moreover, the diversity of signaling pathways associated with GPCRs' transmission gives neuropeptides a much broader and more diverse spectrum of biological effects and functions (Hazell et al., 2012). This diversity of signaling pathways also provides vast opportunities for developing new pharmacological targets and treatment strategies.

The role of tachykinins in the consolidation of fear memory and their therapeutic potential for preventing PTSD development

The tachykinins are a group of peptides sharing a carboxy-terminal sequence; they serve as neuromodulators and neurotransmitters in the mammal brain (Beaujouan et al., 2004). The Tachykinin 1 (*Tac1*) gene encodes a pro-protein that, on post-translational cleavage, produces two peptides: substance P (SP) and neurokinin A. The tachykinin 2 (*Tac2*) gene encodes neurokinin B (NkB) (Floor et al., 1982). SP binds preferentially to the neurokinin 1 receptor (Nk1R), whereas neurokinin A binds preferentially to the neurokinin 2 receptor and NkB preferentially binds at the neurokinin 3 receptor (Nk3R) (Khawaja and Rogers, 1996). SP and Nk1R appear to regulate emotional stress responses, and SP in the CSF correlates with PTSD severity (for review, see Dunlop et al., 2012). In addition, the Nk3R receptor regulates fear memory in healthy mice and a PTSD-like model (Dias et al., 2014). Drugs targeting the tachykinin receptors are generally safe and well tolerated in humans (Malherbe et al., 2011; Yuan et al., 2016), raising hopes that they could be used to treat PTSD. To date, however, investigational drugs targeting tachykinin receptors (e.g., the Nk1R antagonist GR205171) have failed to show clinical efficacy in PTSD (Mathew et al., 2011). But unlike Nk1R, which is expressed in multiple areas of the human brain (Beaujouan et al., 2004), Nk3R expression is mainly restricted to the amygdala in mice, rats, rhesus monkeys, and humans (Mileusnic et al., 1999; Duarte et al., 2006; Nagano et al., 2006). Thus, pharmacological targeting of the Nk3R may be a more effective candidate for PTSD treatment. This hypothesis is supported by the discovery that the Tac2 pathway (Tac2, NkB, and Nk3R) plays an important role in fear processing.

A full gene expression analysis of the amygdala after auditory fear conditioning uncovered molecular pathways involved in memory consolidation processes. The top gene candidate identified was *Tac2*, which was upregulated 30 min after fear acquisition, while its protein product, NkB, was upregulated at 2 h. Additional experiments revealed that Tac2 is necessary and sufficient for fear memory consolidation in male mice (Andero et al., 2014). Systemic or intra-CeA blockade of the Tac2 pathway via administration of an Nk3R antagonist reduced fear expression, suggesting it impaired fear memory consolidation. Concordantly, Designer Receptors Exclusively Activated by Designer Drugs (DREADDs)-mediated inhibition of Tac2-expressing neurons in the CeA after fear acquisition resulted in diminished fear memory consolidation. In a follow-up study, optogenetic stimulation of channelrhodopsin-expressing CeA-Tac2 neurons during fear acquisition resulted in impaired memory consolidation (Andero et al., 2016). These data highlight the potential of compounds targeting the Tac2 pathway for preventing and/or treating fear-related neuropsychiatric disorders (Fig. 1*A*). In particular, Nk3R antagonists, such as osanetant, show potential as an early post-trauma intervention against PTSD development because they impair fear memory consolidation in the amygdala.

Future studies on the Tac2 pathway and fear memory should consider the effects of this pathway on sex hormones. Indeed, the oral Nk3R antagonist ESN364 has recently been shown to decrease gonadal hormone levels (testosterone and estradiol/progesterone, respectively) in healthy men and women (Fraser et al., 2016). This is not surprising, given numerous previous reports

that the Tac2 pathway modulates sex hormones in both male (Danzer et al., 1999) and female rodents (Sahu and Kalra, 1992). Notably, a new study shows that, whereas osanetant impairs fear memory in male mice, it enhances the memory in females (Florido et al., 2020).

The role of Tac2 in trauma-induced aggression

As described above, Tac2 signaling in the CeA has been shown to play a key role in fear memory consolidation (Andero et al., 2014, 2016). In addition, recent work has implicated Tac2 in encoding the brain state produced by social isolation stress. More specifically, Zelikowsky et al. (2018b) found that prolonged social isolation stress is sufficient to upregulate Tac2 expression across a number of brain regions, and that this upregulation is conserved across species, occurring in mice and fruit flies alike (Zelikowsky et al., 2018a). Furthermore, region-specific loss-of-function perturbations of $Tac2^+$ cells, NK3Rs, and Tac2 signaling (using chemogenetics, local Nk3R antagonism, and shRNAi approaches) revealed dissociable roles for the anterior dorsal BNST, dorsomedial hypothalamus, and the CeA in the control of isolation-induced persistent fear, enhanced aggression, and acute fear, respectively. Collectively, these data suggest that Tac2 acts in parallel across multiple brain regions to mediate the effects of social isolation stress on a variety of behaviors.

Of particular interest is the role of tachykinins in isolation-induced aggression. In addition to the findings that Tac2 signaling in the Dorsomedial hypothalamus (DMH) DMH is required for such aggression, Zelikowsky et al. (2018b) demonstrated that virally mediated, brainwide overexpression of Tac2 combined with chemogenetic activation of $Tac2^+$ cells was sufficient to increase aggressive behavior in otherwise docile group-housed mice. This gain-of-function effect has also been observed in fruit flies (Asahina et al., 2014; Wohl et al., 2020), suggesting a conserved function for tachykinins in controlling aggressive behavior across species.

In addition to examining the role of Tac2 in social isolation-induced aggression, recent studies by Zelikowsky et al. (2018b) have begun to examine the role of Tac2 in mediating aggression produced by an acute stressor. Using a rodent model of PTSD known as stress-enhanced fear learning, these investigations found that a series of inescapable, unsignaled, randomized foot shocks produce a subsequent enhancement in aggressive behavior. This stress-enhanced aggression was found to be mediated by Tac2 signaling.

Despite a role for Tac2 in both isolation-induced aggression and stress-enhanced aggression, the nature of these contributions is distinct. Nonetheless, compounds targeting the Tac2 pathway might provide promising therapeutics for trauma-induced aggression (Fig. 1*A*). This is important because veterans with PTSD exhibit higher incidence of aggressive behavior relative to their non-PSTD veteran counterparts (Chemtob et al., 1994; Jakupcak et al., 2007). Future studies will aim to understand the role of Tac2 in various forms of aggression and its therapeutic potential for attenuating trauma and stress-induced aggression as it relates to PTSD.

The role of angiotensin II in fear extinction and therapeutic opportunities for PTSD

Growing evidence suggests that the renin angiotensin system (RAS), a regulator of blood pressure and fluid homeostasis, is another potential therapeutic target for PTSD (Khoury et al., 2012; Nylocks et al., 2015; Terock et al., 2019; Zhou et al., 2019). Recent clinical studies demonstrate that losartan, a blocker of the angiotensin type 1 receptor (AT_1R), modulates amygdala activity and emotional processing (Pulcu et al., 2019; Zhou et al., 2019) and accelerates fear extinction (Zhou et al., 2019). These clinical studies support many earlier rodent studies demonstrating that brain angiotensin receptors are potent mediators of anxiety-like behavior and stress responsiveness (Okuyama et al., 1999; Shekhar et al., 2006; Saavedra et al., 2011; de Kloet et al., 2016a, 2017).

Angiotensin II is the principal effector peptide of the RAS. Its actions are mediated by binding to its primary receptor subtypes, the AT_1R and the angiotensin Type 2 receptor (AT_2R). These GPCRs are expressed in the periphery and throughout brain circuits involved in fear and anxiety, including the hypothalamus, amygdala, hippocampus, and medial prefrontal cortex (mPFC) (Lind et al., 1985; Gonzalez et al., 2012; de Kloet et al., 2016b). Angiotensin II and associated peptides act on their receptor subtypes following synthesis from enzymatic cleavage of the precursor angiotensinogen (Yang et al., 1999; Grobe et al., 2008). All of the enzymatic components for the synthesis of angiotensin II exist in the brain, including renin, angiotensin converting enzyme (Mendelsohn et al., 1990; Grobe et al., 2008; de Kloet et al., 2015), and more recently discovered (pro)renin and (pro)renin receptor (Xu et al., 2016). Compared with other classic neuropeptides discussed here, brain angiotensin II is therefore unique in that a network of different brain cells (vs one cellular phenotype) may contribute to the synthesis and storage of brain angiotensin II, and thus to its contributions to various physiological and pathophysiological functions, in a region- and cell-specific manner. For further reading, on cellular localization of brain RAS, function, and interaction with other brain cell types, the reader is referred to a recent review (de Kloet et al., 2015).

Brain AT_1Rs are expressed by neurons involved in stress responses (e.g., the hypothalamic pituitary axis) (Krause et al., 2011) and in limbic regions important for the emotional regulation of fear (Hurt et al., 2015). Notably, inhibition of AT_1Rs has been shown to facilitate fear extinction, a process necessary for recovery from PTSD in both rodents (Marvar et al., 2014; Parrish et al., 2019) and humans (Zhou et al., 2019) (Fig. 1*A*). Translating between rodent and human studies, Zhou et al. (2019) recently demonstrated that losartan (an AT_1R antagonist) improved early extinction learning through increased ventromedial PFC (vmPFC) activity and functional connectivity between the vmPFC and the BLA in humans. This enhanced vmPFC-BLA coupling could be an important mechanism by which angiotensin II signaling improves fear extinction. Future clinical studies are needed for improving the efficacy of targeting the RAS in fear-based disorders, while application of modern neuroscience technologies will be critical for elucidating the circuits as well as cellular and molecular mechanisms involved in the role of the brain RAS in fear- and anxiety-based disorders (Stout and Risbrough, 2019).

The role of brain Type 2 receptor (AT_2R) in fear learning was recently investigated by Yu et al. (2019) using AT_2R BAC-eGFP reporter mice. The authors demonstrated that AT_2R-$eGFP^+$ neurons were predominantly expressed in the medial amygdala and the CeM, with little AT_2R-eGFP expression in the BLA or CeL. In addition, AT_2R-expressing GABAergic neurons in the CeA were found to project to the PAG, a midbrain region controlling defensive responses to threat, such as freezing (Yu et al., 2019). These findings suggest that CeM AT_2R-expressing neurons may modulate CeA outputs that play a role in fear expression, and they provide new evidence for an angiotensinergic circuit and CeM cell type in the defensive threat response. Brain

AT_1Rs and AT_2Rs may therefore differentially modulate fear memory and threat responding, possibly via inhibitory and excitatory CeA circuits and cortical inputs. Additional studies are needed to test this hypothesis, as well as to further understand angiotensin II signaling pathway interactions with other neuropeptide systems described here.

The role of oxytocin in fostering accurate fear discrimination and strengthening fear responses to predictable threats

The nonapeptide oxytocin is a hormone and a neuromodulator produced in the PVN, supraoptic nucleus, and an accessory nucleus of the hypothalamus. Oxytocin is released in the extended amygdala, including the CeA and the BNST (Ebner et al., 2005; Martinon et al., 2019), among many other brain regions, where it acts on its single GPCR, the oxytocin receptor (OTR). Oxytocin has shown anxiolytic properties in animal models (Bale et al., 2001; Ring et al., 2006) and human studies (Ellenbogen et al., 2014; for review, see Janeček and Dabrowska, 2019). However, the role of oxytocin in the regulation of fear responses appears more complex (Toth et al., 2012; Guzmán et al., 2013; Lahoud and Maroun, 2013; Campbell-Smith et al., 2015; for review, see Olivera-Pasilio and Dabrowska, 2020). Several studies to date have shown that oxytocin neurons in the hypothalamus are activated during cued and contextual fear conditioning and during fear recall, indicating the recruitment of the endogenous oxytocin system in fear learning in male and female rats (Zhu and Onaka, 2002; Hasan et al., 2019; Martinon et al., 2019). Notably, activation of these oxytocin neurons has been shown to influence the level of contextual fear. For example, as demonstrated using the vGATE system (virus-delivered genetic activity-induced tagging of cell ensembles), optogenetic stimulation of CeL-projecting ensembles of oxytocin neurons activated during fear-conditioning (tagged via vGATE) accelerates extinction of contextual fear in female rats (Hasan et al., 2019). This is consistent with the majority of behavioral studies reporting that activation of OTRs in the CeA reduces contextual fear in male and female rats (Viviani et al., 2011; Knobloch et al., 2012; Terburg et al., 2018).

In apparent contrast, in male rat BNST, OTR neurotransmission has been shown to facilitate cued fear measured as FPS. In the rat FPS paradigm, an acoustic startle reflex (a whole-body jump, which occurs <200 ms after a white noise burst) is potentiated by an exposure to a cue (CS, e.g., 3.7 s light) that has previously been paired with foot shocks (US) during a fear-conditioning session. During the FPS test, rats are presented with startle-eliciting bursts in the presence or absence of the CS (mixed in a pseudorandom order) (Davis et al., 1993; Davis, 2001; Walker and Davis, 2002), and both cued fear and noncued fear are measured. Whereas startle potentiation during cue presentations represents cued fear, startle potentiation observed in between the cue presentations reflects noncued fear. However, the latter startle response does not occur until after the cue is presented (Missig et al., 2010; Moaddab and Dabrowska, 2017; Janeček and Dabrowska, 2019; Walker and Davis, 2002). Therefore, a ratio between cued and noncued fear can be used as a proxy for proper fear discrimination (Janeček and Dabrowska, 2019; Martinon et al., 2019). Notably, studies have also shown that noncued fear (or background anxiety) is independent of contextual fear (Missig et al., 2010; Ayers et al., 2011).

A selective OTR antagonist administered before fear conditioning (acquisition) significantly reduced cued fear and tended to increase noncued fear measured during FPS recall the next day, overall reducing fear discrimination (Moaddab and Dabrowska, 2017; Janeček and Dabrowska, 2019) (Fig. 1*A*). Conversely, systemic administration of oxytocin was shown to reduce background anxiety (noncued fear) measured in male rat FPS (Missig et al., 2010; Ayers et al., 2011). These ostensibly contrasting behavioral effects support growing evidence that oxytocin promotes fear discrimination by reducing sustained fear responses (contextual fear and noncued fear) yet strengthening fear responses to signaled, predictable, or imminent threats (Janeček and Dabrowska, 2019; for review, see Olivera-Pasilio and Dabrowska, 2020). Indeed, recent studies investigating the BLA support the role of OTRs in facilitating accurate fear discrimination by selectively strengthening fear responses to discrete cues (CS^+) (Fam et al., 2018). OTR-mediated transmission in the CeA has also been shown to mediate a switch from passive freezing to active escape behaviors when an animal is confronted with an imminent, yet escapable, threat, while reducing reactivity to distant or diffuse threats (Terburg et al., 2018).

In search of potential mechanisms of these oxytocin effects, electrophysiological studies in the CeA and the BNST have demonstrated that there are two groups of oxytocin-responsive neurons: one group of interneurons that is directly excited by oxytocin and another group of output neurons that is inhibited by oxytocin via an indirect pathway (Huber et al., 2005; Viviani et al., 2011; Knobloch et al., 2012; Francesconi et al., 2020). In the dorsolateral BNST, oxytocin selectively increases the excitability and spontaneous firing of Type I dorsolateral BNST interneurons, and inhibits two classes of projection neurons, including Type II neurons, which project to the CeA (Francesconi et al., 2020). Because BNST activation was shown to induce sustained fear and reduce cued fear (Meloni et al., 2006), activation of OTRs in the BNST might facilitate cued fear and reduce sustained fear responses by inhibiting the BNST output. Thus, reciprocal connectivity between the CeA and the BNST plays a major role in modulating fear discrimination.

In conclusion, oxytocin appears to increase the salience of imminent threat-signaling environmental cues and thereby promote adaptive defensive behaviors while reducing fear responses to unsignaled, distant, or diffuse threats. This is important because increased reactivity to unpredictable threats and impaired fear discrimination are two hallmarks of PTSD. In addition, as patients suffering from PTSD demonstrate increased BNST activity (Awasthi et al., 2020), by ameliorating BNST hyperactivity and improving fear discrimination, oxytocin is a promising target for PTSD pharmacotherapy in humans.

Clinical translation of the fear-modulating effects of oxytocin

While there is a plethora of pharmacological strategies to modulate oxytocin signaling, the most established approach in humans is through activation of brain OTRs through intranasal administration of synthetic oxytocin (IN-OT) (Gulliver et al., 2019). IN-OT increases both blood and CSF concentrations of the peptide (Striepens et al., 2013), which accumulates in brain tissue along the trajectories of the olfactory and trigeminal nerves (M. R. Lee et al., 2020). There is also emerging evidence for blood-to-brain transport of oxytocin (M. R. Lee et al., 2018; but see Neumann et al., 2013), which is regulated by the receptor for advanced glycation end-products on brain capillary endothelial cells (Yamamoto and Higashida, 2020).

Current concepts guiding the clinical translation of IN-OT to the treatment of anxiety disorders and PTSD emphasize the following: (1) identification of the neural targets, (2) definition of the most effective dosage needed for target engagement, and

(3) comparison with clinically established traditional anxiolytics, such as benzodiazepines (Insel, 2016). Given that fMRI-based meta-analyses implicate hyperactivity of the amygdala in response to perceived threats as a common pathophysiological denominator of anxiety disorders and PTSD (Etkin and Wager, 2007), inhibition of the amygdala appears to be essential for the therapeutic control of these conditions with IN-OT. In line with this premise are analyses of oxytocin-pathway gene networks in human postmortem brains, which demonstrate enriched OTR gene expression in subcortical regions, including the amygdala (Quintana et al., 2019).

While there is meta-analytic evidence that IN-OT modulates amygdala responses to perceived threats (Wang et al., 2017), fMRI data characterizing the dose–response profile of this effect were collected only recently. A study conducted in male human subjects found that IN-OT-induced inhibition of amygdala responses to threats was most effective after administration of 24 IU, whereas 48 IU evoked an increase in amygdala reactivity (Spengler et al., 2017). The latter was also observed in females after administration of 6, 12, or 24 IU (Lieberz et al., 2020), suggesting that IN-OT effects likely vary as a function of dose and sex.

Notably, interplay between the mPFC and the amygdala has been identified as a hallmark of fear extinction learning, which is thought to mediate the efficacy of exposure therapy for anxiety disorders and PTSD. Recently, 7T ultra-high-field fMRI was used to test IN-OT (24 IU) against the benzodiazepine comparator lorazepam (1 mg by mouth). While both lorazepam and IN-OT inhibited the centromedial amygdala, only IN-OT effects extended to a functional network, including precuneus and dorsomedial mPFC (Kreuder et al., 2020) (Fig. 1*B*). Crosstalk between these regions during fear extinction learning was increased by IN-OT (24 IU), along with inhibitory effects on the amygdala per se (Eckstein et al., 2015).

One of the clinical core symptoms of PTSD is intrusive reexperiencing, which can be modeled over days in healthy volunteers exposed to filmed violence. Based on this paradigm, it was shown that IN-OT (24 IU) not only enhanced functional connectivity between the amygdala and mPFC, but also diminished intrusions, at least in subjects who deliberately talked to their peers about what had scared them (Scheele et al., 2019).

A recent meta-analysis confirmed the principle efficacy and safety of IN-OT treatment for PTSD; however, as reflected by preclinical evidence (Lieberz et al., 2020), IN-OT exerts differential, sometimes even opposing, effects in male and female patients with PTSD (Peled-Avron et al., 2020). Modulatory effects of IN-OT (24 IU) on amygdala reactivity (Labuschagne et al., 2010), amygdala-mPFC connectivity (Sripada et al., 2013), and decision-making (Hurlemann et al., 2019) have also been reported for social anxiety disorder; however, the influence of sex as well as the optimal therapeutic dose range for IN-OT in social anxiety disorder are unclear. As a consequence, future clinical trials of IN-OT for anxiety disorders and PTSD should take dose–response as well as person-related effects into account (Andari et al., 2018). Defining the biological determinants of IN-OT treatment will not only inform the clinical translation of oxytocin neuroscience, it will also contribute to establishing personalized care by identifying subgroups of patients with anxiety disorders and PTSD who would benefit most from this novel therapy.

Modulation of unpredictable threat processing by vasopressin

Preclinical research suggests that the neuropeptide vasopressin may contribute to PTSD, as evidenced by its association with relevant brain regions as well as hormonal and behavioral defensive responses. Neurons in the PVN, suprachiasmatic nuclei, medial amygdala, and BNST synthesize vasopressin (Lu et al., 2019), and vasopressinergic projections are found in the lateral septum and CeA (Hernández et al., 2016; Bredewold and Veenema, 2018). Furthermore, vasopressin plays an important role in activation of the hypothalamic-pituitary-adrenal axis (Rotondo et al., 2016; Nishimura et al., 2019). In rodents, aversive stimuli (e.g., foot shocks) increase vasopressin levels in the PFC and amygdala (Karakilic et al., 2018) and increase vasopressin 1a receptor (V1a) binding in the anterior hypothalamus (Ross et al., 2019). Moreover, intracerebral administration of vasopressin increases anxiety-like behavior (Hernández et al., 2016; Hernández-Pérez et al., 2018), while administration of vasopressin receptor antagonists or knocking out vasopressin receptors decreases anxiety-like behavior (Neumann and Landgraf, 2012; Hodgson et al., 2014; Bayerl et al., 2016). Finally, vasopressin in the lateral septum and BNST enhances aggression (for review, see Carter, 2017; Kompier et al., 2019).

Clinical research on vasopressin has been limited by inconsistent assay methods and restricted pharmacological tools. Nevertheless, researchers have found that early-life stress affects the vasopressin system in both humans and rodents (Hernández et al., 2016; Kompier et al., 2019). Further, vasopressin modulates human neural and physiological responses to negative stimuli across many experimental paradigms (Thompson et al., 2006; Zink et al., 2010; Brunnlieb et al., 2013; R. J. Lee et al., 2013; Motoki et al., 2016). For example, intranasal vasopressin increased physiological arousal (measured with frontalis EMG) during trauma recall in veterans (Pitman et al., 1993). Specific to PTSD, in a longitudinal study of 232 war-exposed children, risk alleles on three genes (*AVPR1a*, which encodes the vasopressin V1a receptor; *OXTR*, the OTR; and *CD38*, the cluster of differentiation 38) predicted PTSD development (Feldman et al., 2014). In contrast, plasma vasopressin levels did not predict postdeployment development of PTSD in military subjects (Reijnen et al., 2017). Cross-sectionally, de Kloet et al. (2008) found that veterans with PTSD had higher plasma vasopressin levels than controls and that levels positively correlated with avoidance symptoms. However, police officers with PTSD had similar salivary vasopressin levels to trauma-controls (Frijling et al., 2015); and in another study, civilian urinary vasopressin levels negatively correlated with PTSD severity (Marshall, 2013). Discrepant results may stem from type of assay used, timing of assessments relative to disease state, and/or population differences.

The development of a novel and specific V1a receptor antagonist, SRX246 (Azevan Pharmaceuticals), permits the experimental validation of vasopressin's role in the regulation of anxiety and fear in humans. In a proof-of-concept study, T.R.L. et al. (unpublished data) examined the effects of SRX246 in a translational paradigm of fear (i.e., the phasic response to imminent threat) and anxiety (i.e., a sustained response to potential threat) using startle potentiation as a behavioral measure. Each subject ($n = 36$, 16 males, 20 females) received placebo and 300 mg of SRX246, in a counterbalanced order, over 5-7 d. The study used a double-blind, crossover, washout design. Researchers administered the NPU (neutral, predictable, unpredictable) threat test to probe physiological responses to threat. During neutral periods, participants are safe from shock (i.e., threat). During predictable periods, any geometric shape on a screen ("cue") indicates risk for shock, and the absence of any shape ("no-cue") indicates safety. During unpredictable periods, participants are at risk for shock at all times. Anxiety-potentiated startle was operationally

defined as the change in startle scores during no-cue from neutral to unpredictable conditions, and FPS as the change from no-cue to cue during predictable times. Results indicate that SRX246 decreases anxiety-potentiated startle compared with placebo (Fig. 1*C*). Participants with the highest subjective anxiety scores had the greatest decrease of subjective anxiety with SRX246 compared with placebo. Given that PTSD patients demonstrate higher startle reactivity to unpredictable threat compared with control patients (Grillon et al., 2009), the V1a receptor antagonist may be a novel promising treatment target for PTSD and anxiety.

Conclusion

In conclusion, in this review, we discussed the unique translational potential of limbic neuropeptides and their receptors for the prevention and treatment of PTSD. We described the role of tachykinins in strengthening fear memory consolidation and the promising effects of Nk3R antagonists as an early post-trauma intervention against PTSD development. We discussed how Nk3R antagonists might also act against stress- and social isolation-induced aggression. We reviewed the unique potential of angiotensin II antagonists in accelerating fear extinction in both preclinical and clinical studies. Because one of the hallmarks of PTSD is deficit in threat discrimination, we discussed how oxytocin fosters accurate discrimination by strengthening fear responses to predictable or imminent threats yet attenuating fear responses to diffuse or distant threats. We further emphasized the therapeutic potential of intranasal oxytocin, which strengthens functional connectivity between the amygdala and the mPFC in humans, and therefore might facilitate proper fear extinction similarly to angiotensin II antagonists. Finally, we described studies showing that vasopressin V1aR antagonist attenuates anxiety in the face of unpredictable threats in both male and female human subjects and thus might serve as a new treatment for PTSD (Fig. 1*A–C*). Collectively, these studies identify multiple neuropeptides as novel and promising targets for the treatment of PTSD and anxiety disorders. However, given the heterogeneity of PTSD symptoms and clinical manifestation, it is likely that therapeutic targeting of one neuropeptide system may show promise for subsets of PTSD-related symptoms. This suggests a need to establish personalized care by identifying subgroups of patients who would benefit most from each treatment. A combination of compounds targeting neuropeptidergic receptors might provide a more comprehensive treatment approach for other patients. For these reasons, further preclinical and clinical studies on interactions among limbic neuromodulators and circuits described here are essential.

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