Review Article

Chronic Stress
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Oxytocin and Stress-related Disorders: Neurobiological Mechanisms and Treatment Opportunities

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Abstract

Novel pharmacotherapies that improve outcomes for individuals with stress-related psychiatric disorders are needed. The neurohormone oxytocin (OT) is a promising candidate given its influence on the social–emotional brain. In this review, we present an overview of evidence supporting OT's utility for treating major depressive disorder and posttraumatic stress disorder. We first discuss endogenous OT, which research suggests is not yet a reliable biomarker of stress-related disorders. Second, we review effects of intranasal (IN) OT on processes relevant to stress-related disorders in healthy populations (anhedonia, reward processing, psychosocial stress reactivity, fear/anxiety, and social behavior) and their neurobiological mechanisms (e.g., the salience network and hypothalamic–pituitary–adrenal axis). Third, we present the sparse but promising findings from clinical populations, followed by discussion of critical moderating variables to consider in the service of maximizing the therapeutic potential of OT (e.g., patient sex and child maltreatment). We also identify heterogeneous findings and limitations of existing research, including reliance on single-dose studies in psychiatrically healthy samples and unanswered questions regarding the effectiveness of IN drug delivery and dosing schedules. Well-controlled multidose studies including women and measures of potentially moderating variables are sorely needed and would inform our understanding of the utility of OT for preventing and treating stress-related psychiatric disorders.

Keywords

Intranasal oxytocin, pharmacology, posttraumatic stress disorder, major depressive disorder, anxiety, psychotherapy, fear, reward, sex, context

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Introduction

The stress response is composed of cognitive, behavioral, and physiological processes that restore homeostasis and ensure survival. Cognitive appraisal of perceived threats and environmental stressors is mediated by the brain to determine cardiovascular, immune, and neuroendocrine processes, all of which can be adaptive or maladaptive.[1,2] Brain areas involved in the stress response include the hippocampus and hypothalamus, both targets of glucocorticoids (e.g., cortisol); the brain stem, which mediates autonomic stress responses; the prefrontal cortex (PFC), which downregulates neurobiological stress responses; the amygdala, which regulates threat appraisal and coordinates automatic neurophysiological and behavioral responses to threat; and the striatum, which mediates threat appraisal value. Acute stress resulting from a specific event or situation and chronic stress resulting from

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repeated exposure to stressful situations increases risk for the development of psychopathology, as well as social dysfunction that can maintain psychopathology.[3] Posttraumatic stress disorder (PTSD) can develop following exposure to trauma, a specific type of acute stressor that includes actual or threatened death, serious injury, or sexual violation and results in trauma-related intrusions, avoidance of trauma cues, changes in cognitions and mood, and hyperarousal.[4] Major depressive disorder (MDD), which is characterized predominantly by sad mood and loss of interest, has been proposed to develop from perceived uncontrollable stress.[5] PTSD and MDD share a number of mechanisms,[6] including anhedonia,[7,8] psychosocial stress reactivity,[9,10] anxiety,[11] and alterations in social behaviors, such as low social support,[12] social withdrawal,[13] reduced trust,[14] and poorer bonding and attachment,[15,16] which may serve as risk and maintenance factors for stress-related psychopathology.

The neurohormone oxytocin (OT) is associated with or influences processes implicated in MDD and PTSD, making the oxytocinergic system potentially relevant to the development, maintenance, and treatment of these disorders. In this review, we examine the role of OT in stress-related disorders, with emphasis on experimental studies of the effects of intranasal (IN) OT on relevant neurobiological and behavioral processes. We first review existing evidence for the role of endogenous peripheral OT in stress-related disorders. Second, we review effects of IN OT on processes relevant to stress-related disorders in healthy populations and their potential neurobiological mechanisms. Third, we review findings in clinical populations and discuss critical moderating variables that should be considered in the service of maximizing therapeutic potential of OT for stress-related disorders. Throughout the review, we highlight oxytocin's capacity to amplify responses to salient stimuli, irrespective of valence, as well as heterogeneity in findings. Given the brevity of this review, evidence that OT receptor distribution in the brain varies in a species-specific manner,[17] and extensive basic science and translational research in animal models,[3,18] we will focus on human subjects research.

Oxytocin

OT, a nine amino acid peptide hormone produced by the hypothalamus, plays a vital role in many physiological functions, including labor induction and lactation.[19] OT, in dynamic interplay with arginine vasopressin (AVP), also regulates human emotions, social cognition, and social behaviors,[20] thus spanning two Research Domain Criteria (RDoC) domains proposed by the U.S. National Institute of Mental Health: negative valence systems and social processes.[21,22] OT is released to several brain areas relevant to stress-related disorders, including the amygdala, hypothalamus, hippocampus, nucleus accumbens, insula, and striatum,[23]and effects of OT are mediated by OT receptors found in these regions.[17]

Endogenous OT

Given lack of access to central measures of OT, investigators have measured endogenous peripheral OT in urine, saliva, or plasma to examine which factors precipitate OT release. While debate remains about whether peripheral measures of OT relate to central measures,[24,25] animal research has revealed coupled central and peripheral OT release during stress[26] and axonal projections from magnocellular OT neurons to forebrain structures, the amygdala, and the posterior pituitary.[27] Stimulation of these projections has also been found to lead to an increased release of OT to the periphery and the brain, with accompanying reductions in fear-related behavior mediated by the amygdala.[27] In humans, peripheral OT has been shown to increase during acute stress,[28,29] in response to affiliative touch,[30] and following interpersonal stress,[31] perhaps promoting affiliative behaviors that facilitate relationship repair.[32] However, as will be evident throughout this review, findings are not entirely consistent; for example, several studies did not detect significant stress-,[33] touch-,[34] and interpersonal interaction–related[35] changes in peripheral OT concentrations.

Existing evidence suggests that peripheral OT is currently not a reliable biomarker for psychiatric disorders. Studies of plasma OT in depressed individuals, for example, have revealed both elevated and reduced levels, and studies of plasma OT in PTSD have shown a lack of main effects,[36] but revealed important moderating variables.[37,38] A recent systematic review of eight studies revealed an inverse relationship between peripheral OT and depressive symptom severity in pregnant women, but associations between depressive symptom severity and high, low, and variable OT levels in non-pregnant women.[39] In men, peripheral OT and depressive symptoms were positively but not significantly associated. A meta-analysis of 64 studies of several psychiatric disorders, including MDD but not PTSD, showed no significant differences in peripheral OT between healthy and psychiatric groups (except in anorexia).[40] Compared with trauma-exposed controls, lower peripheral OT levels have been observed in men, but not women, with PTSD,[37] and among PTSD patients without childhood trauma (whereas PTSD patients with a history of childhood trauma were found to have higher plasma OT levels relative to controls).[38]

Existing studies of peripheral OT and psychopathology have been limited by small samples; a high degree of methodological heterogeneity, including measurement of basal versus post-challenge levels; correlating plasma

OT with symptom severity versus diagnosis; variability in patients' other treatments that may have affected OT levels; inclusion of only women instead of both sexes; and questionable reliability of assay methods.[41,42] For example, there are large discrepancies in OT levels measured from unextracted and extracted plasma.[43] Values derived from unextracted samples have been found to be two orders of magnitude higher, likely because molecules besides OT are tagged and detected.[42]

Exogenous OT

Intravenous or intranasal administration of exogenous OT allows for experimental examination of the causal effects of OT on human behavior. To date, most experimental research on OT has utilized intranasal administration (IN OT) given its convenience, noninvasiveness, and safety.[44] IN OT pharmacokinetics are not fully understood, and definitive evidence for how much OT, a large peptide, reaches target brain areas via IN delivery is lacking;[23] however, there is accumulating evidence for nose-to-brain pathways exerting neural and behavioral effects in both animals[45,46] and humans.[47] The first delivery sites of IN OT are the olfactory bulbs and brainstem, which output to the amygdala via local GABAergic circuits.[48] IN OT may thus enter the central nervous system, mimicking "neurohormonal" OT release; alternatively, IN OT may act peripherally to affect behavior via OT receptors.[25] The presence of OT receptors in many sites in the periphery suggest that it has broad effects,[25] but possible long-term neuronal and molecular side effects have not been systematically measured. Further, other methods of administration (e.g., aerosol[49]) may prove to be more optimal given the many factors that can influence the effectiveness of transmucosal nasal drug delivery[50] and the very modest amount that reaches cerebrospinal fluid (CSF; 0.0005% within 1 h of administration),[25] though IN OT may penetrate brain regions without entering CSF.

IN OT Increases Reward Processing

Stress reduces hedonic capacity and reward responsiveness.[51] As such, PTSD and MDD are both characterized by anhedonia and dysregulation of the brain's reward system.[9,52] Accordingly, the inability to inhibit the influence of negatively valenced stimuli on cognitive and emotional responses is thought to contribute to the onset and maintenance of MDD.[53] IN OT has been shown to increase motivational salience due to association with reward[54] and neural responses to generic and personalized friendly faces in reward pathways (e.g., ventral tegmental area, striatum, and insula).[55–57] IN OT has also facilitated detection of implicitly presented happy faces[58] and improved recognition of positive emotions,[59] which may serve as mechanisms of increased approach behavior toward positive social stimuli after IN OT.[60,61] However, some studies have reported null effects with respect to facial affect recognition,[62] improved recognition of fear, but not other emotions (including happiness),[63] and increased responding of the reward pathway in response to loss or punishment.[64]

IN OT Reduces Psychosocial Stress Reactivity

Psychosocial stress and accompanying neurobiological changes elicited by tasks like the Trier Social Stress Test (TSST; a psychosocial stressor paradigm including a mock job interview and mental arithmetic test in front of judges) appear to be modulated by IN OT. In cocaine-dependent individuals, the positive association between early life stress and cortisol reactivity to the TSST was reduced among participants administered IN OT.[65] Using related tasks, IN OT was shown to reduce anticipatory anxiety[66] and cortisol release.[67] Other studies have shown opposite effects: for example, IN OT was found to increase post-TSST cortisol in men, potentially due to OT binding with receptors for a structurally similar hormone AVP, which is associated with cortisol release.[68]

IN OT Reduces Fear and Anxiety

IN OT has been shown to have anxiolytic effects, likely mediated by effects on the limbic system, including modulation of serotonin (5-HT) activity within the amygdala,[69] within which OT receptors are dense.[70] IN OT has been shown to promote fear extinction recall,[71,72] a critical mechanism of exposure-based therapies. IN OT has also been found to reduce amygdala activation in modulation of autonomic fear[73] and in response to stimuli that were aversively conditioned.[74] Meta-analytic findings suggest that IN OT increases activity in prefrontal cortical areas that mediate emotion regulation and fear inhibition.[75] IN OT has also been found to increase connectivity between the amygdala and prefrontal areas responsible for fear inhibition[76] and decrease activity between the amygdala and brainstem regions implicated in autonomic and behavioral manifestations of fear.[77] However, IN OT has also been shown to enhance fear conditioning when administered before the conditioning phase,[78] to potentiate acoustic startle responses to negative social stimuli,[79] and to impede response to a single-session exposure treatment for arachnophobia.[80]

IN OT Affects Social Cognition and Behavior

Meta-analytic findings have shown that IN OT improves facial affect recognition.[81] IN OT is also associated with increased prosocial behavior,[82] including increases in positive communication[83] and trust,[84] though the validity

of these latter results have been challenged.[85] IN OT has also been linked to increased willingness to share emotions related to a painful memory,[86] increased recall of positive social affiliation memories,[87] and indicators of pair bonding and relationship outcomes.[88] In a recent study, participants currently in a romantic relationship recalled fewer memories of previous partners following IN OT versus placebo, and participants who recalled more conflict memories of their current partner after IN OT administration were more likely to have ended their relationship by 18-month follow-up.[88]

However, IN OT appears to enhance both adaptive and maladaptive approach behavior.[89] For example, IN OT was found to be associated with increased approach toward angry faces,[90] increased inclinations toward intimate partner violence in trait aggressive individuals,[91] increased aggressive behavior,[92] and increased envy and gloating.[93] IN OT is proposed to enhance socially salient cues, with salience informed by baseline individual differences,[94,95] which may explain these findings, as well as decreased trust and cooperation behavior among individuals to whom social cues regarding abandonment and trust are highly salient (i.e., with borderline personality disorder).[96] Mixed findings may also be due in part to use of stimuli that conflate emotion and social cue processing[97]; social stimuli are inherently ambiguous, and can be a sign of both safety and direct (anger faces) and indirect danger (fear faces).

Neurobiological Mechanisms

IN OT may exert its behavioral effects via a number of interacting neurobiological mechanisms that also interact with stressor-elicited biological and psychological responses.

Salience Network

The brain's salience network, which comprises the amygdala, anterior insula, and dorsal anterior cingulate cortex, is a target circuit for OT. The salience network is responsible for identification of the most relevant information from the environment to guide behavior,[98] and as previously noted, IN OT effects on salience processing may explain the seemingly contradictory findings for effects of IN OT on emotional processes.[95] A recent positron emission tomography (PET) study revealed that IN OT increased 5-HT_{1A} receptor binding potential in the amygdala/hippocampal complex, insula, dorsal raphe nucleus, and orbitofrontal cortex,[69] suggesting a possible therapeutic target for stress-related disorders. While a systematic review revealed small effects of IN OT on the amygdala, voxel-based meta-analytic findings based on 11 placebo-controlled imaging studies indicated no direct effects of IN OT on the amygdala.[99] Null findings may have been due to variability in task type (i.e., implicit vs. explicit stimuli presentation), nature of analysis (i.e., whole-brain versus region-of-interest or small volume correction), participant sex, and widespread effects of IN OT in other brain areas.[99] Further, heterogeneous findings concerning OT effects on amygdala responses may be due to differential effects on amygdala subregions[100]; high-resolution functional magnetic resonance imaging could be useful for elucidating region-specific OT effects. IN OT effects on the left insula and temporal lobes, however, were shown to be consistent across task types and participant sex. IN OT may promote plasticity in salience network brain regions that mediate sensitivity to environmental cues, particularly social cues. Increasing the salience of social cues in different contexts may have different implications for emotional and social well-being.[94] In positive social contexts, IN OT may be beneficial for remediating stress-related psychiatric symptoms, but in negative contexts, IN OT may exacerbate sensitivity to negative cues and increase these difficulties (see Figure 1).

Neurotransmitters

IN OT-related neural activity in the salience network is mediated by neurotransmitter activity, with evidence for OT effects on the dopamine (DA),[101] serotonin,[41,102] and norepinephrine systems.[41]IN OT may enhance reward salience and reduce fear and anxiety via actions on DA neural circuits.[101,103] OT appears to promote rewarding effects of social interactions via impact on dopaminergic activity within mesocorticolimbic circuitry, including the PFC and nucleus accumbens,[104] within which OT receptor density is particularly high.[70]

HPA Axis

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis is associated with stress-related disorders,[105] with cortisol, a steroidal hormone, attracting the most empirical attention in human subjects research. Both reduced and elevated levels of cortisol have been observed in psychiatric populations, in part due to methodological heterogeneity.[106,107] A meta-analysis of 18 randomized, placebo-controlled IN OT studies revealed a modest, nonsignificant effect size for effects of IN OT on cortisol levels.[108] While IN OT did not lower post-task cortisol concentrations, it attenuated release of cortisol during lab tasks, particularly lab challenge tasks known to robustly stimulate the HPA axis (e.g., TSST). The IN OT effect was larger among clinical populations, including those with MDD and borderline personality disorder [Hedges $g = 0.74$, 95% CI $(-1.41, -0.08)$], suggesting possible utility of IN OT for dampening stress responses among individuals with stress-related disorders. However, in these studies, acute stress-induced cortisol may have promoted release of endogenous OT, complicating

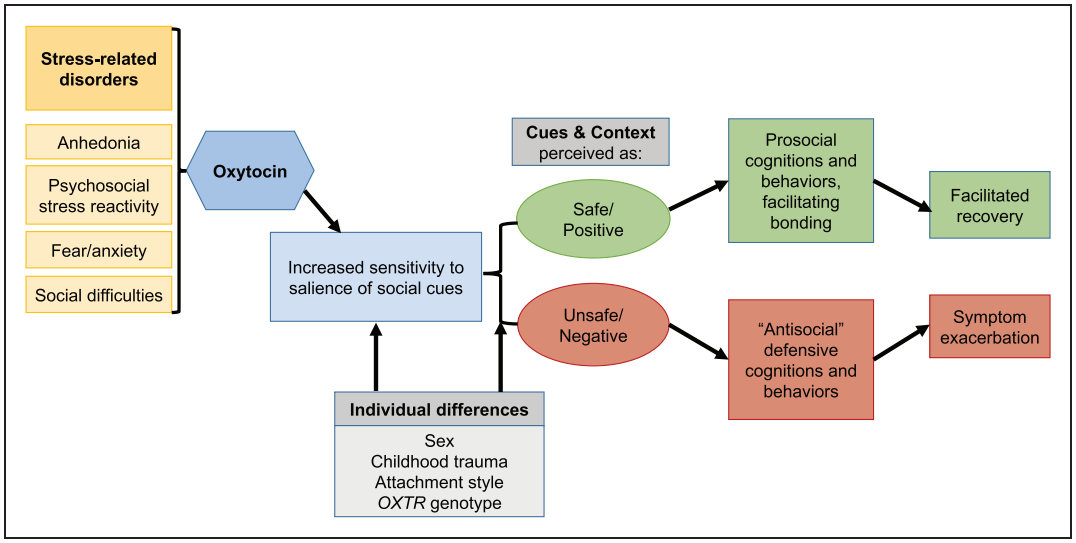

Figure 1. Mechanisms of stress-related disorders that may be modified by intranasal oxytocin and moderated by individual differences and contextual cues. Source: Adapted with permission from Olff et al.[38]

conclusions about direct effects of IN OT. This point is not unique to cortisol; most studies have not been able to parse direct effects of IN OT from indirect effects on other neurotransmitter or neurohormone systems that may mediate reduced stress hormone reactivity.

Inflammation

Burgeoning research suggests that IN OT has anti-inflammatory effects, which is highly promising for stress-related disorders given evidence of elevated pro-inflammatory cytokine levels in patients with MDD[109] and PTSD.[110] Intravenous OT has been shown to attenuate cytokine responses in healthy men.[111] In animals, OT facilitated wound healing among isolated hamsters, whereas administration of an OT antagonist delayed healing among socially housed animals.[112] These findings suggest that IN OT administered after stressful events could reduce inflammation and subsequent risk of developing stress-related disorders.

Treatment Opportunities

IN OT has been proposed as a potential pharmacological agent for the prevention and treatment of PTSD,[113,114] MDD,[41,115] and other psychiatric disorders, with several promising reviews and commentaries published in the past few years.[24,116–118]

IN OT as a Prophylactic Agent

IN OT-enhanced trust and social support seeking could promote adaptive social coping methods to preclude development of stress-related disorders. To our knowledge, however, there are no published studies examining IN OT as a prophylactic for MDD, though recruitment for such studies is ongoing (see clinicaltrials.gov). With respect to trauma, after the baseline visit of a randomized clinical trial testing the effects of 40 IU of twice-daily OT on the development of symptoms of PTSD among emergency department patients within two weeks of trauma, a single dose of IN OT was shown to increase amygdala reactivity to fearful faces,[119] and, in response to trauma reminders, reduced amygdala-ventromedial PFC connectivity and increased amygdala–insula functional connectivity.[120] This is potentially due to increased salience of fear stimuli during the sensitive post-trauma recovery period.[121,122] However, effects of single versus repeated administration appear to differ, with repeated IN OT administration potentially required to achieve clinically significant effects among high-risk individuals. Specifically, in this same sample, individuals who reported high acute PTSD symptoms had significantly lower PTSD symptoms severity at six month follow-up than individuals treated with placebo.[123]

IN OT-Enhanced Psychotherapy

While evidence-based psychotherapies and antidepressant treatments for stress-related disorders have meaningful effects, some of which may actually be mediated by effects on OT,[124] treatments could be improved regarding reduction of side effects, facilitation of more rapid response, and the percentage of individuals who reach and maintain symptom recovery.[125,126] IN OT could thus serve multiple functions that enhance outcomes for psychotherapies for stress-related disorders, including reducing exaggerated fear, facilitating fear extinction, increasing reward salience

of social cues, and promoting therapeutic alliance.[114] However, most existing IN OT studies have been single-dose investigations of IN OT as a pharmacological probe in healthy samples of primarily men, thus compromising generalizability to clinical populations, to women (who may require different dosing than men, and who are at increased risk of MDD, PTSD, and comorbid anxiety disorders[127]); and to typical courses of multidose pharmacological treatment. Doses of 20–24 international units (IU) have shown the strongest effects, whereas lower (10 IU) and higher (48 IU) doses show blunted effects,[128–130] the latter potentially due to excess OT binding to AVP receptors.[19]

Major Depressive Disorder

While a single dose of IN OT facilitated flexible shifting of attention away from sad faces in healthy controls,[131] IN OT enhanced processing of sad faces in depressed individuals,[132] perhaps due to stimulus salience. Similarly, under IN OT, postnatally depressed mothers were sadder and more often described their babies as difficult, but reported that quality of relationship with infant was more positive.[133] IN OT was associated with slower attributions in an emotion recognition task among patients with MDD, with accompanying enhanced neural activation within the superior frontal gyrus and insula, suggesting enhanced neural representation of affective states.[134] These effects may be mediated by OT's effects on empathy, which is elevated in MDD[135]; OT-facilitated empathy may be helpful for healthy individuals, but harmful for individuals already experiencing difficulty regulating sad mood. Severity and course of MDD may also be meaningful qualifiers for use of IN OT. In an open trial without a placebo control group, chronically depressed patients who had not responded to an eight-week trial of 40 mg of escitalopram were given 16 IU of IN OT (in addition to continued escitalopram) for four weeks and reported subsequent increases in life enjoyment and satisfaction.[136] In a recent study of chronically depressed patients, IN OT reduced attention to angry faces and increased attention toward happy faces, specifically under conditions of heightened awareness,[137] suggesting that IN OT may be useful for improving social interactions in chronic MDD.

Only one study has examined IN OT within a psychotherapy context for MDD, with *anxiogenic* effects. MacDonald and colleagues[115] administered 40 IU IN OT or placebo to 17 male outpatients with MDD before a videorecorded session with a therapist. Subjective anxiety increased over the course of the session, potentially due to the combination of IN OT-related increase in motivation to affiliate (indicated by reduction in social avoidance/looking away) with a subsequent lack of warmth from the therapist.[138] IN OT also improved performance on a theory of mind task.[15] Taken together, these results suggest that IN OT may enhance processing of affective cues and reduce subtle behavioral avoidance that can interfere with affiliation, suggesting that it may be useful for subsets of severely depressed individuals experiencing emotional numbing and deficits in social connection. However, IN OT may be contraindicated in depressed individuals with pre-existing sensitivity to social cues or difficulties managing strong emotions.

Posttraumatic Stress Disorder

While there are currently no published studies of IN OT-enhanced psychotherapy for PTSD, single-dose studies with PTSD samples are promising. In a pilot study of 18 individuals with PTSD, IN OT decreased PTSD symptoms, improved mood, and increased desire for social interaction.[139] Trend-level reductions in physiological responses to combat imagery were observed in a study of Vietnam-era veterans with PTSD; however, IN OT did not increase responses to pleasant images.[140] Among police officers with PTSD, IN OT dampened amygdala activity to emotional faces, regardless of valence,[141] normalized amygdala functional connectivity,[142] increased striatal, dorsal anterior cingulate, and insula responses to monetary reward,[143] and normalized left anterior insula responses to social reward, while also increasing responses in the right putamen.[64]Additional studies of the effects of IN OT on threat perception in PTSD samples are needed, given its role in the development and maintenance of PTSD,[144] OT-related increases in salience processing,[94] and evidence that IN OT *increases* anxiety to unpredictable threat.[145] IN OT may also have distinct effects at different stages of information processing—for example, evidence from a single-dose fear conditioning study suggested that during extinction training, IN OT may first enhance threat perception (indicated by increased electrodermal responses and PFC signals to conditioned fear in the early phase of extinction) before reducing fear during late-phase extinction to levels lower than those observed under placebo.[72]

Moderating Factors

Observations of null and inconsistent main effects of IN OT led to the recognition that OT effects, like those of many pharmacologics, are often moderated by characteristics of the individuals to whom IN OT is administered, as well as the context in which the medication is administered.[95]

Participant Sex

While some studies have shown that men and women do not differ with respect to basal OT levels,[146] or even that

men have higher OT levels than women,[147] it has been proposed that OT may be more biologically relevant to women,[32] who, as some studies have shown, have higher levels of circulating OT than men.[148] Observed higher OT levels in women are likely due to gonadal steroids like estrogen,[149] which upregulates central release of OT and the expression of the OT receptor in the brain.[150,151] Levels of estradiol vary across the menstrual cycle, presumably increasing responsivity to IN OT throughout the cycle. Sex-specific effects of IN OT have been observed across domains, including resting-state functional connectivity,[152] responses to social stress,[153] empathy,[154] responses to interactive social games,[155] salience of social attributes,[156] and changes in anxiety.[157] A study of a three-week course of daily IN OT administration showed significant decreases in anxiety scores in men but *increases* in anxiety among women.[157] IN OT was also shown to *increase* amygdala reactivity compared with placebo in response to negative emotional stimuli in healthy women,[158,159] and to increase amygdala – medial PFC connectivity during rest in young women, but not older women or men of any age.[152] Another study found sex-specific patterns of functional connectivity in PTSD patients that were normalized with one-dose IN OT administration in both men and women.[142] Other studies have not revealed sex differences,[160,161] potentially due in part to investigators not controlling for natural variation in estrogen levels across the menstrual cycle.[161] Sexually dimorphic effects of IN OT may be due to evolutionary-based adaptive values[75,162]; among men, reduced fear of social threat may be beneficial for successfully competing with other men (mediated by decreases in amygdala reactivity), whereas among women, increased sensitivity and a high level of fear of social threats may help them avoid danger, maintain social ties (including relationships that are valued but at risk),[32] and secure offspring survival against predators via defensive aggression (mediated by increases in amygdala reactivity).[162]

Childhood Adverse Events and Attachment Security

Childhood abuse and neglect are associated with elevated risk for MDD[163] and PTSD.[164] Early caregiving experiences may influence working models and subsequent perception of others as either a source of threat or safety,[165] processes which are then enhanced and reinforced by IN OT via effects on salience processing. Early maltreatment has been associated with lower CSF OT levels,[166] reductions in social support coping behaviors that could stimulate endogenous OT activity,[16] and dulled or reversed effects of IN OT. For example, early life stress was associated with increased cortisol responses and limbic deactivation after IN OT.[167] Among men with a history of early parental separation compared with controls, IN OT attenuated cortisol decreases.[168] Compared with controls, IN OT did not affect use of excessive force during listening to infant cries among women who experienced harsh parental discipline.[169] Similarly, anxiously attached individuals remembered their mothers as less caring and close following OT versus placebo, compared with securely attached individuals, who remembered their mothers as more caring and close in childhood following IN OT versus placebo.[170]

Alternatively, some studies suggest utility of IN OT among individuals with childhood adversity. IN OT-related improvements in social cognition and corresponding neural activation in the insula and superior temporal gyrus were *only* observed in women reporting higher levels of maternal love withdrawal.[171] IN OT induced a negative shift in TSST-induced functional connectivity between the amygdala and hippocampus in participants with higher levels of emotional abuse; findings were reversed in individuals with low emotional abuse.[172] IN OT increased levels of attachment in the majority of men classified as having insecure attachments,[173] and avoidantly attached individuals showed greater increases in self-perceptions of being communal after IN OT than other participants.[174] IN OT increased cooperation and trust in healthy men who scored high on attachment avoidance, but not among men with high attachment anxiety.[175] Studies of resting state connectivity[176] and cortisol levels[168] suggest that childhood experiences moderate IN OT effects even in the absence of social stimuli, suggesting that childhood adversity fundamentally affects the oxytocinergic system via neurological pathways or methylation of the oxytocin receptor gene (*OXTR*).

Genetic and Epigenetic Variability

IN OT leads to variations in the final active concentration of OT in the brain, but effects are dependent on OT receptor density in critical brain regions, which is influenced by genetic variability in *OXTR*. OT receptor expression is also highly regulated by the methylation of its coding gene, which in turn is influenced by numerous factors.[177] Accumulating research suggests an association between stress-related behavioral phenotypes and *OXTR* single nucleotide polymorphisms (SNPs).[178] *OXTR* SNPs linked to environmental sensitivity may interact with early-life adverse events to increase risk for stress-related disorders[179,180] or could serve as biomarkers for therapeutic IN OT effects.

The *OXTR* rs53576 SNP (minor allele: A, major allele: G) has gained the most attention to date. Compared with A/A carriers, individuals with G/G and A/G genotypes have been shown to be more likely to seek emotional support when distressed,[181] to exhibit higher trust-related behaviors,[182] and to more greatly benefit from social support.[183] Specifically, male G allele carriers have been

found to have less pronounced cortisol responses to the TSST after *in vivo* social support than A/A carriers.[183] The A allele has also been found to be linked to morphometric alterations of the hypothalamus and amygdala, which were in turn associated with increased functional connectivity between these structures during processing of emotionally salient social cues.[184] This variant may function to modulate risk for psychopathology via influence on limbic system reactivity to social cues. However, a recent study found no effect between rs53576 and depressive symptoms among undergraduate students, but did find that the A/A genotype of a SNP on the CD38 gene that controls OT release was associated with feelings of alienation from parents and peers and increased levels of suicidal ideation.[185] Studies using genome-wide association, polygenic, and gene-by-environment approaches; studies identifying the functional consequences of genetic variation in *OXTR*; and studies of associations between stress-related disorders and *OXTR* signaling pathways, *OXTR* molecular cascades, and interactions between the OT system and other neurotransmitters are needed.

Dispositional Traits and Skills

Finally, with respect to individual differences, OT effects have been shown to differ as a function of dispositional traits and skills. For example, effects of IN OT were shown to be moderated by emotion regulation abilities, with individuals with poorer (vs. better) emotion regulation abilities showing reduced cortisol response to stress after IN OT.[186] IN OT has predicted greater perceived social connection, more positive responses to help, and greater trust, but only for individuals low in extraversion.[187] Several studies have also shown that autistic-like traits moderate OT effects, though the direction of effects vary. For example, among individuals with greater autistic traits (i.e., poorer social cognitive skills), IN OT has shown both stronger social effects, including improved empathic accuracy[188] and attention toward positive faces,[189] as well as blunted effects on perceived hedonic value of interpersonal touch[190] and reversed effects on consumers' relationships with brands.[191]

Context of IN OT Administration

IN OT administered in a competitive, threatening, or affiliative context has varied effects. IN OT promoted increased cooperation and trust toward in-group members in a financial decision-making game, but increased defensive behaviors toward competing out-group members.[192] IN OT also reduced cooperation in men by enhancing fear, suggesting that OT promotes fear and distrust of unfamiliar individuals.[193] Safe social support may need to be available for IN OT to exert its full anxiolytic effects,[194] and similarly, the lack of social support may impede effects. During recall of negative autobiographical memories, among women but not men, IN OT decreased perceived emotional support.[195] This effect was stronger among women motivated to affiliate with the experimenter and reversed among women who received social contact from the experimenter. Further, single- and multiple-dose studies may differentially interact with context; it is possible that, in a multidose treatment context, if a patient does not feel increasingly safe with the clinician over time, IN OT could enhance these concerns and impede treatment response. Alternatively, it may be more critical for the patient to feel safe *before* administering IN OT for it to have beneficial effects.

Clinical Applications and Future Directions

Existing evidence suggests that IN OT pharmacotherapy could be part of strategic and targeted therapeutic approaches. IN OT could be administered to individuals identified as having dysregulated OT system activity via the Regensburg Oxytocin Challenge, which characterizes OT system responsiveness to a variety of challenges.[29] IN OT could be combined with psychosocial interventions that target specific cognitive or behavioral outcomes or features of stress-related disorders that may be responsive to IN OT. For example, depressed patients with comorbid anxiety symptoms and low levels of social attachment[102] and individuals for whom stressors involve negative social interactions or in which social isolation is the presenting problem may be good candidates. As an adjunct to time-limited psychotherapy, IN OT may be most effective when used at therapeutic dosage in the context of a warm, supportive clinician to target specific social learning (e.g., perspective-taking in interpersonal psychotherapy or cognitive reappraisal in cognitive-behavioral therapy) and cognitive processes (e.g., preferential attention to negative faces, attentional avoidance of facial expressions). Alternatively, providers could promote behaviors that stimulate the endogenous OT system, such as social support interventions. Evidence for the roles of attachment and childhood adversity on the effects of IN OT in clinical populations is sparse, and would inform personalized approaches to treatment; for example, IN OT may be beneficial for individuals with dismissive attachment (i.e., high avoidance and low anxiety) but contraindicated for individuals with more fearful attachment (high avoidance and high anxiety).[96]

Clinical trials of IN OT with demonstration of target engagement (i.e., demonstrated activation of a proposed therapeutic mechanism at a clinically effective dose) are needed.[196] In addition, given publication bias of positive IN OT findings,[197] poor reproducibility of effects,[198] and retractions of seemingly promising meta-analytic findings,[199,200] caution in recommending IN OT for patients

with stress-related disorders is warranted. Improved research standards including increased statistical power and reporting on trials without expected results are needed before IN OT can be utilized as a first-line treatment for stress-related disorders.[201]

Conclusions

As IN OT enhances affiliation, reward salience, and emotion regulation at both the behavioral and neural levels, it may promote natural recovery from traumatic and chronic stress, mitigating risk of stress-related disorders, as well as facilitate symptom reduction in the context of psychotherapy. IN OT appears to act on a number of neurobiological systems relevant to stress-related disorders, including the HPA axis, limbic system, neurotransmitters, and immune functioning. Despite the proliferation of IN OT studies in the past two decades, our understanding of the therapeutic value of IN OT remains limited in ways that are meaningful to the application of IN OT to stress-related disorders. IN OT does not have uniform effects on all individuals. The potential for sexually dimorphic effects of IN OT and evidence of sex-specific responses to stress necessitate examination of sex as a biological variable in IN OT studies. Further, given evidence that hormone levels, menstrual phase, and hormonal contraceptive status influence OT levels[202] and psychiatric symptoms (including PTSD),[203] concerted efforts to measure or monitor these factors are needed to make accurate conclusions about the potential therapeutic role of IN OT for women with stress-related disorders. Examination of biomarkers of adaptive responses to IN OT is needed, including those related to childhood adversity, as developmentally informed interpretation of social cues as "safe" may promote prosociality but interpretation of cues as "unsafe" may promote defensive, potentially maladaptive emotions and behaviors.[37] Examination of moderators of response to IN OT will contribute to development of strategic, targeted, sex-specific, and developmentally sensitive IN OT treatment approaches for stress-related disorders, in which increasing the salience of social and emotional cues may improve, maintain, or worsen social cognition and behavior, depending on current context and/or the patient to whom the IN OT is administered.

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