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Mood Disorders (C Nemeroff and J Newport, Section Editors)

The Role of Oxytocin in Early Life Adversity and Later Psychopathology: a Review of Preclinical and Clinical Studies

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Abstract

Purpose Oxytocin is a peptide hormone integral in parturition and milk let-down, and is increasingly recognized as an important regulator of human social behaviors including bonding, trust, fear, and stress. There is an increasing evidence that oxytocin is intricately involved in a broad array of neurophysiological functions and may be a common system implicated in multiple psychiatric disorders. This review examines the putative role of oxytocin in early life adversity-mediated risk for later development of subtypes of psychiatric conditions. Several lines of evidence are reviewed including oxytocin levels, response to exogenous oxytocin administration, and genetic studies.
Recent findings To date, most studies report lower levels of peripheral and central oxytocin in a dose-response manner in adults exposed to early life adversity. Individuals exposed to early life adversity seem to have a differential response to exogenous oxytocin administration, sometimes with negative outcomes. Several polymorphisms in the oxytocin receptor and emerging epigenetic studies point to a link between oxytocinergic systems and psychiatric disorders.

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Summary Specific limitations of the studies in the field are highlighted, and areas for future research are described. Considerably more research is needed to understand the complex role of the oxytocin system in early life adversity and its consequences.

Introduction

Traumatic experiences in early life are regrettably widespread and have significant implications for individuals and society. Worldwide, approximately 30% of adults report being maltreated as children [1], and roughly five children die every day due to abuse or neglect in the USA [2]. Definitions of early life adversity vary yet typically include various degrees of abuse, neglect, or family dysfunction [3]. It is now well established that exposure to these experiences can lead to significant morbidity and mortality including increased risk of neuropsychiatric disorders, cancer, diabetes, heart disease, and stroke among others [3–5]. In particular, burgeoning data suggests that exposure to early life adversity and traumatic experiences predispose or increase vulnerability to stress later in life which may further contribute to the development of trauma, mood, and anxiety disorders [5–11].

The mechanisms by which early life adversity confer vulnerability to later psychopathology is subject to intensive on-going investigation. Several mechanisms for early life stress programming have been proposed including impaired hypothalamic-pituitary-adrenal (HPA) axis signaling, altered glutamatergic neurotransmission, oxidative stress, and epigenetic changes among others [12, 13]. Evidence is emerging at a more granular level addressing how the timing, duration, severity, and type of early adverse events (environmental factors) differentially interact with resilience and genetic factors. Furthermore, burgeoning data is beginning to implicate the oxytocinergic system in early life adversity [14, 15].

Understanding more fully the environmental and biological mechanisms involved in early life adversity will allow for more targeted prevention and treatment strategies. This review summarizes evidence associating oxytocin with early adversity and the subsequent development of psychiatric illness. We first provide a brief foundational overview of the neurobiology of oxytocin to lay the groundwork for understanding its potential role in neuropsychiatric disorders. Then, we highlight the current understanding of oxytocin's association to early life adversity exposure and psychopathology. We conclude with an overview of the current state of the literature, including advances and limitations, and suggested directions for future research.

Basic overview

Oxytocin is a nonapeptide structurally similar to vasopressin. The oxytocin and vasopressin systems are highly conserved in vertebrates and, in particular, in mammals [16]. First recognized in the early 1900s as a powerful substance causing uterine contraction, in the 1930s and 1950s, oxytocin was isolated and structurally characterized, enabling exploration of its function beyond parturition.

The oxytocin gene encodes a preprohormone that is processed to oxytocin and its carrier neurophysin [17]. Oxytocin is primarily produced in the paraventricular and supraventricular nuclei of the hypothalamus and is released from nerve terminals in various brain regions including the nucleus accumbens and amygdala [17, 18]. Oxytocin is also stored in the posterior pituitary for direct circulatory release in response to various stimuli. In females, oxytocin is also produced in the ovaries and uterus, and in males in the testes. Oxytocin has

one receptor and vasopressin has three receptors: V1a, V1b, and V2. In some animal species, vasopressin has been shown to bind to the oxytocin receptor as well, effecting behavioral changes that seem to be sex-dependent. Preclinical studies have demonstrated that oxytocin's roles across species, within-species, and between sexes vary significantly; this is largely due to differing oxytocin and vasopressin receptor expression patterns in the central nervous system (CNS) [16]. Furthermore, steroid hormones, including sex hormones such as estrogen and testosterone, directly upregulate or downregulate the expression of oxytocin and vasopressin receptors.

The oxytocin receptor is a G protein-coupled receptor identified across species in multiple brain regions including the nucleus accumbens and ventral pallidum (reward and reinforcement), amygdala and bed nucleus of stria terminalis (emotion and fear processing), and ventromedial hypothalamus, septum, and brainstem (autonomic and neuroendocrine responses) [19]. Outside the CNS, oxytocin receptors have been identified in females in the corpus luteum, placenta, and mammary tissue, and in males in the interstitial cells of Leydig. Oxytocin receptors have also been found in the retina, adrenal medulla, thymus, and pancreas [20–24].

In humans, evidence of oxytocin receptor distribution from post-mortem tissue studies indicates that the oxytocin receptor is highly expressed in the hypothalamic medial preoptic area, paraventricular and ventromedial nuclei, amygdala, cingulate cortex, and the solitary and spinal trigeminal nuclei in the medulla [25, 26•, 27, 28]. The lack of radioligand tracers for oxytocin and vasopressin receptors has precluded in vivo studies of oxytocin receptor distribution and stimulus responses using imaging techniques such as positron emission tomography (PET). However, such ligands are currently under development [29]. Unfortunately, human oxytocin studies to date are largely limited to measuring oxytocin concentrations in plasma or cerebrospinal fluid (CSF), assessing responses to exogenous administration, and evaluating genetic polymorphisms.

Oxytocin function

The best understood function of oxytocin occurs during parturition. Oxytocin production and release are induced by the stretching of the cervix, vagina, and uterus during labor, which in turn induces myometrial contraction. Furthermore, nipple stimulation during breastfeeding induces pulsatile release of oxytocin, which promotes milk ejection [30]. Beyond parturition and lactation, oxytocin is increasingly recognized as an important neurotransmitter in regulating social behaviors and processing sensory stimuli in a social context (e.g., social memories, social cognition) [31]. Behaviors in which oxytocin has been implicated include pair bonding (maternal-infant, partner, group bonding), social behaviors (empathy, generosity, perspective taking), protective aggression, sexual behaviors, stress regulation, trust, fear, and anxiety [9, 32–35].

Oxytocin's role in psychopathology

Oxytocin's role in social behaviors and stress regulation has led to hypotheses that aberrant oxytocinergic systems may contribute to the pathogenesis of

psychiatric illnesses. The role of oxytocin in neuropsychiatric disorders is likely complex, symptom/circuit specific, and interactive with other systems. Specifically, oxytocin may modulate particular social deficits exhibited in neuropsychiatric disorders.

Currently, the role of oxytocin in the pathophysiology and treatment of psychiatric disorders is best understood in autism spectrum disorders (ASD) and schizophrenia, conditions with marked social-behavioral impairments. There is increasing scrutiny of oxytocin's role in mood, anxiety/trauma/obsessive-compulsive, and substance use disorders [36, 37]. The current review focuses on research linking oxytocin to early life adversity and psychopathology. Several lines of evidence will be reviewed including preclinical and human data on 1) oxytocin or oxytocin-binding protein levels (peripheral and/or central), 2) behavioral and imaging correlates in response to exogenous oxytocin administration, and 3) genetic studies of oxytocin and oxytocin receptors (including polymorphisms, candidate gene approach, epigenetics) in individuals with past or present exposure to early life stress and with or without psychopathology.

Preclinical studies of early life adversity on oxytocin

Animal models examining oxytocinergic pathways in early adversity include maternal separation, enriched/impoverished social environment (e.g.., limited bedding/nesting) and quantitative/qualitative differences in maternal care (e.g., low vs high licking and grooming) [38–40], bearing homology to aberrant parenting behaviors (e.g., withdrawal, decreased sensitivity) seen in depressed parents as well as foster care and infant neglect cases in humans.

Preclinical studies of early life adversity demonstrate persistent alterations in the oxytocinergic system. Female rat pups receiving less maternal care exhibit lower oxytocin receptor expression in the hypothalamus, amygdala, and lateral septum, as well as reduced dopaminergic projections from the ventral tegmental area and dopamine receptors in the nucleus accumbens [41–44]. Alterations in oxytocin concentrations have also been reported in maternal separation models with rat pups exhibiting increased serum and hypothalamic oxytocin levels induced by separation that persist following placement with foster mothers [45]. Maternally-separated/nursery-reared rhesus macaques exhibit decreased cerebrospinal fluid (CSF) oxytocin concentrations compared with maternally-reared controls [46]. The effect of early adversity on oxytocinergic systems is enduring as low oxytocin receptor mRNA expression in neonatally-stressed rats persists into adolescence [47]. These long-lasting changes can have intergenerational effects via epigenetic modifications of oxytocin and cortisol genes [48•, 49].

Preclinical studies demonstrate that exogenous oxytocin administration can improve depressive-like and anxiety-like symptoms [9, 50–53]. Furthermore, effects of exogenous oxytocin administration can be examined in animal models of early adversity. For example, intranasal administration of oxytocin remediated depression-like behaviors and socio-affective deficits in adult rats previously exposed to maternal deprivation [54•]. Future animal models will further characterize distinct biological and behavioral phenotypes induced by early life adversities with varying frequencies, timing, and duration of exposure,

and enhance understanding of environmental and genetic resilience factors, including those involving the oxytocin system.

Endogenous oxytocin in humans exposed to early life adversity and psychopathologic correlates

Numerous clinical studies have evaluated baseline endogenous levels of oxytocin in association with early traumatic experiences. Because oxytocin assay methodology is highly heterogeneous, a cursory review of oxytocin measurement is warranted. Peripheral oxytocin levels have been measured in serum, urine, saliva, amniotic fluid, and milk via radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA) with and without prior oxytocin extraction by high performance liquid chromatography (HPLC) and gel filtration chromatography. The reliability and validity of these techniques have been debated by analytical chemists with a consensus emerging for chromatographic oxytocin extraction followed by RIA [55–57]. Moreover, the source of oxytocin measured in plasma, urine, and saliva remains obscure and must be elucidated. Other variables affecting oxytocin measurement variability include time of collection, fasting vs, post-prandial sampling, and sample storage conditions [55].

Central oxytocin levels can be measured directly in CSF or indirectly by quantifying oxytocin's carrier protein, neurophysin. There is considerable debate as to whether peripheral oxytocin is a reliable index of central oxytocin levels. A recent meta-analysis showed that peripheral and central oxytocin concentrations are correlated ($r = 0.29$) after experimental stress induction but not at baseline [58••].

Despite methodologic inconsistencies in oxytocin assay, operationalization of adverse events, and population studied, most studies report lower levels of peripheral and central oxytocin in adults exposed to early life adversity. Furthermore, the number of early life stressors often inversely correlates with oxytocin levels in a dose-dependent manner. Specifically, lower CSF oxytocin levels have been found in adult women who reported childhood maltreatment, particularly those with exposure to sexual abuse [59]. CSF oxytocin concentrations were also negatively correlated with anxiety symptoms in that study [59]. In peripheral oxytocin studies, lower oxytocin levels were found in adult males with more severe prepubertal stressors; oxytocin was inversely associated with current symptoms of depression and anxiety but not adolescent or current stressors [60, 61]. Other studies have shown that less severe forms of childhood physical abuse were actually positively correlated with urine oxytocin levels in adults [62]. Additionally, in a recent study exploring the relationship between oxytocin and CNS morphology in individuals with and without early life maltreatment, although there were no group differences in blood oxytocin levels, the pattern of oxytocin association with brain morphology varied by early maltreatment exposure. In individuals without childhood maltreatment, gray matter volume in the nucleus accumbens and hypothalamus were positively correlated with oxytocin levels; however, oxytocin levels were not correlated with gray matter in the nucleus accumbens and were negatively correlated with hypothalamus gray matter volume and amygdala volume in those with childhood maltreatment histories [63]. These cross-sectional studies with

retrospective reporting in adults suggest that the type, timing, and duration of adversity may have a differential effect on oxytocinergic systems and brain morphology underlying variations in oxytocin activity. Therefore, it is also important to study how these early life stressors affect the developing brain in children.

Studies in children, albeit few in number, also seem to show overall lower basal oxytocin levels, and atypical oxytocin response patterns to acute stress following early life adversity. One study in children (4–5 years old) with and without early neglect (i.e., having lived in orphanages since birth for an average of 16 months), showed lower oxytocin urine levels in neglected children than controls following interaction with their adoptive or biological mothers, respectively [64]. Of note, baseline urine oxytocin levels were not different but vasopressin levels were lower in neglected children. Moreover, their response to familiar caregivers was different than in children not exposed to neglect. Similarly, in an adolescent sample with significant trauma exposure currently living with their biological family ("unsettled") vs. residential care homes ("settled") vs. unexposed to trauma ("control"), unsettled children had lower salivary oxytocin levels both in the morning and evening compared to other groups, whereas settled children had higher evening oxytocin levels only [65]. This may indicate that when taken away from an abusive or neglectful environment, children's oxytocin may hyper-regulate and potentially modulate other systems [65].

In a sample of low-income children and their mothers, maternal oxytocin effects on positive parenting behaviors differed based on maternal early adversity history [66••]. Mothers with low exposure to early adversity had higher oxytocin levels after a play interaction and more positive parenting behaviors during the play. However, mothers with histories of high early adversity and high oxytocin levels after dyadic play surprisingly showed less positive parenting [66••]. Similarly, a longitudinal study of chronically depressed vs non-depressed mothers (controls) and their children showed that children of mothers with depression, and their mothers, had lower salivary oxytocin than controls. These children were also more likely to have a *DSM-IV* axis I disorder (61% vs. 15%) than children of non-depressed mothers [67].

The oxytocinergic response to acute stress also appears to be affected in both children and adults exposed to early childhood maltreatment with sex differences. In one study, adults exposed to child abuse or cancer in childhood or adolescence had higher oxytocin levels in response to a laboratory social stressor, i.e., the Trier Social Stress Test (TSST), than controls. Furthermore, those exposed to cancer in childhood had overall different response patterns than those exposed to child abuse [68]. In children, girls (but not boys) aged 8–11 years old with histories of physical abuse had higher levels of urinary oxytocin following the TSST [69]. It has been speculated that oxytocin increases during stress may constitute a neurobiological means to attain social support when under duress.

Overall, a number of studies have evaluated baseline and response-to-stimuli oxytocin levels in adults, parents, and children exposed to early life adversity. These studies suggest there are distinct patterns of oxytocin alterations in response to early life adversity in adults and children, with higher early adversity showing overall lower baseline peripheral and central oxytocin levels in adults but inconsistency in children. Clearly, future studies are needed to

untangle effects of early life adversity on the adult and developing brain on baseline oxytocin function, including sexual dimorphism and differences in the nature, severity and context of adversity. Additionally, given that oxytocin levels can be either negatively or positively correlated with depressive and anxiety symptoms [70, 71] and that these disorders are associated with early life stress [72], future studies evaluating oxytocin in clinical populations stratified by early life stress exposure may help elucidate subtypes of psychopathologies.

Exogenous oxytocin administration effects in humans exposed to early life adversity and psychopathologic correlates

Studies of exogenous oxytocin administration include both healthy participants with or without early life stress and those with various psychopathologies. In human studies, exogenous oxytocin is usually administered intravenously or intranasally. Studies are typically double-blind randomized placebo-controlled with varying doses of oxytocin. Most use intranasal oxytocin given its convenient application and successful blinding. Furthermore, it is thought that intranasal administration may have higher central effects [73, 74]. However, many have raised concerns about the dosing of exogenous oxytocin, producing levels higher than endogenous oxytocin that could thus induce some of the observed effects through peripheral rather than central mechanisms [75]. Experimental psychological paradigms in these studies usually involve an emotional stimulus such as facial expression images, video clips or others. Study outcomes include functional brain imaging, performance on behavioral tasks, and/or participant perceptions.

Briefly, a meta-analysis of 23 studies of exogenous oxytocin administration in healthy individuals showed that oxytocin enhances recognition of emotional facial expressions with a small effect size and elevates in-group trust with a moderate effect size [37]. Other studies have demonstrated that oxytocin administration decreases anxiety in the TSST and reduces amygdala activation in fMRI with fear-inducing visual stimuli, though there is variability in response to exogenous oxytocin [37, 76, 77].

Some have proposed that these varying effects are related to experimental context, participant characteristics, and early life adversity exposure [37]. Regarding experimental context, participant knowledge of other players or level of threat in behavioral game paradigms may alter the effect of exogenous oxytocin on trust perception. In addition, oxytocin-induced improvement in emotion recognition tasks is specific for individuals with lower social-cognitive competence. Finally, clinical trials indicate that exogenous oxytocin produces different effects in those with vs. without early adversity. For example, the prosocial effects of exogenous oxytocin are greater in, and perhaps limited to, individuals with supportive family backgrounds (and presumably lack of early trauma) [37]. In some studies, only participants reporting low maternal love-withdrawal in childhood, as a form of early life stress, respond in prosocial ways in response to exogenous oxytocin [78, 79]. Similarly, the strength of their hand grip when listening to infant cries is unchanged following oxytocin administration in individuals with histories of harsh parental discipline but decreased in those without such histories [80].

Biological differences in response to exogenous oxytocin have also been reported in individuals with early life adversity. A study of 19 healthy men showed that participants with a history of early parental separation had an increase in salivary cortisol, whereas controls experienced a decrease, in response to intranasal oxytocin administration [81]. A study evaluating oxytocin effects on acute stress responses showed that exogenous oxytocin increased limbic deactivation and heightened cortisol responses to a laboratory stressor in adults exposed to moderate to severe early life adversity but produced opposite effects in those without early adversity [82]. Similarly, a functional connectivity study demonstrated that individuals without early adversity had higher resting-state connectivity between the right amygdala and anterior cingulate cortex (ACC) and greater ACC deactivation during a laboratory stressor, which was attenuated by intranasal oxytocin; conversely, those with histories of emotional abuse had reduced resting-state amygdala/ACC connectivity and exogenous oxytocin demonstrated no effect on post-stressor activation [83].

A separate line of inquiry has examined whether the affiliative effects of oxytocin may enhance parenting behaviors, affording protection against early adversity as a consequence of aberrant parenting. A study of fathers and toddlers showed that intranasal oxytocin increased fathers' responsiveness to children during play and tended to decrease hostility [84]. Similarly, another study showed that oxytocin administration to the father not only increased father's salivary oxytocin and supportive parenting behaviors but also increased salivary oxytocin and social engagement in children in response to paternal behavior [85]. In a study of maternal depression, which commonly affects maternal-child bonding and attachment, mothers randomized to intranasal oxytocin reported subjective improvement in their relationship with their infant but also reported being sadder and that their babies were more difficult [86]. These studies did not evaluate the possible moderating role of early life adversity in the effects of oxytocin on parent-infant relationships.

Oxytocin genetic studies in humans exposed to early life adversity and psychopathologic correlates

The human oxytocin receptor gene, located at 3p25-3p26, has four exons and three introns [87]. At least 44 single-nucleotide polymorphism (SNPs) have been reported in the human oxytocin receptor, mostly in intronic regions [88, 89••]. Oxytocin receptor genetic studies have used a candidate gene approach, which has been questioned with regard to generalizability and validity. The oxytocin receptor polymorphisms most often investigated include rs53576, rs2254298, rs2268498, rs139832701, and rs1131147. Oxytocin receptor SNP rs53576 has been associated with a broad range of social behaviors and has also been implicated in PTSD, response to recent traumatic experiences, anxiety, depression, and related stress phenotypes [90–93].

In particular the G allele of rs53576 has been associated with increased empathy, optimism, and trust [94]. It has been argued that G allele carriers might be more socially sensitive and perhaps more sensitive to adverse effects of early adversity, or alternatively, that A allele carriers may be resilient to untoward effects of early adversity. For example, a study of adult males

demonstrated that appropriate paternal care during childhood was associated with heightened social sensitivity to the sound of a female cry, but only among G/G homozygotes [95]. In a sample of low-income African American adults, individuals with exposure to multiple types of childhood trauma and the G/G genotype were more likely to exhibit emotional dysregulation and disorganized adult attachment styles [96]. In a study of university students, those with histories of childhood maltreatment had increased depressive symptomatology only if they were G allele carriers [97]. Among adolescents with histories of early adversity, G/G homozygotes perceived lower social support and reported higher internalizing symptoms compared to maltreated A-carriers [98]. In children, the AA/AG genotype was associated with increased resiliency in maltreated children [99]. Lastly, in order to further investigate the biological underpinnings of risk conferred by the G-allele, a study evaluating the interaction between SNP genotype, early adversity severity, and imaging data, revealed that GG homozygotes, but not A-allele carriers, had marked gray matter reduction in the ventral striatum with increasing adversity scores and also increased amygdala responsiveness to an emotional facial expressions task [100].

Conversely, a recent study of three oxytocin receptor SNPs including rs53576, rs2254298, and rs2268498 failed to demonstrate moderating effects on the relationship between childhood maltreatment and psychopathology [101]. Other oxytocin receptor SNPs, rs139832701, and rs11131147, were correlated with higher levels of anxiety, stress, and depression scores among those with early adversity [102].

There has been little scrutiny, to date, of the relationship between epigenetic modification of oxytocin receptor genes, early adversity, and psychopathology. Recently, a study of 393 African American adults, showed that oxytocin receptor methylation did not mediate but did moderate (at five CpG sites) the relationship between child abuse history and psychopathology [89••].

Overall, although replications are needed, these studies suggest that the G-allele in rs53576 of the oxytocin receptor constitutes a vulnerability factor for individuals with adverse childhood experiences and support the hypothesis that the oxytocin system plays a role in the pathophysiology of psychiatric disorders among those with early life adversity.

Conclusions, limitations, and future directions

In this review, we examined the literature linking early life adversity to oxytocinergic dysregulation as a mechanism involved in the susceptibility to later psychopathology. In particular, we evaluated studies of oxytocin levels, response to exogenous oxytocin administration, and oxytocin genetic variations in adults and children with histories of early life adversity. Overall, the data indicates that early adversity produces persistent effects on oxytocinergic pathways. Specifically, studies of early life adversity demonstrate 1) differences in peripheral and central oxytocin levels, 2) altered responses to exogenous oxytocin administration, and 3) moderating influence of oxytocin receptor polymorphisms and epigenetic changes on vulnerability to psychopathology. At this juncture, the hypothesis that oxytocinergic mechanisms underlie the risk for psychiatric illness attributable to early life adversity remains preliminary and warrants continued investigation.

The studies reviewed have several methodological limitations including small sample sizes, cross-sectional designs, inconsistent sampling and assay methodologies, highly variable age groups and populations, hindering definitive conclusions. In particular, there is a dearth of studies in children or those employing longitudinal designs, which would enhance examination of causality. Furthermore, although preclinical studies clearly demonstrate sex differences in the oxytocin system, few clinical studies have evaluated potential sexual dimorphisms.

Of particular concern is the inconsistent operationalization of early adversity, inviting discrepant results and thus generating confusion. Studies utilize an array of terms including adverse childhood events, early life stress, early life trauma, childhood trauma, childhood maltreatment, sexual abuse, physical abuse, emotional abuse, and exposure to harsh parenting. Often debated is whether studies should conflate childhood traumatic experiences with other stressful childhood experiences, e.g., parental divorce, poverty, and death of a parent. Moreover, there is a growing recognition that the context in which stressful events occur is impactful; thus, individual, family, and environmental context and resiliency factors should be evaluated. Additionally, childhood stressors are assessed using an array of psychometric instruments that often do not capture the timing, duration, or intensity, of acute response to these events. Moreover, the stability of retrospective data collection regarding childhood adversity using such instruments may arguably be biased by recent stressors [103]. More nuanced and detailed evaluations of these stressors and their context, a common language for referencing them, and measurement of resiliency factors, are needed to advance this field of inquiry.

With regard to oxytocin research specifically, questions remain as to whether peripheral oxytocin levels provide relevant insight into central oxytocinergic function. Furthermore, radioligands to enable in vivo assessment of central oxytocin activity are clearly needed as oxytocin levels may not necessarily correlate with oxytocin receptor expression and activity [29]. This is particularly important in the field of early life adversity which, for example, may lead to down-regulation of oxytocin receptor expression.

Furthermore, the pharmacokinetics and pharmacodynamics of exogenous oxytocin administration remain poorly understood. How much oxytocin actually enters the CNS and the mechanisms by which oxytocin exerts its observed effects remains obscure. Systematic evaluation of oxytocin delivery methods, doses, clearance, and binding affinities are needed. The mechanism(s) by which those with early adversity respond differently, and sometimes negatively, to exogenous oxytocin is unexplained. Preclinical studies evaluating oxytocin receptor expression may be particularly helpful in elucidating some of these questions. Meanwhile, human studies of exogenous oxytocin in various clinical populations should routinely control for early life adversity.

Finally, future epigenetic studies of oxytocin and early adversity should be extended beyond DNA methylation to incorporate expression of non-coding RNA and histone modification. Ultimately, epigenetic inquiries are arguably best-suited to elucidate the mechanisms underlying intergenerational transmission of adversity [104••].

Compliance with ethical standards

Conflict of interest

Dr. Londono Tobon has nothing to disclose.

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Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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