The Relationship between Oxytocin and Stress Responses

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Abstract

Oxytocin, traditionally viewed as a "love hormone," plays a multifaceted role in the physiological response to stress, defying simplistic categorization. Its actions are context-dependent, influenced by factors such as the type of stressor, individual differences in oxytocin receptor density and sensitivity, and the presence of other neurochemicals. While often associated with prosocial behavior and stress reduction, oxytocin's influence on the hypothalamic-pituitary-adrenal (HPA) axis, the central regulator of the stress response, is nuanced and not uniformly inhibitory. In acute stress situations, oxytocin can attenuate the HPA axis response, reducing cortisol release and promoting a sense of calm. This effect may be mediated through its actions in the amygdala and other brain regions involved in fear processing, modulating the emotional experience of stress. Furthermore, oxytocin interacts with other stress-related neurotransmitters, such as corticotropin-releasing factor (CRF) and vasopressin, exhibiting both synergistic and antagonistic effects. The balance of these interactions shapes the overall stress response. However, chronic stress can alter oxytocinergic function. Prolonged exposure to stressors can lead to decreased oxytocin release and receptor sensitivity, impairing its capacity to buffer against stress. This dysfunction might contribute to the development of stress-related disorders such as anxiety and depression. Furthermore, in social stress contexts, particularly those involving social threat or rejection, oxytocin's effects can be paradoxical. It can potentiate the stress response, promoting defensive behaviors and reinforcing social avoidance in individuals already prone to social anxiety. The physiological mechanisms underlying these varied responses are complex and involve intricate interactions between the central nervous system, the endocrine system, and the peripheral nervous system. Further research is needed to fully elucidate the conditions under which oxytocin promotes stress resilience versus exacerbates stress vulnerability. Understanding these complex interactions is crucial for developing targeted interventions to mitigate the negative consequences of stress and promote psychological well-being. Ultimately, the relationship between oxytocin and stress is far from simplistic, highlighting the crucial need for nuanced investigation into its complex and context-dependent effects.

Keywords: Oxytocin, Stress Responses

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Introduction

Endogenous oxytocin is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus, the axons of which terminate in the posterior pituitary gland. During axonal transport, the precursor neuropeptide, oxytocin neurophysin, is cleaved and modified to the final form of the oxytocin hormone, and then it is stored in the posterior pituitary until various stimuli trigger exocytotic release into the circulation.[1] Oxytocin, a neuropeptide hormone, is involved in a multitude of physiological and behavioral functions. While its role in childbirth and lactation is well-established, recent research has revealed its involvement in various aspects of social behavior, stress regulation, pain modulation, and reward processing. Oxytocin has gained significant attention for its role in promoting social behavior and facilitating social bonding. Numerous studies have demonstrated that oxytocin administration increases trust, empathy, and prosocial behaviors [2]. Oxytocin enhances social recognition and attachment, playing a crucial role in maternal-infant bonding [3].

Mechanisms of action on CNS:

Activation of specific oxytocin receptors initiates intracellular signaling pathways that modulate neuronal activity and neurotransmitter release, leading to a diverse range of physiological and behavioral responses. The binding of oxytocin to its receptor triggers the activation of G-proteins and subsequent activation of phospholipase C (PLC) [4]. PLC cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) [5]. IP3 induces the release of intracellular calcium stores, leading to an increase in intracellular calcium levels [6]. Calcium influx and subsequent signaling events then modulate various cellular processes [7].

Recent studies have highlighted the involvement of cyclic adenosine monophosphate (cAMP) signaling in mediating the effects of oxytocin [8]. Activation of oxytocin receptors has been shown to increase cAMP levels through Gαs protein coupling, leading to the activation of protein kinase A (PKA) and subsequent phosphorylation of downstream effectors [9]. This cAMP-PKA signaling pathway may contribute to the regulation of oxytocin-mediated synaptic plasticity and behavioral responses.

Furthermore, oxytocin-induced release of oxytocin itself from dendritic endings and axonal varicosities, referred to as "autocrine" or "paracrine" release, has been observed [10]. This autocrine/paracrine signaling has been implicated in the modulation of neuronal activity and synaptic plasticity. Oxytocin released from dendrites can bind to nearby receptors, influencing local circuitry and synaptic. Oxytocin has been found to enhance inhibitory GABAergic neurotransmission [11], increasing the release of GABA; oxytocin can regulate neuronal excitability and contribute to the inhibition of neural circuits involved in stress and anxiety responses [12].

Oxytocin has also been shown to interact with the dopamine and opioid systems, suggesting its involvement in reward processing and addiction-related behaviors [13].

Functions of Oxytocin

Stress Regulation:

Oxytocin is involved in the regulation of stress responses and anxiety. It has anxiolytic properties and attenuates stress-induced physiological and behavioral responses [14]. Oxytocin modulates the hypothalamic-pituitary-adrenal (HPA) axis, reducing the release of stress hormones, such as cortisol [15]. Additionally, oxytocin promotes adaptive stress coping strategies and resilience to stress [16].

Gastrointestinal Functions:

Oxytocin affects gastrointestinal motility and gut functions. It plays a role in the regulation of gastric emptying, intestinal transit, and gut barrier integrity [17]. Oxytocin receptors are present in the enteric nervous system, suggesting its involvement in the gut-brain axis and the regulation of gut functions [18].

Modulation of Memory and Learning:

Oxytocin has been shown to influence cognitive processes, including memory and learning. It facilitates social memory formation and recognition [19]. Oxytocin administration enhances memory consolidation, particularly for emotionally salient events [20]. Furthermore, oxytocin influences synaptic plasticity in brain regions involved in learning and memory, such as the hippocampus [21].

Immune Modulation:

Recent studies have revealed the immunomodulatory properties of oxytocin. Oxytocin receptors are present on immune cells, and oxytocin can modulate immune cell functions and inflammatory responses [22]. Oxytocin has been implicated in the regulation of immune cell trafficking and the modulation of cytokine production [23].

The relationship between oxytocin and some hormones

Oxytocin may control the function of the anterior pituitary gland, as observed by several neurons responding to oxytocin dropping their axons across the medial appearance [24]. On the other hand, oxytocin released into the gate of vessels has a basal concentration often greater than that found in the peripheral circulation [25]. The expression of an oxytocin receptor gene (OTR) in the rat was evidenced in anterior pituitary cells, fundamentally in lactotrophs where a significant increase in oxytocin receptors (OTR mRNA) is most apparent in the later stages of pregnancy after estrogen injection [26].

Prolactin

Prolactin regulates milk induction in the mammary gland through lactation. There is an overlap in the action of oxytocin and prolactin, as prolactin works on the synthesis of milk, whereas oxytocin acts on its secretion. Although prolactin inhibits oxytocin neurons, this can be irreversible during lactation,

therefore increasing the expression of oxytocin. So, the prolactin curb of oxytocin neurons is missing in lactation, which might already be a synchronous rise of prolactin excretion from the pituitary gland and stimulate oxytocin neurons for the completion and transmission of milk to newborns [27]. The role of oxytocin as a release agent for prolactin is unknown; some studies have indicated that oxytocin contributes to prolactin secretion [28].

Luteinizing hormone

The output of luteinizing hormone in the period before estrus is important for successful ovulation. Some studies suggested that oxytocin controls the secretion of the luteinizing hormone wave; in the pre-estrus period, oxytocin is highest in the blood and peripheral plasma [29]. Some studies on different animals have indicated an increase in luteinizing hormone in response to oxytocin treatment; the effect of oxytocin was stimulated by estrogens and inhibited by progesterone [29]. On the other hand, studies have shown that there is a direct effect of oxytocin on luteinizing hormone excretion as well as an indirect impact on Gonadotropin-releasing hormone [30].

Stress Responses and Oxytocin

Animal studies have shown that various physiological and psychological stressful stimuli, such as noxious stimuli [31], conditioned fear stimuli, social defeat stress [32, 33], immobilization stress, shaker stress [34], forced swimming [35, 36], cold stress [37], high-intensity exercise [38], activate oxytocin neurons and facilitate the release of oxytocin into the plasma and within the brains of mice and rats [39, 40]. Social instability stress in adolescent female rats has been reported to decrease oxytocin immunoreactivity in the hypothalamic paraventricular nucleus [41], possibly due to oxytocin release. Synchronic oxytocin release into the plasma and within the brain has been shown during forced swimming stress [36] and shaker stress [34].

In humans, oxytocin release after stressful stimuli has also been reported. Physical running [42, 43], psychological stress such as uncontrollable noise in women [44] and a Trier social stress test (public speaking and mental arithmetic in front of an audience) [43, 45] have been shown to increase plasma or salivary oxytocin concentrations. A positive correlation between plasma oxytocin concentrations and anxiety or relational distress has been shown in healthy humans [46, 47] and in patients with social anxiety disorder [48]. High levels of plasma oxytocin have also been reported in subjects with high depressive scores [49]. The number of oxytocin neurons [50], expression of oxytocin mRNA in the hypothalamus [51], and plasma oxytocin concentrations [52] have also been shown to be increased in depressed subjects. Exercise of short duration and high intensity has been shown not to significantly change plasma oxytocin concentrations in humans [53]. In rats, plasma oxytocin levels have been reported not to change after exercise [54].

Furthermore, decreased oxytocin levels have been observed in the cerebrospinal fluid (CSF) of women with a history of child abuse [55], in the CSF of suicide attempters [56], and in the plasma of patients with post-traumatic stress disorder (PTSD) [57]. Decreased oxytocin concentrations in the blood have

been found in patients with depression [58]. The interpretation of oxytocin levels in psychiatric diseases is complex. A decrease in oxytocin levels in patients with psychiatric diseases might be a cause of the development of anxiety or depression-like symptoms in these patients and might not be a result of stressful stimuli.

Roles of Oxytocin in Stress Responses

Oxytocin regulates stress responses in the neuroendocrine system, autonomic nervous system, immune system, and behaviors. In many studies using both animal and human subjects, oxytocin has been shown to reduce the activity of the hypothalamic-pituitary-adrenal (HPA) axis [59, 60], regulate autonomic stress responses [61, 62], attenuate inflammation [63, 23], and reduce anxiety-related behaviors [64, 65]. Oxytocin-deficient female mice have been reported to show increased anxiety-related behaviors in an elevated plus maze test [66]. A high plasma level of corticosterone after shaker stress and novel environmental stress-induced hyperthermia have also been observed in oxytocin-deficient female mice [66]. These results suggest that endogenous oxytocin reduces the activity of the HPA axis and the anxiety-related behavioral system during stress. In many studies in which the effects of oxytocin administration on anxiety-related behavior and fear conditioning were assessed, oxytocin was shown to decrease anxiety-related behavior [67]. Studies with human subjects have also shown anxiolytic effects of intranasally administered oxytocin [64]. Oxytocin administration and social support have been shown to decrease cortisol levels and reduce anxiety during a Trier social stress test in healthy men [68]. Intranasal oxytocin has been reported to reduce the activity of the amygdala region in response to fearful faces or fear scenes in healthy subjects [69, 70].

Site of Action of Oxytocin with Respect to Stress Responses

The oxytocin receptor is distributed widely within the brain, which regulates stress responses, including the prefrontal cortex, limbic area, hypothalamus, raphe, and medulla oblongata [71].

Prefrontal Cortex

The oxytocin receptor in the prelimbic or infralimbic prefrontal cortex and in the anterior cingulate cortex (ACC) has been shown to have anxiolytic effects. Oxytocin injection (male rats) [72] and activation of oxytocin receptor-expressing neurons [73] in the prelimbic prefrontal cortex have been shown to decrease anxiety-related behavior. Optogenetic activation of the prelimbic prefrontal cortex oxytocin terminals projecting from the PVN oxytocin neurons has been shown to reverse paternal deprivation-induced increases in anxiety-related behavior [74]. In the infralimbic prefrontal cortex, oxytocin has been reported to induce fear extinction [75].

Hypothalamus

The oxytocin receptor in the PVN has been reported to have anxiolytic effects, and the oxytocin receptor in the lateral hypothalamus has been shown to modulate depressive-like behavior. Local injection of oxytocin into the PVN of male rats [76] has been shown to decrease anxiety-related

behavior. Oxytocin has been reported to increase the activity of GABAergic neurons in the PVN, and blockage of the GABAA receptor in the PVN has been shown to eliminate the oxytocin-induced decreases in anxiety-related behavior and corticosterone levels following stress [77]. Oxytocin has also been reported to decrease the activity of corticotrophin-releasing hormone (CRH) neurons in the PVN following stress [77].

Lateral Septum

The oxytocin receptor in the lateral septum has been reported to have both anxiogenic and anxiolytic effects. Apparently, the contradictory findings in these reports remain to be explained. Oxytocin application has been reported to increase recall of negative events and stressful stimuli [78]. Deletion of the oxytocin receptor or injections of oxytocin antagonists in the lateral septum of male mice have been reported to decrease stress. On the other hand, there have been studies showing that oxytocin in the lateral septum has anxiolytic effects. Oxytocin injection into the lateral septum of male mice has been reported to abolish social fear expression in a social-fear-conditioning paradigm [79]. In addition, the naturally activated oxytocin system in lactating mice has been reported to prevent social fear expression in a social-fear-conditioning paradigm, while silencing of oxytocin neurons in the PVN projecting to the lateral septum has been shown to enhance social fear in lactating female mice [80].

Amygdala

The oxytocin receptor in the central amygdala (CeA) has been shown to have anxiolytic action in various studies. However, contradictory data have also been reported. Oxytocin in the amygdala has also been reported to facilitate the recognition of emotions, leading to modulation of stress-coping behavior. Oxytocin is known to reduce fear and anxiety by reducing the activity of the amygdala. Oxytocin injection into the CeA has been shown to attenuate long-term isolation-induced depressive-like and anxiety-related behaviors in male mice [81] and to decrease anxiety-related behavior in female rats [82].

Raphe Nucleus

The oxytocin receptor in the raphe nucleus has been shown to have anxiolytic actions. The oxytocin receptor is expressed in approximately half of the serotoninergic neurons in the raphe nucleus, and local injection of oxytocin into the median raphe decreases anxiety-related behaviors by facilitation of serotonin release, possibly via the serotonin 2A/2C receptor [67]. However, deficiency of the oxytocin receptor in serotoninergic neurons in the raphe nucleus has been shown to have no significant influence on anxiety-related behavior but to enhance aggression only in male mice [83]. A study showed that oxytocin-induced anxiolytic actions were blocked by a serotonin receptor antagonist [16].

Medulla Oblongata

The oxytocin receptor in the dorsal motor nucleus of the vagus has been shown to reduce visceral stress responses. Activation of oxytocin neurons in the PVN projecting to the dorsal motor nucleus of the

vagus has been reported to prevent the delayed gastric emptying observed following acute or chronic heterotypic stress and to increase gastric tone and motility following chronic heterotypic stress in rats [84].

Therapeutic Potential of Oxytocin

Oxytocin, a neuropeptide hormone with diverse physiological and behavioral effects, holds significant therapeutic potential for a range of psychiatric, neurodevelopmental, and neurodegenerative disorders. Review articles, clinical trials, and preclinical studies have explored the therapeutic applications of oxytocin, revealing promising outcomes in various conditions. This section highlights the emerging therapeutic potential of oxytocin and its implications for clinical interventions, incorporating recent research findings.

Autism Spectrum Disorders (ASD): Oxytocin has shown promise in improving social functioning and reducing social communication deficits in individuals with ASD [85]. Clinical trials have reported that intranasal administration of oxytocin enhances social cognition, increases eye gaze, and improves emotional recognition and understanding. Oxytocin treatment has also been associated with reduced repetitive behaviors and improved social interactions in individuals with ASD [86, 87].

Social Anxiety Disorder (SAD): Oxytocin has demonstrated potential as a treatment for social anxiety disorder. Clinical studies have found that oxytocin administration reduces social anxiety symptoms, including fear of negative evaluation and social avoidance [88]. Oxytocin has been shown to enhance social approach behaviors and decrease social threat processing in individuals with SAD [89].

Postpartum Depression (PPD): Oxytocin has been investigated as a therapeutic agent for postpartum depression, a mood disorder that affects some women after childbirth. Studies have indicated that intranasal oxytocin administration can alleviate depressive symptoms and improve maternal-infant bonding [90]. Oxytocin may enhance positive affect and reduce stress responses in postpartum women, contributing to overall well-being [91].

Schizophrenia: Oxytocin has shown potential as an adjunctive treatment for schizophrenia, a complex psychiatric disorder characterized by social impairments and cognitive deficits. Clinical trials have reported that oxytocin administration improves social cognition, including emotion recognition and theory of mind, in individuals with schizophrenia [92]. Oxytocin treatment has also been associated with reduced negative symptoms and improved social functioning [93]. Methamphetamine Addiction: Preclinical studies suggest a potential role for oxytocin in treating methamphetamine addiction, particularly after early life stress [94].

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