Oxytocin: From milk ejection to maladaptation in stress response and psychiatric disorders. A psychoneuroendocrine perspective

Ocytocine : de l’éjection de lait à la réponse inadaptée au stress et aux troubles psychiatriques. Perspective psychoneuroendocrinienne

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Résumé

L’ocytocine est impliquée dans la réponse au stress et le comportement social. La contribution relative de l’ocytocine au contrôle de la sécrétion d’ACTH pourrait avoir d’importantes répercussions dans les conditions physiologiques et pathologiques liées à l’axe hypothalamo-hypophyso-surrénalien. L’ocytocine est également liée au comportement affiliatif, sexuel, à la formation du lien mère–enfant, à l’anxiété, l’humeur, l’appétit et la mémoire. De nombreux troubles psychiatriques sont fortement influencés par des variables sociales, comme les attaques de panique, la dépression et les troubles de santé mentale. L’ocytocine a aussi montré des propriétés anxiolytiques, analgésiques et sédatives. Cet article synthétise les données actuelles de la littérature et les intrications entre l’ocytocine, la réponse au stress, les effets comportementaux, les troubles psychiatriques et les perspectives thérapeutiques.

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Mots clés : Ocytocine ; Anxiété ; Comportement social ; Dépression majeure

Abstract

Oxytocin (OT) is implicated in stress reduction as well as in social behavior. It inhibits the stress-induced activity of the hypothalamic-pituitary adrenal axis responsiveness. OT is involved in social affiliation, sexual and maternal-infant binding, anxiety, mood, feeding control and memory. Several lines of evidence suggest a role of OT in psychiatric disorders. Various psychiatric disorders are strongly influenced by social variables, such as panic attacks, depression and early childhood autism, and seem to exhibit a particularly close connection with the brain dynamics that underlie social emotions. This paper proposes an overview of OT in psychiatric disorders through the links with the stress response and prosocial behavior.

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Keywords: Oxytocin; Anxiety; Affiliative behavior; Major depression

1. Introduction

Homologs of oxytocin (OT) and vasopressin (AVP) existed at least 700 million years ago, but only recently have scientists begun to dissect the roles of OT, AVP, and their related receptors in human social behavior [1]. In mammals, they are produced primarily within hypothalamic brain regions and then are shuttled to the pituitary for peripheral release or projected to various brain regions. OT and AVP play a developmental role in the regulation of the hypothalamic-pituitary adrenal (HPA) axis and could directly or indirectly influence emotioanlity or social behaviors [2].

Central effects of OT include an involvement in social affiliation, sexual and maternal-infant binding, anxiety, mood, feeding control and memory [3]. Intracerebral OT inhibits the stress-induced activity of the hypothalamic-pituitary adrenal axis responsiveness and the activity of the amygdala in the modulation of the autonomic fear. Recent studies suggest that in
human, OT modulates social perception; social cognition, and social behavior, thereby possibly promoting social approach and affiliation [4].

Several lines of evidence suggest a role of OT in psychiatric disorders [5]. The pathophysiology of stress-related diseases, including depression and anxiety disorders, is thought to involve both endogenous predisposing factors and a dysregulated response to stress. OT clearly promotes bonding. OT may play an important role in the etiology and treatment of a number of clinical disorders involving social deficits and disrupted attachment, such as panic attacks, depression, and early childhood autism. The supposition is that social bonding ultimately involves the ability of young organisms to experiment separation distress. There is preliminary evidence suggesting that genetic alterations of neuropeptide receptors and developmental challenges (e.g. early adverse experience) interact in the etiology and development of these disorders.

The discovery of the amazing behavioral functions OT regulates makes this neuromodulator/neurotransmitter system of the brain a promising target for psychotherapeutic intervention and treatment of numerous psychiatric illnesses [6]. This paper reviews links between OT, vulnerability to stress, prosocial behavior and psychiatric disorders.

2. Physiological implications

2.1. OT neuroanatomy

OT and vasopressin (AVP) are nonapeptides that are evolutionarily well conserved across phyla. They are synthesized in separate populations of the magnocellular neurons of the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus. Oxytocinergic neurons in the PVN are of two types: the magnocellular and parvocellular neurons. The former projects to the posterior pituitary; the parvocellular neurons, also project to many areas within the brain, including other nuclei within the hypothalamus, the median eminence, the limbic system, the raphe nuclei, the striatum [7]. OT is also produced in peripheral tissues. OT stimulates uterine smooth muscle contraction during labor and milk ejection during lactation (Fig. 1). It is a potent stimulator of spontaneous erection in rats and is involved in ejaculation. OT is also expressed by thymic epithelial and nurse cells of different species and could play a role in developing T cells [8]. Until now, only one OT receptor (OTR) has been identified which is a typical class of G protein-coupled receptor.

OT and OTR expression is usually higher in females. The central roles of OT on behaviors and physiology are strongly dependent on steroid hormones and gender. OT gene promoters contain estrogen-response elements and are stimulated by estrogen and thyroid hormones [9].

2.2. OT and lactation

Evidence the posterior pituitary peptide OT plays a pivotal role in three behaviors of human females in which bonding often occurs (birth, breast-feeding and sexual behavior) initially led to suggestion that OT may regulate aspects of social bonding [10]. The oxytocinergic neurons undergo morphological changes in response to the intense stimulation caused by pregnancy, labor and suckling. Tactile, olfactory, visual and perhaps other types of sensory stimuli contribute to the adaptive changes in mother–child interaction [11]. OT is likely to play a role in the development of the mother’s bond to her fetus [12]. OT levels at early pregnancy and the postpartum period were related to a clearly defined set of maternal bonding behaviors, including gaze, vocalizations, positive affects, and affectionate touch; to attachment related thoughts; and to frequent checking of the infant [13]. Levine et al. [14] have shown an increase in OT levels from early to late pregnancy correlated with higher maternal-fetal bonding. In pregnancy, parturition and lactation, the circadian variation in HPA axis activity is dampened, whereas response to stressors is attenuated. Lactation is a state of HPA axis hyporesponsiveness that is maintained by the suckling of the young [15]. Recently, White-Traut et al. [16] suggested that OT increases in anticipation of breast-feeding and that the release of OT can become conditioned to cues associated with breast-feeding or the infant. Moreover, it seems that a mother’s milk odors relieve pain in her own newborn, but not in other newborns [17].

2.3. OT, stress and anxiety

The inhibitory effect of exogenous OT on ACTH and cortisol release has supported the hypothesis of a reciprocal balance modulation of behavioral and neuroendocrine function by OT [18]. OT has an overall anti-stress effect and it functions to attenuate behavioral and endocrine response to stress [19,3,20]. OT has been shown to inhibit the stress-induced activity of the HPA axis responsiveness (Fig. 2) and pharmacological activation of...
endogenous OT release might be considered as a way of alleviating stress [20]. These effects of OT may be influenced by stress background of the individual as chronic stressor exposure mediated through GR activation can down-regulate the OT system [21]. Intranasal OT was found to reduce endocrine and psychological response to social stress [22]. The neural correlate for the anxiolytic effects of OT has been suspected in limbic areas. OT has been found to attenuate amygdala reactivity to emotional and social stimuli and to reduce brainstem activity [23].

2.4. OT and prosocial behavior

Research in animals has implicated OT in processes of parental, pair, and filial bonding [24,25]. Expression levels and innervation of OT are similar between species, whereas distribution of OT receptor (OTR) is highly variable between species and may explain species differences in social behaviors such as parental care and formation of pair bonds [26,27]. Prairies voles (which exhibits high levels of affiliative behavior) have a high density of OTR in the nucleus accumbens (a brain region associated with reward) whereas montane voles (which exhibit low levels of affiliative behaviors) have virtually none in this site [28].

Little research has addressed the role of OT in human bonding. OT is observed in brain regions implicated in attachment and functions to integrate autonomic states with social behavior. OT is thought to play a special role in the initiation of bonding, possibly by decreasing stress, increasing trust, and integrating psychobiological and physiological states that enable calmness and approach [29]. Selective bonding, including pair bonding and some mother–infant bonding, is hypothesized to result from concurrent neuropeptide modulation of pathways regulating reward and reinforcement and those involved in processing social information [1]. OT has special properties to increase the sensitivity of brain opioid system. Positive social emotions and social bonds are mediated by opioid-based, naturally occurring addictive processes within the brain [30]. Bell et al. [31] have also shown a positive correlation between the reward dependence temperament dimension of the temperament and character inventory (TCI) developed by Cloninger, and plasma OT levels. Recently, Tops et al. [32] have found a positive association between attachment subscale of the reward dependence scale of the TCI and plasma OT levels. These results confirm an association between attachment scores and oxytonnergic function, as was originally suggested by Cloninger [33].

Recent studies suggest that in humans, OT modulates social perception; social cognition, and social behavior, thereby possibly promoting social approach and affiliation [4]. Peripheral OT has been associated with bonding-related factors, such as empathy, closeness, and trust [34] and early parental neglect was found to alter peripheral [35] and CSF OT [36]. OT is also involved in a range of socially related thoughts and behaviors, including partner support [37], and the ability to read the mental states of others [38]. Across pregnancy and the postpartum period, oxytocin may play a role in the emergency of behaviors and mental representations typical of bonding in the human mother [13].

Heinrichs et al. [39] have argued for a biological-evolutionary model that suggest that OT enhances the perception of cues important for social interaction and bonding, while reducing the impact of socially aversive and threatening cues.

3. Clinical implications

Various psychiatric disorders are strongly influenced by social variables. Some such as panic attacks, depression and
early childhood autism, seem especially closely connected to the brain dynamics that underlie social emotions [30]. Abnormal manifestations of social behavior are social withdrawal in depression and decreased social cognition in autism. A number of studies show that the availability of OT is associated with socio-cognitive functioning in autistic spectrum disorder. OT receptor gene might be involved in the development of autism [4].

3.1. Mood disorders

There are speculations that some of the symptoms commonly reported in depression (social withdrawal, reduced appetite, cognitive impairment) may reflect central OT dysfunctions. Depressive episodes are thought to result from interplay of multiple genes interacting with environmental factors, such as stressful life events or social isolation. The few data concerning OT in depression have shown decreased levels of OT [40], but also no difference in a larger group of patients, compared with healthy subjects [41]. Scantamburlo et al. [42] found a negative association between anxiety and OT levels in a small sample of depressive patients. Topps et al. [32] have shown that attachment mediates a negative association between plasma OT and state anxiety. Heim et al. [43] summarized findings of clinical studies conducted on the neuroendocrine consequences of childhood trauma and their relationship with major depression. They suggest that childhood trauma is associated with persistent sensitization of the stress responses as well as altered dynamics of the HPA axis, which in turn are related to symptoms of depression. Genetic dispositions and early-life stress interact in shaping a vulnerable phenotype with change in cortical-limbic-brainstem circuits. Upon stress or trauma, maladaptation in these circuits leads to increased endocrine-autonomic and behavioral-emotional responses. Social support and successful treatment modify the stress response system in different components.

3.2. Anxiety disorders

Recently, Hoge et al. [44] found higher circulating OT levels with greater social dissatisfaction and increased severity among individuals with social anxiety disorder. They hypothesize that patients with social deficits due to anxiety or autism may have higher than normal levels of OT perhaps as a compensatory mechanism in the face of multifunctioning OT receptors. Research has shown that OT plays a key role in promoting positive social cognition over social threat [45]. Guestella et al. [46] argue for a bio-cognitive model of OT emphasizing its biological-evolutionary [39] in promoting processing for positive social-cues and reducing threat when there is opportunity to conceptually process meaning at top-down levels of processing.

3.3. Autism spectrum disorder

While the plasma OT data are consistent with the hypothesis that disruptions in the OT system contribute to the social behavioral phenotype in autism, it is also equally plausible that the differences in OT levels may be the consequence of altered cognitive processing in autistic patients [47]. There is some modest evidence suggesting a possible association of the OTR gene with autism. As OT is critical to social cognition, it is not surprising that polymorphisms in oxytocin receptor gene (OXTR) are also associated with autism in multiple cultural populations [48,49]. A number of studies have emphasized the 3p25 region containing the OXTR as the most promising linkage site for autism spectrum disorder (ASD) [4]. A study with Chinese Han families suggests an association between ASD and two single polymorphisms (rs2254298 and rs53576) [49]. Recently, Gillath et al. [50] showed that these polymorphisms are not correlated with attachment insecurities.

3.4. Therapeutic targets

There is relevance to suggest a role for OT as an endogenous antidepressant/anxiolytic hormone [29,51,23,7]. Emiliano et al. [52] have demonstrated overlap of OT-labelled neurons and serotonin-transporter-labelled fibers in the paraventricular, magnocellular, dorsal and posterior subdivisions of the PVN and provided neuroanatomic support for the idea that SSRI-s therapeutic effects on social affiliation and anxiety may be mediated in part through components of the OT system. It is possible that the efficacy of SSRI-s in restoring interest in social interactions is due, in part, to their actions on the reward circuit via the OT system. A large body of evidence supports the idea that stimulation of OT receptors inhibits HPA axis activation and that OT mediates anxiolytic-like affects after central infusion in rats [53]. Implicit in these results is potential therapeutic opportunity of targeting the central oxytoninergic system in the development of novel anxiolytics for humans [54]. OT has little potential as a therapeutic agent if its route is invasive (e.g. central; intravenous). An alternative is intranasal administration, which presents a viable, non-invasive delivery method. Neuropeptides have been shown to enter the cerebrospinal fluid directly after intranasal administration [55]. Recent work has demonstrated that OT infusion (24 IU) and social support during public speaking reduces stress responses [22]. The oxytocin and dopaminergic systems may act in concert to reduce anxiety in response to social and environmental stressors. OT receptors in the central nucleus of amygdala are tonically activated by dopamine D1 receptors in this nucleus. Meinschmidt and Heim [56] have shown altered central sensitivity to the effects of intranasal OT (24 IU Syntocinon®) after early parental separation and attenuated cortisol decreases in these subjects. Altered central OT sensitivity might interfere with protection against stress, promotion of health, and social adaptation, contributing to individual vulnerability to psychiatric disorders after early social adversity. In ASD, two studies suggest that systemic infusions of OT reduce repetitive behavior in ASD [57] and improve emotion recognition in ASD [58]. Recently, Guastella et al. [46] have shown that the administration of OT given as an adjunct to exposure therapy improves mental representations of self.

Studies on the behavioral effects after systemic administration of OT receptor ago- or antagonist are missing. Preliminary
results support the development of novel therapeutics targeting the central OT system to prevent pathologic effects of early loss and promote resilience against stress [43]. Finally, there are a number of interesting observations from human studies, suggesting an association between plasma OT levels and anxiolytic, antidepressant and as well as antinociceptive actions [59,22,56].

4. Futures directions

Biopsychobiological models have attempted to explain the influence of secure attachment on health in humans via altered stress physiology [38]. Gordon et al. [24] have suggested that one mechanism by which OT buffers stress and depression across lifespan is through its association with the attachment system. Future work focusing on male/female differences or looking at childbirth and lactation history could be done. Neuroendocrine research is needed to elucidate the mode of action of OT, its anti-stress properties, and the interactions with the HPA axis and the monoaminergic system in depression. Future research should further elucidate the neural and molecular basis of increased risk after childhood trauma, and integrate these mechanisms with neuroendocrine features and clinical symptoms. The development of specific radioactive labelling of neuropeptides in positron emission tomography will be needed to understand how OT receptors are mapped in the human brain [4]. The therapeutic potential of manipulating the OT system remains to be explored in clinical trials, and the development of potent, selective agonists that penetrate the blood brain barrier would be an important advancement towards this goal. Future studies should explore other OT polymorphisms and also examine possible interactions of various genes and polymorphisms. Research suggests a modulatory role of OT on amygdala responses to facial expressions. Another interesting study is how far genetic factors, like serotonin transporter-promoter, may influence amygdala volume. With continued investigations, the research may lead to novel pharmacological treatments for stress-related disorders.

Conflicts of interest

No such conflict exists.

References


