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REVIEW

Oxytocin: a therapeutic target for mental disorders

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Abstract We review here that oxytocin (OT) is released into blood and within distinct brain regions in response to stressful and social stimuli, and has been shown to have an antidepressant-like effect in animal studies. Clinical reports suggest OT to be a promising drug for psychiatric diseases such as depression, anxiety disorders, schizophrenia, and autism. OT may also have therapeutic potential in the treatment of major depressive disorders, even though OT administered into blood does not readily cross the blood–brain barrier. Physiological functions such as sexual activity and mating induce the release of OT in the central nervous system. A drug for the treatment of sexual dysfunction, sildenafil, enhances the electrically evoked release of OT from the posterior pituitary. This drug has antidepressant-like effects through activation of an OT signaling pathway. These results suggest that sildenafil may have promise as a potential antidepressant.

Keywords Oxytocin · Depression · Sildenafil · CREB · MAP kinase

Introduction

Oxytocin (OT) is a peptide hormone composed of nine amino acids, synthesized in magnocellular and parvocellular neurons of the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus. OT is an acknowledged hormone for uterine contractions during labor and for milk ejection during lactation in mammals [1–4]. The hormone synthesized in magnocellular neurons is secreted into capillaries in the posterior lobe of the pituitary, whereas the hormone synthesized in parvocellular neurons is transported to various areas of the brain in addition to the pituitary [1]. The OT receptor (OTR), a member of the G protein-coupled receptor family, is expressed widely in the central nervous system (CNS), especially in the ventromedial nucleus of the hypothalamus, the central nucleus of the amygdala, the head of the caudate-putamen and the hippocampus [2, 5]. Therefore, OT acts as a neurotransmitter/neuromodulator to regulate a range of CNS functions in males and females, including emotional [6, 7], parental [8–10], affiliative [11, 12], and sexual [2] behaviors, as well as spatial and social memories [1, 5].

Oxytocin mediates an antidepressant-like effect in male mice, which disappears in OTR knockout (KO) mice [13, 14]. In humans, moreover, there is a significant association between plasma OT levels and major depressive disorders (MDD) [15–17]. A polymorphism in *OTR* is associated with MDD in adolescent girls [18]. These results imply that OT may have therapeutic potential in the treatment of MDD. In fact, clinical studies have shown that nasal administration of OT improves some symptoms of psychiatric diseases such as depression, anxiety disorder, schizophrenia, and autism [17–20]. However, it is difficult to apply OT orally and intravenously because plasma OT does not readily cross the blood–brain barrier (BBB). Recent studies have shown that sexual activity and mating with a female induced the release of OT in the CNS of male rats [21] and that sexual activity and orgasms increase

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plasma OT levels in humans [22]. A drug for the treatment of human sexual dysfunction, sildenafil, enhanced the electrically evoked release of OT from the posterior pituitary of rodents [23]. In this review, we will describe the antidepressant-like effect of OT and the potential of OT as a promising drug for treating mental disorders.

Animal studies of the antidepressant-like effect of OT

A number of animal studies have showed antidepressant-like effects of OT since the first report by Arletti and Bertolini [24]. Both acute and chronic treatment with OT decreased immobility time in the forced swim test (FST) [25, 26]. This antidepressant-like effect was blocked by an OTR antagonist and was absent in OTR KO mice [13, 14, 27]. An antidepressant-like effect of OT was also demonstrated in the tail suspension test [28].

Clinical studies of OT in MDD

Clinical studies have attempted to correlate the levels of OT circulating in plasma with depressive symptomology. Reduced plasma OT concentrations were observed in patients with MDD compared with controls [15, 16]. A similar finding was recently made in a female cohort study of patients with MDD [29, 30]. Moreover, plasma OT concentration during pregnancy is associated with the development of postpartum depression [31].

Sexual activity shows antidepressant-like effects through increases in OT secretion

Oxytocin levels in plasma increase during sexual responses, and nighttime OT levels are significantly lower in patients with MDD. Although sexual activity and mating are accompanied by a high level of arousal, anecdotal and experimental evidence demonstrates that sedation and calmness are common in the post-coital period in humans [22, 32, 33]. Sexual activity and mating in male rats mediated anxiolysis via the release of OT in the CNS, specifically within the PVN [21]. A recent study showed that OT mediated the antidepressant-like effect of sexual activity and mating behavior in male mice [13]. For non-mating behavioral experiments, a male was placed with a female into a cage partitioned by a perforated acrylic wall allowing auditory, visual, and olfactory communication, but not physical contact. The duration of immobility did not differ between non-mating behavior mice and control males placed with another male in the FST apparatus. In contrast, mice showing sexual activity and mating behavior had a significantly reduced duration of immobility at 1 h compared with control males. No reduction in the duration of immobility was seen 24 h after the mating behavior. However, the mice showing long-term mating behavior had a significantly reduced duration of immobility both 1 and 24 h after the termination of cohabitation compared with control mice [13]. In addition to the PVN, other regions of the brain, notably, the hippocampus, amygdala, and spinal cord, release OT to mediate sexual behavior [21]. During sexual arousal, stimulation of the mesolimbic dopamine system via OT released in the hippocampus and amygdala in turn activates incertohypothalamic dopamine fibers innervating the medial preoptic area, SON, and PVN of the hypothalamus [2]. These results suggest that OT mediates the antidepressant-like effect of sexual activity and mating behavior in males (Fig. 1).

Antidepressant-like effect of sildenafil

Sexual dysfunction is one complication associated with depression. Although selective serotonin reuptake inhibitors (SSRIs) are widely used to treat MDD, these drugs have serious side effects including sexual dysfunction [34, 35]. Sildenafil citrate (Viagra®; Pfizer, NY, USA) is a selective inhibitor of the cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) enzyme and is widely used to treat erectile dysfunction [36]. Recent studies have shown that sildenafil modulates neural functions in the CNS, especially OT signaling. For instance, sildenafil enhances the electrically evoked release of OT from the posterior pituitary through cGMP-mediated modulation of K^+ channels in the neurohypophysis [23] and enhances OT expression in the PVN without a sexual

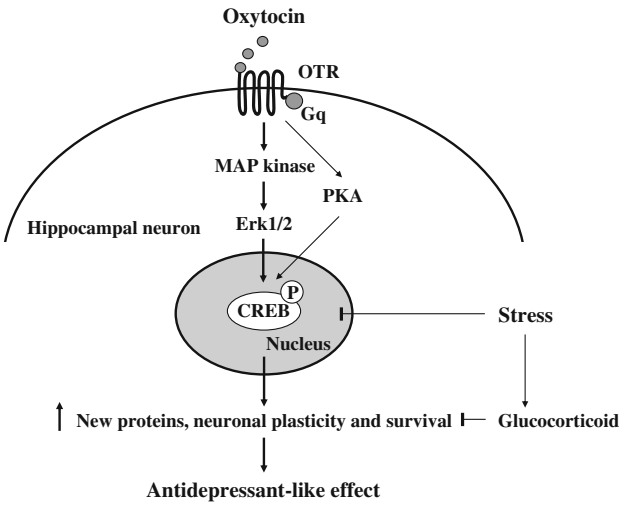

Fig. 1 Possible molecular mechanism underlying the antidepressant-like effect of OT

response [37]. In a previous study, to test its potential as an antidepressant drug without sexual side effects, sildenafil was intraperitoneally administered to male mice and antidepressant-like effects were measured in the FST [14]. Wild-type males exhibited reduced depression-related behavior after administration of sildenafil, but OTR KO males did not. These results suggested that sildenafil has an antidepressant-like effect through the activation of OT signaling, and that it is a promising drug for the treatment of depression.

Molecular mechanism of the antidepressant-like effect of OT and sildenafil

Increases in neurogenesis, neuronal plasticity, and survival through the activation of a MAP kinase cascade and subsequent enhanced phosphorylation of cAMP response element-binding protein (CREB) in the hippocampus have been proposed as common mediators of antidepressant efficacy [38–40]. Moreover, OT induces phosphorylation of CREB through activation of MAP kinase signaling and induces neuronal plasticity in the hippocampi of mice [5]. In rodents, direct hippocampal infusion of brain-derived neurotrophic factor (BDNF) has anxiolytic and antidepressant-like effects [41]. BDNF gene expression was also found to be up-regulated in primary cultured neurons treated with OT by microarray analysis [42]. In addition, stress and corticosterone strongly influence the phosphorylation of CREB in the hippocampus. Chronic stress blocks the expression of BDNF [38]. Blood BDNF levels are decreased in subjects diagnosed with major depression, but antidepressants reverse this neurobiological change [41, 43]. These results suggest that OT has antidepressant-like effects through the activation of a MAP kinase cascade and subsequent induction of BDNF expression (Fig. 1).

Sildenafil induces activation of a MAP kinase cascade and increased the phosphorylation of CREB in the hippocampi of male mice [14]. A MAP kinase inhibitor attenuated the reduction in immobility time induced by sildenafil in male mice. Sildenafil increased the phosphorylation of CREB in the hippocampus compared with vehicle, and an OTR antagonist inhibited sildenafil-induced phosphorylation of CREB. Moreover, sildenafil had no effect on CREB phosphorylation in OTR KO mice. These results show that sildenafil activates MAP kinase signaling and induces subsequent phosphorylation of CREB via an OT-mediated signaling pathway.

Conclusion

Oxytocin has a potent antidepressant effect following its secretion in the CNS, including the hippocampus and amygdala. However, its inability to penetrate the BBB reduces its potential use as a drug for treating MDD. Sildenafil passes the BBB and has an antidepressant-like effect. The results of recent studies suggest that sildenafil has promise as a potential drug for treatment of psychiatric diseases such as depression, anxiety disorders, and schizophrenia. Verification of its safety and effectiveness are needed.

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