Scientific Research Publishing

World Journal of Neuroscience, 2023, 13, 192-209
https://www.scirp.org/journal/wjns
ISSN Online: 2162-2019
ISSN Print: 2162-2000

The Function of Oxytocin in Memory

—A General Review of Oxytocin's Effect on Memory

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How to cite this paper: Gao, F. (2023) The Function of Oxytocin in Memory. *World Journal of Neuroscience*, **13**, 192-209.
https://doi.org/10.4236/wjns.2023.134013

Received: September 19, 2023
Accepted: November 7, 2023
Published: November 10, 2023

Abstract

Introduction: While oxytocin (OT) is widely recognized for its pivotal role in reproductive behavior and the formation of social bonds, there remains a significant gap in our understanding of its potential influence on learning and memory processes, encompassing both social and non-social aspects. Thus this paper serves as an attempt to investigate the comprehensive role of OT in Physiological, Cognitive, and Behavioral processes. **Method:** A comprehensive literature review was conducted to assemble evidence related to the influence of OT on learning and memory. Studies encompassing both social and non-social memory were incorporated into the analysis. Additionally, molecular mechanisms through which OT could potentially impact neuronal activity in the hippocampus and amygdala, consequently affecting learning and memory, were also investigated. **Results:** Our review reveals a spectrum of evidence that both supports and contradicts the theory that OT plays a significant role in social and non-social memory. While certain studies suggest a positive impact of OT on memory, others present findings that argue otherwise. However, multiple potential molecular mechanisms were discovered that may elucidate OT's effects on learning and memory, particularly its potential to modulate neuronal activity in the hippocampus and amygdala. **Conclusion:** Despite the mixed evidence, OT might have a significant role in both social and non-social memory. Identified molecular mechanisms propose potential ways in which OT could influence learning and memory. The key role appears to be the modulation of neuronal activity in the hippocampus and amygdala by OT. Furthermore, it is plausible that OT's function in memory is crucial for the social behaviors previously associated with it. Future research is necessitated to fully unravel the exact mechanisms and implications of OT's role in learning and memory.

Keywords

Oxytocin, Learning and Memory, Long-Term Memory, Short-Term Memory,

Emotion

1. Introduction

Oxytocin (OT) has a fascinating history that dates back to its discovery by Sir Henry Dale in 1909. He found that this hormone, extracted from humans, could contract the uterus of a pregnant cat; he named it Oxytocin, meaning "fast" and "birth" in Greek. In 1953, Vincent du Vigneaud sequenced oxytocin, making it the first peptide hormone to be sequenced and earning him a Nobel Prize [1] [2] [3].

The effects of OT on reproductive and non-reproductive behaviors have been extensively studied. The role of OT in social bonding is particularly intriguing. Studies have shown that the direct application of OT in virgin female mice induces maternal behavior [4] [5], while inhibition through its antagonist abolishes it [6]. Additionally, OT facilitates female lordosis behavior and leads to sexual receptivity in females [7]. The specificity and duration of these effects are still under debate.

Some of the results have been inconsistent. Comparative studies between socially monogamous and non-monogamous voles suggest that OT receptor expression plays a vital role in social attachment and bonding [8]. Recent findings have challenged this notion. A study using CRISPR to generate three distinct null mutations in oxytocin receptors in prairie voles found that they still exhibit social bonding and parental behaviors [9]. These conflicting results suggest a more complicated function of oxytocin and oxytocin receptors in social bonding, which warrants further investigation.

While oxytocin's discovery by Sir Henry Dale in 1909 and Vincent du Vigneaud's sequencing of the hormone in 1953 marked significant milestones in our understanding of its physiological roles, the story of oxytocin is far from complete. In fact, as we delve deeper into the complexities of this remarkable molecule, we encounter a tapestry of intriguing yet sometimes conflicting findings. These inconsistencies and unresolved questions in oxytocin research have sparked ongoing debates in the field.

As oxytocin research continues to evolve, addressing these unresolved questions and reconciling conflicting findings will be crucial to unlocking the full scope of oxytocin's influence on behavior, physiology, and social interactions. It is in these gaps and controversies that the true intricacies of oxytocin's function await discovery, promising not only a deeper understanding of this remarkable hormone but also potential insights into its therapeutic applications.

2. Distribution of Oxytocin Neurons and Receptors

Oxytocin is primarily released by magnocellular neurons of the hypothalamic paraventricular nucleus (PVH) and the supraoptic nucleus (SON) [10]. The

oxytocin receptor, a G protein-coupled receptor [11], is responsible for mediating the effects of oxytocin. OT receptors are largely expressed in the hippocampus and modulate neuronal excitability, network oscillatory activity, synaptic plasticity, and social recognition memory [12]. These findings suggest that oxytocin may play a crucial role in learning and memory and highlight the importance of the hippocampus in these processes. OT has also been reported in astrocytes [13]. Oxytocin receptors have also been found in breast cancer cells and bone cells myoblasts and cardiomyocytes and endothelial cells [14].

3. Oxytocin in Learning and Memory

Research has shown that oxytocin plays a critical role in regulating social memory. Popik (1991) found that social memory in rats was impaired by injection of synthetic oxytocin antagonists (MeCAOT and MePAOT) and facilitated by local injection of oxytocin in a wide range (03 - 1000 pg) within the medial preoptic area of the hypothalamus [15]. In addition, OT gene mutation in mice leads to impaired social memory formation, which could be rescued by oxytocin treatment, indicating that oxytocin is necessary for the normal development of social memory in mice [16]. Moreover, OT improved learning and memory impairment caused by 3-NP (some brief description), induced Huntington's disease [17].

Studies aimed to investigate the effects of OT on Pavlovian fear conditioning showed that OT strengthened conditioning on both the behavioral and neural levels. The subjects exhibited faster task-related responses and enhanced skin conductance responses to fear-associated stimuli in the late phase of conditioning, which was paralleled by heightened activity in cingulate cortex subregions, but no changes in amygdala function were observed. This suggests that oxytocin enables rapid and flexible adaptation to fear signals in social contexts, which could confer evolutionary advantages but may also elevate vulnerability to the pathological sequelae of interpersonal trauma. The study highlights the complex and multifaceted effects of oxytocin on human behavior and the need for further research to fully understand its therapeutic potential [18].

Furthermore, OT has also been suggested to be able to facilitate amygdala-dependent, emotion-related memory. Emotional empathy was greatly increased in response to both positive and negative stimuli after OT treatment. It is also found that the OT-sensitive behavioral components required a normal functional amygdala. Patients with selective bilateral damage to the amygdala were impaired on the OT-sensitive aspects of learning and empathy tasks but performed normally on non socially reinforced learning and cognitive empathy. The previous study provides evidence that OT can facilitate amygdala-dependent, socially reinforced learning and emotional empathy [19]. This emotion-dependent enhancement by OT was found to be true for human subjects, in which participants were more likely to remember emotional faces, particularly for positive faces than negative faces [20]. In addition, studies using emotional stimuli showed an

improvement of long-term memory performance, while studies using non-emotional stimuli found no effect or even worsening in memory [21].

Additionally, studies examined the OT effect on long-term potentiation showed that the oxytocin receptor (OXTR) is crucial for long-term potentiation in social recognition memory; the complete deletion of OXTR caused a defect in forming long-term potentiation at the synapses between the entorhinal cortex and CA2 pyramidal neurons [22]. On the same hand, other studies have supported this evidence by showing that OT enhanced long-term potentiation induction in a dose-dependent manner and functioned as a gate to modulate the establishment of NMDA receptor-dependent LTP at the mitral-to-granule cell synapse in the Accessory Olfactory Bulb (AOB) [23]. Furthermore, study has also shown that OT could reverse the A-beta induced hippocampal long-term potentiation (LTP) impairment, possibly through ERK phosphorylation and Ca+ permeable AMPA receptors [10]. Meanwhile, despite the fact that OT could reverse hippocampal long-term potentiation (LTP) impairment, it could also facilitate longer long-term potentiation (LTP), and this effect is blocked by MAP kinase inhibitors [10].

While there was a wealth of evidence showing that OT improves memory, there were also studies that found that OT impairs memory in certain circumstances. One study found that OT induces a cholinergic hypofunction state, resulting in an impairment of inhibitory avoidance memory formation, a process for which the cholinergic system is crucially necessary. This study investigates the effect of OT and its antagonist on the inhibitory avoidance response of mice and their interaction with the cholinergic system. The study replicates and validates previous results of peripheral administration of OT and anti-oxytocin receptor (AOT) and extends the investigation through central administration. Furthermore, this study finds that central administration of OT impairs and anti-oxytocin receptor (AOT) enhances behavioral performance on an inhibitory avoidance response evaluated 48 hours after training in a dose-dependent manner. Additionally, the study shows that anticholinesterase inhibitors, activation of muscarinic acetylcholine receptors, and increase of evoked acetylcholine release reverse the impairment of retention performance induced by OT [24].

Studies have demonstrated that oxytocin can enhance social memory in rodents, foster rapid adaptation to fear signals in social contexts, and facilitate emotional empathy in humans. Furthermore, oxytocin has been linked to the modulation of long-term potentiation (LTP), a crucial process underlying memory formation, in various brain regions.

Yet, the story is far from straightforward. Oxytocin's effects on memory can be dose-dependent, and the timing of administration relative to memory tasks may yield different outcomes. The relationship between oxytocin and cholinergic systems introduces another layer of complexity, with some studies suggesting impairments in inhibitory avoidance memory under oxytocin administration.

This mixed evidence regarding the effects of oxytocin on memory may be at-

tributed to the diverse contexts and paradigms used in various studies. Studies have examined oxytocin's effects on various types of memory, including social and non-social memory, and used different memory tasks, such as recall, recognition, and learning tasks. Additionally, studies have used different doses and routes of administration of oxytocin, which can affect the magnitude and duration of oxytocin's effects on memory. These factors, in combination with individual differences in participants' neurochemistry, genetics, and behavior, could contribute to the mixed findings regarding the effects of oxytocin on memory [16] [25] [26]. Therefore, it is crucial to carefully consider the specific context and paradigm used in studies when interpreting the effects of oxytocin on memory.

4. Oxytocin and Memory Extinction

Fear and anxiety are natural emotions that can help protect us from danger, but in some cases, they can become overwhelming and interfere with daily life. Pharmacological compounds that can reduce fear and anxiety and promote fear memory extinction have been the focus of numerous studies in recent years. Among these compounds, OT has shown promise as a potential agent in memory consolidation that enhances fear extinction.

Previous studies have suggested that OT could be a promising agent in memory consolidation that enhances fear extinction. Furthermore, changes in endogenous OT signaling may also reduce fear expression in different brain targets, including the dorsal hippocampus and the amygdala [27]. Amir Bazaz and colleagues investigated the release of endogenous OT during fear extinction and the effects of exogenous OT on the hippocampus-medial prefrontal cortex circuit and brain-derived neurotrophic factor (BDNF). They found that exogenous OT in the dorsal hippocampus (dHPC) enhanced fear extinction. They also suggest that activation of the hippocampus-medial prefrontal cortex pathway, consequently leading to the release of BDNF in the infralimbic cortex, which could enhance the effects of OT on fear extinction [28]. Another study examined the modulation effect of OT on the prefrontal cortex and amygdala, they found that oxytocin increased prefrontal cortex signals to conditioned fear in the early phase of extinction and enhance the decline of skin conductance responses in the late phase of extinction. Oxytocin also inhibited amygdala responses in both phases, making it a promising candidate for enhancing extinction-based therapies for anxiety disorders [29].

In an animal behavior study, low-dose oxytocin immediately after the acquisition phase improves memory consolidation and extinction enhances fear extinction in rodents and could lead to impairment of reversal learning when OT receptors are deficient. However, results in humans have been inconsistent, perhaps due to administration design and lack of dosage curve [30]. A human behavior study that investigated the effects of OT on fear conditioning and extinction found that intranasal spray of OT before extinction training resulted in in-

creased fear-potentiated startle responses during the earliest stage of extinction training. However, the OT group showed higher recall of extinction 24 hours later compared to the placebo group. These findings suggest that OT may facilitate fear extinction recall and support further investigation of OT as a potential adjunctive treatment for extinction-based therapies in fear-related disorders [31].

In summary, while the mechanisms behind pharmacological compounds that can reduce fear and anxiety and promote fear memory extinction are not fully understood, oxytocin has shown promise as a potential agent in memory consolidation and fear extinction. The effects of oxytocin have been examined in both animals and humans, with studies showing that it enhances fear extinction and could potentially be used to treat anxiety disorders. Furthermore, the activation of the hippocampus-medial prefrontal cortex pathway and release of brain-derived neurotrophic factor (BDNF) may enhance the effects of oxytocin on fear extinction. While inconsistent results in human studies suggest a need for further investigation into the optimal dosage and administration of oxytocin, the findings suggest that it may be a promising adjunctive treatment for extinction-based therapies in fear-related disorders. Overall, the potential therapeutic effects of oxytocin on fear extinction are exciting and warrant further investigation.

We suspect these inconsistencies could be part due to several intertwined factors. Dosage and method of OT administration, individual variability in response, and the timing of OT administration relative to fear-related procedures all contribute to the variability in outcomes. The complexity of fear and anxiety, influenced by multiple brain regions and neurochemical systems, further complicates the interpretation of results, with interplays between the amygdala, prefrontal cortex, hippocampus, and more. Species differences between rodents and humans, coupled with variations in experimental design and methodological approaches, also add to the challenge of establishing consistent effects.

In conclusion, the study of OT's role in memory consolidation and fear extinction represents a promising avenue for advancing our understanding of fear-related disorders. While challenges and inconsistencies exist, the potential therapeutic applications of OT are encouraging and merit further exploration. Continued research efforts will be vital in uncovering the precise mechanisms and conditions that govern the effects of OT on fear and anxiety, potentially offering novel strategies for addressing these conditions in both animal and human populations.

5. Oxytocin and Neural Activity

The effect of oxytocin on the neuronal activity is mostly studies in rodent models. Oxytocin has been shown to play a crucial role in regulating neuronal activity and synaptic plasticity in the brain [4] [32] [33]. Recent studies have highlighted its involvement in a range of neural processes, such as long-term poten-

tiation [22] [23] [34]. Oxytocin's effects on plasticity have been observed in various brain regions, including the hippocampus, amygdala, and prefrontal cortex, and have been linked to various behavioral outcomes, such as social recognition memory, maternal behavior, and stress resilience. These findings suggest that oxytocin may be a key mediator of experience-dependent plasticity.

Recent findings have shown that oxytocin plays a crucial role in regulating neuronal activity and synaptic plasticity in the hippocampus, particularly in social recognition memory. One study demonstrated that PVN oxytocin neurons promote alloparenting through social transmission, suggesting that oxytocin may be involved in acquiring maternal behaviors in virgin mice [4]. Another study investigated the mechanisms of oxytocin-dependent social deficits and found that Magel2tm1.1Mus-deficient mice showed deficits in social memory, with co-expression of Magel2 and oxytocin receptor in the DG and CA2/CA3 hippocampal regions [32]. Additionally, the study demonstrated that increased activity of GABAergic CA3-pyramidal cells is associated with an increase in the quantity of oxytocin receptor of somatostatin interneurons [32]. Furthermore, oxytocin has been shown to enhance the salience of social stimuli and increase signal-to-noise ratios by modulating spiking and synaptic plasticity [33].

The importance of the oxytocin receptor (OXTR) in social recognition memory (SRM) and long-term potentiation (LTP) has been extensively studied in mice. In male mice, conditional deletion of OXTR from the forebrain or CA2/CA regions led to impaired social recognition memory SRM, while complete deletion of OXTR resulted in a defect in forming LTP. Moreover, OXTR deletion caused a reduced complexity of basal dendritic arbors of CA2 pyramidal neurons, but no alteration in the density of apical dendritic spines. These findings suggest the critical role of OXTR in the CA2/CA3 regions for long-term potentiation LTP in social recognition memory (SRM) [22].

In vitro experiments have shown that oxytocin-perfused hippocampal slices exhibit long-lasting LTP, and *in vivo* injection of oxytocin improved long-term spatial memory. However, this effect could be blocked by oxytocin antagonists, indicating that the positive effects of oxytocin on memory are receptor-mediated [34].

Moreover, a study on female mice revealed that oxytocin enhances the strength of synaptic transmission from mitral to granule cells in the accessory olfactory bulb (AOB) during mating. The researchers found that oxytocin enhanced LTP induction in a dose-dependent manner and modulated the establishment of NMDA receptor-dependent LTP at the mitral-to-granule cell synapse in the AOB. This study highlights the potential therapeutic applications of oxytocin in treating disorders associated with impaired social recognition [23].

Oxytocin also enhanced inhibitory postsynaptic currents in CA1 pyramidal neurons and regulated the excitatory-inhibitory balance in local neuronal networks. These findings suggest that oxytocin receptor signaling may help attenuate neonatal neural death in NHIE patients [35].

Slice recording suggested that activation of oxytocin terminals could activate local GABAergic neurons thus inhibiting CeA output. *In vivo*, study shows that activation of oxytocin neurons decrease freezing behaviors in fear-conditioned rats. Oxytocin neurons could be excitatory due to the nature that it activate GABAergic neurons in CeA [36].

In conclusion, the current state of knowledge underscores the multifaceted impact of OT on neuronal activity and synaptic plasticity, with promising therapeutic potential in various domains. Yet, ongoing research is essential to bridge the gaps in our understanding, particularly regarding the precise mechanisms and clinical applications of OT modulation in both animal and human contexts.

6. Molecular Mechanism Underlying the Function of Oxytocin

Oxytocin has been shown to influence multiple molecular signaling pathways. Oxytocin reduced the intensity of TOPRO-3 (fluorescent dye) staining and delayed the onset time of anoxic depolarization in the hippocampal CA1 region [35]. Oxytocin treatment suppressed stress-induced alternations of phosphorylated protein kinase (pERK), suggesting a potentially therapeutically effective for stress [37]. Meanwhile, oxytocin could reverse the A-beta induced hippocampal LTP impairment, possible through ERK phosphorylation and Ca+ permeable AMPA receptors [10]. Moreover, oxytocin-perfused hippocampal slices exhibit long-lasting LTP and phosphorylation of CREB, which can be blocked by MAP kinase inhibitors [34].

7. Gender Difference and Oxytocin

Anatomically, studies suggest that both oxytocin neurons in both male and female showed highly similar synaptic inputs that are sex-conserved [38]. However, behavioral studies observed sex dimorphism. One study aimed to investigate the effects of oxytocin on social affective perception and learning, specifically looking at how gender may affect these effects. The study involved 47 male and female participants who were randomized to receive either intranasal oxytocin or a placebo. The participants completed two tasks that involved evaluating faces paired with affective stimuli. The first task involved evaluating faces presented with "unseen" affective stimuli, while the second task involved learning affective associations between neutral faces and affective acts through a gossip learning procedure. The participants then rated the faces based on affective dimensions. The study found that gender moderated the effects of oxytocin, with male participants in the oxytocin condition rating faces more negatively than placebo and female participants rating faces more positively in the oxytocin condition than placebo. These findings contribute to a growing body of research that suggests differential effects of oxytocin in men and women [39]. The other study found that oxytocin improved learning and memory impairment caused by 3-NP (in-

duced Huntington's disease). In the presence of pre-natal stress, oxytocin only improved learning and memory impairment caused by 3-NP in female rats [17].

8. Oxytocin and Its Effect on Specific Brain Structures

The presence of oxytocin in different brain areas functions differently. For example, the knockout of oxytocin in the medial amygdala impairs mice's ability to recognize conspecifics [40]. Oxytocin receptor in dentate gyrus and anterior CA2/CA3 of mice are necessary for discrimination of social stimuli [41] [42]. Oxytocin has been proposed to treat anxiety and depression-related mental disorders or abnormal social dysfunction. Several evidences were summarized, OT and anxiolytic and anti-stress effects by acting within the central amygdala (CEA) and paraventricular Hypothalamus (PVH) [43]. OT has effect on fear-related amygdala activity [44]. Oxytocin reduces amygdala activity measured by fMRI [45]. Infusion of oxytocin receptor antagonists would suppress this behavior partner-directed grooming behavior toward familiar conspecifics [46]. A fMRI imaging study found that intranasal administration of oxytocin in female would increase signal in the amygdala, the fusiform gyrus and the superior temporal gyrus [47]. Bilateral microinjection of OT in the CeA produced a significant increase in time spent in the treatment quadrant during the conditioned place preference test, indicating positive reinforcement. In addition, OT significantly increased the time spent in the open arms during the elevated plus maze test, indicating anxiolytic effects. These effects were blocked by prior treatment with the selective OT receptor antagonist. The study suggests that OT has dose-dependent, positive reinforcing, and anxiolytic effects in the CeA, mediated via its receptor [48].

9. Oxytocin and Addition

Due to the early discovery of oxytocin in learning and memory, it is proposed that oxytocin could be involved in addition, based on the conceptualization that addition is pathological learning. Oxytocin could effectively attenuate long-term neuroadaptation related to opiate and psychostimulant addiction [49]. Oxytocin decreases methamphetamine demand and seeing, and these effects depend on OT signaling in the nucleus accumbens for rats [50]. Meanwhile, OT reduced nicotine aversion and increased intake in rats [51], and inhibited the changes induced by oxycodone, and attenuated the rewarding effects induced by oxycodone [52]. These studies have suggested that OT treatment can ameliorate a wide range of drug-induced neurobehavioral changes. In addition, OT not only suppress the reward in the binge stage of drug addiction, it also reduces stress responses and social impairments during withdrawal, thus OT serve as an excellent agent at treating clinical addiction [53].

10. Social Recognition

Oxytocin receptor in dentage gyrus and anterior CA2/CA3 of mice are necessary

for discrimination of social stimuli [41]. Oxytocin could enhance the salience to social stimuli and increase signal-to-noise ratios by modulating spiking and synaptic plasticity [33]. Oxytocin could change emotional response to social cues (e.g., speech) [54]. Subcutaneous injection of low doses of oxytocin in adult male residents facilitated social recognition by showing decreased social investigation behavior when the same juvenile is encountered again. This decreased behavior was not observed when adult male residents were encountering with a novel juvenile [55]. Oxytocin knock-out mice fail to consolidate social recognition, which could be restored using OT treatment. OT given before, not after, social interaction restores social recognition. Using Cfos staining, medial amygdala shows higher activation in wild-type (WT) animal compared with OT knock-out mice. While OT knock-out mice shows higher activation in somatosensory cortex, hippocampus, suggesting differential processing [40].

11. Involvement in General Social Behavior

Oxytocin coordinates the onset of maternal nurturing behavior at parturition and plays a role in mother-infant bonding [8]. Recent studies revealed a general role for oxytocin in modulating affiliative behavior and regulate alloparental care and pair bonding in female voles. In human, oxytocin increase gaze to the eye region of human faces and enhances trust [56], improves empathic accuracy [57]. Disruption of Oxytocin system might lead to pathological social behavior by affecting learning of prosocial outcomes [58]. Human studies start to suggest that variation in genes encoding OT receptors may contribute to variation in human social behavior [59]. Human study, intranasal administration of oxytocin would increase positive communication between heterosexual couples [60]. By using viral-genetic approaches, one study reported that hypothalamic oxytocin neurons are essential regulators of the parental caregiving behavior of male mice. The excitatory neural connections from the lateral hypothalamus to oxytocin neurons were also drastically strengthened when male mice became fathers, suggesting the cell-type specific spasticity of neutral connection within the hypothalamus [61]. Several theories have been proposed to explain the social effect of oxytocin, including prosocial theory, fear/stress theory, and group cooperation theory to explain the effect of oxytocin in human behavioral studies [62].

12. Oxytocin and Emotion, Stress, Anxiety

Oxytocin has been suggested to be able to regulate emotion [63]. Oxytocin has been proposed to treat anxiety and depression related mental disorders or abnormal social dysfunction. OT exhibits anxiolytic and anti-stress effects by acting within CEA and PVH [43] [64] [65]. Oxytocin seems to enhance the buffering effect of social support on stress responsiveness [66]. Recent research suggests that oxytocin, a hormone involved in social bonding, may have anxiolytic effects by reducing anxiety and stress. One study used functional magnetic resonance imaging (fMRI) to investigate the effects of intranasal oxytocin admin-

istration on the amygdala response to facial expressions. The findings showed that oxytocin suppressed the amygdala's response to emotional stimuli, indicating its potential role in regulating emotional processing [67]. Oxytocin could also regulate aggression levels. Mouse with null mutations in the OXTR gene in general shows normal behavior. Female shows deficit in lactation and maternal nurturing. Male shows increased aggression [68].

13. Oxytocin and Autism

Oxytocin and its receptor shows positive effect in autism [69]. Intranasal administration improves emotion recognition in autism children [70]. Meanwhile, genetic analysis revealed that oxytocin receptor gene nucleotide polymorphisms are associated with autism susceptibility [71]. Autistic population responds more strongly to others and exhibit more appropriate social behavior and affect under oxytocin treatment [67] [72].

14. Oxytocin and Energy Metabolism

Oxytocin receptors have been suggested to be involved in energy metabolism [73]. Oxytocin reduced caloric intake with a preferential effect on fat intake and increased levels of the anorexigenic hormone cholecystokinin without affecting appetite or other appetite-regulating hormones [74]. Oxytocin reduced food consumption and time spent eating and increased the latency to the first meal in rats fasted for 21 hr [75].

15. Oxytocin and Stimuli

Several studies suggested that oxytocin could modulate the perception of external sensory stimulation. Oxytocin modulates cortical responses to pup calls specifically in the left auditory cortex [5]. A single dose of intranasally administered oxytocin enhances detection of briefly presented emotional stimuli [76]. Oxytocin treatment enhanced stimulus-induced pupil dilation, consistent with oxytocin enhancement of attention towards socially relevant stimuli [77].

16. Discussion on the Inconsistent Results on Oxytocin

Inconsistent results regarding the oxytocin have been reported. We argue that such inconsistencies can, in part, be explained by variability across experiments in the degree to which potential extraneous confounds have been controlled, the different methods upon which studies assessed cognition, and the extent to which the focus of investigation has been on group-based outcomes [78].

17. Administration Routes of Oxytocin

The intranasal administration is now widely adopted in most of the human study. Evidence shows that intranasal oxytocin: 1) produces no detectable subjective changes in recipients, 2) produces no reliable side-effects, and 3) is not associated with adverse outcomes when delivered for short term use in con-

trolled research settings [79]. One study also suggested that aerosolized (AE) route is the most effective method for increasing central OT concentrations in monkeys, and may also be an effective route, alternative to intranasal, for administering OT to some human populations [80].

18. Oxytocin and Schizophrenia

Oxytocin has been believed to be potentially helpful in terms of treating schizophrenia, but results have been mixed [81]. Different dosages of oxytocin and different administration protocols may lead to divergent results in previous studies, and the lack of clarity regarding oxytocin's therapeutic benefit in schizophrenia warrants the dissemination of negative findings to guide future investigations [82].

Acknowledgements

I would like to express my sincere gratitude to Dr. Guangwei Zhang for his assistance and guidance on my way of writing this paper.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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CCS Concepts

Human-centered computing -> HCI (human-computer interaction) -> User studies -> User-centered design