On the Possibility to Use Oxytocin as A Potential Therapeutic Approach for Memory-Related Psychological Disorders

Shahab A. Zarei [1,2], Carlos Tomaz [3*], Carlos Vasconcelos[4], Maria Clotilde H. Tavares[5], Melika Sarani[6]

1. Institute of Neuroscience, The Center of Excellence in Brain and Intelligence Technology, State Key Laboratory of Neuroscience, Key Laboratory of Primate Neurobiology, Chinese Academy of Sciences, Shanghai, China.
   E-mail address: sh.zarei@sbmu.ac.ir
2. Department of Dana Brain Health Institute, Iranian Neuroscience Society-Fars Chapter, Shiraz, Iran.
3. Laboratory of Neuroscience & Behavior and Graduate Program in Environment, CEUMA University - UniCEUMA, São Luís 65075-120 MA, Brazil. E-mail address: ctomaz@ceuma.br
4. Federal University of Pernambuco, Health Sciences Center, Department of Nutrition, LNED, Recife, PE, Brazil. E-mail address: vasconcelos984@gmail.com
5. Laboratory of Neurosciences and Behavior, Department of Physiological Sciences, Institute of Biology, University of Brasilia, CEP 70910-900 Brasilia, DF, Brazil. E-mail address: mchtavares@gmail.com
6. Modeling in Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran. E-mail address: sh.sarani@yahoo.com

Abstract

Studies have indicated that oxytocin has an influence on cognitive functions such as attention, memory and emotional regulation, particularly in the context of social and communicative behavior. There is a growing interest in the use of oxytocin as a treatment for memory-related psychological disorders and social cognitive disorders. The ease of access to the brain intranasally, numerous positive evidences and widely advertised as a wonder drug, foster this interest. However, recent studies also have shown that the effect of oxytocin could varied, even leading to reverse results. The factors that lead to the effects of oxytocin and its underlying processes on such variables are still uncertain. The inconsistent evidence of general oxytocin effects on memory and neuropsychological conditions is an important issue in considering oxytocin as an adjunct therapy. Therefore, understanding the effects of oxytocin, within various emotional and social context, is important before oxytocin could be efficiently used for improving learning and communication impairment or managing neuropsychological disorders. Here, we intend to review various theories regarding the effect of oxytocin on memory, accompanied by its mechanisms which are proposed in human and animal experiments. Based on evidence from these studies, we explore the potentials and limitations of oxytocin's pharmacotherapeutic applications as a treatment to improve neuropsychological disorders.

Keywords: Oxytocin, Memory, Contextual factor, Psychological disorders, Cognitive function.

Introduction

Oxytocin is labeled as "love hormone" or "cuddle hormone", because it plays a determining role in social bonding, feelings of love and well-being. Oxytocin is a nonapeptide that is mostly produced by the supraoptic and paraventricular nuclei of the hypothalamus. It is store and secrete by the posterior pituitary gland. From the posterior pituitary, it is released into the bloodstream to act as a hormone and influence body functions [1].

For years, oxytocin was known as a crucial factor underlying childbirth, maternal behaviors, and, lactation [2]. As well as peripheral actions, oxytocin also has a neuromodulator and neurotransmitter actions in the brain. It has been observed that endogenous concentrations of oxytocin in the brain are as much as a thousand times greater than peripheral concentrations [3]. The main source of oxytocin in the brain is the dendritic release from hypothalamus into the extracellular space, as well as direct projection from parvocellular neurons in the paraventricular nucleus to other brain areas [4]. Oxytocin receptors are expressed in the spinal cord and many areas of the brain, including amygdala, suprachiasmatic nucleus, hippocampus, striatum, bed nucleus of stria terminalis and brainstem [5], which regulate motivations, emotions, reward processing and support mnemonic and executive functions [6]. Several studies have reported that oxytocin plays a key role in some behaviors, such as increasing of trust [7], empathy [8], sexual arousal [9], social behavior [10], cognitive function [9], modulating stress and metabolic/nutritional homeostasis system [11,12] and also some antisocial states such as fear, aggression, jealous and pride [13–15].

One important area where oxytocin plays a major role is its impact on learning and memory. Memory is a fundamental cognitive function that help people to constantly access relevant information and adjust their behavior appropriately after the encoding of experiences. In the social behavior, memory helps individuals to maintain relevant information in different social situations, and, consequently, adapt to social interactions in the future. Therefore, if oxytocin plays a significant role in human social cognition, it will also affect the encoding of new information [16]. These findings convey the feasibility of using oxytocin as a memory enhancer and potential treatment for memory-related disorder, such as amnesia, Alzheimer's disease, dementia, mild cognitive impairment and so on.

However, existing findings concerning oxytocin effects on memory and suggested mechanisms include numerous contradictions. This is an important issue in considering oxytocin as an adjunct therapy for cognitive deficits, because these disorders might be even exaggerated by using oxytocin. Therefore, understanding all aspects oxytocin' effects on cognitive functions, within various emotional and social context is important, before it can be efficiently used for improving learning and communication impairment or managing neuropsychological disorders.

Here, we compare the results of different healthy and clinical groups of humans, animal studies and also its suggested mechanisms for certifying the role of oxytocin in three hypotheses; Impairing hypothesis, facilitates hypothesis and selective hypothesis. We discuss therapeutic potentials as well as limitations of the (adjunct) use of oxytocin in treatment of neuropsychological disorders, with emphasis in memory.

Impairing Hypothesis

Several studies revealed the negative effects of oxytocin on memory processes. In a preliminary study on participants who performed a neutral verbal task, it was found that exogenous oxytocin had a negative effect on human memory performance in retaining a list of words [17,18]. Administration of high dosages of oxytocin to human subjects also showed that while learning did not appear to be affected, but subsequent recall (recalling 20 nonsense four-letter words and recognition of facial images earlier seen) was impaired [17]. In another study with verbal stimuli, oxytocin decreased memory efficiency for a category of sex- and baby-related phrases. [19].

In a clinical study on post-traumatic stress disorder (PTSD) patients, significant effects of a single dose of oxytocin on PTSD symptoms and on desire for social interaction were found [20]. It was concluded that oxytocin significantly decreased the frequency of recurrent thoughts about the traumatic experience. Mood was also elevated and feelings of anxiety reduced.

With regard to detrimental effects on certain memory-related functions, oxytocin may be engaged in the forgetting of mother-related delivery pain [21].

Animal studies have also shown that oxytocin consumption in inhibitory avoidance testing after exercise could significantly reduce memory efficiency in mice. While using an oxytocin receptor antagonist after practice, the authors observed enhanced memory performance [22]. Oxytocin also had a detrimental effect on the social memory in male rats, so that, rats who received oxytocin, were less likely to recall the mice that they had encountered before [23].

Although, the mechanism of Impairing hypothesis is not fully understood, several studies have indicated that oxytocin decreased the initial storage of information and the amount of storage [24]. In this line, studies also have suggested that reducing the speed and performance in tasks after administration of oxytocin was due to its sedative effects [25,26]. Complementarily, it was proposed that oxytocin is an effective factor in these modifications by reducing the cortisol levels and anxiety in response to physical stress [27]. In humans, the observation of emotional visual stimuli was accompanied by activation of the amygdala, but oxytocin significantly reduced this activation [28] and enhanced information processing in other brain areas [29].

Developmental findings indicate that oxytocin has a physiological effect on mental functions during delivery and breastfeeding, by focusing maternal attention on the maternal-fetal and maternal-infant units. These effects would be achieved by oxytocin to isolate the mother from external stimuli [17].

With regard to these studies, some authors suggested that the detrimental effects of oxytocin on remembering past memories might help the situation for those who had an unpleasant memory of their lives such as social anxiety, post-traumatic stress disorder, and etc. However, there is still an urgency for understanding the exact mechanism and its implementation.

Facilitating Hypothesis

In fact, the above mentioned mechanisms did not cover the results of many other studies describing the role of oxytocin in facilitating recognition, learning, memory, and decision making [6,30]. Thus, in a study on schizophrenia patients, two cognitive tests were applied to test the amnesic effects of oxytocin treatment:

the California Verbal Learning Test and the Letter Number Sequence [31]. Tests were performed at the beginning and after 3 weeks of treatment by oxytocin. No evidence of an amnesic effect was observed. In the oxytocin condition, patients showed even better performance on two subtests. In a related vein, after using oxytocin, the amount of certain personal memory retrieval and its details increased in the autobiographical memory test [32]. Oxytocin has also shown its ability to intensify the men's early memories of their mothers [33].

Various studies have shown that oxytocin has distinct effects on memory performance for social behavior [34]. In particular, intranasal oxytocin administration could enhance recognition memory for faces regardless of emotion expression [35], and this improvement was not correlated to response biases, gender or mood changes [36]. In a clinic study schizophrenic patients showed that oxytocin administration improved emotion recognition (happiness, surprise, fear, sadness, disgust and anger) independent of type of emotion and morphing status [37].

In animal studies, oxytocin has demonstrated facilitatory effects on memory and social recognition. In a research on mice, during their maternity where the level of oxytocin was naturally high, their spatial memory improved significantly [38]. Oxytocin knock-out mice failed to recognize familiar conspecifics after repeated social exposures and social recognition [39]. It is reported that oxytocin was required for the normal development of social memory and the ability to identify a familiar individual in mice [40].

Moreover, it has been reported that oxytocin modulate reactions to fear by increasing social memory recall. Rats that are genetically modified to have a surplus of oxytocin receptors has shown a greater response to fear of a previously conditioned stressor [41].

A dominant mechanism proposed that oxytocin enhanced the salience of emotional and social information of stimuli which led to a faster response, since these signals are especially important for the survival and development of social behavior [42]. A related model suggested that oxytocin increased attention to emotional and social issues [43]. According to this hypothesis, oxytocin, through the dopaminergic mechanism of attention, regulate orientation towards stimuli that are perceived as socially salient [44]. On the other hand, attention to social cues was due to relationship of oxytocinergic circuits with the dopaminergic system. It has also been shown that oxytocin could increase dopaminergic activity in VTA in response to social symptoms [45]. Oxytocin could reduce amygdala activation, but increased functional connectivity between posterior amygdala and superior colliculus to enhance the proportion of the gaze shifts over negative and positive emotions towards the eyes. So, oxytocin may help detect fear or happiness from subtle cues around the eyes [46].

Results of several studies have demonstrated that oxytocin could enhance the social approach, intimacy and bonding by strengthening encoding through the recall of positive social information [47]. In contrary, some studies showed increased memory only for faces with neutral or negative expressions [34].

Intranasal administration of oxytocin rescued stress-induced impairments in long-lasting synaptic plasticity and recognition memory. The authors reported the rescue effect of oxytocin on synaptic dysfunction in hippocampal slices from stressed animals. These findings indicated that posttreatment with oxytocin after experiencing a stressful event may preserve synaptic plasticity and cognition function, suggesting the therapeutic potential of oxytocin for stress-related disorders, including posttraumatic stress disorder [48]. Therefore, a better understanding of the key role of oxytocin on the cognitive functions can provide an

impetus for more successful interventions for learning impairments and communication or management of psychological disorders. For example, using oxytocin for autism spectrum disorders (ASD) to enhance memory performance, attention to emotional and social cues and more attention towards the eyes.

Selective Hypothesis

Based on contradictory findings that highlighting the increased or reduced effects of oxytocin on memory, some studies suggested that oxytocin administration in humans can lead to both improvement or impairment in perception [49] and memory tasks [32,47] depending the cognitive demand. So that, oxytocin could significantly and specifically enhance recognition of happy faces, but not disgust, fear, anger and sadness [36]. In this regard, also, a study was shown that the effects of oxytocin on social stimuli (angry and smile faces) or nonsocial (colored lights) were different. Oxytocin intake could only promote socially reinforced learning but not neutral stimuli [8].

This dual effect of oxytocin also has been debated about inter- and intra-group behaviors, such as cooperation and competition between and within groups. The administration of oxytocin in humans in-group trust and collaboration, defensive and aggression toward competing out-groups [50] as well as human ethnocentrism [51]. In a recent study, functional MRI and measurements of endogenous oxytocin in participants who viewed an ingroup and an outgroup member's suffering were evaluated. It showed that intergroup conflict that experienced by the revenge group is associated with an increased level of oxytocin in saliva. Moreover, the medial prefrontal activity in response to ingroup pain in the revenge group, but not in the control group mediates the association between endogenous oxytocin and the propensity to give painful electrical shocks to outgroup members, regardless of whether or not they were personally involved in the conflict [52].

Oxytocin also modulate rodent and monkeys' performance in memory tasks, and both increased and reduced effects were reported [53–57]. The effects of oxytocin on the perception and evaluation of social stimuli greatly was dependent on the emotional/social valence of stimuli [58] and it is suggested that oxytocin's effect is context-dependently in monkeys [58,59]. In our recent study that associated with the effects of oxytocin on macaque monkeys' memory performance, findings showed that the effect of oxytocin was dependent on the emotional content of stimuli. Thus, the oxytocin increased the adverse effects of negative stimuli on recalling, but, moderated this effect for positive stimuli. The results of our research on monkeys did not support models indicating a general effect of oxytocin in enhancing salience or declining of attention to social stimuli. Instead, our findings showed that the cognitive effects of oxytocin were related to the emotional valence of contextual factors [60]. It proposed that the neuropeptide oxytocin modulates the salience of emotional/social stimuli and consequently influences the processes of perception, attention, and learning which underlie social behavior.

There are few explanatory mechanisms regarding this theory, however, in a study [61], elevated oxytocin levels showed reduced activation in the amygdala during infant laughter. But it enhanced functional connectivity between the amygdala and the orbitofrontal cortex, the hippocampus, the anterior cingulate, the supramarginal gyri, the precuneus and the middle temporal gyrus. Increased functional connectivity between the amygdala and regions involved in emotion regulation will reduce negative emotional arousal

while enhancing the infant laughter salience [61]. It appears that oxytocin has influenced the processing of both positive and negative information differently.

Other Variables

Despite all these results, oxytocin still showed a different effect depending of task demand and individuals [62]. Thus, inconsistencies in oxytocin effects on memory performance could be partly due to the stimuli and type of memory test [19]. In addition, the context- and person-dependent effects of oxytocin also affect the memory performance [63]. Therefore, the contradictory effects of the oxytocin might be due to the individual differences (e.g. different empathy score) and diverse populations (males, females, healthy, clinical, etc.). Studies in humans and other species show that the effects of oxytocin on the perception and assessment of social stimuli depend greatly on the emotional/social valence of stimuli [58,64], and the internal situation (having stress and anxiety) in which the subject encounters the emotional stimuli [65,66]. Several studies showed that female subjects responded differently to oxytocin administration than male. It might be due to sex differences in circulating levels of oxytocin (women tend to have higher levels of oxytocin than men) and due to the regulatory effect of sex hormones on the oxytocinergic system [67]. Since the menstrual cycle can affect the outcome of oxytocin administration, much more oxytocin studies have been conducted with male participants than with females. Nevertheless, the limited female research also showed contradictory findings.

The individual dependent nature of the effects of oxytocin administration has been observed in several studies. For instance, only in people with low subjective socioeconomic status (SES) backgrounds oxytocin boost emotional theory of mind. This shows that individual differences moderate oxytocin's role on social behaviors [68]. The attachment type (dependence, closeness and anxiety) also identified as a major personality regulator of oxytocin effects in humans [33,69–71] and it is confirmed by research regarding the effect of oxytocin on processing new information into memory. In humans, attachment style has been related to individual levels of oxytocin and genetic oxytocin receptor polymorphisms, so it seems to represent an endophenotype that defines the sensitivity of an individual's oxytocin system [44,70]. In fact, oxytocin improved memory accuracy for low-dependence score participants (people who feel insecure depending on others) but decreased memory accuracy for high-dependence score participants (people who feel relaxed depending on others). The authors claimed that oxytocin would have more beneficial effects for the less proficient than those of the more proficient [42]. It is also argued that the positive effects of oxytocin on prosocial behavior were only restricted to persons with supportive family backgrounds [72]. It has been indicated that positive oxytocin effects on neurobiology or behavior are reduced or absent in persons with negative caregiving experiences. Suffering in early life can alter the function of basal oxytocinergic system, and likely involves changes at the level of the oxytocin receptor. Altered receptor density, affinity or function at the level of oxytocin receptor may be linked to experience-dependent methylation level of the oxytocin receptor (OXTR) gene regulating the oxytocin system. In addition, differences in genetic expression can lead to reduced sensitivity to intranasal oxytocin [63]. From these studies, it may be concluded that oxytocin administration does not generate positive effects in individuals who as a consequence of unfavorable early caregiving.

Therefore, the inconsistencies of these results would probably be dependent of additional factors, including gene polymorphism, early life experiences as well as motivational status [73,74]. It showed that OXTR had genetic differences with different effects on individual behavior. The polymorphism of OXTR occurs in three types: GG, AG, AA. A-allele associated with more sensitivity to stress, fewer social skills, aggressive behavior and more mental health issues than the GG-carriers [75]. GG carriers, with their naturally higher levels of oxytocin, empathy and "Reading the Mind in the Eyes" test, better able to distinguish between emotions, more optimism, mastery, and self-esteem, higher in human sociality [76].
In a recent study it has been shown that subjects with the GA genotype have a poorer memory for surprise recognition than subjects with the GG genotype. Interestingly, subjects with the GA genotype showed faster recognition memory for fear than subjects with the GG genotype. This study indicates that polymorphisms may affect memory processes of emotion-recognition and can contribute to a further understanding of social behavior [77]. However, its effect on memory and cognitive functions need more investigations.

Conclusion

Taking into account the above revised studies, we propose that using oxytocin as a memory and cognitive modulator for treatment or adjunct therapy in some neuropsychological situation such as PTSD, amnesia, Alzheimer's disease, dementia and so on, is not far-fetched. The possibility to use oxytocin in the light of its great variability and even contradictory outcomes, showing that its administration must take into account some variables such as arousal-emotional state, past experience, motivation and lifestyle of the participants (their stress level, exercise, smoking food/drink and their sleep pattern). We hope this working hypothesis can generate studies to elucidate the neural mechanisms underlying oxytocin memory/cognitive properties.

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