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Selective amnesic effects of oxytocin on human memory

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Abstract

The neuropeptide oxytocin is essential for mammalian parturition and lactation. Recent animal studies suggest that oxytocin is also implicated in the central nervous control of behavior including learning and memory. There has been little investigation, however, of the impact of oxytocin on human memory. The purpose of this study was to investigate the effect of a single dose of intranasal oxytocin on implicit and explicit memory in humans. In a placebo-controlled, double-blind study, 38 healthy men were randomly assigned to receive intranasal oxytocin (24 IU) or placebo 50 min before the study phase (incidental learning). Memory was measured using three different memory tests: an implicit perceptual test (word stem completion), an implicit conceptual test (category-cued semantic association), and an explicit test (cued recall). Due to the reproductive-biological role of oxytocin and the impact of adequate environmental conditions for the stimulation of behavioral effects of oxytocin known from animal research, we used semantic word stimuli with reproduction-related vs. neutral meaning. Oxytocin significantly impaired recall performance as compared with placebo treatment irrespective of the meaning of words in the cued recall test. In the implicit conceptual test, characterized by a deepened information processing, compared with placebo, oxytocin significantly impaired only the overall generation of associated target words with reproduction relevant meaning, whereas no significant difference between oxytocin and placebo was obtained for neutral words. These findings concur with data from animal research suggesting that central oxytocin selectively influences memory performance depending on the kind of memory test used and, more importantly, the psychobiological relevance of stimuli.

Keywords: Oxytocin; Peptide; Intranasal; Implicit memory; Explicit memory; Amnesic; Learning; Cognition; Reproductive

1. Introduction

Four decades ago, David de Wied [1], one of the pioneers in behavioral neuroscience, showed that in the rat, the neuropeptide oxytocin plays a central role in behavioral regulation in general, and in learning and memory in particular. Subsequently, numerous studies went on to demonstrate that in addition to its most well-known peripheral role in parturition and lactation, oxytocin promotes positive social interaction (e.g., pair bonding, maternal behavior, sexual behavior, social attachment), inhibits stress-responsive neuroendocrine systems (e.g., hypothalamic–pituitary–adrenal axis), and modulates cognitive performance (e.g., learning, memory) [2–14].

Oxytocin belongs to a family of nine-amino-acid peptides that have been identified in all classes of vertebrates and many invertebrate species [15]. Oxytocin and the closely related nonapeptide arginine-vasopressin are the only members of this family of peptides that are identified in mammals. Oxytocin is synthesized in magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus [16,17]. The peptide is processed from its precursor form, together with the carrier protein, along

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the axonal projection to the posterior pituitary, from which it is secreted into the systemic circulation [18]. In addition, oxytocin is widely distributed throughout the central nervous system from smaller parvocellular neurons, influencing many neurobehavioral functions [10,19–21]. Prominent oxytocin receptor binding has been found in various brain regions, in particular the hippocampus and the septum [19,22–27]. These findings suggest that the brain is a target organ for oxytocin and that this peptide may function as a neurotransmitter or neuromodulator in the central nervous system.

The neuropeptides oxytocin and arginine-vasopressin may have opposite roles, the former impairing memory and learning processes, and the latter improving cognitive performance [28,29]. However, recent studies in animals suggest that oxytocin and vasopressin may be differentially involved in cognitive behavioral regulation depending on the behavioral test, the application or endogenous stimulation of the peptide, and the area of the brain under study [30]. Similar to the studies in animals, studies in healthy humans also showed inconsistent effects of oxytocin on memory function. Whereas some studies report impaired memory following oxytocin administration [31,32], others were not able to confirm such memory effects [33–35].

Human memory has been subdivided into two categories, implicit and explicit [36]. Whereas explicit tests require subjects to retrieve previously studied items, implicit tests do not mention the study episode and measure retention indirectly as a facilitation of performance in a seemingly unrelated task. This facilitation is known as priming. Direct tests of memory, such as recall or recognition tasks, are used to measure explicit memory, while indirect tests of memory, such as word stem completion, are used to measure implicit memory. Implicit tests of memory can further be classified as perceptual or conceptual. While the cues in perceptual tests have a perceptual relation with their studied targets (e.g., din- for dinosaur within a word stem completion task), the cues in conceptual tests have a conceptual or semantic relation (e.g., reptiles within a category-cued association task). The distinction between implicit and explicit tests is supported by numerous findings of dissociations between performance under implicit and explicit conditions [36,37]. For example, amnesic patients are severely impaired in explicit tests but not in most of the implicit measures of memory [38].

In the present study, we investigated the effects of oxytocin on implicit and explicit memory functions in healthy men. It should be noted within this context that neuropharmacological research has demonstrated that several pathways to the brain pass the blood–brain barrier, and there is convincing evidence that peptides gain access to the brain after intranasal administration in humans [6,39–43]. In the present study, we therefore used double-blind, placebo-controlled intranasal administration of the neuropeptide to induce central nervous effects. Due to the reproductive role of oxytocin and the impact of adequate environmental conditions for the stimulation of behavioral effects of oxytocin, as known from animal research [12,44–46], we used semantic word stimuli with and without reproduction-related meaning.

2. Methods

2.1. Subjects

A total of 38 healthy men (mean age=23.7 years, S.D.=3.0) were recruited by local advertisements for paid participation in the study. The study was conducted at the University of Trier, Germany. Before entering the study, all subjects underwent a standardized interview to screen out chronic diseases, mental disorders, medication, and drug or alcohol abuse. Subjects were instructed to abstain from food and drink (other than water) for 2 h before they reported to the laboratory, and from alcohol, smoking, and caffeine during the 24 h before the experiment. The study protocol was approved by the institutional ethics committee. All subjects gave written, informed consent prior to participation.

2.2. Procedure

The experimental session consisted of four phases, a study task and three memory tests. Subsequent memory testing was not mentioned at the beginning of the session (incidental learning). Based on random assignment, participants received intranasal oxytocin or placebo 50 min before the study phase (see Substance administration). In the study phase of the experiment, subjects were told that they would see a series of 24 words presented separately by slide projection, which they were to rank on a four-point scale with regard to their frequency in everyday life. They were also informed that erotic pictures of women would be presented in conjunction with the projected words and were asked to rank the degree of eroticism of the pictures on a 10-point scale. Exposure time was 15 s for words and 90 s for pictures, allowing each picture to be presented alone for 30 s, followed by four word slides presented at the bottom of the picture. Visual presentation was followed by memory testing (see Assessment of memory performance). The experimental session lasted for approximately 2.5 h. At the end of the session, participants were debriefed about the purpose of the experiment.

2.3. Substance administration

In a placebo-controlled, double-blind study design, participants received a single dose of 24 IU oxytocin (Syntocinon-Spray, Novartis, Basel, Switzerland) intranasally or placebo. Intranasal administration took place 50 min before the study phase; a dose of 12 IU was sprayed into each nostril (three puffs per nostril, each with 4 IU oxytocin). The methodology of the administration used has been described elsewhere [41]. Intranasal oxytocin is widely prescribed in lactating women and has been used in several experimental studies in humans (e.g., Refs. [6,31,34,47]).

2.4. Stimulus material

A set of 48 common German nouns was selected for study items. One of two lists, each consisting of 24 nouns, was used for the two randomized subgroups. The words in the two lists had an equal number of syllables and were semantically similar (e.g., mother vs. father). As analyses revealed no significant differences between the two randomly assigned word lists, data for statistical analyses were collapsed across lists. Each study list was derived from two semantic categories, 'reproduction' and 'neutral' (12 words each). In order to generate more semantic variance within both categories, the category 'reproduction' consisted of words associated with 'sex' (e.g., orgasm) and 'baby' (e.g., pacifier) (six words each). The category 'neutral' also included words from two subcategories, 'sweets' (e.g., cake) and 'car' (e.g., brake) (six words each). The sets of word categories were selected on the basis of a pilot study with eight male subjects who did not participate in the experiment. Only those words that were correctly assigned to the categories were selected for the final list. The order of word presentation was pseudorandomized with the constraint that there were no more than two consecutive trials of the same category. All word stems consisted of the first two letters of each word. Each word stem was unique within the context of the materials presented and could be completed with at least 8 alternative German nouns in addition to the target. Since there were no significant differences between the two semantic word topics within both word categories, data for statistical analyses were collapsed across the word topics. In order to generate standardized environmental conditions related to the reproductive role of oxytocin (e.g., sexual behavior, pair bonding), as known from animal research (e.g., Refs. [12,44–46]), each word stimulus was projected by slide onto pictures with reproductive significance. Six slides showing erotic stimuli (erotic pictures of women) were presented in random order. From the aforementioned pilot study, pictures were accepted as erotic stimuli if they obtained a score of 8 or more on a 10-point scale. All stimuli were presented separately by slide projection onto a screen 3 m from the subject's eyes.

2.5. Assessment of memory performance

Each participant studied one list of words derived from two semantic categories and performed an implicit perceptual test with word stem completion of studied and nonstudied words. They then performed an implicit conceptual test with a category-cued association task relating to the word categories. Finally, subjects performed a cued recall test with word stems as cues for the recall of studied words.

2.5.1. Implicit perceptual test

Subjects were told that they would be given a list of 48 word stems composed of the first two letters of whole words. The test was introduced as a test of spontaneity; subjects were instructed to complete each stem with the first noun that came to mind. In order to counteract any cognitive strategies, subjects were told that their performance would be timed and that they should neither skip ahead nor return to any item. Proper nouns and foreign words were to be avoided. Of the 48 word stems, 24 referred to words presented in the prior study list, while the other stems referred to the 24 words of the nonstudied list.

2.5.2. Implicit conceptual test

In this category-cued association task, subjects were told that they would see the names of four categories (sweets, car, sex, baby) on a sheet of paper and that they were to write down the first 12 nouns of each category that came to mind. All individuals were shown an example of an appropriate type of test item that had not been presented during the study phase. Categories were equal to the four semantic word fields of the study phase (see above); subjects were shown six nouns from each category of this test at the beginning of the session. As the nonstudied list also contained 24 words with six nouns in each category, the two lists were closely related in terms of construction and semantics, and because the conceptual test was assessed to reveal general semantic associations, statistical analyses on the number of associated words were collapsed across the two item types. Thus, the number of category-cued associated words in this test was at most 48.

2.5.3. Cued recall test

Subjects were given a written list of the 24 two-letter word stems referring to words presented in the prior study list. They were reminded of the study phase at the beginning of the experimental session and were instructed to use the

Table 1
Mean percentages and priming (studied minus nonstudied) of word stems correctly completed under implicit perceptual retrieval instructions

Word category	Item type					
	Studied words		Nonstudied words		Priming score	
	Oxytocin	Placebo	Oxytocin	Placebo	Oxytocin	Placebo
Neutral	13	15	3	10	10	5
Reproduction	18	20	9	8	9	12

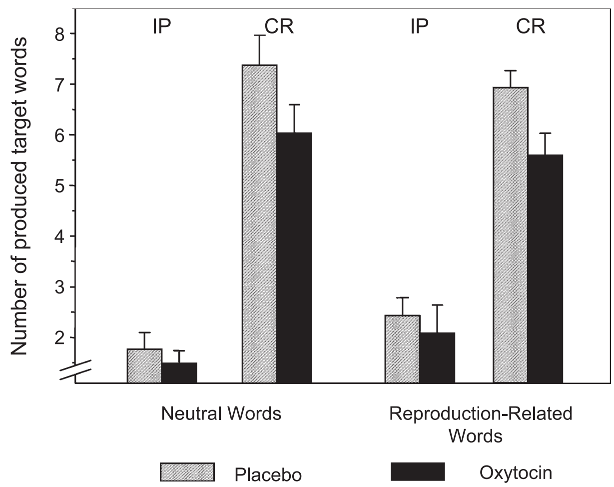

Fig. 1. Mean (±S.E.M.) scores of correctly produced words as responses under implicit perceptual (IP) and cued recall (CR) instructions.

stems as cues to remember the nouns previously studied (explicit memory). They were told not to guess and to be relatively certain that they had studied the item before they wrote down its name.

2.6. Psychometric measures

Psychometric instruments included the German versions of the State-Trait Anxiety Inventory (STAI [48]) and the Self-Rating Depression Scale (SDS [49]). Both questionnaires are standard screening measures for psychopathological symptoms of anxiety and depression. In addition, we used a mood questionnaire that is especially suited for repeated measures of mood, wakefulness, and calmness within several minutes or hours [50]. State anxiety and mood were assessed before substance administration and after memory testing.

2.7. Statistical analyses

Effects of oxytocin on memory performance were evaluated using a 2 (oxytocin vs. placebo as between-subjects factor)×2 (neutral vs. reproduction as within-subjects factor)×2 (studied vs. nonstudied words as within-subjects factor) analysis of variance for the implicit perceptual and the implicit conceptual test. To determine effects of oxytocin in the cued recall test, a 2 (oxytocin vs. placebo as between-subjects factor)×2 (neutral vs. reproduction as within-subjects factor) analysis of variance was

Table 2
Mean percentages of word stems correctly completed under explicit cued recall instructions

Word category	Studied words	
	Oxytocin	Placebo
Neutral	50	62
Reproduction	47	58

conducted. Single time point data were compared using *t*-test. In order to reveal state anxiety and mood before substance administration and after memory testing for both groups, analyses of variance with repeated measurement were calculated. The statistical significance level was set at 5% for two-sided tests.

3. Results

3.1. Description of subjects

As described in Methods, participants were randomly assigned to either the oxytocin or placebo group. Groups did not differ significantly in age and education. In addition, there were no significant differences between the two groups (mean±S.D.) with respect to anxiety (38.10±9.78 vs. 36.33±7.81; $t(36)=-.61$, $p=.55$) or depression (34.00±6.46 vs. 33.10±4.87; $t(36)=-.48$, $p=.64$). Trait anxiety (37.26±8.83) and depression scores (33.58±5.70) of all subjects were within the normal range of the general population. Analysis of variance with repeated measurement revealed no differences between groups in state anxiety levels before substance administration and after memory testing. No significant treatment effects were observed in repeated measurement of mood and activation.

3.2. Memory tests

3.2.1. Implicit perceptual test

Three-way analyses of variance revealed a significant priming effect, indicating that participants provided more previously studied target items than nonstudied target items ($F(1,36)=18.71$, $p<.001$). There were no differences in priming between groups and word categories (neutral and reproduction). The percentages for studied and nonstudied words correctly produced in both groups and for both word categories with the respective priming scores are presented in Table 1. There were no significant interaction effects

Table 3
Mean percentage and priming (studied minus nonstudied) of category-cued words correctly associated under implicit conceptual retrieval instructions

Word category	Item type					
	Studied words		Nonstudied words		Priming score	
	Oxytocin	Placebo	Oxytocin	Placebo	Oxytocin	Placebo
Neutral	38	35	18	19	20	16
Reproduction	25	32	14	22	11	10

between groups, item type (studied vs. nonstudied), and word category. Mean scores of correctly produced studied words under implicit perceptual instructions are depicted in Fig. 1.

3.2.2. Cued recall test

A significant group effect was obtained under cued recall instructions ($F(1,36)=5.78$, $p<.05$), with fewer recalled words in subjects who received oxytocin compared with those who received placebo. There was no significant interaction effect. As shown in Fig. 1, more target words were produced with the same word stems under cued recall instructions than under implicit perceptual retrieval instructions. The percentages of word stems correctly completed in both groups and for both categories are presented in Table 2.

3.2.3. Implicit conceptual test

Significant priming was observed using three-way analyses of variance ($F(1,36)=41.24$, $p<.001$). Priming was comparable for both groups and both word categories. The overall percentages for correctly associated studied and nonstudied words in both groups and for both word categories with the respective priming scores are shown in Table 3.

Remarkably, intranasal administration of oxytocin significantly impaired the overall number of associated target words with reproduction-related meaning compared with placebo, whereas no significant differences between oxytocin and placebo were found regarding neutral words (interaction word category×group: $F(1,36)=7.60$, $p<.01$). Fig. 2 depicts the means and standard errors of correctly associated words under implicit conceptual instructions. Notably, this interaction effect cannot be explained by priming, because oxytocin impaired the overall number of both studied and closely related nonstudied words with reproduction-related meaning.

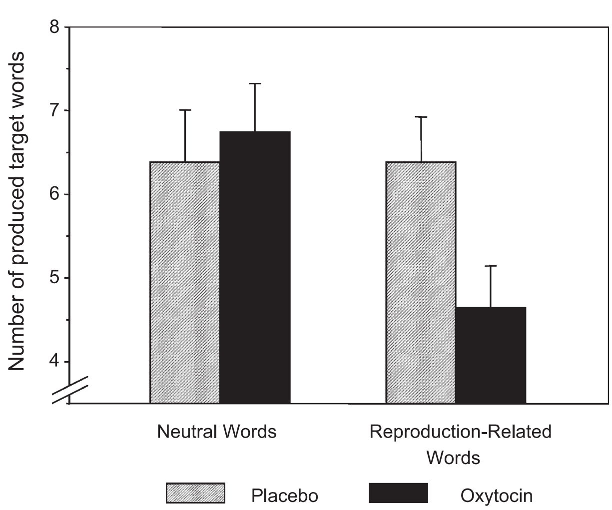

Fig. 2. Mean (±S.E.M.) scores of correctly associated words as responses under category-cued association instructions.

4. Discussion

The effects of intranasally administered oxytocin reported above suggest that central oxytocin in humans selectively influences memory performance depending on the kind of memory test and the psychobiological relevance of stimuli. There was a memory impairing effect on recall performance of studied words in the cued recall test in those who received oxytocin relative to the placebo group. However, the impaired cued recall performance was unrelated to the meaning of words, i.e., neutral and reproduction-related words were similarly affected by oxytocin. In the implicit conceptual test with a category-cued association task relating to distinct semantic word categories, compared to placebo, oxytocin significantly impaired only the overall generation of words with reproduction-related meaning, whereas no significant difference between oxytocin and placebo was revealed for neutral words. These findings lead to the conclusion that intranasal oxytocin selectively impairs semantic implicit memory depending on the meaning of words when examined in a test that requires a heightened depth of processing. As central nervous effects of oxytocin vary depending on the type of memory testing but anxiety, mood, and activation were not significantly influenced, there is no support for attributing the cognitive effect of the neuropeptide to substance-related decreased vigor and vigilance as speculated in previous studies (e.g., Ref. [31]). Furthermore, due to intact priming measures, oxytocin seems to affect memory retrieval, rather than the learning of reproduction-related words.

The present data support and extend previous findings regarding cognitive effects of oxytocin in animal research. Numerous studies in rodents demonstrated impairing effects on memory processes (e.g., Refs. [8,51,52]). Besides studies using intracerebroventricular administration of oxytocin, studies on endogenous oxytocin showed improving effects on consolidation and retrieval processes using antioxytocin serum [29]. On the other hand, oxytocin seems to specifically improve spatial memory during motherhood in mice [53]. Summing up these data, recent studies in animals show that oxytocin may be differentially involved in memory performance depending on the behavioral test, the application or endogenous stimulation of the peptide, and the area of the brain under study [30]. In addition, the cognitive effects of oxytocin seem to be dose- and time-dependent [51].

Whereas the effects of oxytocin on memory have been investigated very actively in animals, research in humans remains relatively limited. Moreover, the small number of studies that were carried out in humans reported inconsistent findings on the effects of oxytocin on human memory. Ferrier et al. [32] found a memory impairing effect of intranasal oxytocin in a small sample of four men and two women. In addition, Bruins et al. [31] reported attenuated memory functions from intranasal oxytocin, but used different memory tests to those implemented by Ferrier et al. [32]. Other studies using intravenously injected or intranasally administered oxytocin were not able to show any memory effects [33–35]. Overall, the few available studies are difficult to compare given the variety of the experimental methods, including differences in stimulus material, memory testing or dose, route, and timing of substance administration (for review, see Refs. [28,41]). In the present study, we therefore administered oxytocin intranasally in order for it to directly enter the cerebrospinal fluid, bypassing the bloodstream [39–41]. By using a battery of different memory tests in our study, including implicit and explicit memory, we circumvented the limitations of unidimensional memory measurement. Furthermore, this is the first study to consider the prominent role of specific environmental stimulation in triggering behavioral effects of oxytocin in humans, as known from animal research [12,44–46]. Accordingly, we used reproduction-related and neutral word stimuli projected onto pictures with reproductive significance.

Aside from pharmacological studies on the central mediation of oxytocin in memory functioning using agonists and antagonists, the knowledge of the effects of oxytocin has recently been extended by the development of oxytocin knockout mice [54]. Mice with a null mutation of the oxytocin gene fail to recognize familiar conspecifics after repeated social encounters, whereas olfactory and non-social memory functions appear to be intact. Remarkably, central oxytocin administration into the amygdala of these transgenic mice restores social memory [55]. In accordance with this strong prosocial central effect of oxytocin in animals, we recently demonstrated that intranasal oxytocin in men significantly enhances the buffering effect of social support on endocrine and subjective responses to psychosocial stress with increased calmness and decreased cortisol levels and anxiety [6]. These seemingly conflicting findings of the above reported impaired cognitive performance in the presence of improved social memory or social behavior could be related to specific effects of the neuropeptide in distinct brain regions, including different receptor sensitivity, depending on the relevance of environmental characteristics [56]. Future studies in humans and animals should further explore the role of oxytocin for the relationship between social behavior and memory processes.

Clear indications from animal research suggest that intracerebrally released oxytocin is involved in behavioral performance that is cued by olfactory signals and appears to be causally related to reproduction and socio-sexual behavior [2,3,7,44,57–59]. From an evolutionarybiological point of view, reproduction belongs to the basic demands of living systems and olfactory signals are salient stimuli of sexual behavior in many species [60]. It could be possible that a close coupling between olfactory cue acquisition and mating behavior was established during evolution and involved a sharing of the same neuronal circuits including their neurotransmitters or neuromodulators [30]. Thus, one might have expected improved memory performance with regard to reproduction-related stimulus material due to increased biological saliency of sexual stimuli. On the other hand, the amnesic properties of oxytocin may have important value in the context of specific reproductive conditions (e.g., Refs. [8,41]). For example, oxytocin is released not only into the blood but also within the brain during lactation [61,62].

Interestingly, some human studies reported temporary impairment in memory function in women throughout pregnancy and in the postpartum period [63–67]. In light of these findings, short-term amnesic effects of central oxytocin might have important biological functions in the peripartum period by inhibiting acquisition and/or consolidation of aversive (e.g., painful) experiences during labor and by isolating the mother from distracting stimuli in the environment during lactation, which may in turn facilitate the focussing of maternal attention on the interaction between mother and fetus or infant [5]. The effect of oxytocin in reproduction-related memory in men, however, has not yet been investigated. Our findings suggest that a single dose of intranasal oxytocin selectively inhibits the implicit recall of sexual and baby-related word stimuli. The fact that those subjects who received oxytocin displayed a reduced number of studied and matched nonstudied target words with reproductive significance suggests that oxytocin extensively affects both target words and close semantic associations of reproductive stimuli. It might be speculated that there are gender-specific differences in deepened cognitive processing of reproduction-related information, related to the evolutionary role of this information. It is noteworthy that the highest endogenous oxytocin levels are reported at male orgasm in humans [68], and it might be that there is a reduced sociobiological necessity of encoding or retrieval successful reproductive behavior in males.

Considered together, a critical analysis of the current knowledge of the behavioral effects of oxytocin in humans indicates the need for further research on the role of the peptide in interneuronal communication underlying learning and memory. Interestingly, some studies reported alterations in brain oxytocin in degenerative neurologic disorders in which disturbances of memory are a clinical hallmark. For example, Mazurek et al. [69] found increased oxytocin concentrations in postmortem brain tissue from histologically confirmed cases of Alzheimer's disease in the hippocampus and temporal cortex. Although there is most likely no causal relationship between oxytocin and Alzheimer's disease, further studies should explore the role of oxytocin in amnesic disorders.

The findings described here indicate that a single intranasal administration of oxytocin in humans impairs explicit memory irrespective of the content of the words, whereas the neuropeptide selectively impairs semantic association for words with reproduction-related meaning. As these data are suggestive rather than conclusive, additional cross-disciplinary investigations of human memory should use psychological, neuroendocrinological, and neuroimaging methods in order to understand the differential role of central oxytocin depending on the social context and the kind of memory performance.

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