

Learning About Oxytocin: Pharmacologic and Behavioral Issues

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Despite the accumulating evidence suggesting that the neuropeptide oxytocin (OT) plays a role in neuropsychiatric disorders characterized by social dysfunction, the influence of OT on the nonsocial aspects of learning and memory have been less investigated. To foster research in this area, we review the effects of OT on learning and memory in animal models and humans. In healthy animal models, OT improves memory consolidation and extinction, but only if given at a low dose immediately after the acquisition phase. On the contrary, OT effects in healthy humans have been inconsistent; although, in this case, OT was always given before the acquisition phase and no dose-response curves have ever been drawn up. Interestingly, a specific impairment in the reversal of learning has been found in mice devoid of OT receptors and OT has been demonstrated to enhance fear extinction in rodents. All together, these data suggest that OT plays a role in elementary forms of behavioral flexibility and adaptive responses and support its therapeutic potential in neuropsychiatric disorders characterized by cognitive inflexibility and/or impairment (autism, schizophrenia, Alzheimer's disease, Parkinson disease, stroke, posttraumatic stress disorder). Accordingly, OT has been shown to improve cognitive flexibility in OT receptor-deficient mice, and scattered findings indicate that intranasal OT has positive effects on the memory of patients with schizophrenia or posttraumatic stress disorders. Further studies of the therapeutic potential of OT as an enhancer of learning and memory are warranted.

Key Words: Animal models, consolidation, flexibility, learning and memory, neuropeptide, neuropsychiatric disorders, oxytocin

This review will concentrate on aspects of learning and memory other than social behavior and social cognition, because the involvement of oxytocin (OT) in shaping and regulating the social brain have been extensively covered by a number of excellent and exhaustive reviews (1–4). It first reviews experimental data relating to learning and memory paradigms in animal and humans and then summarizes what is known about its neurochemical substrates in rodents. Finally, it discusses a few critical issues in the hope of encouraging the successful therapeutic use of OT in neuropsychiatric disorders.

Oxytocin in Learning and Memory

Animal Studies

Table 1 and Tables S1 and S2 in Supplement 1 provide a comprehensive overview of all of the reviewed papers describing the administration of OT to animal models (mainly rodents, but also birds and molluscs). Table 1 shows the studies reporting enhanced learning and memory (5–10), while Table S1 and Table S2, respectively, in Supplement 1 show the studies reporting impaired learning and memory (6,11–21) or no effect (10,13,15,22–27). Most papers consider the effects of OT on learning and memory in mice and rats, but findings in elderly monkeys indicate that OT (4–128 µg/kg) subcutaneously (SC) administered 30 minutes before the task impaired memory in three of the six but led to subtle but replicable improvements in the number of correct choices in two monkeys (28). It is surprising that there are no data concerning memory (other than social

memory) in prairie and mountain voles (*Microtus ochrogaster*), which are among the most widely used models for investigating the biological roots of mating and other social behaviors (29). Furthermore, although few data are available concerning other species, the findings in birds (pigeons and chicks) and molluscs (*Sepia officinalis*) are in line with those of rodents. These studies have led to the development of a vasopressin (AVP)/OT central memory theory that suggests AVP enhances and OT inhibits memory consolidation and retrieval. However, the exact involvement of these molecules in learning and memory is still very controversial (30), mainly because the experiments have used different doses and administration routes. Furthermore, learning and memory processes involve many distinct phenomena that can be distinguished on the basis of the stimulus (spatial, aversive, or rewarding), context (nonsocial, social), and/or timing (acquisition, consolidation, retention, extinction, recall).

Dosage. As has often been observed in behavioral studies, the dose-response curves of OT's effects have an inverted-U shape. In mice and rats, a moderate OT dose (100–300 ng/kg) impairs passive avoidance, whereas lower (10 or 30 ng/kg) or higher doses (1000 ng/kg) have no effect (13,16). Similarly, the extinction phase of pole-jumping behavior is inhibited by high SC doses of OT (1000–3000 ng per rat) given during consolidation, whereas lower doses (<1000 ng) have no effect or tend to facilitate extinction (6). Oxytocin has a biphasic effect on social behavior: very low peripheral doses (in the pg-ng/kg range) improve social memory but higher (µg-mg/kg) doses disrupt it (31–35). Finally, the intracerebroventricular (ICV) administration of the selective OT agonist [Thr4,Gly7]-oxytocin to *Oxtr*^{+/-} mice improves social recognition deficit at a dose of .0005 ng/mouse, whereas higher doses (.005–.5 ng/mouse) and a lower dose (.00005 ng/mouse) do not (35). The U-shaped, biphasic, or even more complex dose-response curves may be due to various factors. High doses of OT may activate AVP V1a and/or V1b receptors, as observed in *Oxtr*^{-/-} and *Oxtr*^{+/-} mice (36,37), and the release of other neurotransmitter/hormone systems may be modulated. When given before extinction, OT delays fear conditioning extinction in rats in a bimodal manner, depending on the levels of corticosterone released (16), whereas AVP has no significant effect on the corticosterone response to noise stress (38). Finally, some of the studies cited above used very high doses of OT peripherally

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Table 1. Improving Effect of OT on Memory in Different Tasks

Species	Route	Dose	Test	Affected Memory Phase	Reference
Male Mice	SC	.1 ng/kg	Novel object recognition	Consolidation	(5)
Rats	SC	.01 ng	Passive avoidance	Consolidation	(6)
Sepia <i>Officinalis</i>	Peripheral	3000–60000 ng/kg	Passive avoidance	Consolidation	(7)
Chicks	Intracerebral	5 pg–50 ng	Conditioned taste aversion	Consolidation	(8)
Wistar Rats	DSN	.05 ng	Passive avoidance	Consolidation	(9)
Virgin Female Mice	ICV	2 ng for 12 days	Radial maze	Long-term memory	(10)

DSN, dorsal septal nuclei; ICV, intracerebroventricular; OT, oxytocin; SC, subcutaneous.

(Table S1 and Table S2 in Supplement 1) without considering the risk of interfering with overall behavioral performance, whose integrity is essential in all memory paradigms. In this regard, it has been reported that a very high peripheral dose of 3000 ng per rat significantly reduces all measures of general activity (6), as confirmed by our unpublished data indicating that 1 ng per mouse ICV reduces general arousal. The effective dose on any specific behavioral parameter should be experimentally ruled out on the basis of carefully planned dose-response curves.

Administration Routes. Two important issues that need to be clarified is whether peripherally administered OT reaches the brain because of its very limited passage through the blood/brain barrier (BBB) (39), and the brain OT levels required to have a mnemonic effect. Small amounts of OT may cross the BBB (40), and it has been calculated that .002% of SC or intravenous OT reaches the cerebrospinal fluid (CSF) of freely moving rats within 10 minutes of administration. However, after 30 years of research, there is still no irrefutable proof that peripherally administered OT (and related peptides) actually does cross the BBB: for example, there is intense controversy as to whether this is true of intranasally administered OT and AVP, and two papers reported conflicting results in the space of 2 months in 2013 (41,42). However, although the mechanisms by which peripherally administered OT acts within the brain are not known, there is no doubt that central effects are observed after intranasal, SC, and intravenous administration in various animal species. Animal studies of the intranasal route (the preferred route in humans) have only considered social behavior, but it is interesting to note that 25 IU of OT intranasally administered to rhesus macaques increased the frequency of prosocial choices associated with reward to another monkey 2 hours after inhalation (43), and in the same study, CSF OT levels doubled within 35 minutes (43), thus supporting the idea that endogenous OT in the CSF comes from central and not peripheral sources. In prairie voles, the acute effects of intranasal OT resemble those found in many human studies (an increase in prosocial behavior and engagement), but when given for 21 days at three doses (.08, .8 or 8.0 IU/kg), it impaired the formation of pair-bond behavior (44) and this detrimental social consequence persisted far longer than the treatments themselves.

It is very difficult to estimate the brain OT levels required to have an effect on memory. It has been shown that an ICV injection of 1 pg can begin to restore social memory deficit in *Oxt*^{-/-} mice, although better results are obtained using 1 ng (45). Accordingly, a very low SC dose (.1 ng/kg) improves the consolidation of episodic memory in mice engaged in the object recognition task (5). Unfortunately, no data are available concerning OT levels during memory tasks.

Learning Paradigms and Phases of Memory. An important finding is that OT does not appear to play a key role in spatial learning because the acquisition phase of spatial memory is not impaired in *Oxt*^{-/-} mice evaluated using the Morris water or a two-trial Y-maze (46), and *Oxtr*^{-/-} mice and their wild-type littermates have similar spatial memory acquisition rates when performing an appetitive-motivated T-maze task (36). Accordingly, repeated injections of OT (2 ng ICV for 12 days) do not impair short-term memory in virgin female mice undergoing a radial maze task (10). However, in the same experimental setting, OT significantly improves long-term memory, thus suggesting it enhances consolidation, a central attribute of hippocampal function to which OT and AVP may contribute (47). Consolidation is the processes of stabilizing a memory trace after initial acquisition and consists of two specific phases: synaptic consolidation (within the first few hours of learning or encoding) and system consolidation, during which hippocampus-dependent memories become independent of the hippocampus over a period of weeks or years. Retrieval and extinction are two other strictly connected processes associated with consolidation: retrieval is the only way memory can be measured, and extinction is the process by which a conditioned response diminishes over time. To determine whether a drug is involved in consolidation or retrieval, it can be administered before or after different phases of training and/or testing. A careful examination of the few published reports indicates that OT can improve memory but only under certain conditions (Table 1): a low dose given immediately (or at most 1 hour) after the acquisition phase (5,9,10). Similarly, a very low SC OT dose (.1 ng/kg) given to mice performing the object recognition task improves the consolidation of episodic memory, and this effect is antagonized by a selective oxytocin receptor (OTR) antagonist (5). In the wake of findings regarding the enhancing effects of OT-like peptides on memory consolidation, a recent study of *Sepia officinalis*, a cephalopod mollusc known for its remarkable learning abilities, showed that a peripheral injection of cephalotocin (an OT analogue) 1 hour after training facilitated long-term memory in a passive avoidance task (7). Accordingly, intracerebral administration of OT (5 pg–50 ng/animal) to chicks enhances retention in a dose- and time-dependent manner, with 5 ng being the best dose when given 1 minute after acquisition (8).

Other forms of memory are improved by OT if the above parameters are followed. For example, OT enhances memory in the passive avoidance task when injected 30 minutes after learning into the lateral septum of rats but not when injected into other brain areas (Table S3 in Supplement 1) (9). The septum is one major brain structure in which endogenous OT and AVP exert their behavioral effects (30,48): it receives OT and AVP fibers originating from the bed nucleus of the stria terminalis and the

amygdala (49) and contains OT and AVP receptors (50–52). The septal region also contributes to reference memory, particularly the encoding and consolidation of information and/or its subsequent recall (53). Finally, intraseptal OT facilitates social recognition in rats (54). When acutely administered after acquisition, OT facilitates fear extinction in a fear conditioning test (55), although the very high ICV doses used (1 µg per rat) do not exclude the participation of arginine vasopressin receptor 1 subtype a/arginine vasopressin receptor 1 subtype b (V1aR/V1bR).

Response inhibition and extinction learning can also be considered elementary elements of behavioral flexibility, a set of strategies aimed at assuring successful performance in unfixated and challenging environments. Tests of behavioral flexibility in mice are represented by reversal learning and set shifting, in which a previously learned response or rule needs to be suppressed to redirect attention to a previously irrelevant stimulus or stimulus dimension. It is worth noting that *Oxtr*^{-/-} mice are impaired in the reversal phase of an appetitively motivated T-maze test, whereas *Oxtr*^{+/+} (37) or *Oxtr*^{+/-} mice are not (36). Such impairments can be due to perseveration or a reduced ability to acquire or maintain a new strategy. Given the relevance of perseveration and behavioral rigidity to human psychopathology, we believe that the role of OT in behavioral flexibility merits particular attention. It is also worth noting that *Oxtr*^{+/-} mice, which express only 50% of brain OTRs (36), show impaired sociability but normal cognitive flexibility and are not aggressive, thus indicating that the number of OTRs affects these phenotypical manifestations. In addition to OT release, the level of OTR expression in the brain may be a key factor in determining OT-mediated behaviors.

A functional AVP/OT-like signaling system has been found in the nematode *Caenorhabditis elegans*. Mutant worms lacking nematocin (an AVP/OT-related neuropeptide) or its receptor were subjected to an associative learning paradigm using a short-term gustatory plasticity assay (56). The results suggested that defects in the nematocin signaling cascade disrupted gustatory associative learning and the facilitated experience-driven modulation of sodium chloride chemotaxis. Although there are few comparative data, the findings described above indicate that the effects of OT on memory are similar in different species.

Human Studies

In humans, OT has been preferentially administered intranasally, but different studies are difficult to compare for various reasons: the limited dose range, single versus repeated administrations, and the use of different cognitive tasks.

The studies based on nonsocial stimuli (e.g., words) have found a memory-impairing effect or none at all. A very low dose of OT (.038 IU) had inconsistent effects on memory and mood functions in healthy male volunteers when evaluated 1 hour after treatment by means of attentional and visual analogue scales tests (57). Higher and repeated doses (15 IU three times a day for 50 days) did not affect the learning of a word list but impaired subsequent recall in six healthy subjects, a transient effect that was the opposite to that induced by AVP (58). Similar results were obtained in another study (59) in which the subjects received nasal sprays of OT (40 µg, corresponding to 24 IU) 1, 24, or 48 hours before the acquisition phase of a memory test. The impairing effect of OT on the long-term memory of healthy subjects (evaluated by the free recall of verbal memory) has been confirmed by a study in which OT (40 µg) was administered 10 minutes before acquisition (60).

Various memory tests have been carried out in human healthy subjects using social (reproduction-related words associated with gender or faces) or nonsocial stimuli (a list of words, houses, or neutral pictures). The administration of OT 24 IU 40 to 50 minutes before the acquisition phase had no effect (61–63) or impaired (64) the recall of nonsocial stimuli but impaired or improved the recall of social stimuli: this difference could only be partially explained by differences in the types of faces (neutral versus emotional) or objects (houses versus sculptures and landscapes).

Apart from the study using the very low dose of .038 IU (57), none of the human studies have used doses other than the usual 15 to 24 IU, and this has prevented the construction of a dose-response curve. However, as animal studies suggest that the effects of OT are dose-dependent, studies directly comparing more than one dose (and preferably a range of doses) would be useful. Furthermore, as OT improves memory in animals when given within 1 hour of acquisition, it would be interesting to investigate the human effects of OT during the consolidation phase.

One open question is how long brain OT levels remain elevated after intranasal administration. It has been shown that CSF levels of the cognate peptide AVP increase for up to 80 minutes and remain above baseline levels for 100 to 120 minutes (65). However, there are no data concerning OT itself. It is worth noting that no convincing evidence of a direct correlation between central and peripheral OT levels has been reported in humans, which suggests caution when interpreting associations between peripheral levels and psychiatric conditions. Furthermore, the lack in reliability of commercially available methods for OT determination raises serious concerns about their validity (66,67).

Although accumulating evidence suggests that OT plays a role in many neuropsychiatric disorders (particularly those involving social dysfunction, such as autism spectrum disorders, social anxiety disorders, obsessive-compulsive disorders, attachment disorders, depression, and schizophrenia), its therapeutic potential is still intensely debated (68). Cognitive deficits are a prominent and disabling component of schizophrenia, and the efficacy of current pharmacologic treatments is limited. Plasma OT concentrations are lower in schizophrenic patients than in normal subjects and negatively correlate with psychotic symptoms (69,70). The first evidence of the beneficial effect of OT on memory comes from a small group of schizophrenic patients treated with intranasal OT (20 IU) twice a day for 1 week and then with 40 IU twice a day for a further 2 weeks (71), who showed a striking improvement in short-term but not long-term verbal memory as assessed by the California Verbal Learning Test and the Letter Number Sequence. In another study (72), intranasal OT (24 IU) twice daily for 14 days reduced the effects of psychotic symptoms and improved social cognition in schizophrenic patients. However, it is currently impossible to discern how much of the beneficial effect of OT on verbal memory is due to specific procognitive effects and how much is secondary to the OT-induced reduction in the patients' core schizophrenia symptoms. Nevertheless, although the use of different cognitive tests makes it difficult to compare the studies, the positive results appear promising.

Few studies have reported brain OT system alterations in aging subjects or those with degenerative neurological disorders (of which memory disturbances are a clinical hallmark). Studies of rats (73) and monkeys (74) have found an age-related decrease in central OTergic activity, but no human data are available. Postmortem studies of brain tissue taken from elderly subjects

affected by Alzheimer's disease have led to mixed findings of decreased (75), increased (76), or unchanged OTergic activity (77), thus leaving the field open to further investigation.

Oxytocin may have a beneficial effect on posttraumatic stress disorder (PTSD). The memory impairments associated with PTSD may be related to functional and morphological changes in the brain structures involved in episodic memory function, including the frontal cortex, hippocampus, and amygdala (78). An enhancing role of OT in extinction is consistent with the finding that the intranasal administration of OT (48 IU) inhibited memory retrieval in 43 male veterans of the Vietnam war with PTSD (79). A very recent study (80) involved 44 healthy subjects who underwent a conditioned fear acquisition procedure before receiving acute treatment with OT (24 IU); 45 minutes later, they underwent extinction training and they were tested for extinction recall after a further 24 hours. It was found that OT facilitated extinction recall, which supports its potential use as adjunctive treatment to extinction-based therapies for fear-related disorders.

Although preliminary clinical trial results indicate that OT is beneficial in schizophrenic patients, much work is still needed to advance its therapeutic development in other neuropsychiatric or neurological disorders.

The Neurochemical Substrates of OT-Induced Effects on Learning and Memory

Although it has been clearly established that OT plays a role in learning and memory in animal models, the cellular and molecular mechanism(s) underlying its action are much less well known. Oxytocin can influence learning and memory at different times and in different ways (by establishing neural networks during development, by cooperating with classical neurotransmitter systems, and by directly mediating plasticity phenomena in target neurons), and animal studies are beginning to provide some clues concerning these substrates, particularly at neurochemical and electrophysiological levels.

There is virtually no OT immunoreactivity in the developing brain (81), and the first exposure to OT occurs perinatally or postnatally. Interestingly, some evidence indicates that OT plays both neuroprotective and neurodevelopmental roles in the postnatal period. At about the time of delivery, it temporarily switches gamma-aminobutyric acid (GABA) neurotransmission from its excitatory to its inhibitory form, thus potentially protecting hippocampal neurons from anoxic insults (82); this protective effect on immature cultured hippocampal neurons has recently been confirmed by an oxygen/glucose deprivation challenge (83). It has also been elegantly shown that OT triggers the appearance of the coherent activity pattern in the developing hippocampus (84), thus suggesting that it plays a role in the maturation of neuronal microcircuits. Data showing an imbalance in GABA/glutamate synaptic contacts in cultured postnatal hippocampal neurons obtained from *Oxtr*^{-/-} mice (37) also support the possibility that OT plays a role in regulating GABA signaling at the end of the second postnatal week, in concomitance with the final shift of GABA from depolarization to hyperpolarization (85).

The contribution of OT to the formation of new connections and synaptic contacts may also influence learning and memory processes in the mature brain. An OT-induced improvement in hippocampus-dependent plasticity has been described in motherhood (10), and this is in line with accumulating evidence that late pregnant and lactating rats have denser populations of hippocampal dendritic spines than virgins and that maternal

experience alters hippocampal plasticity to ensure the better care of the pups (86). It is also worth mentioning that OT stimulation of neurogenesis has been found in adult rat hippocampus (87). Finally, functional magnetic resonance imaging studies have started to shed light on the OT-induced modulation of functional connectivity in the human brain, as extensively reviewed elsewhere (88).

A number of studies of the effect of OT on basal neurotransmission in adult hippocampus have found an inhibitory action mediated by the activation of GABAergic interneurons (89–92), and a few studies have also found that OT acts on activity-dependent hippocampal synaptic plasticity. In the medial prefrontal cortex, OT converts long-term depression to long-term potentiation (LTP) (93), and in the cornu ammonis 1 (CA1) pyramidal neurons of adult rats, it prolongs the duration of LTP (10,94). Surprisingly, this latter finding was obtained in the dorsal hippocampus of male and female rats aged 4 to 5 weeks, a region in which no OT fibers have been found in adult female rats (95). It can therefore be postulated that OT fibers are present at puberty and then disappear or that it is AVP that physiologically mediates these effects. It is known that AVP plays a role in the hippocampal activity-dependent plasticity mediated by V1aRs and V1bRs (89,96–99), and the use of high concentrations of agonists and antagonists in the above-mentioned studies does not rule out the possibility of overlapping V1aR/V1bR-mediated effects. Further studies are required to assess if OT has a direct effect on the activity-dependent synaptic plasticity involved in LTP and/or long-term depression (the neurobiological substrates of memory), or if it participates in learning and memory processes by acting on other neurotransmitters/neuromodulators.

Critical Issues and Strategies

On the basis of the reviewed literature, it is still too early to draw any definite conclusions concerning the role(s) of OT in regulating cognitive functions such as learning and memory for a number of reasons.

First of all, animal studies indicate that low doses of OT can improve memory in healthy subjects only when given during the first phase of consolidation (within 1 hour), but it has not yet been given to healthy humans during the consolidation phase and so no verification of a possible improving effect is possible.

Second, the cognitive effects of OT follow an inverted U-shaped dose-response curve that is typical of many peptides tested in animals, whereas studies of healthy humans have only tested single doses or a very narrow range of doses chosen on the basis of their ability to improve the recognition memory of faces. Future studies using a wider range of doses could provide more information about optimal OT doses for improving learning and memory.

Third, most human studies have used intranasally administered OT, which is the best noninvasive route for drugs that have poor systemic bioavailability after oral administration. However, nasal sprays are limited in terms of controlling dosing and absorption and consequently drug response (4). Furthermore, on the basis of recent data indicating that the detrimental social consequences of intranasal OT treatment in prairie voles persisted for much longer than the treatments themselves, we believe that caution is required when chronically administering intranasal OT to humans (44). Further animal studies are needed to examine doses, timing of administration, gender-related differences in efficacy, and the developmental timing of OT therapeutics. It is

also worth remembering that interspecies differences in nasal cavity structures can limit the ability to extrapolate findings from animals to humans.

Finally, another very important issue is how OT affects cognition in normal and impaired subjects. Many drugs only enhance cognition in impaired animals and have no measurable effect (or even reduce performance) in normal rodents and nonhuman primates: no effect in a normal animal therefore does not necessarily preclude a beneficial effect in an impaired model (100). Studies of the effects of OT in animal models of neuropsychiatric disorders are urgently needed and could greatly aid the planning of clinical trials to investigate the hormone's potential benefits in humans with psychiatric disorders.

In conclusion, there are the premises for OT to become a successful pharmacologic treatment for patients with selected psychiatric and neurodevelopmental disorders. Learning how OT works in the brain will guide the transfer of its therapeutic potential from the laboratory to the clinic.

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