Differential effects of estrogen on memory processes and learning strategies: A selective review of animal studies

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ABSTRACT

Estrogen has differential effects on learning and memory. The direction of these effects depends on a variety of factors including the type of memory process, task specific demands, dose and time course of treatment. While some processes, including working memory, spatial memory and place learning, are improved in high estrogen conditions, other processes such as amygdala-dependent associative memory, reference memory and response learning are impaired. Furthermore, learning strategy is sensitive to the effects of estrogen. Specifically, high estrogen conditions promote the use of a hippocampus-dependent strategy, while low estrogen levels bias learning towards a response strategy. In humans, the evidence for effects of estrogen on cognitive function is controversial and the mechanisms of action are not fully understood. This review will discuss major findings from animal studies, highlighting the modulatory effects of estrogen on learning and memory, possible neurobiological mechanisms underlying these effects and the implications of these findings for future investigations of the cognitive effects of estrogen in humans.

KEYWORDS

Estrogen, memory, Learning strategies, Hippocampus, Striatum

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INTRODUCTION

Although normally thought to regulate reproductive behaviors, the steroid estrogen also plays a crucial role in learning and memory (*1*). Investigating the effects of estrogen on learning and memory has been motivated by observations of changes in the cognitive performance of female rats during different phases of the estrus cycle (*2, 3*), estrogen induced neuronal alterations in brain regions associated with learning and memory (*4*), and most importantly, epidemiologic observations indicating that estrogen replacement therapy enhances certain cognitive functions and delays the onset of memory disorders in post-menopausal women (*1*). In recent decades, the effects of estrogen on learning and memory have been the subject of extensive investigation. This paper reviews the major findings from animal studies regarding the modulatory role of estrogen in various memory processes, its effects on competing learning strategies and the potential neurobiological mechanisms that underlie these effects.

EFFECTS OF ESTROGEN ON VARIOUS MEMORY PROCESSES

It is generally accepted that different types of memory are mediated by distinct neural systems (i.e., interconnected brain structures). Support for this view comes from human and animal studies which show dissociations between spatial, response, working and reference memory processes following selective lesions to the hippocampus, striatum and the prefrontal cortex, respectively (*5*). Similarly, the steroid estrogen has been shown to modulate different memory processes by differentially affecting distinct brain regions implicated in memory (*6*).

WORKING AND REFERENCE MEMORY

In 1998, Fader *et al* investigated the effects of estrogen on the performance of ovariectomized female rats in the radial arm maze (*7*). In this task the same subset of arms were baited in each trial and the remaining arms always remained unbaited. A working memory error constituted reentry to a baited arm and a reference memory error was committed when the animal entered an arm that was never baited. Half of the animals received estrogen injections that produced circulating levels typical of diestrus, the phase of the estrus cycle in which estrogen level is intermediate. The results showed that the animals receiving estrogen committed significantly fewer working memory errors than those who did not receive estrogen but that estrogen had no significant effect on reference memory. Estrogen-induced improvements in working memory have also been observed in other variations of the radial arm maze tasks (*8, 9*). In contrast, a study by Davis *et al.* showed that high levels of estrogen significantly improve reference memory but have no effect on working memory in the radial arm maze task (*10*). Interestingly, different doses of estrogen were used in these studies. In light of the slight differences in the experimental designs across these studies, it is important to consider whether the effects of estrogen on working and reference memory are dose-dependent.

In 2002, Holmes *et al.* designed an experiment to determine whether variable doses of estrogen result in different effects upon working and reference memory processes (*11*). Ovariectomized female rats were injected with high physiological doses (1.00 μg and 5.00 μg) and low physiological doses (0.32 μg) of estrogen and were tested on the working and reference memory versions of the radial arm maze. The results indicated that high physiological doses of estrogen impaired working memory whereas low physiological doses enhanced working memory. On the other hand, there were no significant differences between the high and low dose groups for reference memory. The evidence demonstrates that estrogen has a dose-dependent influence on working memory but the mechanisms through which different doses modulate this memory process are poorly understood.

ASSOCIATIVE LEARNING AND MEMORY

It has been shown that the amygdala plays a critical role in various forms of associative learning and memory (*12*). Though, only a few studies have investigated the role of estrogen on amygdala-dependent associative memory, the results consistently suggest that estrogen disrupts this type of memory function.

Conditioned place preference, a type of amygdala-mediated associative memory, is adversely affected by high levels of estrogen (*13*). In a study by Galea *et al.*, ovariectomized female rats were trained in a radial arm maze task in which only two non-adjacent arms were open. One of the arms was baited during all training trials and both arms were left unbaited during the test trial. Preference for an arm was determined by the amount of time the rat spent in each arm during the test trial. The results indicated that ovariectomized rats treated with vehicle (i.e., non-estrogen treated group) had a significant preference for the arm that was baited during training trials, while estrogen treated rats showed no preference for either arm. In other words, estrogen-treated rats were impaired in the task.

Contextual fear conditioning is another form of amygdala-dependent memory process. In one study, for example, male rats exhibited faster fear conditioning than female rats (*14*). Thus, it appears that high estrogen conditions disrupt amygdala-mediated memory functions. This view is further supported by reports which demonstrate that estrogen attenuates contextual fear memory in female rats (*15, 16*).

SPATIAL LEARNING AND MEMORY

It is generally accepted that the hippocampus processes spatial and contextual information (*5, 17*). Various lesion and pharmacological treatment studies indicate that this region is critical for spatial learning and memory (*18-21*). The effects of estrogen on spatial memory processes are not fully understood and the results are inconsistent; while some studies report estrogen induced enhancements in spatial memory, others demonstrate the opposite.

Packard *et al.* examined the effects of peripheral and intrahippocampal injection of estrogen on spatial memory in a Morris water maze task (*22*). In this task, a platform is submerged in an opaque liquid so that it is hidden from view. The rat is placed in the maze from different starting positions and must learn the location of the platform using distal cues in the environment (*23*). This experiment, which used ovariectomized female and intact male rats, showed that peripheral and intrahippocampal estrogen injections enhanced memory retention at 24 hours post-training, but only if the injection occurred immediately after training and not after a 2-hour delay. In contrast, other studies using the same task have reported that high circulating levels of estrogen impair spatial learning (*24-27*). It is important to note that in these

studies, levels of circulating estrogen were manipulated before rather than after training. Thus, it is possible that high estrogen conditions impair *performance* but not *acquisition* of the task. Korol and colleagues observed that rats in the water maze with high circulating levels of estrogen have an increased tendency to swim along the walls compared to rats with low levels of circulating estrogen (*25*). This behavior may predispose the animal to use an inefficient search strategy that can result in poor performance on the task. Thus, this impairment in performance may then be falsely interpreted as a disruption in learning.

EFFECTS OF ESTROGEN ON LEARNING STRATEGIES

While studies that manipulate estrogen levels during learning and performance of a task are inconclusive with regards to memory retention and rate of acquisition in certain tasks, they can be effective in determining the influence of estrogen on the learning strategy used to solve a task. Learning the location of an object in a maze may be solved by two different strategies: the spatial strategy involves learning the location of the object in relation to distal cues in the environment and is dependent on the hippocampus, while the response strategy involves learning the location of the object in relation to one's self and is dependent on the function of the striatum (*5*). Learning the place and the response tasks *require* the use of spatial and response strategy respectively.

In a study by Davis and colleagues, performance on the place and response version of the eight-arm radial maze was compared between ovariectomized female rats receiving estrogen replacement (OVX + E) and ovariectomized females without estrogen replacement (OVX) (*10*). Estrogen was administered systemically via 60-day release pellets. Learning rate was considered the number of training days the rat required to reach criterion. The results showed that OVX + E rats acquired the place task significantly faster than the OVX rats. On the other hand, OVX rats required fewer days to learn the response task and showed impairment in learning the place task compared to estrogen-treated rats. These outcomes are in agreement with the observations reported by Korol and colleagues (*28*), and support the hypothesis that hippocampus-dependent learning (spatial learning) is facilitated by high estrogen states, whereas striatum-dependent learning (response learning) is enhanced in low estrogen and impaired in high estrogen conditions.

Further studies have shown that place and response learning are impaired by lesions to the hippocampus and the striatum respectively (*29*). Moreover, compromising hippocampal function promotes response learning, while dysfunction of the striatum facilitates place learning (*30, 31*). These inverse findings suggest that there may be a competitive interaction between the hippocampus and the striatum during learning, such that intact function of one structure somehow obstructs the relative contributions of the other to the task. Similarly, estrogen may modulate the relative contribution of the hippocampus or the striatum to task learning, biasing selection of one strategy over the other (*32*).

In a dual solution T-maze task, which can be solved by a spatial or a response strategy, female rats in proestrus (the estrous cycle phase during which circulating estrogen levels are high) have an increased tendency to use a spatial strategy to solve the task. Conversely, rats in estrus (the low estrogen phase of the cycle) are more likely to use a response strategy. Rats in diestrus (intermediate estrogen phase) show no bias towards either strategy (*33*). These findings support the notion that high levels of estrogen bias learning towards a spatial strategy, whereas low estrogen levels promote the use of response strategy. Further support for this finding comes from a study that used a dual solution version of the water maze task. Similar to previous findings, rats with high circulating estrogen levels exhibited a preference for the spatial strategy whereas, low levels of estrogen promoted the use of the response strategy (*34*).

SITE OF ESTROGEN'S EFFECTS

In the studies discussed above, estrogen administration was manipulated systemically, resulting in a model comparable to intact rats that went through the estrous cycle regularly. Specifically, estrogen was present throughout the nervous system including both the hippocampus and the striatum in all tasks; thus, the exact mechanism by which estrogen affects learning strategies is not clear. One possibility is that estrogen affects only the hippocampus to improve place learning and that impairment in response learning is a consequence of the increased competitive edge of the hippocampus over the striatum. An equally plausible explanation is that estrogen modulates learning through site specific effects: it directly targets the hippocampus and the striatum to improve place learning and impair response learning, respectively (*32*).

A study by Zurkovsky and Brown was conducted to further investigate the mechanism by which estrogen alters place versus response learning. Estrogen was injected bilaterally into the hippocampus or the dorsal striatum of ovariectomized female rats. The animals were trained and tested on the response and the spatial learning version of the Y-maze task. In the response version of the task, the location of the reward changes in each trial and the animal enters the maze from a position such that the reward is always located on its right hand side. In the spatial version of the task, the location of reward is constant in all trials and the animal enters the maze from a different starting position in every trial. Thus, the animal must learn the reward location

relative to distal cues in the room. The results of this experiment demonstrated a simple dissociation: intrahippocampal estrogen infusion only enhanced place learning without affecting response learning, whereas intrastriatal estrogen infusion only impaired response learning and did not influence place learning. The data from this experiment suggest that estrogen modulates response and place learning by directly acting on the striatum and the hippocampus respectively, most likely through independent molecular mechanisms at these brain regions (*29*).

NEUROBIOLOGICAL MECHANISMS UNDERLYING EFFECTS OF ESTROGEN ON LEARNING STRATEGIES

In addition to behavioral observations, neurobiological investigations have attempted to explain the differential effects of estrogen on learning and memory (*6, 35*). It has proven to be a challenge, however, to produce a precise working model of how estrogen interacts with the hippocampus and the striatum to modulate learning strategies. Various neurotransmitters including acetylcholine and dopamine, NMDA receptors and processes involved in synaptic plasticity have been implicated in mediating the effects of estrogen in the brain.

ACETYLCHOLINE

Substantial evidence indicates the important function of the cholinergic system in learning and memory (*36-38*). In 1997, Packard *et al.* observed that memory enhancing effects of estrogen may be blocked by small doses of an acetylcholine receptor antagonist. Furthermore, injections of sub-effective doses of an acetylcholine agonist along with estrogen produce synergistic memory enhancing effects (*39*). The results suggest that estrogen modulates hippocampus-dependent memory processes through interactions with the cholinergic system. Further evidence suggests that administration of estrogen enhances learning-induced acetylcholine release during place tasks and increases acetylcholine levels in ovariectomized rats (*40*). The estrogen-driven increase in acetylcholine reduces the overall transmission of the inhibitory neurotransmitter GABA, which results in reduced inhibition of CA1 pyramidal neurons in the hippocampus (*10*). This reduction in inhibition increases the overall excitability of the region, enhancing the function of the hippocampus which may ultimately result in improvement in place learning (*41*).

NMDA RECEPTOR AND LONG TERM POTENTIATION

In the past two decades numerous studies have proposed that long term potentiation and synaptic plasticity are (amongst) the underlying molecular mechanisms of learning and memory (*42, 43*). Both these mechanisms involve altering synaptic activity: long term potentiation refers to the strengthening of synapses based on recent patterns of activity, and plasticity refers to overall structural and functional changes at the synapses. It has been shown that blocking long term potentiation impairs learning and memory and that this process is dependent on the functional integrity of the N-methyl-D-Aspartate (NMDA) receptors (*44-46*). High estrogen levels in the hippocampus increase NMDA receptor binding density (*47*). Furthermore, estrogen replacement can reverse the reduction in NMDA binding density produced by ovariectomy. Finally, long-term potentiation is strongest during high estrogen states (*48*) and estrogen alleviates detriments in long term potentiation that are caused by NMDA receptor antagonists (*49*). Thus, it appears that high estrogen conditions produce a series of interacting effects that facilitate excitability and synaptic plasticity in the hippocampus, which ultimately enhance hippocampus-dependent learning. In contrast, estrogen in the striatum reduces NMDA receptors binding density which may impair long term potentiation and synaptic plasticity in this structure and ultimately resulting in deficits in response learning (*47*).

DOPAMINE

The mechanisms through which estrogen affects striatum-dependent learning are less understood. The striatum lacks α and β estrogen receptors (*50*), implying that a direct effect via estrogen receptors is unlikely and that other mechanisms must be involved. The most widely reported effect of estrogen on the striatum is by interactions with the dopamine system. Numerous studies have shown that estrogen increases the levels of dopamine in the striatum (*51*). Behavioral findings indicate that intrastriatal administration of amphetamine, a treatment which increases dopamine release, enhances striatum-dependent learning (*52*). Given that estrogen increases dopamine release in the striatum and that dopamine agonists such as amphetamines improve response learning, it is quite puzzling that estrogen has detrimental effects on striatum-dependent learning.

It is likely that other neurotransmitter systems also play a role in mediating the effects of estrogen on the striatum. Acetylcholine is a good candidate since estrogen has been shown to modulate its transmission in the striatum; low levels of estrogen decrease acetylcholine levels by reducing the concentration of the acetylcholine-synthesizing enzyme choline acetyltransferase (*53*). Acetylcholine is used by the tonic (constantly) active striatum interneurons. These interneurons persistently inhibit the dopaminergic cells, resulting in low basal levels of dopamine in the striatum (*10*). Thus, in low estrogen conditions, reduced cholinergic transmission reduces inhibition of dopaminergic neurons resulting in an increased basal levels of dopamine (*54, 55*). So far, it appears that both high and low estrogen states ultimately result in increased dopamine transmission in the striatum. It is important to note however, that high estrogen levels result in an overall increase in tonic basal levels and may not affect the

phasic dopamine release in the striatum (*56*). Phasic dopamine release, characterized by high frequency and transient activity of dopaminergic neurons, results from perception of novel environmental stimuli and is thought to be important for response learning (*10, 57*). Therefore, it is possible that in high estrogen conditions basal dopamine levels are so high that they masks the phasic release of dopamine in the striatum, resulting in impairment of striatum-dependent (response) learning.

DISCUSSION

Several lines of evidence from animal studies indicate that estrogen differentially modulates memory processes. While estrogen improves some processes such as working and spatial memory, it may cause impairment in others such as amygdala-dependent associative memory. The direction of estrogen's effect on these processes is further complicated by variables including dose of treatment and task specific demands such as use of a certain strategy.

Increased estrogen levels promote spatial strategy and impair the use of response strategy. Importantly, relatively low levels of estrogen do the exact opposite, impairing spatial strategy and facilitating the response strategy. Findings from studies of estrogen infusion into the hippocampus and striatum indicate that the effects of estrogen on these structures are direct and site specific. More importantly, the data show that estrogen's effects on place and response learning are independent from each other and that impairment in response learning is not simply a consequence of improved hippocampal function. It is not known, however, whether estrogen deprivation, which improves response learning, acts on the hippocampus and the striatum in a similar direct and site specific manner (*32*). Estrogen differentially affects plastic processes (e.g. receptor binding density, long term potentiation) across neural structures. In the hippocampus, estrogen interacts with the cholinergic system to reduce transmission of GABA and increase excitability of this structure. Furthermore, estrogen increases NMDA receptor binding density which enhances long term potentiation and synaptic plasticity. In the striatum, however, estrogen interacts with the acetylcholine and the dopamine systems to produce a series of effects which result in reduced NMDA binding density and plasticity.

The nature of estrogen's effect on plasticity is not fully understood; the hippocampus contains both α and β estrogen receptors while the striatum does not, suggesting that the effects of estrogen on this structure may be through an indirect mechanism. Despite this, neurons in both structures respond very rapidly to estrogen (*58, 59*), implying non-genomic effects through cytoplasmic signaling pathways following membrane or extracellular receptor activation. Thus, it is unknown whether the effects of estrogen in these brain structures are carried through similar or different receptor or subcellular mechanisms.

The effects of estrogen are made even more complex by the evidence that suggests that duration of estrogen exposure or deprivation, and the age of the animal all play a role in determining the cognitive and neurobiological efficacy of estrogen. In a dual solution task, continuous estrogen administration to young adult female rats for eight weeks failed to produce a bias towards spatial strategy that is seen following a shorter term estrogen regimen (*32*). Long term estrogen deprivation due to ovariectomy was also ineffective in producing a response strategy bias. These findings suggest that effects of estrogen on learning strategy change over time. Differential effects of treatment duration have also been seen in aged rats. Cyclic or short term versus long term estrogen regimens are more effective in stimulating plastic changes (*60*), modulating cholinergic function (*61*) and learning and memory (*62*) in older rats.

In sum, animal studies show that effects of estrogen on learning and memory are extremely complex and that the direction of these effects are dependent on specific variables including memory type, learning strategy, dose and time course of treatment as well as age. The notion that estrogen has distinct effects on different memory processes may provide a different interpretation of the findings by the Women's Health Initiative Memory Study which showed no cognitive improvements, or in some cases impairment, in post-menopausal women taking estrogen (*63*). It is possible that the tests used in these investigations failed to detect task-specific actions of estrogen on cognition known to exist in humans (*64*). Using a more complete battery of neuropsychological tests that are more sensitive to the effects of estrogen may reveal different findings in which both improvements and impairments due to estrogen are observed. In depth investigation of these effects may provide a better framework for understanding individual differences in learning styles and cognitive changes that occur in aging post-menopausal women and foster the development of more effective treatments for aging related memory disorders.

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