Available online at www.sciencedirect.com
SCIENCE DIRECT®
Neurobiology of Learning and Memory 84 (2005) 132–137
Neurobiology of Learning and Memory
www.elsevier.com/locate/ynlme

Differential effects of estrogen on hippocampal- and striatal-dependent learning

D.M. Davis, T.K. Jacobson, S. Aliakbari, S.J.Y. Mizumori *

Department of Psychology, University of Washington, Seattle, WA 98195, USA

Received 31 March 2005; revised 7 June 2005; accepted 9 June 2005

Abstract

Estrogen's role in learning and memory may be to predispose animals to use specific cognitive strategies (Korol & Kolo, 2002). Specifically, estrogen may facilitate hippocampal-dependent learning, while at the same time attenuate striatal-dependent learning. As a stringent test of this hypothesis, place or response learning on an eight-arm radial maze was compared between ovariectomized (OVX) female Long–Evans rats and rats with chronic estrogen replacement (OVX + E; 5 mg 17-β estradiol 60-day release tablet). Reference and working memory errors were monitored separately for both place and response learning tasks. OVX + E rats learned the place task significantly faster than the response task, and faster than OVX rats. OVX rats required fewer days to reach criterion on the response task than OVX + E rats. Estrogen selectively enhanced reference memory performance, but only during place learning. The specific pattern of estrogen effects on learning suggests that future studies include verification of cognitive strategies used by animals.

Keywords: Estrogen; Memory systems; Working memory; Reference memory; Cognitive strategy

1. Introduction

Many studies have investigated the effects of estrogen on an animal's ability to learn and remember (for review, see Dohanich, 2002). While this research has produced somewhat conflicting results, generally speaking, experiments that tested hippocampal (HPC)-dependent memory showed improved performance with estrogen (Gibbs, 1999, 2000; Korol & Kolo, 2002) while experiments that tested striatal (STR)-dependent and amygdala-dependent learning showed deficits (Galea et al., 2001). To account for some of the variation in the reported estrogen effects, however, Korol and Kolo (2002) proposed that estrogen differentially impacts the strategy preference that an animal chooses to solve a task. Daniel and Lee (2004) tested this idea by examining estrogen's effects on strategy use during the acquisition of a nonspatial (i.e., cued) water maze task (Pearce, Roberts, & Good, 1998). Estrogen replacement in ovariectomized rats impaired learning when a landmark cue was used to identify a hidden platform. Probe trials in which the landmark was removed did not affect performance of estrogen-treated animals, yet it disrupted performance in control rats. Therefore, estrogen levels seem to affect the strategy an animal chooses to solve a water maze task, which in turn impacts the learning ability. The present study aimed to provide a more stringent and detailed test of the hypothesis that estrogen differentially impacts HPC- and STR-dependent processes as reflected in the efficient use of different strategies (Korol & Kolo, 2002). Moreover, we extended the original hypothesis by testing whether long-term administration of estrogen results in similar strategy biases as those observed following short-term estrogen treatment (Korol & Kolo, 2002).

* Corresponding author. Fax: +1 206 685 3157.
E-mail address: mizumori@u.washington.edu (S.J.Y. Mizumori).

1074-7427/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.nlm.2005.06.004

2. Methods

Five-month-old females rats (Long–Evans) were handled daily upon arrival. Once it was determined that the animals experienced normal estrous cycles, their food was restricted so that they were at 85% of their ad lib body weights. Then, animals were acclimated to the experimental environment, maze, and the chocolate milk reward. Rats were randomly assigned to either ovariectomized (OVX) or ovariectomized with estrogen replacement (OVX + E) groups. Both groups received bilateral ovariectomies. OVX + E animals received a 0.5 mg 60-day release pellet (IRA) that releases 45–80 pg/ml of estrogen. The remaining OVX animals did not receive estrogen replacement. Animals were given 7–10 days to recover from surgery before training. Vaginal smears were performed following recovery to ensure that ovariectomies and estrogen pellets were working, to sustain either low or high estrogen states (Butcher, Collins, & Fugo, 1973). Also to ensure that the estrogen pellets were working estrogen group's weights were compared following the estrogen manipulation to show that estrogen significantly decreased the OVX + E animals weights ($t(16) = -6.691$, $p < .05$).

All animals, for both tasks, were trained on an eight-arm radial maze that was enclosed by a black curtain. Visual cues (e.g., posters and a broom) were hung in various locations around the maze. Animals to be trained on the HPC-dependent place task were given 3–4 days of pretraining. Pretraining consisted of 15-trials/day in which two randomly selected arms, each day, were made available to the rat: a start and goal arm. The purpose of pretraining was to teach animals the motor skills needed to run on the maze and to teach them to search for a food reward on the maze. The pretraining environment was the same as the testing environment. Cues were left in the room so that when task training began the learning seen could be attributed to learning the task strategy or rules, and not due to familiarity with the cues. Goal locations during pretraining were randomly located across the maze so that animals would not learn to prefer a single location on the maze. Place training began by each rat in the spatial learning group being placed on randomly selected start locations, and then being trained to seek a reward that could be found at a constant goal location (the location varied between rats). Upon arrival at the central platform of the maze, rats selected the goal arm from seven possibilities. Rats were run for 15 trails daily (30 s ITI). Before each day's training animals were given 30-s exposure to the goal location (i.e., placed at the goal location) with a reward to serve as a reminder. A trial began by placing the animal on the maze facing the surrounding curtain, and ended when the animal reached the goal location and began consumption of the reward. Reference memory errors were considered as entries into a non-goal arm. Working memory errors were defined as any re-entry into a previously visited arm within a trial. Animals were run to the criterion of 80% of the trials performed without either type of error. Fig. 1A shows examples of typical trials for this task.

Past studies of response strategy use by rats on a plus-maze typically start rats from one of two locations, from which the rat learns to make either a right or left turn at a choice point to find reward. The common interpretation is that rats trained according to this protocol have learned an egocentric response. It is also possible that the rats learned a condition place strategy such that the start location dictates at which place rewards can be found. To minimize the contribution of a conditional place strategy, we developed a different test of response learning. The (STR-dependent) response task was performed on the same maze as that used to test place learning.

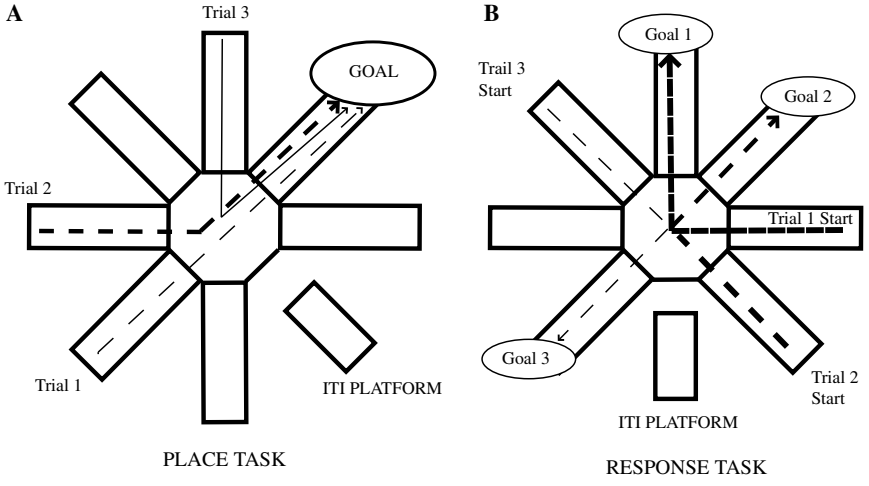

Fig. 1. (A) Three sample trials for an animal performing according to the place task paradigm in which the start location varied, but the goal location was held constant. (B) Three sample trials performed according to the response task paradigm in which a rat learned to turn 90° to the right regardless of the start location.

Also, the same visual cues were present. Training involved first determining the rat's preferred direction of turn on the maze. This was done by exposing an animal to a T-maze arm arrangement and recording which direction (i.e., right or left), the animal first turned. Then, all animals were trained to turn toward their non-preferred direction upon entering the central platform from a start arm. About 3–4 days of pretraining were required before rats readily traversed the maze. During pretraining a different set of two arms was tested each day with the constraint that the two arms formed a right angle. Fifteen trials were tested per day. For response training all seven maze arms were made available from the central platform and each animal ran 15 trials per day with random start locations. The goal location was always 90° to the right (or left for some rats) of the start arm. Trials were separated by a 30 s ITI. To serve as a reminder, at the beginning of each daily session, animals received two forced choice trials on two arms raised to form a 90° in their non-preferred direction. Trial times, trials to criterion, and working and reference memory errors were calculated as described above for the place task. Fig. 1B shows typical trials for the response task.

Since rats were trained to specified criteria, they experienced different numbers of days of training. Therefore, the statistical analyses were performed only for those days during which all animals were undergoing training.

3. Results

Using versions of T-maze training that could only be solved effectively by using a place or response strategy, we confirmed that estrogen has differential and opposite effects on HPC-dependent and STR-dependent learning. Place learning was faster in the OVX + E group, while the response trained OVX animals learned faster (Fig. 2; $t(7) = 6.37$, $p < .05$). On average, OVX + E rats learned the spatial task in 3.2 days, while OVX rats required 10.0 more days of training. In contrast, OVX + E rats required 23.0 days to learn the response task while OVX rats learned it in 10.8 days ($t(7) = 2.58$, $p < .05$). The differential effects of estrogen on place and response learning following long-term estrogen replacement in this study is similar to the differential effects of estrogen following short-term replacement (Korol & Kolo, 2002).

In addition to estrogen effects on select learning systems, we tested the possibility that estrogen preferentially impacts working or reference memory functions within each of the learning systems during acquisition of a task. Working memory errors on the place task significantly declined across Days 1–5, $F(1,4) = 5.67$, $p < .05$ (see Fig. 3). There was no overall effect of estrogen, nor was there an interaction effect of estrogen and day of training (p's > .10, ns). Reference memory errors significantly decreased across Days 1–5, $F(1,4) = 11.70$, $p < .05$.

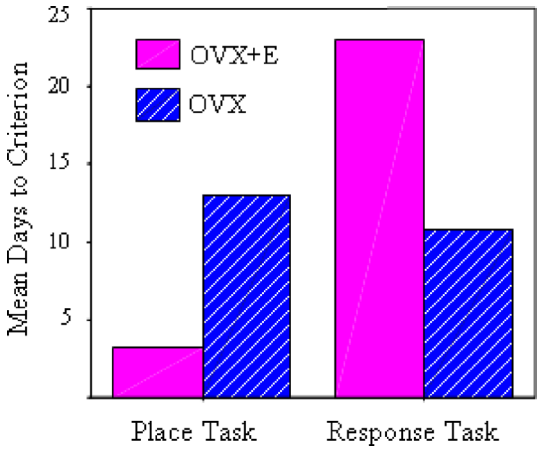

Fig. 2. Number of days to criterion performance for rats trained according to the place and response paradigm. On the place task, OVX + E rats reached criterion in 3.2 days while OVX rats took 13 days. For the response task, OVX animals achieved criterion in 10.8 days. OVE + E rats required significantly more days to reach criterion on the response task (23.0 days).

Furthermore, an interaction effect of estrogen and day of training was observed for reference memory errors, $F(1,4) = 5.57$, $p < .05$. Estrogen reduced the total number of reference (but not working memory) errors, only during place task performance (OVX + E = 66.8 reference memory errors, OVX = 226.0 reference memory errors; $t(7) = 2.52$, $p < .05$). Thus, there may be selective effects of estrogen on different types of memory processing (working vs. reference memory) and this may be conditional depending on the cognitive strategy.

4. Discussion

We tested the hypothesis that elevated estrogen facilitates HPC-dependent learning, while a low estrogen state enhances STR-dependent learning. In contrast to past studies of this issue, we used a variation of the T-maze task that reduces the likelihood that animals solve the response task by using a conditional place strategy. The findings of this study provided support for the original hypothesis: OVX rats treated with estrogen replacement showed enhanced spatial learning and poor response learning relative to OVX rats that were not given estrogen replacement. Moreover, it appears that estrogen has selective enhancing effects on reference memory aspects of spatial processing, but not working memory components. These findings also provide strong verification of the claim that elevated estrogen levels bias rats to use HPC-dependent learning strategies, while low estrogen levels bias rats to use STR-dependent strategies during learning (Korol & Kolo, 2002). A neurobiological explanation of these differential effects on learning has been a challenge given that estrogen receptors are found in both HPC and STR. The following section presents a

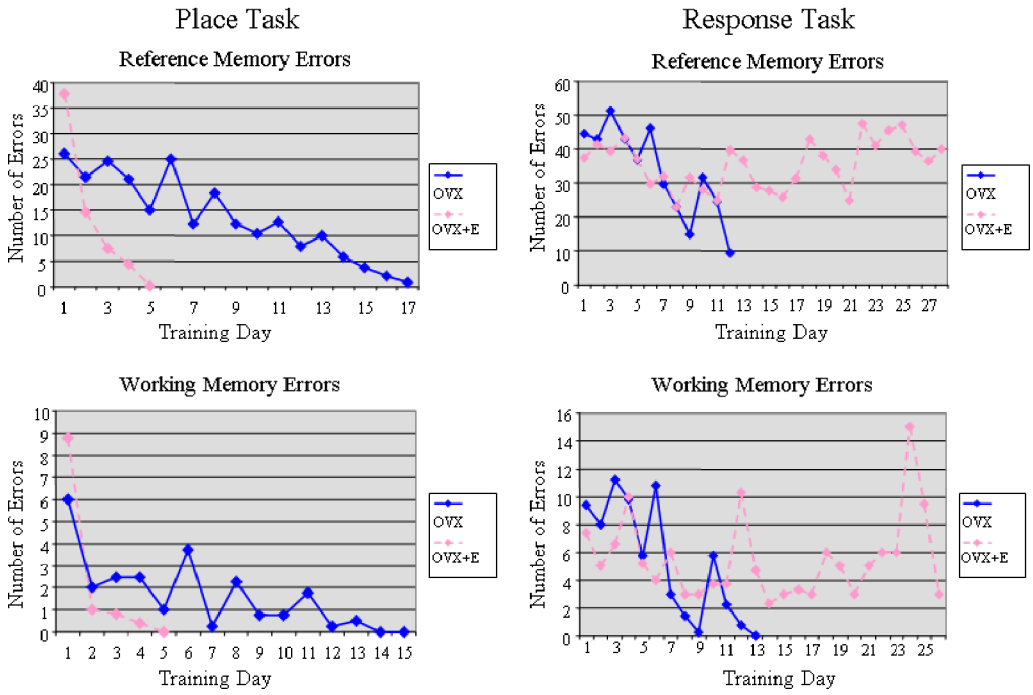

Fig. 3. Summary of working memory (bottom row) and reference memory (top row) errors committed during place task (left) and response task (right) acquisition. Estrogen treatment produced a more rapid reduction of reference, but not working, memory errors during the first 5 days of training, each training day consisting of 15 trials. This pattern was observed only during place learning. Thus, estrogen appears to affect memory systems selectively.

working model that can be used to explain the pattern of behavioral results observed in this study.

4.1. Differential effects of estrogen in hippocampus and striatum

Estrogen increases the synaptic efficiency and output of the HPC for multiple reasons. Estrogen increases the density of synaptic spines in the CA1 region of HPC, and this increase varies with the phase of the estrous cycle (Woolley & McEwen, 1992). HPC cell excitability may be further enhanced by estrogen via its disinhibition of CA1 pyramidal cells and increased decay time of IPSCs (Rudick, Gibbs, & Woolley, 2003). This disinhibition appears related to the decrease in synaptic GABA release by HPC interneurons, which in turn reduces the amplitude of pyramidal cell IPSCs (Rudick et al., 2003). Estrogen can also exert dramatic effects on HPC cholinergic functions. Estrogen increases potassium-stimulated release of acetylcholine (ACh; Gabor, Nagle, Johnson, & Gibbs, 2003), and enhances learning-induced ACh release during a place task (Marriott & Korol, 2003). Estrogen replacement in OVX rats can cause a significant increase in ACh levels (Gabor et al., 2003). Conversely, a lack of estrogen in knockout mice causes a 24% decrease in HPC ChAT (Tam, Danilovich, Nilsson, Sairam, & Maysinger, 2002). The ACh increase that is driven by estrogen may in turn diminish GABAergic inhibition, resulting in disinhibition of CA1 pyramidal neurons (Daniel & Dohanich, 2001). Estrogen-mediated increases in ACh may also enhance NMDA receptor binding (Daniel & Dohanich, 2001) since increased NMDA agonist binding is observed in CA1 after exposure to estrogen (Weiland, Orikasa, Hayasaki, & McEwen, 1997). Estrogen alleviates detriments in LTP that are caused by blockade of NMDA receptors (Gureviciene et al., 2003), and LTP may be strongest during high estrogen states (Warren, Humphreys, Juraska, & Greenough, 1995). Finally, ovariectomies decrease NMDA receptor binding, and treatment with estrogen can restore the binding (Cyr et al., 2001). Thus, high estrogen conditions produce a number of interacting conditions that ultimately increase HPC synaptic excitation and efficiency, which in turn likely contributes to estrogen's positive effects on HPC-dependent learning.

The direct effects of estrogen in STR are less well understood. The most widely reported effect is upon the dopamine (DA) system. Estrogen has been shown to increase DA levels (reviewed in Korol, 2004). While DA agonists are thought to improve performance on STR tasks, research shows that estrogen negatively impacts STR-dependent maze performance (Korol & Kolo, 2002). Korol (2004) suggests that the elevated DA increases D2 receptor activation, and that this causes a decrease in STR-dependent performance. However, DA may not be the only determinant of estrogen's effects on STR-dependent learning; other neurotransmitters likely play a role as well. ACh is a good candidate in this

Table 1
A summary of the effects of estrogen (A) or a lack of estrogen (B) on ACh and DA functions in the STR

(A) Estrogen present	(B) Low or no estrogen
• ⇓AChE → ⇓activity of nACh receptor → ⇓DA release	• ⇓ACh → ⇑nACh receptor activation → ⇑DA release
• ⇓AChE → ⇑ACh induced inhibition of MSN → ⇓STR output	• ⇓ACh induced inhibition of MSN → ⇑STR output
• ⇑mACh activation → ⇓GLU induced excitation → ⇓STR output	• ⇓mACh activation → ⇑GLU excitation → ⇑STR output
• ⇓AMPA binding → ⇓GLU induced excitation → ⇓STR output	• ⇑AMPA binding → ⇑GLU excitation → ⇑STR output

We propose that the cumulate effect of all of these changes may be the underlying reason that OVX rats outperform the OVX + E group on the STR-dependent response task. Also, these effects likely contribute to the finding that OVX + E rats learn the spatial task faster than OVX rats. When estrogen levels are elevated, striatal output could be expected to be reduced. On the other hand, when estrogen levels are low, striatal output may be increased. These differences in output strength presumably impact the relative strengths of different neural systems for control of behavioral expression systems (Mizumori et al., 2004). MSN, medium spiny neurons; DA, dopamine; GLU, glutamate; ACh, acetylcholine; AChE, acetylcholinesterase; mACH, muscarinic cholinergic receptors; nACh, nicotinic cholinergic receptors.

regard since estrogen has clear effects on STR ACh function. For example, knockout mice that cannot produce estrogen show a 50% reduction in the synthesizing enzyme for ACh, choline acetyltransferase or ChAT (Tam et al., 2002). Also, Tomas-Camardiel et al. (2002) found decreased acetylcholinesterase (AChE) fiber density when estradiol was injected into the STR. A high concentration of AChE normally terminates the cholinergic signal. ACh is used by the tonically active STR interneurons. A reduced cholinergic signal removes the tonic inhibition on nicotinic receptors. This disinhibition in turn results in an increased potential for DA release following afferent (glutamatergic) input (Windels & Kiyakin, 2003; Zhou, Wilson, & Dani, 2002). It appears, then, that *both* high and low estrogen conditions have the potential to elevate DA function. However, an important difference might be that during high estrogen states, a higher level of DA is sustained when compared to low estrogen states (Fernandez-Ruiz, Hernandez, de Miguel, & Ramos, 1991). This higher level may affect tonic levels of DA and not phasic changes. Phasic activity is thought to be more important for learning; perhaps the level of DA in a high estrogen condition is too high such that phasic changes are masked. This could lead to reduced contributions of the STR to learning. It is worth noting that estrogen-induced activation of the cholinergic system also leads to increased stimulation of mACh receptors, which in turn inhibits glutamatergic afferent input (Hersch, Gutekunst, Rees, Heilman, & Levey, 1994; Malenka & Kocsis, 1988). Estrogen also decreases glutamatergic excitation directly by decreasing AMPA binding in the STR (Cyr et al., 2001). Thus, multiple mechanisms may underlie an estrogen-induced reduction in STR throughput. Table 1 presents a summary of the complex array of effects of estrogen on STR output.

4.2. Differential effects of estrogen during working and reference memory function

The differential effects of estrogen on reference and working memory show that estrogen may target reference memory processing more than working memory functions. Previous research has indeed shown that estrogen may improve reference memory in young and aged animals when estrogen was given over an extended amount of time (Frick, Fernandez, & Bulinski, 2002; Martin, Jones, Simpson, & van den Buuse, 2003). However, spatial working memory has also been shown to improve with constant levels of estrogen (Bimonte & Denenberg, 1999; Daniel, Fader, Spencer, & Dohanich, 1997; Fader, Johnson, & Dohanich, 1999). Our results did not show estrogen effects on working memory errors. It could be that the estrogen rats learned the place task so quickly that a floor effect prevented us from observing effects on working memory. In the future, it would be interesting to study the consequences of increasing the working memory demand of this task. In the response task reference and working memory errors were similar across both estrogen groups. This may be due to the fact that the solution to this task emphasized the development of strong motor habits (i.e., a 90° turn), and not hippocampal-dependent reference or working memory functions.

5. Conclusion

The findings of this study support the hypothesis that estrogen exerts differential and selective influences over mnemonic structures of the brain such as the STR and HPC. OVX rats treated with estrogen replacement showed enhanced spatial learning and poor response learning relative to OVX rats that were not given estrogen replacement. Estrogen's effects on place learning may target reference memory processing compared to working memory processing. Therefore, to facilitate future comparisons across studies that employ different learning tasks, special emphasis should be placed on testing and then verifying the cognitive strategy employed. This is the case following both acute and chronic estrogen administration. A model is presented to explain the differential effects of estrogen on HPC- and STR-dependent learning. When estrogen levels are elevated, HPC output is stronger than STR output, and when estrogen levels are low, STR output is stronger than HPC output. In other words, estrogen may regulate the relative out-

put strengths of HPC and STR, thereby biasing their relative influence over behavioral expression systems (Mizumori, Yeshenko, Gill, & Davis, 2004).

Acknowledgments

This research was supported by NIMH Grant MH 58755 and Grant #2980 from the University of Washington Royalty Research Fund.

References

Bimonte, H. A., & Denenberg, V. H. (1999). Estradiol facilitates performance as working memory load increases. *Psychoneuroendocrinology, 24*, 161–173.

Butcher, R., Collins, W., & Fugo, N. (1973). Plasma concentration of LH, FSH, prolactin, progesterone, and estradiol-17β throughout the four day estrous cycle of the rat. *Endocrinology, 94*, 1704–1708.

Cyr, M., Ghribi, O., Thibault, C., Morissette, M., Landry, M., & Di Paolo, T. (2001). Ovarian steroids and selective estrogen receptor modulators activity on rat brain NMDA and AMPA receptors. *Brain Research Brain Research Review, 37*, 153–161.

Daniel, J., & Lee, C. (2004). Estrogen replacement in ovariectomized rats affects strategy selection in the Morris water maze. *Neurobiology of Learning and Memory, 82*, 142–149.

Daniel, J., & Dohanich, G. (2001). Acetylcholine mediates the estrogen-induced increase in NMDA receptor binding in CA1 of the hippocampus and the associated improvement in working memory. *Journal of Neuroscience, 21*(17), 6949–6956.

Daniel, J., Fader, A., Spencer, A., & Dohanich, G. (1997). Estrogen enhances performance of female rats during acquisition of a radial arm maze. *Hormones and Behavior, 32*, 217–225.

Dohanich, G. P. (2002). Gonadal steroids, learning and memory. In *Hormones brain and behavior* (pp. 265–327). San Diego: Academic.

Fader, A., Johnson, P., & Dohanich, G. (1999). Estrogen improves working but not reference memory and prevents amnestic effects of scopolamine of a radial-arm maze. *Pharmacology Biochemical Behavior, 62*, 711–717.

Fernandez-Ruiz, J., Hernandez, M., de Miguel, R., & Ramos, J. (1991). Nigrostriatal and mesolimbic dopaminergic activities were modified throughout the ovarian cycle of female rats. *Journal of Transmission Genetics Section, 85*, 223–229.

Frick, K., Fernandez, S., & Bulinski, S. (2002). Estrogen replacement improves spatial reference memory and increases hippocampal synaptophysin in aged female mice. *Neuroscience, 115*, 547–558.

Gabor, R., Nagle, R., Johnson, D., & Gibbs, R. (2003). Estrogen enhances potassium-stimulated acetylcholine release in the rat hippocampus. *Brain Research, 962*, 244–247.

Galea, L., Wide, J., Paine, T., Holmes, M., Ormerod, B., & Floresco, S. (2001). High levels of estradiol disrupt conditioned place preference learning, stimulus response learning and reference memory but have limited effects on working memory. *Behavioural Brain Research, 126*(1–2), 115–126.

Gibbs, R. B. (1999). Estrogen replacement enhances acquisition of a spatial memory task and reduces deficits associated with hippocampal muscarinic receptor inhibition. *Hormones and Behavior, 36*, 222–233.

Gibbs, R. B. (2000). Long-term treatment with estrogen and progesterone enhances acquisition of a spatial memory task by ovariectomized aged rats. *Neurobiology of Aging, 21*, 107–116.

Gureviciene, I., Puolivali, J., Pussinen, R., Wang, J., Tanilia, H., & Ylinen, A. (2003). Estrogen treatment alleviates NMDA antagonist induced hippocampal LTP blockade and cognitive deficits in ovariectomized mice. *Neurobiology of Learning and Memory, 79*, 72–80.

Hersch, S., Gutekunst, C., Rees, H., Heilman, C., & Levey, A. (1994). Distribution of m1-m muscarinic receptor proteins in the rat striatum: light and electron microscopic immunocytochemistry using subtype specific antibodies. *Journal of Neuroscience, 14*, 3351–3363.

Korol, D. (2004). Role of estrogen in balancing contributions from multiple memory systems. *Neurobiology of Learning and Memory, 82*, 309–323.

Korol, D., & Kolo, L. (2002). Estrogen-Induced changes in place and response learning in young adult female rats. *Behavioral Neuroscience, 116*, 411–420.

Malenka, R., & Kocsis, J. (1988). Presynaptic actions of carbachol and adenosine on corticostriatal synaptic transmission studied in vitro. *Journal of Neuroscience, 8*, 3750–3756.

Martin, S., Jones, M., Simpson, E., & van den Buuse, M. (2003). Impaired spatial reference memory in aromatase-deficient (ArKO) mice. *Learning and Memory, 14*, 1979–1982.

Marriott, L., & Korol, D. (2003). Short-term estrogen treatment in ovariectomized rats augments hippocampal acetylcholine release during place learning. *Neurobiology of Learning and Memory, 80*, 315–322.

Mizumori, S. J. Y., Yeshenko, O., Gill, K. M., & Davis, D. M. (2004). Parallel processing across neural systems: Implications for a multiple memory system hypothesis. *Neurobiology of Learning and Memory, 82*, 278–298.

Pearce, J., Roberts, A., & Good, M. (1998). Hippocampal lesions disrupt navigation based on cognitive maps but not heading vectors. *Nature, 396*, 75–77.

Tam, J., Danilovich, N., Nilsson, K., Sairam, M., & Maysinger, M. (2002). Chronic estrogen deficiency leads to molecular aberrations related to neurodegenerative changes in Follitropin receptor knockout female mice. *Neuroscience, 114*, 493–506.

Tomas-Camardiel, M., Sanchez-Hidalgo, M., Sanchez del Pino, M., Navarro, A., Machado, A., & Cano, J. (2002). Comparative study of the neuroprotective effect of dehydroepiandrosterone and 17beta-estradiol against 1-methyl-4-phenylpyridium toxicity on rat striatum. *Neuroscience, 109*(3), 569–584.

Rudick, C., Gibbs, R., & Woolley, C. (2003). A role for the basal forebrain cholinergic system in estrogen-induced disinhibition of hippocampal pyramidal cells. *Journal of Neuroscience, 23*(11), 4479–4490.

Warren, S., Humphreys, A., Juraska, J., & Greenough, W. (1995). LTP varies across the estrous cycle: Enhanced synaptic plasticity in proestrous. *Brain Research, 703*, 26–30.

Weiland, N., Orikasa, C., Hayasaki, S., & McEwen, B. (1997). Distribution and hormone regulation of estrogen receptor immunoreactive cells in the hippocampus of male and female rats. *Journal of Comparative Neurology, 388*, 603–612.

Woolley, C., & McEwen, B. (1992). Estradiol mediates fluctuation in hippocampal synapse density during the estrous cycle in the adult rat. *Journal of Neuroscience, 12*, 2549–2554.

Windels, F., & Kiyakin, E. (2003). Modulatory action of acetylcholine on striatal neurons: microiontophoretic study in awake unrestrained rats. *European Journal of Neuroscience, 17*, 613–622.

Zhou, F., Wilson, C., & Dani, J. (2002). Cholinergic interneurons characteristics and nicotinic properties in the striatum. *Journal of Neurobiology, 53*(4), 590–605.