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An Integrative Review of Estradiol Effects on Dendritic Spines and Memory over the Lifespan

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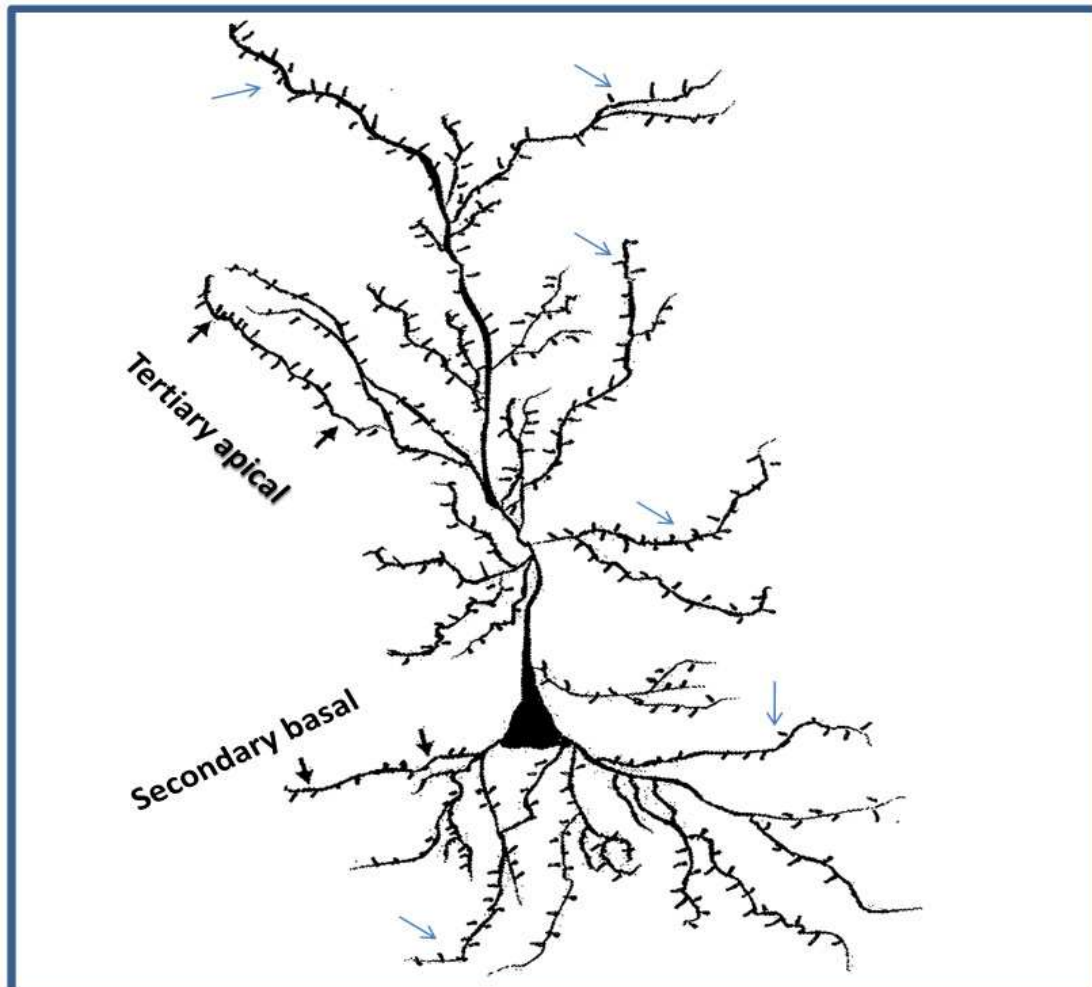
1. Introduction

Estradiol enhances some aspects of learning and memory in both humans and animal models. These enhancements are present throughout the adult lifespan (Luine, 2008) and extend into old age (Frick, 2008). While many neurochemicals and neurotrophins have been shown to be regulated by estrogen, the mechanism(s) responsible for estrogen's positive effects on cognition remain elusive. It has, however, been demonstrated that gonadal hormones, both estrogens and progestins, influence neural morphology in areas important for cognitive function such as the hippocampus and medial prefrontal cortex (PFC). Spines, which are located on the dendrites of pyramidal neurons in both of these areas, have been shown to contribute to cognitive function (Morgado-Bernal, 2011). Therefore, we will review estradiol's effects on dendritic spine density in the hippocampus and PFC in relation to cognitive function. Moreover, we also consider whether changes in spine density are important for estrogen's role in the maintenance of memory. The studies are primarily from our own laboratories, but, when available, data from other labs are compared. In our studies, spine density has been investigated by Golgi impregnation, and memory has been evaluated using the spatial memory tasks of radial arm maze and object placement, and non-spatial memory has been assessed by object recognition. In most of the studies to be discussed, both morphology and cognitive function were assessed in the subjects. This current research provides substantial data suggesting a relationship between hormones, spines and cognitive function, but we point out the need for further research to establish causal relationships between these variables and to identify how spines promote memory consolidation and are integrated into memory networks.

2. Dendritic spines and memory

Neuron to neuron communication occurs mainly when axons synapse on dendrites. Dendritic spines are small protrusions of the dendrite which receive the majority of synaptic input. Although dendritic spines are present on many neurons, they are extremely numerous on pyramidal cells of both the hippocampus and the PFC (See Figure 1, schematic

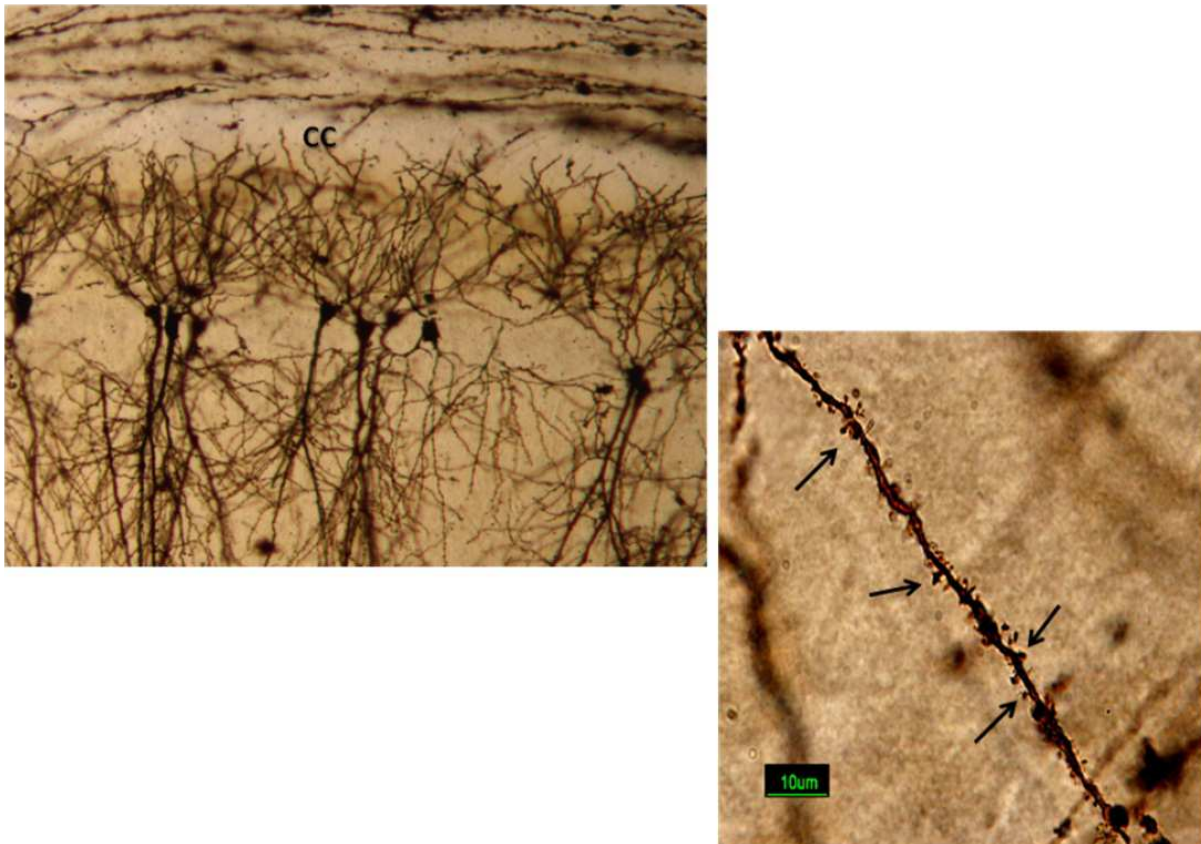
of pyramidal neuron). Most excitatory synapses occur on dendritic spines where there is a concentration of neurotransmitter receptors.



Shown are the parts of the apical and basal trees that are used for Golgi analysis in our studies. Blue arrows denote dendritic spines. Drawn by Landry McMeans.

Fig. 1. Schematic of a pyramidal cell.

Several subtypes of dendritic spines are recognized. The classification varies depending on the author but generally dendritic spines consist of a protrusion and either have a bulbous termination (mushroom spines) or not. One may also distinguish between thin spines with a smaller head and stubby spines that lack any terminal enlargement (reviewed by Bourne and Harris 2008). Golgi impregnation is used to study spine density because it labels the cell body and the adjacent dendritic structures completely (See Figure 2, photomicrograph of a pyramidal neuron). Using this technique it has been clearly demonstrated that dendritic spine density and the type of dendritic spines observed actually change with many conditions such as hormone state (Gould et al., 1990; Kinsley, 2008; Li et al., 2004; Woolley et al., 1990), stress (Radley et al. 2008) and drug administration (Robinson et al., 2001; Robinson and Kolb, 2004; Frankfurt, et al., 2011).



Left: CA1 region of the adult rat hippocampus. CC = corpus callosum. 10x magnification. Right: Photomicrograph of golgi-impregnated dendrites taken under oil (100x). Arrows denote spines. Frankfurt, Unpublished.

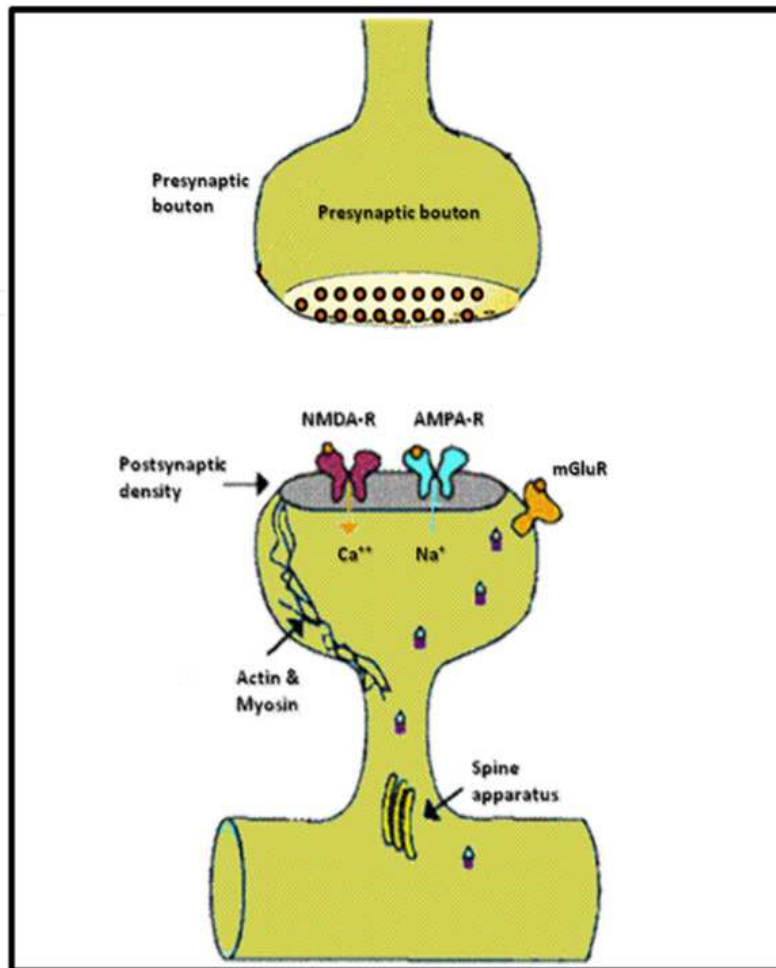
Fig. 2. Examples of Golgi impregnation.

3. Use of golgi impregnation techniques to study spines

There is increasing evidence that the processes underlying learning and memory involve neural plasticity, which includes neurogenesis and dendritic remodeling. Ultimately memory seems to require dendritic remodeling which leads to an increase in LTP and synaptic strength (See Figure 3, schematic of a spine). This idea that memory requires alterations in dendritic spines is supported by the demonstration that the acquisition of new memories is associated with changes in dendritic spine density in the CA1 hippocampal region in adult male rats (Leuner et al, 2003; Jedlicka et al, 2008; Beltran-Campos, 2011). In addition, there is increasing evidence that existing spines undergo structural alterations that result in LTP (Jedlicka et al, 2008; Morgado-Bernal, 2011). Spine assembly involves a complex sequence of events and many proteins which have been demonstrated to be altered following memory tasks (Hotulainen and Hoogenraad, 2010; Morgado-Bernal, 2011). For example the polymerization of actin, which is highly concentrated in dendritic spines, appears to be required for the induction of LTP (reviewed by Fortin et. al, 2011).

4. Estrogens and spines

The hippocampal region not only contains a high density of spines, but these spines are plastic, i.e. their numbers fluctuate depending upon the state of the host. A dramatic 30%



The axon terminal contains vesicles which release their contents, then bind to the post synaptic receptor and then initiate a series of events that induce structural changes in the dendritic spine. Drawn by Dr. A. Bornstein

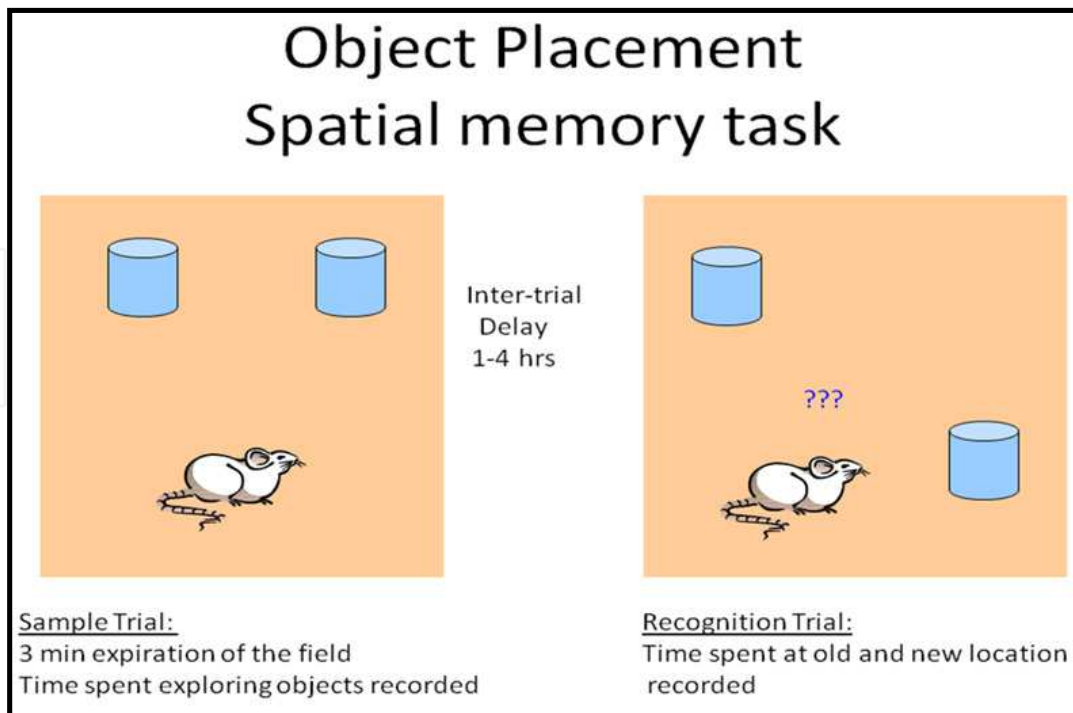
Fig. 3. Schematic representation of the events that occur at the axo-spinous synapse.

change in spine density has been shown in the hippocampus during the 4-5 day estrus cycle of the female rat in concert with the changes in estradiol and progesterone (Woolley, et al, 1990). These changes occur in the CA1, but not the CA3 or dentate gyrus region of the hippocampus and allow for changes in neural traffic through frontal cortex and the hippocampus itself. Ovariectomy (Ovx) is associated with decreased spine density in CA1 (Gould et al. 1990, Wallace et al, 2006), and it has been recently demonstrated that the PFC also undergoes spine (Wallace et al, 2006) and spine synapse (Leranth et al, 2003) loss following gonadectomy. Since memory function undergoes similar changes with alterations in gonadal hormones (see Estrogens and memory below), dendritic spines in CA1 and the medial PFC may be important in mediating gonadal hormone influences on cognitive function in females.

5. Estrogens and memory

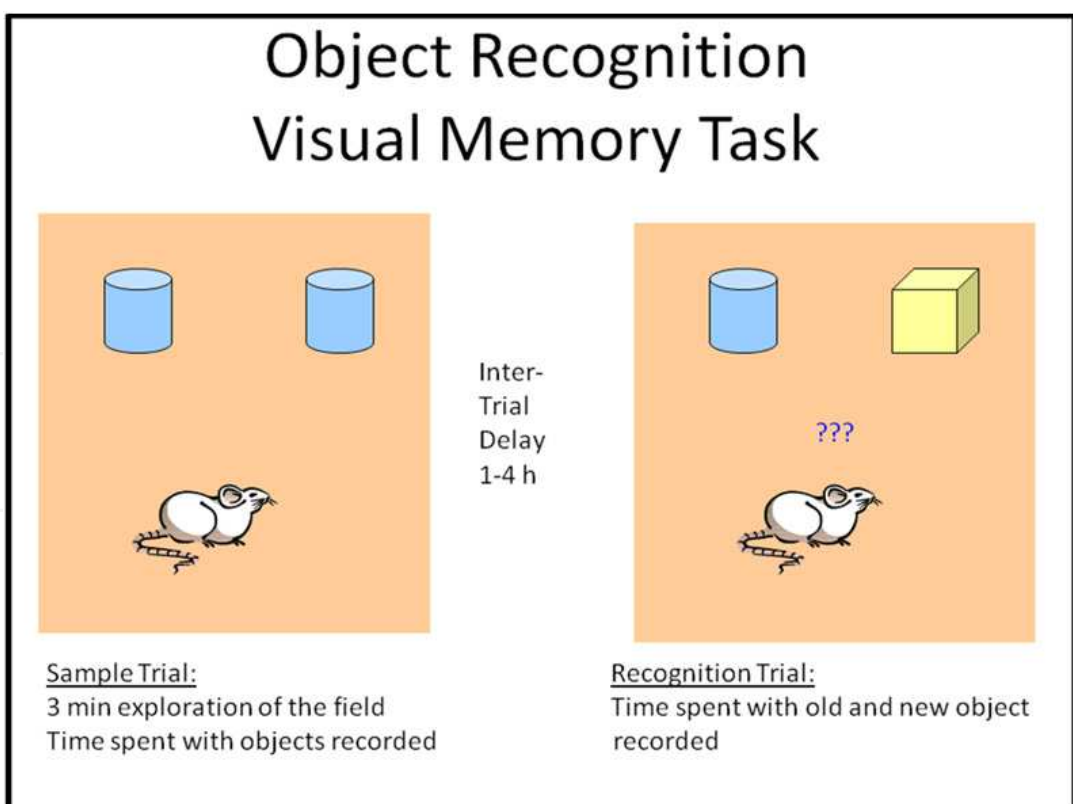
A substantial literature has demonstrated that gonadal hormones, mainly estradiol, influence cognition function during development, at adulthood and during aging (Luine,

2008; Frick, 2008); however, the changes are often small in magnitude. Nonetheless, estradiol administration to Ovx rats or mice has been shown to enhance performance of radial arm maze, T-maze, Morris water maze, and object recognition/placement tasks (see Dohanich, 2002 for review). A critical consideration is that hormones do not usually enhance all aspects of cognition. For example, learning to play a card game like Bridge (*acquisition* of the extensive rules of play) is different from playing the game and remembering which cards have been played (*short-term/working memory*). Thus, acquisition/learning is different than memory, and it appears that estradiol may not enhance both (Luine, 2008). In understanding memory in animal models, it should be noted that the rats face the same issues when they learn a task and then use memory to solve or complete the task. Thus, it is important to consider both learning and memory when examining the influence of gonadal hormones on cognitive function. In this review, we focus on the role of hormone-dependent changes in spines in mediating memory function. Thus, we have applied tasks which utilize memory to female rats, but there are also different types of memory. Spatial memory is the most widely assessed form of memory in rodents, and a variety of tasks have been developed for its measurement, for example, radial arm maze, Morris water maze and object placement. These strongly hippocampal-dependent tasks rely on the innate ability of rodents to know and defend a territory by utilization of salient environmental landmarks to establish a cognitive map which resides within hippocampal neurons or networks. Thus, if the hippocampus is ablated, the rats can no longer perform spatial tasks (Broadbent et al, 2004). We have applied the object placement task because this task, unlike other tasks, requires minimal learning and it also does not entail use of positive (food) or negative (drowning) rewards which might inadvertently influence performance through stress or other influences. Object placement relies on the observation that rats seek novelty and readily explore their environment. When a delay is interspersed between presentation of objects in a new as compared to an old location, then memory can be assessed by determining whether the subjects spend more time exploring the object in the new location than in the old location (Ennaceur et al, 1997). The task is conducted as depicted in Figure 4. Rats spend three minutes exploring two identical objects on an open field in the sample trial (T1). After inter-trial delays of 1 to 4 h, the subject is returned to the field where one object has been moved to a different location (retention trial or T2). The time spent exploring the object in the old and in the new location is noted. Spending significantly more time exploring at the new vs. the old location indicates that the rat remembers the old location and hence explores at the novel location, i.e. significantly discriminates between locations. Object placement memory can also be reported using the exploration ratio (time exploring new place/time exploring old + time exploring new place) where ratios of 0.5 indicate chance performance (poor memory) and ratios higher than 0.5 indicate that subjects remember the old location and significantly discriminate between the locations. This task can also be configured as a visual memory task which relies on visual associations by the prefrontal cortex as well as integration of the PFC with hippocampal memory circuits (Broadbent et al, 2004; Ennaceur et al, 1997). See Figure 5. The sample trial is the same as in object placement, but in the retention trial, a new object is switched for one of the two identical objects. Scoring in the retention trial is as in object placement. Estradiol, given to Ovx rats or mice, has been shown to enhance memory in these tasks by a number of laboratories (Luine et al, 2003; Li et al, 2004; Walf et al, 2006, 2007; Frye et al, 2007; Scharfman et al, 2007; Jacome et al, 2010).



The rat is shown on an open field with objects to be explored.

Fig. 4. Depiction of the object placement memory task.



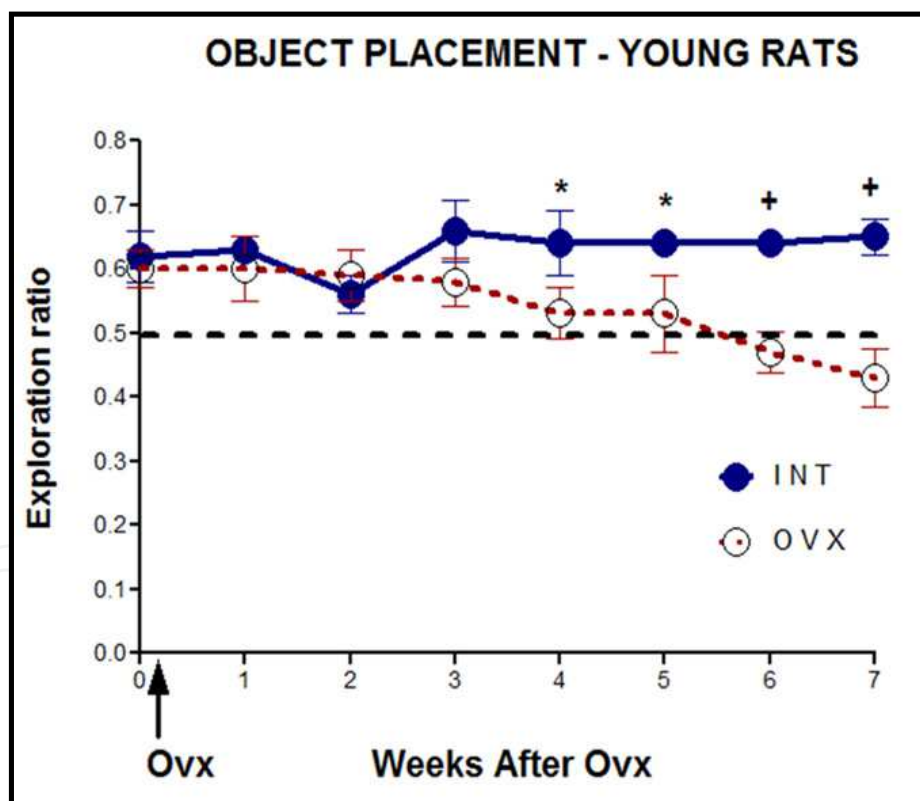
The rat is shown on an open field with objects to be explored.

Fig. 5. Depiction of the object recognition memory task.

6. Estrogens, memory and spines

6.1 Declines in estrogen following Ovx

As indicated earlier, some cognitive functions appear optimal in the presence of circulating gonadal hormones, but whether maintenance of dendritic spines at critical levels contributes to gonadal hormone influences on cognition has not received extensive investigation; however, we assessed the effects of gonadectomy on recognition memory (object recognition) and spatial memory (object placement) and spine density in the medial prefrontal cortex (PFC) and in hippocampal sub-regions (Wallace et al, 2006). Prior to Ovx, rats could significantly discriminate between old and new objects and between objects in new and old locations when tested 4 hours after first viewing the objects. One week following surgery, Ovx females showed impaired object recognition memory because they could not discriminate between old and new objects (ratio less than 50%) while gonadally intact females still discriminated in the task (Wallace et al, 2006). At this time interval post Ovx, place memory showed different results because both gonadally intact and Ovx rats could significantly discriminate between objects in new and old locations (ratios of approximately 0.65), however by four weeks post-Ovx, rats could not significantly discriminate locations (See Figure 6). These results suggest that gonadal hormones contribute to the performance of the memory tasks. Moreover,



The exploration ratio \pm SEM is shown for gonadally intact, sham (solid circles) and Ovx (open circles) rats before Ovx (0 week) and weeks 1-7 post Ovx. Dashed line at 0.5 indicates chance performance of task (same amount of time spent exploring the object at the old and new locations). Two way ANOVA (group \times week) of ratios showed no significant main effects but a significant group \times week interaction ($F(1,16)=2.22$, $p<0.047$). Post hoc testing by t-tests showed significant differences between groups at weeks 4, 5, 6 and 7, by at least $p < 0.02$. Adapted from Wallace et al. (2006)

Fig. 6. The effect of ovariectomy on object placement memory task.

recognition memory may be more sensitive to ovarian steroids than spatial memory since performance of object recognition was lost faster after Ovx. However, it is important to consider the possible effects of stress on the results because stressing female rats has been shown to enhance object placement (Bowman et al, 2003). Since corticosterone, released during stress, acts within the hippocampus, it is possible that anesthesia-induced stress in this study may have masked any early effects of Ovx on object placement.

The Ovx and gonadally intact subjects were sacrificed 7 weeks post Ovx and brain morphology was analyzed following Golgi impregnation. Spines were counted on tertiary apical and secondary basal dendrites of pyramidal neurons in layer II/III of the medial prefrontal cortex (PFC) and in CA1 and CA3 of the hippocampus (See Figure 1). In the PFC and CA1 (but not CA3), Ovx females had lower spine density in both apical and basal dendrites than intact rats, ranging from 17% decreases in apical CA1 to 53% decreases in apical PFC. Thus, poorer memory in the Ovx subjects was associated with lower spine densities in the hippocampus and PFC. Unfortunately, behavior could not be directly correlated with spine density as the subjects were not sacrificed immediately following behavior testing. Similar results have been reported recently by Beltran-Campos et al (2011) who found that CA1 apical dendrite spines were 55% lower in Ovx as compared to intact rats. Moreover, the Ovx rats were impaired in acquisition of the platform location in the Morris Water Maze spatial memory task.

6.2 Declines in estrogens with aging

Given that gonadal hormones decrease with age, aged rats also provide interesting subjects for assessing relationships between spines and memory. It is well known that aged rats, as well as aged humans, show declines in both learning and memory as compared to young subjects (Frick, 2008). We examined memory function, brain spine densities and estradiol levels in young (four months old) and aged (21 months old) Fischer 344 rats (Wallace et al, 2007; Luine et al, 2011). Fischer 344 rats are maintained by the National Institute for Aging of the National Institutes of Health as a standard model for studies on the physiological and neural aspects of aging. Consistent with many previous studies on spatial memory using tasks like the radial arm maze (Luine and Hearn, 1990) and its water version (Bimonte et al, 2003), Y and T mazes (Aggleton et al, 1980), Barnes maze (Barrett et al, 2009) and the most widely applied spatial memory task, the Morris water maze (Markowska et al, 1999, Veng et al, 2003) the aged females showed poorer object placement performance; they were unable to discriminate between old and new location with 1.5 h inter-trial delay while young rats could discriminate (Luine et al, 2011). Likewise, aged rats are also impaired in visual memory; they could not discriminate between old and new objects at a one hr inter-trial delay (Wallace et al, 2007). Examination of spine densities in the PFC and hippocampus (Table 1) showed that aged rats had 16% decreases, as compared to young rats, in apical dendrites of the PFC and CA1, but no changes in CA3. This decline in densities with aging was smaller than the decline following Ovx. Moreover, the whole pyramidal neuron was affected following Ovx; both apical and basal dendrites were decreased by Ovx, but only apical dendrites were affected with aging. It is notable that the Fischer 344, aged rats (Luine et al, 2011) still had appreciable circulating estradiol levels, 7.9 ± 1 pg/ml serum, a level which is comparable to a young rat at diestrus. With further aging, estradiol levels become negligible, but spine densities have not been examined in this age group so it is not known whether spine densities would further decline with aging to levels seen in young Ovx females.

| Group | PFC Apical | PFC Basal | CA1 Apical | CA1 Basal | CA3 Apical | CA3 Basal |
|-------|--------------|-------------|--------------|-------------|-------------|-------------|
| Young | 8.13 ± 0.40 | 7.80 ± 0.41 | 7.87 ± 0.58 | 5.37 ± 0.21 | 5.42 ± 0.36 | 5.52 ± 0.29 |
| Aged | 6.86 ± 0.52* | 7.19 ± 0.31 | 6.59 ± 0.39* | 5.96 ± 0.15 | 6.30 ± 0.39 | 4.79 ± 0.36 |

Entries are mean number of spines/10 μ m ± S.E.M. for 6-8 rats/group. Young is 4 months and aged is 21 months old. * $p < .05$ by Student's T-test. Data from Wallace et al, 2007 and Luine et al, 2011.

Table 1. Spine density in young vs aged Fischer 344 rats

Von Bohlen et al (2006) also reported decreased CA1 spine density in a group of aged rats of both sexes that had impaired Morris water maze performance. However, our data is different from the only other published study in females. Markham et al. (2005), who applied Golgi techniques, reported no changes in CA1 spine density in rats of a similar age as ours (19-22 mo.) but of a different strain, Long Evans. Nonetheless, it is notable that Markham and Juraska (2002) reported decreased spine density in the PFC of their aged females. In neither of these studies was memory assessed. An important variable which may have contributed to our demonstration of decreased hippocampal spine density with aging is the reproductive history of the females utilized. The Fischer 344 female rats supplied to us by N.I.A. were virgins. In the other studies (Markham and Juraska, 2002; Juraska et al, 2005) retired Long-Evans breeding dams were used. As discussed in detail below, rats that have been pregnant and reared pups (multiparous) generally have better memory abilities than female rats that have never experienced motherhood (virgin or nulliparous; see Macbeth and Luine, 2010 for review). For example, middle-aged rats (12 months old) that have had 4-5 pregnancies and births demonstrated better object placement performance and other memory tasks than age-matched, virgin rats (Macbeth et al., 2008). Reproductive experience also apparently imparts long lasting effects on memory processes because multiparous females show better spatial memory than age-matched virgins at 24 months of age (Kinsley, 2008; Macbeth and Luine, 2010). Moreover, pregnant or lactating females have greater spine density in CA1 than females at all stages of the estrus cycle (Kinsley, et al, 2006; Kinsley 2008). Whether pregnancy-related spine changes are as enduring as the memory changes is, however, unknown, and needs to be investigated. Thus, the reproductive history of female rats may be an important variable when investigating neural and behavioral function.

Overall, our studies indicate that aging in females is accompanied by losses in memory abilities, neural spines and lower estradiol levels. Whether there is a causal relationship among the variables needs further investigation.

7. Increases in estrogens

7.1 Pregnancy

During pregnancy levels of gonadal hormones are elevated so pregnant dams provide an interesting model for further assessing relationships between memory function and dendritic spines. We found that pregnant females on days 7 and 16 of gestation showed better place memory than virgin females (Macbeth et al, 2008). While spine density was not measured in these subjects, there are several reports of alterations in spine density on pyramidal neurons in CA1 and the PFC with pregnancy. Leuner and Gould (2010) demonstrated that pregnant rats had increased dendritic spine density in both apical and basal branches of neurons in CA1 and the medial PFC as well as enhanced cognitive function 20 days after birth when compared to virgin females. However, the effects of pregnancy on

spine density in CA1 have been determined in several studies with variable results. In a recent study, we found that dendritic spine density was decreased on the apical branch of CA1 neurons on the day of birth in dams when compared with the virgin females (Frankfurt et al, 2011) whereas Kinsley et al. (2006) demonstrated that dendritic spine density on the apical branch of CA1 neurons was greatest in late pregnancy and during lactation (day 5) when compared with virgin rats in different stages of estrous. Brusco et al. (2008) demonstrated that, starting at day four postpartum, there were no differences in either spine density or spine type in CA1 between postpartum and virgin Wistar rats. The differences between these studies may be attributed to the fact that the animals were examined at different postpartum times and therefore the gonadal hormone levels also differ.

7.2 Replacement of Estradiol to Ovx rats

As indicated earlier, Estradiol Benzoate (EB) treatment for two days increases CA1 apical spine density (Gould et al, 1990), and estrogens and other gonadal hormones regulate the density of synapses on these CA1 spines (Parducz et al, 2006; MacLusky et al, 2005); however, neither learning nor memory was assessed in these studies. Conrad and colleagues (McLaughlin et al, 2008) examined the effects of two doses of EB, 5 and 10 ug, given twice to Ovx rats on object placement and other cognitive tasks as well as spine densities. The higher doses resulted in significant discriminations in object placement and a doubling of spine density in the apical dendrites of CA1 (but not in the basal dendrites). Interestingly, if rats were Ovx for ten weeks without any hormonal replacement, then estradiol did not alter spine density (memory was not assessed).

We have reported that Ovx females chronically fed regular rat chow (Purina LabDiet), which contains high levels of a variety of phytoestrogens, have better memory function and greater dendritic spine density in some brain areas than Ovx rats fed chow low in phytoestrogens (Teklad 2016) (Luine et al, 2006). Phytoestrogens are plant derived estrogens which have a much lower affinity for the estrogen receptor than estradiol but nonetheless exert some estrogenic effects. Following 7 weeks on the diets, the high phytoestrogen diet group significantly discriminated between objects at old and new locations while the Ovx rats fed the low phytoestrogen diet could not. Interestingly, Ovx rats fed either diet could not significantly discriminate between old and new objects after 6, 8 or 9 weeks on the diets. Thus, phytoestrogens were insufficient to enhance object recognition memory which again suggests that behaviors mediated by the medial prefrontal cortex may be very sensitive to losses in circulating estrogens. Apical spine density was assessed in pyramidal cells in CA1 and the PFC, areas where we previously saw differences between Ovx and gonadally intact rats. Spine density of the low phytoestrogen diet group was 32% lower in CA1 and 21% lower in the PFC than the high phytoestrogen group. Comparison of the two experiments utilizing Ovx rats (Ovx vs. intact rats; low vs. high phytoestrogen diet in Ovx rats) suggests that a reduction of 20-30% in CA1 apical spines is sufficient to impact spatial memory function but that larger declines are necessary in PFC in order to affect recognition memory. However, the relationship between spine density and memory may not be direct since spines were decreased in the low phytoestrogen diet group but object recognition memory was not.

Working with groups at Rockefeller University (Li et al, 2003), we found a somewhat different pattern of estrogen treatment in mice vs. rats. Ovx mice received 1 ug of EB daily for 5 days and then received object placement testing. EB treatment enhanced object placement, but the density of spines in apical CA1 was not increased. Interestingly, the density of mushroom

spines was increased by 38%. Combined with other ICC data, it was suggested that estradiol may be facilitating the spine-maturation process. While this could be a species difference, the longer treatment time compared with McLaughlin et al (2008) is consistent with the notion that estradiol, in general, may facilitate the spine maturation process.

8. Conclusions

The data presented here show that estrogen effects on memory are associated with dendritic remodeling in the hippocampus and PFC. It is impossible, at present, to state conclusively which dendritic spines are involved in mediating a given function because most of the studies done to date include confounding variables. For example, some evidence suggests that learning (Beltran-Campos, 2011) or forming associative memories (Leuner and Shors 2003) increases spine density in CA1, but Beltran-Campos, in the same study, found that spines were not increased by training in Ovx rats, only in gonadally intact rats. Moreover, Frick et al (2004) reported that behavioral training in the water maze interfered with the ability of estradiol to increase CA1 spine synapse density in Ovx rats. While an influence of the stress of swimming cannot be discounted, the above studies indicate a complex interaction between hormones, memory and spines. Since there is some evidence of different hormonal or learning effects on different spines, counting of mushroom, thin and filapodial spines might be informative for future studies. Also critical is the comparison of behaviorally tested vs. non-behaviorally tested subjects and how long the subjects have been without circulating estrogens as well as how long after behavioral testing spine density is analyzed. Nonetheless, estrogenic facilitations of memory functions regulated by the hippocampus and prefrontal cortex provide a rich context in which to examine the mechanisms underlying memory consolidation and retrieval. Using estradiol as a physiological probe, it should be possible to identify the intracellular signals whereby spines are generated, strengthened or shed, and how newly generated spines promote memory consolidation and may be ultimately integrated into memory networks.

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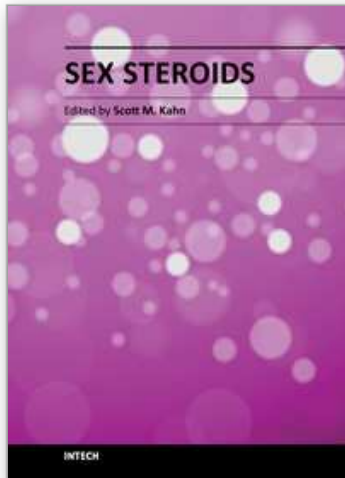
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This book, entitled "Sex Steroids", features a valuable collection of reviews and research articles written by experts in signal transduction, cellular biology, diseases and disorders. "Sex Steroids" is comprised of four sections, "The Biology of Sex Steroids", "Sex Steroids, Memory, and the Brain", "Sex Steroids and the Immune Response", and "Therapy"; individual chapters address a broad range of recognized and predicted functions and applications of sex steroids. "Sex Steroids" is intended to provide seasoned veterans as well as newcomers to this area of research with informative, resourceful, and provocative insights. Readers of "Sex Steroids" should emerge with an appreciation and understanding of the multitude and complexity of biologic processes attributed to these important hormones, and possible future directions of research in this fascinating and ever evolving field.

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