

THE ROLE OF STEROID HORMONES IN LEARNING AND MEMORY

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Abstract - Sufficient evidence has accumulated since the 1970s to support the hypothesis that gonadal steroids can influence processes that allow an organism to learn and remember new information. Although this conclusion quickly leads to exciting implications for our understanding of cognitive function and for the treatment of cognitive disability, it also raises questions regarding the nature, mechanism, and significance of the steroid modulation of learning and memory. In order to support the case that a steroid plays a meaningful role in cognition, several central issues must be addressed : adaptative value (the proposed effect of the steroid on learning and memory should have adaptive value to the organism); strenght of effect (empirical data supporting the role of the steroid in learning and memory should be sufficiently robust in magnitude and replicability); neural substrate (anatomical and physiological substrates should exist to support the actions of the steroid on learning and memory) ; and nonmnemonic processes (processes other than those directly mediating steroid effects on learning and memory systems should be identified) (23).

ACTION OF STEROID HORMONES AT THEIR RECEPTORS

In order for a hormone to modulate the biological functions of its target cells that hormone must first bind to a receptor in the target cell. If a cell has no receptor for a given hormone, that hormone can not influence the activity of the cell. Steroid and peptide hormones regulate the activity of their target cells by different receptor mechanisms. The peptide hormones are large, water soluble (hydrophilic) molecules wich can not pass through the cell membrane, so bind to receptor proteins on the cell membrane (8).

The steroid hormones (androgens, estrogens, progesterone, glucocorticoids, and mineralocorticoids) are small lipophilic (lipid soluble) molecules and, if not bound to carrier proteins, they can readily diffuse through the cell membranes into any cell in the body. Target cells for steroid hormones have intracellular receptors in the nucleus wich bind to the hormones after they enter the cells (37).

Steroid hormone receptors are proteins with a hormone-binding region, wich determines wich hormone will bind to that receptor, and a DNA binding region, wich attaches to the non-histone proteins in the cell nucleus (figure 1). The nuclear theory of steroid hormone action suggests that the receptor proteins exist in a reversible bond with the non-histone proteins in the chromatin of the cell nucleus (63). Non-histone proteins bind directly to the DNA and define the specific genes to be regulated by the hormone-receptor complex (92). When no hormone is bound to the receptor, the hormone-binding region inhibits the DNA-binding region. When a steroid hormone binds to its receptor, this inhibition is removed (26). The location at wich the steroid hormone-receptor complex binds to the non-histone protein is called an “acceptor site” (figure 1). Since each cell contains a complete complement of DNA, enough to replicate all the proteins in the body, the acceptor site is necessary to determine the exact segment of the genomic DNA to be replicated for the synthesis of specific proteins in each target cell.

Once the hormone-receptor complex forms an acceptor site, the receptor undergoes a structural alteration or “transformation”, allowing it to open an “initiation site” on the DNA itself. At the initiation site, the enzyme RNA polymerase transcribes the information from the DNA to a molecule of mRNA (figure 1). The mRNA is then transported to the ribosomes in the cytoplasm where it serves as the template for protein synthesis. The protein synthesized may be hormones, hormone receptors, carrier proteins, and other proteins in the target cell.

STEROID HORMONE RECEPTORS

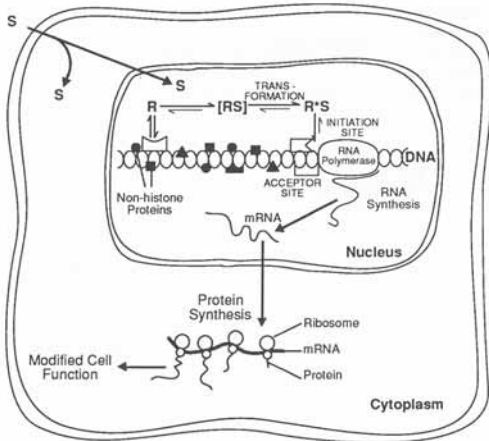


Figure 1 The nuclear model of the steroid hormone receptor .

The steroid hormones (S) are distributed within both cytoplasm and the nucleus of the target cell. The unoccupied receptors (R) are believed to be primarily concentrated in the nucleus in a reversible equilibrium binding state with the non-histone proteins of the chromatin. The binding of the steroid hormone to the receptor results in the transformation of the unoccupied receptor (R) into the biologically active hormone-receptor complex (R*S) at the acceptor site. The transformed receptor then opens an initiation site on the DNA, resulting in the induction (or repression) of mRNA synthesis through the action of the enzyme RNA polymerase. The mRNA then enters the cytoplasm where protein synthesis occurs on the ribosomes, resulting in modified cell function (Brown, 2001).

Unlike the slower process characteristic of genomic steroid action that requires minutes to hours, other mechanisms of steroid action be detected within second to minutes(75). Ultrarapid effects of steroids on membrane excitability occur within seconds of application and reflect steroid action at the membrane via either receptor- or nonreceptor- mediated events (40, 53, 60).

Estrogen, regulates cellular events within minutes through various signal transduction system, probably mediated by the activation of novel membrane receptors or intracellular receptors (51,60).

In one proposed model, the binding of steroids to unidentified membrane receptors activates mitogen-activated protein kinases (MAPK) and protein kinase A (PKA), which stimulate or repress transcription through the phosphorylation of AP-1, the cyclic adenosine monophosphate (AMP) responsive element (CRE), and the steroid receptor element (SRE), as well as other transcriptional factors and coregulators (1,35,51,80,81)(Fig. 2).

The traditional concept of a steroid and its receptors interacting with a sequence of DNA to form new proteins has been extended dramatically by the discoveries of estrogen receptor subtypes ($ER\alpha$ and six isoforms of $ER\beta$), DNA binding elements (ERE, AP-1, CRE and SRE), membrane actions (receptor and nonreceptor-mediated), and intracellular signal transduction (MAPK and PKA). As do other steroids, androgens can exert their actions through intracellular receptors. Although the regional distributions of androgen receptors and their mRNA vary somewhat among species and experiments, studies report high concentrations of receptor and mRNA in pyramidal cells of rats (43), humans (85), and fetal monkeys (65).

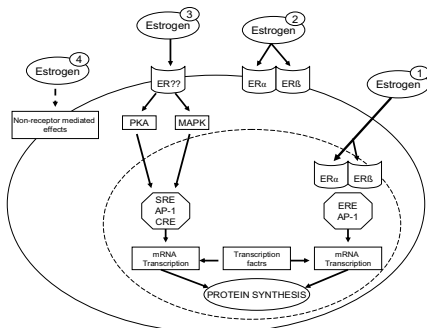


Figure 2 Four types of steroid mechanisms postulated to mediate the effects of estrogen on cellular function.

$ER\alpha$, $ER\beta$ – estrogen receptors, $ER?$ – unknown estrogen receptor; ERE – estrogen-response element; AP-1 – activator protein 1; PKA – protein kinase A; MAPK – mitogen-activated protein kinases; SRE – steroid response element; CRE – cyclic AMP response element(Dohanich,2002)

The density of neurons with androgen receptor mRNA in the hippocampus and cortex is much higher than the density of neurons with estrogen receptor mRNA (79). However, the receptor subtypes and novel mechanisms identified for estrogen action have not been documented for androgens (23).

THE ROLE OF OVARIAN HORMONES AND COGNITION IN NONHUMANS

Although the roles of estrogen, progesterone, and testosterone in the activation and maintenance of reproductive function are well established, emerging evidence indicates that these same steroids influence performance on measures of learning and memory in various species, including humans. These effects are complex and vary with task, gender, and age, as well as the regimens of steroid exposure (23). Estrogen can affect performance on appetitive and aversive tasks; spatial and nonspatial tasks; conditioning; and acquisition, consolidation, and retention. However, the effects of steroids on learning and memory often are moderate in magnitude and can improve, impair or not affect performance on various measures of learning and memory (23). Progesterone has received limited attention in the area of learning and memory. This steroid often augments the actions of estrogen on reproductive functions and may have similar synergistic effects on cognitive performance when combined with estrogen under certain conditions.

As data on the cognitive effects of estrogen and progesterone have accumulated since the 1990s, many researchers and clinicians have become concerned by the complexity of the findings.

Estrogen has been found to improve, impair, or not affect performance on various tasks of learning and memory. Steroids effects are task dependent and possibly memory-dependent, as pointed out by Sherwin (76,77,78) in humans. It also should be noted that the classification of memory types and the underlying neural systems continue to be issues of intense controversy in the general field of learning and memory from which the study of the cognitive effects of steroids is not immune.

Estrogen enhances performance on some appetitively motivated tasks and impairs performance on some aversively motivated tasks, but not consistently. Another proposed framework is based on the division of cognitive tasks as hippocampal vs extrahippocampal (49), supported by evidence that 2 weeks of estrogen treatment in ovariectomized rats impaired hippocampally dependent spatial reference memory in a radial arm maze (32). A third context in which to study steroid effects is based on the division of working memory vs reference memory.

Working memory can be defined as the storage of information that is useful within a single trial and for short durations; reference memory has been defined as the storage of information that is useful over many trials and for long durations. Although this division of memory continues to have its supporters, critics, and indifferents, it provides another model to frame the complex actions of ovarian steroids on learning and memory. Available data indicate that endogenous or exogenous estrogen enhances performance on tasks that depend primarily on working memory, but usually fails to alter or even impairs performance of reference-memory tasks (11,18).

Structural change associated with ovarian steroids

It has been known for some time that estrogen exerts powerful effects on neuronal structure, particularly in developing cells and tissues (86,87), in reproductive regions (30), and during reactive growth following neuronal damage (36,56,84).

One mechanism by which estrogen might influence learning and memory is through the restructuring of dendrites and synapses, particularly in the female hippocampus and cortex. For example, in the dentate gyrus, aged rats ovariectomized for long periods experienced a severe loss of dendritic spines that was restored by short-term, but not long-term, estrogen replacement (52).

The density of synapses and shapes of boutons in the stratum radiatum of the CA1 region also correlated positively with fluctuation of estrogen levels during the estrous cycle or following estradiol treatment (97,98). Based on increases in NMDA receptor binding (93,98) and decreases in GAD (57) induced by estrogen in CA1 of the hippocampus, estrogen appears to act on intracellular or possibly other receptors associated with GABAergic interneurons to reduce their inhibition on nearby CA1 pyramidal cells. This hypothesis was supported by evidence that estrogen-induced spine growth was prevented by NMDA receptor blockers (97) or an estrogen receptor antagonist (50).

The enhanced activity of these disinhibited pyramidal cells is associated with increases in NMDA receptor binding along with changes in the structural and electrical properties of the cell (98). Evidence also indicated that subcortical inputs to CA1 via the fimbria and fornix may contribute to the action of estrogen on spine density (46).

Electrical change associated with ovarian steroids

Endogenous and exogenous estrogen alters the electrical properties of neuronal circuits in cycling female rats. Long-term potentiation is an electrophysiological phenomenon in which strong electrical stimulation of afferents to an area induces long-term changes in synaptic efficiency that have been postulated to represent learning (7).

Several studies reported that at proestrus, when endogenous estrogen levels are elevated, or following exposure to exogenous estradiol, long term potentiation in the CA1 response to Schaffer collateral stimulation was enhanced under both *in vivo* and *in vitro* conditions (17,29,34,91). Additional *in vitro* studies reported no effect of estrogen on long-term potentiation (LTP) parameters in adult rats (2,38), as well as a suppression of LTP by estrogen in prepubertal females (38).

The induction of long-term depression in CA1 was found to be decreased at proestrus *in vivo* (34), but increased in the CA1 of the hippocampus taken from ovariectomized rats treated with estradiol (22).

THE ROLE OF ANDROGENS IN NONHUMAN COGNITION

Compared to estrogen, there is a more limited scientific literature on the role of androgen in learning and memory. Many of existing reports focus on gender differences in performance on a variety of land and water mazes.

Males were reported to outperform females on a number of spatial and nonspatial tasks (3,4,6,19,20,24,41,63,93), although not in all cases (9,42,89). Various nonmnemonic factors, such as activity, anxiety, and pain sensitivity, have been proposed to account for reported differences by some investigators (4,89).

Investigators manipulated the early hormone environment to determine the consequence of perinatal androgen exposure for learning and memory performance in adulthood (89,94).

In a later study, male rats castrated on the first day of life again performed like normal females when tested on a 12-arm radial maze, but performed worse than normal males or females treated with estradiol on the first 9 days of life (94). The results suggested that masculinization of spatial learning and memory depends on the conversion of testosterone to estradiol. In addition, it was proposed that early exposure to androgen or estrogen shifted a female's learning strategy from dependence on both landmark and geometry cues to a more efficient but less flexible dependence on only geometry (94). Alternatively, in humans, women typically used landmarks to learn to navigate a virtual water maze, whereas men used both landmarks and geometry (74).

Administration of testosterone during the first week of life improved the performance of female rats but impaired the performance of males in a radial maze and a water maze, possibly due to its organizational effects on the development of the dentate gyrus (68). Similar organizational effects were described earlier in rhesus monkeys when females treated with testosterone during development showed object discrimination equivalent to that of untreated males (15). These studies indicate a relationship between early androgen exposure and later spatial ability.

The ability of androgen, possibly following conversion to estrogen, to affect the development of cognitive abilities wanes after the first 10 days of life. Furthermore, in gonadally intact adult male rodents, exposure to testosterone or other anabolic steroids for 1-3 months did not affect acquisition or retention in the standard reference memory version of the water maze in male rats or voles (15,31).

Testosterone and anabolic androgens also failed to affect performance in a working memory version of the radial arm maze task, the gonadectomy of male rats (44).

For tasks motivated by shock, testosterone was reported to impair the acquisition and retention of active avoidance behavior (27), whereas testosterone and norandrostenedione improved the retention of passive avoidance responses over short-term and long-term intervals (28,90).

The effects of androgens in human cognition

Gender differences in human cognition have intrigued investigators for many years, driven by both scientific and social factors. Studies have identified weak but significant differences between the overlapping distributions of male and female abilities, with women reported to perform better as a group than men on verbal, perceptual, and fine motor tasks, but poorer than men on spatial and quantitative measures (76).

As suggested by studies in other species, differences in brain structure established during development by the presence or absence of androgen probably account for performance differences between the sexes (58). Based on evidence from studies of adults, it has been suggested that androgen levels correlate negatively with performance on verbal tasks, but positively with performance on spatial tasks.

Endogenous testosterone levels determined from plasma or saliva samples have been positively correlated with the performance of men on spatial measures (12,13,25) and testosterone supplementation selectively improved spatial performance in elderly men and female-to-male transexuals (39,88). There also is evidence that endogenous and supplemental testosterone impaired performance on some verbal measures (12,13,64,88), but improved the object location (66).

Structural change associated with androgens

Both androgens and estrogens support the maintenance of synapses in hippocampus and prefrontal cortex in animal models. For instance, gonadectomy or ovariectomy cause a profound loss of synapse density in hippocampus of male and female rats (46,97) and monkeys (47). In young and middle-aged animals, estradiol replacement restores synaptic density in female animals, but not in male animals. In contrast, estradiol is neuroprotective for ischemia-induced damage if administered just before or immediately after the period of injury in both male and female animals (33).

The effects of androgens in synaptic densities of pyramidal cells from CA1 hippocampal region was study on the ovariectomized rats (47). A weak but significant enhance of synaptic spine density was reported on ovariectomized rats after dehydrotestosterone treatment, an aromatizable androgen (47).

THE EFFECTS OF GLUCOCORTICOIDS ON MEMORY

Given the inverted U-shaped dose-response function observed in many studies (62,67), too much acute stress and excessively high glucocorticoid levels can also be detrimental to memory processes. Furthermore, it is important to point out that the concept of memory also comprises the retrieval phase during which previously learned information is remembered. Anecdotal evidence tells us that stress has a detrimental effect on memory retrieval. Most people have experienced problems remembering certain information when they were nervous and stressed, for example in test situations or job interviews. Experimental evidence confirming this comes from the work of de Quervain and colleagues (61) who found that footshock 30 min prior to a retention test impaired rats performance in the Morris water maze. This effect was blocked by prior administration of the corticosterone synthesis inhibitor metyrapone. Pre-test administration of corticosterone also impaired performance. De Quervain et al. (2000) showed the same effect in humans. Pre-test administration of cortisone impaired delayed free-recall of a word list in a long-term declarative memory study, as compared to the placebo condition.

In other studies, the effects of glucocorticoids on memory retrieval cannot easily be dissociated from effects on extinction and/or expression of memory. Quite a number of studies have investigated the effects of glucocorticoids on extinction in animals and even though the overall impression of these studies is that glucocorticoids might facilitate extinction not all studies may be comparable. Further, there may be overlapping and possibly even opposing effects on retrieval and expression of behavioural inhibition in some studies. For example, some forms of behavioural inhibition such as freezing (16), the ontogenetic development of freezing and acquired immobility in a forced-swimming paradigm are thought to be directly affected by glucocorticoids. In certain experimental procedures this can lead to difficulties in the interpretation of the results. While this might indicate a role of corticosterone in the expression of freezing, it also appears to contradict the finding of de Quervain et al. (1998) that glucocorticoids impair retrieval, as well as those findings mentioned above that reported a facilitative effect on extinction. Given the opposing effects of acute glucocorticoid administration on memory consolidation on the one hand and chronic glucocorticoid administration in general or acute glucocorticoid administration on memory retrieval on the other hand, it is hardly surprising that some confusion exists when talking about the role of glucocorticoids in memory. This further elucidates the importance of considering the experimental design carefully when interpreting the data.

Studies investigating glucocorticoid memory modulation on anatomical and molecular level

A great number of studies investigating the neural loci of glucocorticoid memory modulation have been carried out by Roozendaal and colleagues. In summary, they have proposed a model of glucocorticoid memory modulation according to which glucocorticoids dose- and time-dependently modulate memory consolidation by activating GRs in different brain areas, e.g. in noradrenergic soma, the BLA and the hippocampus. As a result, glucocorticoids facilitate stress-induced noradrenergic neurotransmission and formation of cyclic adenosine monophosphate (cAMP) / protein kinase A (PKA) in the BLA, which coordinates and influences memory storage in other brain areas, such as the hippocampus, possibly involving the nucleus accumbens (NAC) as a site of convergence, through projections via the stria terminalis (ST).

These findings are consistent with recent evidence suggesting that glucocorticoids do not uniformly modulate memory of all kinds of information but, rather, preferentially influence the consolidation of emotionally arousing information (10,59). Glucocorticoid effects on memory consolidation may depend on emotional arousal because of critical interactions with training-induced noradrenergic activation of the amygdala. However, glucocorticoids not only influence the formation of long-lasting memory; there is evidence that they impair the retrieval impairment (61, 69).

Stress exposure or glucocorticoids administered systematically shortly before retention testing induces retrieval impairment of spatial/contextual information in rats and of declarative information in humans. These effects appear to depend predominantly on glucocorticoid activation in the hippocampus as local infusion of the specific glucocorticoid agonist RU 28362 into the hippocampus induces similar memory retrieval impairment. Furthermore, cortisone administration to human subjects shortly before retention testing reduces regional blood flow in the medial temporal lobe (parahippocampal gyrus), an effect that correlated with declarative memory retrieval impairment (21).

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