

# Effects of sex steroid hormones on memory

Assunta Pompili<sup>1,2\*</sup>, Carla Iorio<sup>1</sup> and Antonella Gasbarri<sup>1,2</sup>

<sup>1</sup> Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy, <sup>2</sup> Fondazione Santa Lucia, IRCCS, Rome, Italy,

\* Email: [assunta.pompili@cc.univaq.it](mailto:assunta.pompili@cc.univaq.it)

Many evidences have elucidated relevant mechanisms of action of estrogen, progesterone, and testosterone on cognition, including learning and memory processes, both in animal models and humans. This influence may depend on their modulator role on several neurotransmitter systems, and the extensive presence of their receptors in cerebral areas, involved in cognitive functions, including the amygdala, hippocampal formation, and cerebral cortex. The present brief review summarizes data of our research and others with the aim of clarifying, in mammals, the involvement of sex hormones on memory. In particular, after an introduction illustrating the general mechanisms of sex hormones modulation on memory processes, the specific role of estrogen, progesterone and testosterone in memory is described in three different sections. Besides summarizing the most relevant actions of sex steroid hormones in the modulation of learning and memory, in this review is also emphasized that many aspects and mechanisms are still not completely understood and extensive future research is necessary to elucidate them.

**Key words:** sex hormones, estrogen, progesterone, testosterone, learning and memory

## INTRODUCTION

Sex hormones are steroids produced predominantly by the reproductive glands, either the ovaries or testes, including estrogens, progestogens and androgens. Besides influencing reproductive behavior, gonadal hormones are also assumed to have an influence on many cerebral function (Fig. 1). Gonadal steroids have an impact on many cerebral functions, including brain development, synaptic plasticity, and modulation of neurotransmitter systems, such as acetylcholine (ACh), serotonin (5-HT), dopamine (DA), and gamma-aminobutyric acid (GABA) (Diekhof and Ratnayake, 2016; Marrocco and McEwen, 2016; Lai et al., 2017; McEwen and Milner, 2017) as well as on emotions and cognitive functions, including memory, on animals and humans (Hamson et al., 2016; Marrocco and McEwen, 2016; Pletzer et al., 2019; Kobayashi et al., 2020). Estrogen and progesterone receptors are present in cerebral regions involved with the stress response and mood regulation, such as the hypothalamus, hippocampal formation (HF), amygdala, and prefrontal cortex. A correlation exists

between estrogen and schizophrenia, which is known to be affected by 5-HT function. A deficit in estrogen exposure may influence the thickness of cortical gray matter, which may be reversed by higher levels of estrogen that may induce neuroprotective mechanisms. These results support both the estrogen deficiency and protection hypothesis. Sex hormones directly influence the hypothalamus and HF that are involved in several cognitive functions, including memory and emotion (Haimov-Kochman and Berger, 2014; Marrocco and McEwen, 2016; Heck and Handa 2019).

## Brain anatomy and function: gender differences

Sex steroids are involved in the organization of neural networks during the prenatal period. In men, the overall brain volume is bigger, compared to women, and sex-specific regional differences were also evidenced. In fact, while amygdala and hypothalamus are larger in men, striatum (ST) and HF are bigger in women (Brierley et al., 2002; Hines 2010; Persson et al.,

2014). The distribution of estrogen receptors (ERs) and androgen receptors (ARs) could be responsible, at least in part, of these differences.

Dopaminergic transmission is enhanced in women, compared to men, and the availability of D2 receptor may differ, as a consequence of the oscillations of sex hormones, during the menstrual cycle (Laakso and Vilkmann, 2002; Diekhof and Ratnayake, 2016). The DA transporter, regulating synaptic DA availability, is higher in women than in men (Lavalaye et al., 2000; Mozley et al., 2001; Staley et al., 2001). Healthy women, compared to men, may show higher presynaptic dopaminergic tone in ST, and bigger extra striatal DA receptor density and availability (Kaasinen, 2001; Laasko et al., 2002). Even if less studied, differences between men and women have been reported also for other receptor systems, such as the Ach system (involved in cognition, including memory processes), the GABAergic system (implicated in mood and memory), and the

opioid system (involved in pain and reward processes). Women, compared to men, have higher numbers of cortical muscarinic Ach receptors (Yoshida et al., 2000) and cortical GABA levels, as measured with magnetic resonance spectroscopy (Sanacora et al., 1999). Cortical GABA levels also fluctuate across the different phases of the menstrual cycle: in fact, in healthy women they decrease between the follicular and luteal phase, while in women with premenopausal dysphoric syndrome they increase, suggesting that GABA neurotransmission is strongly related to the specific phase of the menstrual cycle which, therefore, provides an exceptional opportunity to study whether and how minor fluctuations of sex hormones may affect cognition (Epperson et al., 2002; Haimov-Kochman and Berger, 2014). The influence of gonadal steroids may underlie cognitive differences between the sexes, such as the general better performance of men on visuospatial tasks opposed to the better performance of women on verbal, fine mo-

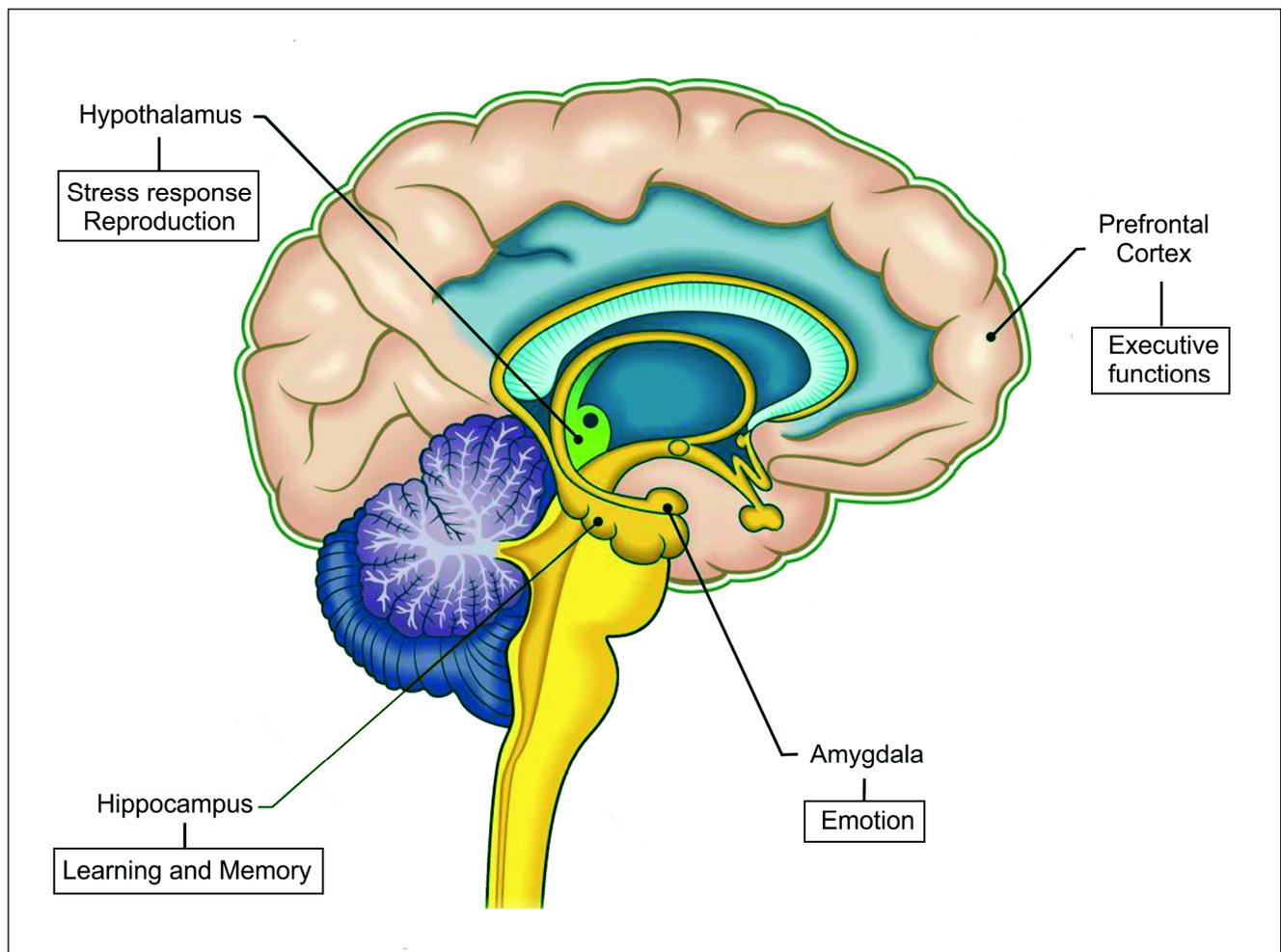


Fig. 1. Effects of sex hormones on different brain areas. Besides influencing reproductive behavior, gonadal hormones are also assumed to have an influence on many cerebral function.

tor and some memory tasks (Sherwin, 2012). In women, cognitive performance in female-favoring tasks is enhanced during the luteal phase, when estrogen level is high and progesterone increases; in contrast, performance in male-favoring tasks is better during the menstrual phase (Warren et al., 2014). In women with polycystic ovarian syndrome, higher serum testosterone levels have been related with better performance in male-favoring cognitive tasks (Barry et al., 2013). In general, while estrogen has a positive influence on cognition (particularly in female-favoring tasks, such as verbal memory), progesterone exerts negative effects (Sherwin, 2012; Hogervorst, 2013). Strangely enough, both sex steroids show neuroprotective effects *in vitro*, probably due to the activation of pro-survival pathways and the inhibition of proapoptotic cascades (Lockhart et al., 2002; Sribnick et al., 2004; Kaur et al., 2007; Yao et al., 2007; Atif et al., 2009). *In vivo*, important findings from naturally healthy cycling women showed different brain activation patterns between the follicular and the luteal phase, that could explain, at least to some extent, the differences in the action on cognitive functions of the two different hormones (Toffoletto et al., 2014). The overall effects of sex female hormones on cognition are very complex, and they may interact in ways still not completely understood.

Finally, even though much of the evidence on gonadal-induced neuroplasticity, related to learning and memory processes, centers on the effect of estrogens, data related to neurotrophic actions of androgens also exist (Colciago et al., 2015).

### Role of estrogens in memory processes

Many studies have suggested that estrogens have a role on many cognitive functions, including learning and memory (Gasbarri et al., 2008a, 2008b, 2009, 2012, 2019; Pompili et al., 2010, 2012, 2016; Toffoletto et al., 2014; Lacreuse et al., 2015; Gervais et al., 2017). These effects may depend, at least in part, on their modulation on different neurotransmitters, such as Ach, catecholamines, serotonin and GABA, both in animals and human/non-human primates (Almey et al., 2015; Diekhof and Ratnayake, 2016; Marrocco and McEwen, 2016; McEwen and Milner, 2017). ERs are present in several limbic areas correlated to learning and memory, comprising the HF, AMY, and cerebral cortex in rodents, monkeys, and humans (Sherwin 2012; Bean et al., 2014; Sheppard et al., 2019). Considering the modulatory effect of estrogen on cognitive processes, their menstrual cycle-related fluctuations may have different actions on numerous cognitive tests. In fact, data obtained in tests of articulator and fine motor skills during the

late follicular and mid-luteal phases evidenced improved performance compared to menses; conversely, impaired performance on tests of spatial ability were reported. Then, differences in estradiol levels can explain, at least in part, these effects (Sandstrom and Williams, 2004). The evaluation of performance during the estrous and menstrual cycles revealed that ovarian hormones affect cognitive functions and cerebral areas, related to learning and memory, in both rodents (Pompili et al., 2010; 2012; Lacreuse et al., 2015; Frick et al., 2018) and human and non-human primates (Gasbarri et al., 2008a; 2008b; Lacreuse et al., 2015; Hara et al., 2018). Even though important progress on the knowledge of the role of estrogen in cognition and neuronal survival have been made, conflicting opinions still exist regarding the efficacy of estrogen replacement therapy as a treatment and protective role for cognitive impairments related to aging, disease and injury (Pike et al., 2009; Azcoitia et al., 2011). Estrogen can induce its effects on cognition by binding specific ERs (ER $\alpha$  and ER $\beta$ ), localized in several brain areas, such as the amygdala, HF, cerebral cortex, basal forebrain, locus coeruleus, midbrain raphe nuclei, cerebellum, central grey matter, and glial cells (Sherwin et al., 2008; Sherwin 2009; Almey et al., 2015). The prevalent presence of ER $\alpha$  in the amygdala and hypothalamus suggests estrogen modulation of autonomic and neuroendocrine, as well as emotional functions; on the other hand, ER $\beta$  is mostly found in the HF, entorhinal cortex and thalamus, suggesting a role in cognition, including learning and memory (Almey et al., 2015). In the rat brain, the presence of both receptors in the cerebral cortex, pituitary and hypothalamus was reported, while the cerebellum contains only ER $\alpha$  and the HF contains mostly ER $\beta$  (Genazzani et al., 2007). Memory represents one of the most important aspects of cognition influenced by estrogens (Gasbarri et al., 2008a; 2008b; Pompili et al., 2010; 2012; Arnone et al., 2011; Gasbarri et al., 2012). The episodic memory could depend on the integrity of the medial temporal lobe (Squire, 2009). Aging often involves a remarkable decrease of episodic memory (Weintraub et al., 2009). The HF, and specially its dorsal part, represents one of the most studied areas involved in memory, which are directly influenced by estrogens. Besides spatial memory, it also controls the formation of episodic memory. In laboratory animals, estrogen affects the HF and its functions; the basal forebrain cholinergic cells, expressing ER $\alpha$  and projecting to HF, are also involved in cognition (Gonzales et al., 2007; Gibbs et al., 2009).

ER $\alpha$  and ER $\beta$  contribute differently to memory mechanisms: in fact, some actions are modulated by  $\alpha$  and  $\beta$  ERs of HF pyramidal cells (Rhodes et al., 2006). It is important to underline that estrogens or ER $\beta$  agonists

improve performance in some hippocampal-dependent memory tasks (Liu et al., 2008). In vivo, selective ER $\beta$  agonists increase the amount of key synaptic proteins in HF; in ER $\beta$  knockout mice or after treatment with an ER $\alpha$  agonist, these effects were not present confirming the action of ER $\beta$  in memory; however, cross-talk between the two ER cannot be excluded.

Previous research studies suggested hypothesized that newly acquired information is transferred to long-term memory over time, and seminal studies by McGaugh (McGaugh, 2000) have revealed that consolidation occurs within 1 to 2 h post training. The impairment or improvement of the consolidation process can occur, if the drugs or hormones are administered within this time, but not later. Estrogenic improvements in consolidation employing post-training paradigms have been evidenced in some memory tasks, such as the Morris water maze, object recognition, and object placement, inhibitory avoidance (Rhodes and Frye, 2006; Walf et al., 2015).

Estrogen not only influences memory formation and maintenance processes in some situations, but also biases the learning strategies employed to resolve a task, therefore altering what and how information is learned, and thus not only how much is learned, e.g., the strength of the memory. Rats with elevated estrogen levels employ place or allocentric strategies quite successfully, outperforming hormone-deprived rats on tasks requiring the configuration and use of extra-maze cues for effective completion. Nevertheless, rats with low estrogen levels have a tendency to utilize response or egocentric strategies during tasks where the use of a directional turn, e.g., left or right, is necessary for acquisition (Korol and Pisani, 2015). Taking into account its wide range of actions on different nervous systems, estrogen may influence cognition by changing the relative involvement of specific memory systems, acting like a conductor, orchestrating the dynamics, timing and coordination of various cognitive strategies during learning (Korol and Pisani, 2015; McGaugh 2000).

The HF is essential for memories involving spatial, relational and contextual information, and it is only needed for consolidation and not the long-term storage of such memories (Boulware et al., 2011). The prefrontal cortex (PFC), mainly the dorsolateral part, is also critically necessary for memory, particularly working memory. However, a great deal of evidence suggests that the PFC subserves a range of cognitive functions broader than the HF, comprising episodic memory and executive function, such as verbal fluency, planning, judgment and mental flexibility. As we have previously mentioned, many studies reported that ER $\alpha$  and ER $\beta$  are expressed in areas that are

essential for learning and memory (McEwen 2002), providing an opportunity for estrogens to influence the functioning of these regions of the brain and the memory mechanisms they subserves. In fact, estradiol may affect performance of learning and memory tasks, as reported in studies on animal models and humans (Daniel, 2006; Luine, 2008). Since estrogen exerts its actions on several systems, complex cognitive processes such as learning and memory could result from the interaction between the influences on many cerebral regions, including the PFC, HF, basal forebrain and ST (Spencer et al., 2008). In particular, the basal forebrain contains Ach neurons projecting to the cerebral cortex and HF, where they have a relevant role in learning, memory and attention. It is very well known that estradiol influences cholinergic neurochemistry in the basal forebrain and HF in different ways; in particular, it increases the affinity choline uptake and choline acetyltransferase activity in the basal forebrain and its projection areas to CA1 and the frontal cortex (Gibbs, 2010); moreover, it regulates Ach release in the HF and the overlying cortex (Luine 2014). Several studies reported a correlation between the capability of estradiol to modulate cholinergic neurotransmission and to cause changes in the CA1 field of the HF (Newhouse and Dumas, 2015). In vivo, learning induces long-term potentiation (LTP) in HF (Whitlock et al., 2006) and estrogen has been shown to induce chemical, morphological, and physiological changes in the HF (Frick et al., 2015; Mukai et al., 2010; Whitlock et al., 2006). The recent research on laboratory animals has evidenced the relevance of ERs as mediators of synaptic plasticity (Arevalo et al., 2015; Brinton 2009). As shown by *in situ* hybridization, although both the ER $\alpha$  mRNA and the ER $\beta$  mRNA are expressed in the HF, ER $\beta$  mRNA is more abundant. Estrogen has an important effect on dendritic morphology in HF synapses. In the CA1 of female rats, the density of dendritic spines on pyramidal neurons and the density of synapses in the stratum radiatum vary according to plasma estrogen levels (Brinton 2009). In rats, hippocampal CA1 contains 30% higher spine density in late proestrus, when estrogen is high, compared to late estrus, when estrogen is low (Gonzales et al., 2007; McEwen and Milner, 2017). Moreover, compared to estrous, during proestrus rats have a higher proportion of mushroom shaped dendritic spines that are considered be a stronger, more mature subcategory of spines (Gonzales et al., 2007). Then, during estrous cycle, there is a natural oscillation in spine density and shape as a consequence of fluctuating levels of gonadal hormones. Comparable results have been shown after exogenous hormones administration to ovariectomized rats (Brinton, 2009). Many findings suggest that the increase in synapse and

spine density in CA1 pyramidal cells is mediated by NMDA receptors (Leuner and Shors, 2004; Shors, 2004; 2016; Brinton 2009; Shors and Millon, 2016). Estradiol treatment increases the sensitivity of CA1 pyramidal neurons to NMDA receptor-mediated synaptic input, which positively correlates with dendritic spine density. Findings indicating a connection between the estrogenic improvement of HF functionality and regulation of dendritic spine dynamics in rats are consistent with findings on non-human primates, suggesting that some estrogen action in the HF is preserved from rodents to non-human primates, raising the probability that they could also be maintained in human primates (Protopopescu et al., 2008).

Estrogen action in learning and memory could consist in predisposing animals to utilize specific cognitive strategies (Korol and Wang, 2017). It is very well known that the multiple memory systems include distinct circuits process and store different informations. For example, spatial information is controlled by a circuit including the HF, while certain aspects of instrumental conditioning depend on the ST (Luine et al., 2008). Even though the direct effects of estrogen in the ST are less known, compared to HF, estrogen could enhance HF-dependent learning, while simultaneously it could impair ST-dependent learning (Korol and Kolo, 2002; Gibbs et al., 2004; Korol and Wang, 2017). The effect upon the DA system is the most extensively reported: specifically, estrogen has been reported to enhance DA levels. DA agonists improve performance on ST tasks, estrogen negatively influences ST-dependent maze performance (Korol and Wang, 2017). The elevated DA levels may increase D2 receptor activation, causing an impairment of ST-dependent performance (Korol, 2004). Nevertheless, DA may not be the exclusive cause of estrogen effects on ST-dependent learning; other neurotransmitters could play a role as well, such as Ach which is a target of the effects of estrogen on ST. It is important to note that estrogen-induced activation of the Ach system causes enhanced activation of muscarinic Ach receptors which, in turn, inhibits the glutamatergic afferent projections (Gibbs, 2010). Estrogen also directly impairs glutamatergic excitation by decreasing  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) binding in the ST (Cyr et al., 2001). Hence, multiple mechanisms may underlie an estrogen-induced reduction in ST output. Learning and memory deficits in rats have been reported after lesions of the Ach nuclei of basal forebrain (Rehman and Masson, 2005). Ovariectomized rats, continuously treated with estradiol, showed enhanced choline acetyltransferase mRNA in the medial septum and nucleus basalis magnocellularis. In these areas, cholinergic neurons contain high-affinity estrogen binding sites,

and a direct action of estrogen on Ach synthesis and/or release could explain the enhancement of memory. Short-term estrogen replacement therapy improved not only cholinergic parameters and spatial memory, but also behavioral impairments connected with cholinergic inhibition (Rehman and Masson, 2005). Even though the connection between estrogen and choline acetyltransferase expression is intricate, it is in agreement with the estrogen sensitivity of Ach neurons (Rehman and Masson, 2005).

The dorsolateral PFC is critical for the performance of working memory tasks in both humans and non-human primates (Funahashi, 2017). Many studies suggested that PFC contains ERs and is a major target for the action of estrogen on the brain (Maki 2005; Joffe et al., 2006). Immunohistochemistry research on the frontal cortex in humans, monkeys and rats evidenced the presence of ER $\alpha$ -positive cells through all layers of the PFC, in pyramidal and non-pyramidal neurons, with both nuclear and cytoplasmic immunoreactivity (Montague et al., 2008). In contrast to the action of aging, dendritic spine density in the dorsolateral PFC in both young and aged ovariectomized monkeys was enhanced by cyclical estrogen administration (Hao et al., 2007). Estrogen has a role in the action of many neurotransmitters in the PFC; in fact, the excitability of PFC pyramidal cells is influenced by DA and 5-HT afferents originating from the brain stem (Maki, 2009). The effect of the physiological fluctuation of estradiol on working memory was examined in healthy young women, demonstrating that estradiol levels influence working memory and the effects are related to baseline DA (Jacobs et al, 2011). Neuroimaging studies have confirmed that estrogen can influence functions dependent on PFC, such as working memory (Maki, 2005; Joffe et al., 2006; Badre and Wagner, 2007).

### Role of progesterone in memory processes

In females, progesterone is synthesized mainly by the ovary, whereas in males it is produced principally in testes and adrenal cortex. The physiological effects of progesterone are correlated to its interaction with particular intracellular receptors (PRs) expressed as two protein isoforms, PR-A and PR-B. Progesterone exerts an important neuroprotective role, which can be effective to counteract the cognitive decline related to aging. Both in adult and developing brain, progesterone contributes to the decrease of HF spines and spine synapses, evidenced through the estrous cycle phases (Murakami et al., 2017). The injection of progesterone in ovariectomized rats has a biphasic action on spine density of CA1 pyramidal neurons: in fact, progester-

one treatment following estrogen at first enhances spine density, but then induces a more severe reduction compared to that evidenced after an acute administration of estrogen alone (Murakami et al., 2017). Neural mechanisms through which progesterone affects HF function and memory formation are still not completely understood. Nevertheless, similarly to estrogen, progesterone can also potentiate neurogenesis (Liu et al., 2009; Zhao et al., 2011), cell-signaling pathways (Orr et al., 2012), and HF LTP (Foy et al., 2008). However, taking into account that progesterone represents an essential precursor for the synthesis of other steroids (including estrogens, androgens, and glucocorticoids), its effects on HF function could depend on the transformation in other steroids that consequently bind to their equivalent receptors. Moreover, progesterone has in common with estrogen the complication that it can bind to two kinds of PR: classical intracellular PRs, involved in slow transcription-mediated events, and plasma membrane-bound receptors, regulating rapid cell signaling-initiated actions (Fig. 2).

Thus, progesterone may influence HF memory in different modalities, such as binding to intracellular PRs that translocate to the nucleus and initiate gene transcription at a progesterone response element, binding to membrane-bound receptors and quickly activating cell-signaling cascades. In the HF, intracellular PRs are situated within cell bodies, dendrites and their spines, axons of main cells in CA1, CA3, and the dentate gyrus, as well as in GABAergic interneurons and glia cells (Mitterling et al., 2010; Murakami et al., 2017). Then, similarly to ERs, PRs action is exerted locally in order to regulate HF function. Actually, when progesterone was injected in the dorsal HF of ovariectomized mice, the activation of extracellular signal-regulated kinase (ERK) and mammalian target of rapamycin (mTOR) cell signaling in the dorsal HF was evidenced within five minutes (Orr et al., 2012). Remarkably, progesterone shows a biphasic effect on p42 ERK activation, enhancing phospho-p42 ERK levels five minutes after infusion and then reducing levels 15 min after infusion, before reaching again the baseline after 30 min (Orr et

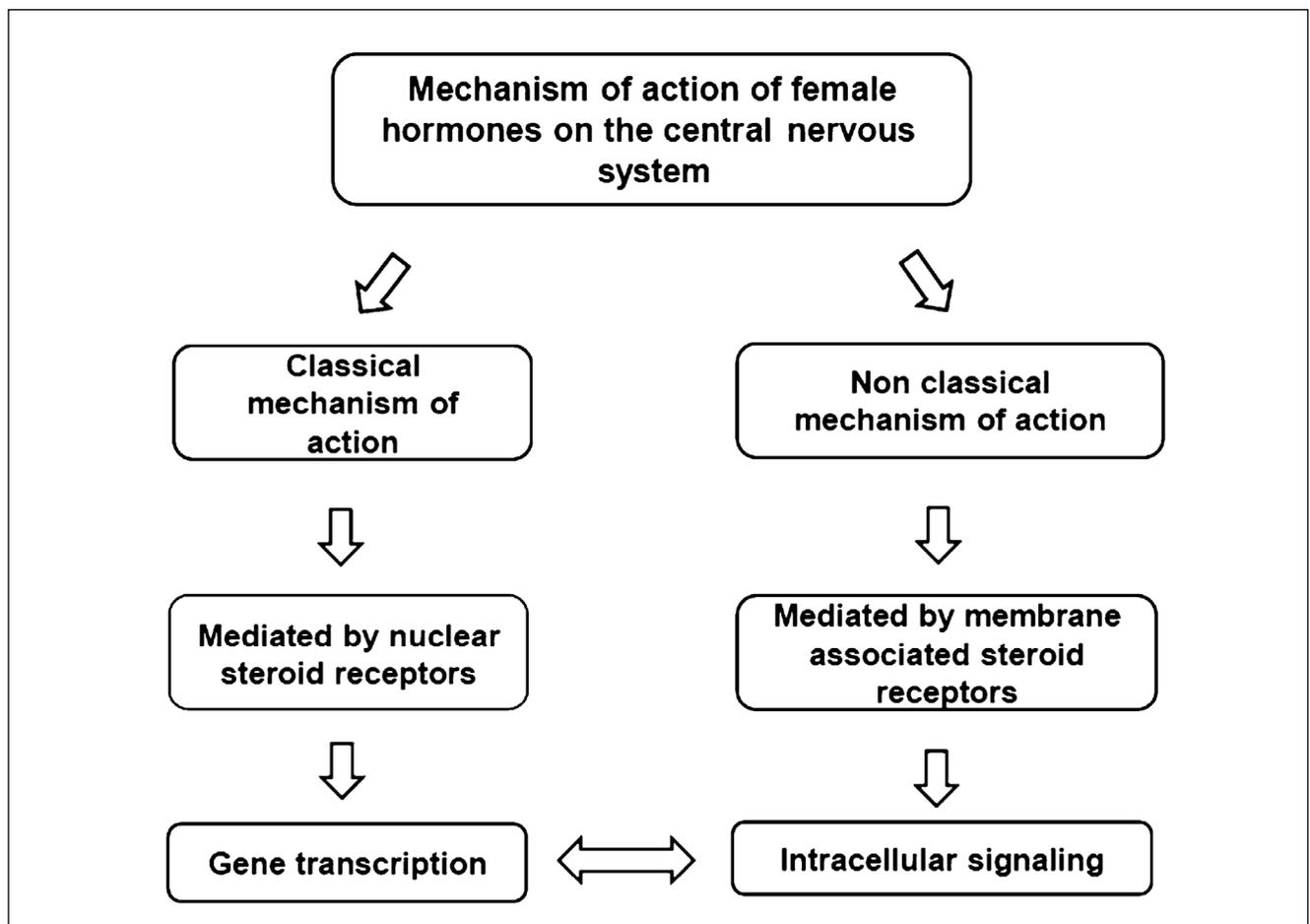


Fig. 2. Action of female hormones in the central nervous system. Genomic (or classical) and non-genomic (or non-classical) mechanisms of action of estrogens and progesterone.

al., 2012). This biphasic effect of progesterone on HF function makes even more difficult to understand how it regulates HF memory. In the two decades since the preliminary indication that ovarian hormones control the dendritic spine density in CA1, much research has focused on the role of progesterone on memory in rodents, human and non-human primates (Barros et al., 2015; Lacreuse et al., 2015; Tuscher et al., 2015; Walf et al., 2015; Gervais et al., 2017). Even though an exhaustive evaluation of this literature is beyond the aim of this review, some wide generalizations may be drawn, principally among rodent studies. The influence of progesterone on HF memory differs according to its administration relative to training and testing. It is important to note that progesterone treatment is often given in combination with estrogen, whose levels increase before those of progesterone, during the physiological estrous cycle. Some studies, utilizing the Morris water maze to evaluate spatial memory in aged female mice, have reported that systemic administration of progesterone immediately post-training prevents the memory-enhancing effects of estrogen (Harburger et al., 2007; 2009), while other studies evidenced that the combined treatment of estrogen and progesterone increases memory on object recognition, in young ovariectomized mice (Harburger et al., 2009). Analogously to those of estrogen, also the molecular mechanisms by which progesterone influences HF memory consolidation are not completely understood. Nevertheless, it was hypothesized that progesterone regulates object recognition memory through cell signaling mechanisms similar to those of estrogen (Petralia and Frye, 2006; Orr et al., 2012). For example, progesterone induces rapid activation of cell-signaling pathways, including ERK (Singh 2001; Orr et al., 2012), phosphoinositide 3-kinase (PI3K) (Singh, 2001), and protein kinase A (PKA) (Petralia and Frye, 2006). It has been suggested that the post-training infusion of progesterone in the dorsal HF of young ovariectomized mice increases the memory consolidation in object recognition due to a rapid dorsal HF activation of ERK and mTOR, suggesting that progesterone may control memory utilizing cell-signaling mechanisms similar to those utilized by estrogen (Orr et al., 2012; Tuscher et al., 2015). However, potential PR mechanisms mediating these effects are not clear. In fact, the progesterone influence on memory and cell signaling may be completely unrelated to PRs, but it could depend on progesterone metabolites, such as estrogen, androgen, and allopregnanolone on estrogen, androgen, and GABAA receptors, respectively. Therefore, further research is necessary to better clarify the molecular mechanisms on the basis of progesterone action on object memory consolidation.

## Role of androgens in memory processes

Androgens have enhancing effects on cognitive performance, both in humans and laboratory animals, as well as a positive effect on mood. Moreover, the relevant decrease of androgen levels with aging and the higher risk of Alzheimer disease (AD) in hypogonadic patients, indicate that androgens could be relevant in preventing neurodegenerative diseases (Carroll and Rosario, 2012; Lei et al., 2018).

The broad spectrum of activity of androgens makes more complicate to understand their effects: in fact, they are the substrate for the synthesis of several active metabolites, whose production enhances and differentiates the intracellular actions of the circulating hormones (Labrie et al., 2003). Testosterone is transformed in estradiol and many 5 $\alpha$ -reduced androgens both in neurons and glial cells (Colciago et al., 2015). The 5 $\alpha$ -dihydrotestosterone (DHT), which represents the immediate product of testosterone reduction, is more effective than testosterone itself in bioassays of androgenic activity. Pyramidal CA1-CA3 neurons and granule DG cells also contain complete steroidogenic systems, catalyzing all the principal steps of steroidogenic pathways. A weak immunostaining of cytochrome P450s in glial cells suggests that their neuro-steroidogenesis activity may be much lower, compared to neurons (Hojo et al., 2011). Steroidogenic enzymes are located in both the presynaptic and postsynaptic terminals of pyramidal CA1-CA3 neurons and granule DG cells, suggesting a possible synaptic synthesis of estrogens and androgens, besides classical microsomal synthesis of sex steroids (Hojo et al., 2011). Then, circulating androgens in the brain may activate both ARs and ERs, according to the enzymatic pattern and the kind of receptors localized in the different brain regions. This happens also for the HF that develops as a dimorphic area according to genetic and hormonal inputs. In addition to the relevant effects of sex steroids on the morphological and functional characteristics of many cerebral regions, such as the HF and the hypothalamus, the expression of some genes, sited on both sex chromosomes and autosomes, affects the cerebral dimorphic development (Colciago et al., 2015). These genes play a role in several biological processes (such as androgens and estrogens signaling pathways, synaptic organization, cell proliferation and death), involved in the sex-related differences in the neural development, cognitive function and neurological diseases (Armoskus et al., 2014).

As far as we know, the presence and the role of ARs in most cerebral regions are not completely understood, even though data exist regarding their high concentration in brain regions known to be implicated in

the control of sexual behaviors, such as the hypothalamus (Scott et al., 2004).

In humans and several animal species, ARs are mostly located in the PFC, amygdala, and HF (Beyenburg et al., 2000). The results of studies, utilizing HF tissue specimens of patients undergoing epilepsy surgery, revealed that AR concentrations are similar to those found in the prostate, representing a classical androgen-dependent organ. Men and women did not present significant differences in AR transcript levels and in the specific lateralization pattern (Beyenburg et al., 2000). Physiologic changes in gonadal androgen secretion across lifespan may be involved in differences of cognitive functions; in addition, the relevant decay of androgen levels with aging, combined to decreased circulating androgens in AD patients, suggest that the conservation of androgen levels could be relevant for reducing the risks of neurodegenerative diseases (Moffat et al., 2004). Hence, several studies tried to elucidate the androgen influence on HF neurons and the specific mechanisms on the basis of these effects, but conflicting results are reported (Nowak et al., 2014). Some studies using the Morris water maze, to examine the effect of intra-HF injection of  $3\alpha$ -diol (a testosterone metabolite) on acquisition of spatial memory in adult male rats, evidenced a memory impairment, possibly via down-regulation of PKA (Assadiannarenji, 2013; Narenji et al., 2015). Sex differences in spatial and cognitive skills are correlated to sex-related differences in HF differentiation and morphology.

The local production of estrogens and androgens have an influence on LTD and LTP (Colciago et al., 2015). The role of androgens in influencing HF synaptic plasticity is still unclear and conflicting results are reported. Taking into account that, in general, testosterone and DHT decrease LTD, an opposite action of estrogens and androgens on synaptic plasticity has been suggested (Harley et al., 2000, Hebbard et al., 2003). It was hypothesized that estrogenic and androgenic neurosteroids are recruited throughout the specific synaptic activation inducing LTP and LTD, respectively, facilitating these mechanisms through interaction with their specific receptors. Actually, the induction of LTD is impaired by ARs antagonists (such as flutamide), while LTP is prevented by the ERs antagonists (such as ICI 162,040) (Pettorossi et al., 2013). An implication of locally synthesized estrogens in the activity-dependent synaptic plasticity has been evidenced (Grassi et al., 2009); however, it is still unclear whether local synthesis of androgenic steroids (testosterone and DHT) has a direct role in synaptic plasticity induced by neuronal activity.

It is well known that the regulation of dendritic connectivity in the HF and the establishing of new syn-

apses is directly related to the formation and maintenance of memory. While it is well known that estradiol modulates the oscillation of CA1 pyramidal cell spine synapse density across the estrous cycle of female rats (Luine and Frankfurt, 2012), the role of androgens on HF spine synapse growth has long been discussed (MacLusky et al., 2006). In HF CA1 neurons, testosterone induces spine density and influences spine maturation (MacLusky et al., 2006; Murakami et al., 2017). Many hypotheses have been suggested for the mechanism of testosterone-dependent spine maturation in the CA1, based on direct or indirect up-regulation of brain-derived neurotrophic factor (BDNF) (Gao et al., 2009; Li et al., 2012). Testosterone up-regulates BDNF expression involved in the dendritic growth of diverse neurons in particular cerebral, in different animal species (Li et al., 2012). The action of androgens is not restricted to the CA1 region; in fact, it has been reported that orchietomy in monkeys differentially influences spine synapse density in the CA3 neurons, inducing an impairment in the synaptogenesis that, compared to other HF regions, may be limited (Mendell et al., 2014). Moreover, it was evidenced that adult male rats, after gonadectomy, show an improvement in excitability, sprouting and plasticity, synaptic transmission and LTP of the mossy-fibers in CA3 cells (Skucas et al., 2013).

Morphology of dendritic spine is a relevant indicator of synaptic maturation and functionality; moreover, variations in dendritic spine morphology are connected with synaptic strength and maturity (Yuste and Bonhoeffer, 2001). At least three kinds of spines can be distinguished among CA1 neurons: thin-type spines, characterized by long and narrow necks, which are considered to be in a transitory morphological stage; stubby-type spines, lacking of a well-defined neck and head, which are probably immature; mushroom-type spines, which are thought to be the most stable type (Li et al., 2012). In CA1 neurons, testosterone induces spine density and controls spine maturation (MacLusky et al., 2006). In fact, castration induces an evident impairment of stable spine density, and an enhancement of the immature spine types (Li et al., 2012).

Dehydroepiandrosterone (DHEA) and its circulating active sulfate metabolite (DHEA-S) are the most important androgens secreted by the adrenal gland in humans. In the adrenal cortex, a pronounced impairment of their production represents the most representative age-related alteration (Goel and Coppola, 2011); therefore, intensive studies, which aimed to prevent the negative actions of DHEA deficit during aging, focused on DHEA and DHEA-S. In humans, also the brain produces these two androgens in substantial amounts. DHEA is reduced to 5-androstenediol in microglia (Jellinck et al., 2007), while it is hydroxylat-

ed to 7 $\alpha$ -hydroxy-DHEA in HF granule cells (Jellinck et al., 2005). In astrocytes, DHEA is transformed to androstenedione, which functions as a precursor to the synthesis of estrogens and androgens. As far as we know, no specific receptor for DHEA has been discovered. Numerous studies report the role of DHEA and DHEA-S on several receptors, such as GABA-R and NMDA-R, and also other relevant receptors probably involved, including glycine receptors, P2X purinoreceptors, ionotropic glutamate receptors, AMPA and kainate receptors, nicotinic Ach receptors (Starka et al., 2014). Therefore, it was suggested that, through the activation of this extensive multiplicity of receptors, DHEA may play significant roles as antioxidant, antilipidperoxidative, anti-inflammatory and, thus, antiaging factor (Starka et al., 2014). Amid the systemic modifications detected in aging, and probably related with DHEA and DHEA-S decrease, cognitive damage seems the most relevant. Some research evaluated the possible neuroprotective role of DHEA to prevent cognitive dysfunctions, as observed in AD. DHEA treatment, utilized in a rat model of vascular dementia, caused a remarkably enhancement in working memory, reference memory, Ach levels and BDNF expression in HF (Sakr et al., 2014). At the cellular levels, DHEA and DHEA-S reinstate age-related spine loss in CA1 neurons (Chen et al., 2014). Considering that DHEA and DHEA-S can be transformed into estrogen derivative products and androstenedione, their actions are regulated both by ERs and ARs (Starka et al., 2014). For example, the action of DHEA in enhancing spine density in CA1 pyramidal cells is related to the *in situ* aromatization and the activation of ERs (Mukai et al., 2006).

Even though several studies focused on cognitive dysfunction and AD in animal models suggest that the DHEA treatment may be useful, the majority of the clinical studies focused on the role of DHEA treatment on cognition evidenced lack of effect or only a minor effect on specific cognitive functions (Samaras et al., 2013). Nevertheless, most of the research was very short (from 2 weeks to 1 year) and was conducted on small groups of patients. Therefore, further studies are needed to better investigate the efficacy of DHEA as a possible treatment in human cognition.

## CONCLUSIONS

The past decades have witnessed an increasing interest of researchers for the role of hormones in cognitive functions, and important and consistent progress has been made in this field; in particular, many studies evidenced that sex steroid hormones, specially estrogens, are relevant for cognitive functions, affecting ce-

rebral areas critically involved in them, such as the HF and PFC.

The findings reported in the present review may give a contribution in elucidating the actions of sex hormones in the modulation of learning and memory, which represent the most relevant aspects of cognition. The knowledge of neurobiological factors of the relationship between sex steroid hormones and memory processes may be beneficial for the development of therapies focused to the treatment of disorders, associated to the phases of menstrual cycle, and also to reduction or prevention of cognitive deterioration in older women, which represents the fastest increasing segment of the population in industrialized countries. In addition, although many progresses have been made in the knowledge of the effects of sex hormones on cognition, in this review is also evidenced that several aspects are still unknown or not completely understood. Therefore, many critical questions remain open for future investigation.

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