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Estrogen Influences on Cognition

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1. Introduction

Sex steroids are hormones produced mainly by the reproductive glands, either the ovaries or testes, which share a similar basic structure of three hexane rings and a pentane ring. They include estrogens, androgens, and progestogens, and each has major effects on reproductive physiology (Henderson, 2009; Osterlund & Hurd, 2001). Estrogens are required for normal female sexual maturation; they promote growth and differentiation of the breast, uterus, fallopian tubes, vagina, and ovaries (Carr, 1998). Male reproductive tissues, such as testis and prostate, are also estrogen target tissues (Clark et al., 1992). In addition, estrogens have an important role in bone maintenance (Turner et al., 1994), and protection of the cardiovascular system (Farhat et al., 1996) .

Even though estrogens (e.g., 17β-estradiol) and progestogens (e.g., progesterone) are classified as female sex hormones and androgens (e.g., testosterone) as male sex hormones, this categorization is misleading. In fact, for example, estrogens are found both in men and women, and they have effects in both sexes; besides, they arise in tissues other than the ovaries (Osterlund & Hurd, 2001).

Among the sex steroids, estrogens are the best studied with respect to human non-reproductive behaviors. They exert a broad range of effects throughout the body, including the central nervous system (CNS), where their actions are not limited to the regulation of reproductive neuroendocrinology and sexual behavior (Henderson 2009, 2010, 2011; Ziegler & Gallagher, 2005). In fact, accumulating evidence points to their involvement in influencing the function of numerous neural systems and, presumably, different behavioral domains (McEwen & Alves, 1999; McEwen et al, 2001; McEwen, 2010; Ziegler & Gallagher, 2005). Recent studies have highlighted a number of important, global issues regarding the influence of estrogen on cognitive functions (Lacreuse, 2006; Luine, 2007, 2008; Markou et al., 2007).

A possible explanation for this effect can be represented by the modulator role exerted by estrogens on several neurotransmitter systems (such as acetylcholine, catecholamines, serotonin, and GABA), both in animals and humans (Amin et al, 2006; Dumas et al 2006). Another reason may lie in the widespread presence of estrogen receptors (ERs) in many regions involved in cognitive processes, such as learning and memory, including the hippocampal formation (HF), amygdala, and cerebral cortex (Genazzani et al 2007; Sherwin, 2003; Shughrue & Merchenthaler, 2000) .

Sex-related differences in cognitive abilities, such as verbal, memory and spatial tasks, have been reported; in addition, several estrogen effects differ qualitatively or quantitatively between the sexes, suggesting that they could be subject to sexual differentiation during pre- or early postnatal development (Gasbarri et al, 2009). Ovarian hormones affect cognition and neural substrates subserving learning and memory functions, in both rodents (Daniel, 2006; Warren & Juraska, 1997) and humans (Janowski et al, 2000), as it was evidenced by studies assessing performances across the estrous and menstrual cycles. Sex-related differences in brain function are also observed in the incidence of some psychopathology, such as depressive illness, which is more frequent in women, antisocial behavior and substance abuse, which are more common in men (McEwen, 2002). The variety of these effects confirms that other brain structures are implicated, besides the hypothalamus, which has been the traditional site for the study of ovarian steroid receptors and their role in the control of reproductive function. For example, the hormonal influences on motor activity involve brain areas such as the nucleus accumbens, striatum, substantia nigra and ventral tegmental area, while the effects on memory processes imply actions on brain structures such as basal forebrain and HF, and those on mood involve, at least in part, the serotonergic system of the midbrain raphe nuclei.

Postmenopausal alterations of the limbic system are related to mood changes, anxiety, depression, insomnia, headaches/migraine, alterations of cognitive functions (Genazzani et al 2002).

Even though there is currently a substantial literature on the putative neuroprotective effects of estrogen on cognitive functions in postmenopausal women, some discrepancy still exists. The critical period hypothesis, validated several years ago, attempts to account for the literature inconsistencies by positing that estrogen treatment can protect aspects of cognition in older women only if treatment starts soon after the menopause. Although it is not totally clear why estrogen administered to women over 65 does not provide any neuroprotection and may even impair cognition, it could be possible that the events characterizing brain aging (such as alterations in neurotransmitter systems and decrease of brain volume, neuronal size, dendritic spine number) represent an adverse background preventing the neuroprotective effect of exogenous estrogen on the brain. Other factors that could have contributed to the discrepancies in the literature include differences in the type of estrogen compounds used, their route of administration, cyclic versus continuous regimens, and the concomitant administration of progestins (Sherwin & Henry, 2008).

2. Neurobiology of estrogen

The identification and mapping of ERs in the brain led to the discovery that they are concentrated in the hypothalamus, hypophysis, HF, cerebral cortex, midbrain, and brainstem (Micevych & Mermelstein, 2008).

Even though a complete description is beyond the scope of the present paper, the mechanisms that are likely the most relevant to explain the cognitive function of estrogen are briefly described here (see McEwen, 2002, for a review).

The nuclear ERs are ligands activated transcription factors belonging to the steroid hormone receptors, included in the nuclear receptor superfamily (Osterlund & Hurd, 2001). Two types of ERs are known: ERα and ERβ, which are similar in their structural organization into

domains, but differ in their binding affinities for diverse ligands and selective ER modulators (Gruber et al, 2002; Rehman & Masson, 2005).
ERα and ERβ are products of different genes and show tissue- and cell-type specific expression (Pettersson & Gustafsson, 2001). Both ERs are widely distributed throughout the body (Rehman & Masson, 2005) and have also been localized in several cerebral areas, such as the cortex, amygdala, HF, basal forebrain, cerebellum, locus coeruleus, rafe, and central grey matter, confirming an involvement of estrogen in controlling cognitive functions in both physiological and pathological conditions (Sherwin, 1997; Sherwin & Henry, 2008).
The cerebral distribution of ERα has been quite well established by steroid autoradiography, immunocytochemistry, and in situ hybridization (Pfaff, 1980) and many studies have shown nuclear and extranuclear ERβ immunoreactivity in several brain regions, especially the hippocampus (Milner et al, 2005; Mitra et al, 2003). The ERα mRNA expression prevail in the hypothalamus and amygdaloid complex, suggesting that the α-subtype could modulate neuronal populations involved in autonomic and reproductive neuroendocrine functions, as well as emotional processes. On the contrary, in the thalamus, HF, entorhinal cortex, and neocortex there is a prevalence of ERβ, indicating a putative role for ERβ in cognition, non-emotional memory and motor functions (Osterlund & Hurd, 2001) The co-localization of ERβ mRNA with cell nuclear ERβ immunoreactivity was revealed in the cerebral cortex, paraventricular nuclei, and preoptic area of hypothalamus, in the rat (Shughrue & Merchenthaler, 2001) It is important to note that the use of I^{125} estrogen, which labels ERs with a higher specific radioactivity compared to ^{3}H estradiol, allowed the detection of label in pyramidal cells of ventral hippocampal CAl and CA3 fields (Shughrue & Merchenthaler, 2000), which are involved in memory processes. Besides its influence on both direct genomic actions, estrogen can also act in the CNS via nonnuclear receptors that implicate interactions of ERs with second messenger systems (Lee & McEwen, 2001; Sherwin & Henry, 2008)
Concerning the subcellular localization of ER, in addition to the nuclear ERs, there is a predominant localization of ERs in proximity to the plasmatic membrane of neuritis, soma, dendritic spines, and axon terminals (Clarke et al, 2000; McEwen et al, 2001). These results also imply that classical ERs may have an intracellular dynamic action and suggest that ERs can be found in different subcellular structures. This is supported by findings showing that estrogen binds and interacts with proteins in the mitochondrial membranes and that ERs are associated with pre-synaptic structures, thus controlling synaptic transmission (Genazzani et al, 2007; Ledoux & Woolley, 2005). In conclusion, estrogen effects on the brain include complex cellular mechanisms ranging from classical nuclear to non-classical membrane-mediated actions. Both forms of cell signaling could be activated separately, even though there is evidence that they are intertwined at several cellular instances and can influence each other reciprocally, yielding synergic effects (Genazzani et al, 2007).
Due to the widespread presence of the ERs in their different forms throughout the brain, estrogen actions are also widespread and affect many neurotransmitter systems including the cholinergic, catecholaminergic, serotonergic, and GABAergic systems (McEwen, 2002). The influence of estrogen on cerebral structures and functions offer possible explanations for the mechanisms of action by which this steroid hormone could affect cognitive functions in women. For example, it was reported that one of the effects of estrogen is to enhance the density of dendritic spine on CAl hippocampal neurons within 24–72 h after its acute administration (Woolley et al, 1990). Moreover, estrogens increase the concentration of choline acetyltransferase (ChAT), critically involved in memory functions and whose levels

are markedly decreased in Alzheimer's disease (AD) (Gibbs & Aggarwal, 1998). The neuroprotective action of estrogen could also be exerted through a modulator effect on molecules involved in apoptosis (Pike, 1999) and its antioxidant action. The potential for the numerous mechanisms of action of estrogen to affect the structure and function of cerebral areas that subserve several cognitive functions provides biological plausibility for the hypothesis that estrogen could protect cognitive functions in aging women.

3. Estrogen and cognition

The term cognition indicates the totality of human information processing, including psychomotor skills, pattern recognition, attention, language, learning and memory, problem solving, abstract reasoning or higher-order intellectual functioning.

In female mammals, including rodents and non-human primates, estrogen effects on non-reproductive behaviors include, besides anxiety and depressive-like behaviors, cognitive behaviors (Spencer et al, 2008; Walf & Frye, 2006) When administered to ovariectomized (OVX) rats, estradiol decreases anxiety and depressant behavior in laboratory tests (Walf & Frye, 2006). The effects of estrogen on cognition depend on the type of task performed and on the brain regions involved. For instance, while estradiol impairs performance on striatum-dependent tasks in female rats (Davis et al, 2005; Korol, 2004) it improves performance on prefrontal cortical-dependent learning in female rats (Luine, 2008) rhesus monkeys (Hao et al, 2007; Rapp et al, 2003) and both young adult and post-menopausal women (Berman, 1997) . It also enhances performance on HF-dependent tasks in female mice (Li et al, 2004; Xu & Zhang, 2006) , rats (Daniel et al, 1997; Sandstrom & Williams, 2004) and rhesus monkeys (Lacreuse et al, 2002; Rapp et al, 2003). Findings showing improved performance after estradiol infusion directly into the HF, but not other cerebral areas (Zurkovsky et al, 2006), provides behavioral evidence that the estradiol enhancement of HF-dependent tasks indeed represents a specific effect on HF function. However, estrogen's roles on cognitive function may result from the sum of interacting influences on numerous cerebral regions, including striatum, HF, basal forebrain, and prefrontal cortex (PFC).

3.1 Estrogen in learning and memory

Signaling pathways and gene expression regulated by estrogen include activation of CREB, GABA-A receptors, NMDA receptors, glutamic acid decarboxylase (GAD), ChAT, and synaptic and spine-associated proteins (Frick et al, 2002; McEwen et al, 2001; Rudick & Woolley , 2003).

Studies in knockout mice using the selective estrogen receptor modulators suggest that ERα and ERβ contribute differently to memory mechanisms (Rhodes & Frye, 2006; Rissman et al, 2002). Several studies have shown estrogen regulation of ERα (Hart et al, 2001; 2007) Moreover, it was reported that selective ERβ agonists increased levels of key synaptic proteins in vivo in the HF, and these effects were absent in ERβ knockout mice or after treatment with an ERα agonist. ERβ agonists also induced morphological changes in HF neurons, such as an enhanced density of mushroom-type spines. Most importantly, estrogen or ERβ agonists improved performance in some HF-dependent memory tasks (Liu et al, 2008). Therefore, these results confirm the role of ERβ in memory, but cross-talk between ERα and ERβ receptors cannot be excluded.

It was also evidenced that rapid improvements in cognition could be mediated by membrane associated estrogen receptors activating mitogen-activated protein kinase

(MAPK) signalling pathways in specific neural sites (Bryant et al, 2006). For example, estrogen enhances performance in tasks such as inhibitory avoidance (IA), object recognition and placement within 4h of treatment; a post-training paradigm evidenced that these effects are due to the facilitatory action of estrogen on memory (Frye et al, 2007; Luine, 2008; Rhodes & Frye, 2006; Walf & Frye, 2006). Previous memory studies hypothesized that newly-acquired informations are transferred to long-term memory over time, and seminal work by McGaugh and co-workers has shown that consolidation takes place within 1–2 h post-training (McGaugh, 2000). In addition, the impairment or improvement of the consolidation process due to drugs or hormones can occur if they are given within this time, but not later. Estrogen-related enhancement of consolidation utilizing post-training paradigms have been shown in some memory tasks, such as Morris water maze (MWM), IA, object recognition and object placement (Frye et al, 2007; Luine et al, 2008; Rhodes & Frye, 2006; Walf & Frye, 2006). Administration of the powerful estrogen agonist, diethylstilbestrol, either immediately before or immediately after the presentation of objects, increased discrimination between previously viewed and never viewed items in the recognition trial. Therefore, temporal relations between hormonal application and performance enhancements are in agreement with memory improvement.

Estrogen not only modulates memory formation and maintenance processes in some contexts, but also biases the learning strategy utilized to solve a task, thus changing what and how information is learned, and therefore not only how much is learned, i.e., the strength of the memory (Gasbarri et al, 2009, Pompili et al, 2010).

Rats with high estrogen levels utilize place or allocentric strategies rather successfully, outperforming hormone-deprived rats on tasks requiring the configuration and use of extramaze cues for successful completion. On the contrary, rats with low estrogen levels tend to use response or egocentric strategies on tasks where the use of a directional turn, e.g., left or right, is required for acquisition (Korol, 2004). Taking into account the actions of estrogen across a large range of neural systems, its modulation on cognition could be exerted by altering the relative involvement of specific memory systems, acting much like a conductor, orchestrating the dynamics, timing and coordination of multiple cognitive strategies during learning (McGaugh, 2000) . Influences on neurotransmitters, such as acetylcholine (ACh), regulating other processes, like inhibitory tone and excitability, reflect one of the mechanisms by which estrogen may orchestrate learning and memory. In fact, the ACh system is also activated by estrogen in cerebral areas that are important for memory, such as the basal forebrain and its ACh-containing projections to the HF and frontal cortex (Gibbs et al, 2004; Luine, 2008).

Even though gonadal hormones influence cognition, these hormone-induced changes are not large (Luine, 2008), and they are reported especially when function is compromised by aging or lesions (Gulinello et al, 2006; Scharfman et al, 2007) however, they do not improve all the different aspects of cognition such as, for example, acquisition during memory processes (Dohanich, 2002; Luine, 2007).

Rodents have been evaluated in different tasks, utilizing several kinds of mazes, and they rely on diverse reinforcements or contingencies (positive food rewards or aversive electric shocks) for the learning phase, and the tasks measure different kinds of memory, such as spatial memory, which requires the establishment of relationships between distant cues in the environment and the reinforcement site (Gasbarri et al, 2009). Other tasks use visual memory, based on visual associations. Nonetheless, many studies show positive effects of estradiol on cognition (Dohanich, 2002) . Spatial memory, which is dependent on the HF, has been extensively evaluated using the radial arm maze (RM) and MWM; studies conducted in OVX subjects show enhancements in performance during the acquisition (Dohanich, 2002; Luine et al. 1998) but, after learning how to solve the task (reference memory), estradiol no longer enhances performance (Fader et al, 1999; Luine et al. 1998) and could even impair spatial memory, although the data are not conclusive (Dohanichn 2002). Consistent estrogen-related improvements are reported in studies utilizing spatial tasks for the evaluation of working memory (WM) (Daniel & Dohanich, 2001; Luine, 2008; Sandstrom & Williams, 2001, 2004; Scharfman et al, 2007) defined as the ability to retain information in the face of potentially interfering distraction, in order to guide behavior and make a response (Baddeley, 1992, 1998).

Results of studies, assessing hormonal effects on learning and memory, evidence the importance that context and / or experience can have on performance, and these considerations may account, at least in part, for some inconsistency in the literature. Therefore, it is hypothesized that stress experienced during task performance may interfere with estrogen enhancements of some spatial tasks (Englemann et al, 2006; Frick et al, 2004). In addition, extensive handling, housing conditions, or environmental enrichment can also mitigate hormonal effects on other spatial tasks (Gresack et al, 2007; Rubinow, et al 2004) Taking into account that cognition represents a complex, multidimensional set of higher-order functions that are sub-served by specific, yet inter-related, cerebral areas, the intervention of other stimuli on the effects of estrogen is not unexpected. It is interesting to note that more recent research, evidencing consistent estrogen-related improvements of memory, use tasks evaluating working or short-term memory, tap into higher order memory or executive function, and also rely on cortical integration with HF fields (Ennaceur, et al 1997; Mumby et al, 2002). In addition, subjects are not exposed to stressful circumstances or negative reinforcers during the task. Therefore, recognition memory tests, where subjects have to discriminate between familiar and unfamiliar objects or objects in familiar or unfamiliar locations, appear to be quite consistently improved by estrogen and its agonists in OVX rats (Luine, 2008) or mice (Fernandez & Frick, 2004; Li et al, 2004).

In agreement with OVX models, pro-estrous rats evidenced better recognition memory compared to rats in a different phase of the estrous cycle (Frye et al 2007; Walf & Frye, 2006) and mice show better spatial memory in pro-estrous (Frick et al, 2001). However, rats in pro-estrous phase are often impaired during acquisition (Bowman et al, 2001; Frye, 1995; Warren & Juraska, 1997). Other researchers did not show modifications over the cycle (Berry et al, 1997; Stackman et al, 1997) this inconsistency could be explaining taking into account that they evaluated reference memory, which seems to be insensitive to hormones after acquisition.

3.1.1 Estrogen and working memory

As evidenced by research assessing performances across the estrous and menstrual cycles, ovarian hormones affect cognition and neural substrates subserving learning and memory, including WM, in both rodents (Craig &Murphy , 2007; Daniel, 2006; Warren & Juraska, 1997) and humans (Bimonte & Denenberg, 1999; Janowski et al, 2000). The decrease of estrogen following ovariectomy or menopause enhances the risk of diseases, such as osteoporosis and vasomotor dysfunction (Timins, 2004; Warren & Halpert, 2004), but could also be involved in the development of cognitive impairments (Markou, 2007; Sherwin,

2003). ERT relieves several menopausal symptoms, but whether its benefits include protection of cognitive functions is still controversial (LeBlanc et al, 2007; Tivis et al, 2001).
In recent years, considerable progress has been made towards specifying the neural mechanisms underlying WM in humans (Baddeley, 1998; Repovs & Baddeley , 2006).
Data from OVX rats treated with estrogen, compared to OVX untreated controls, showed improvements in performance of some tasks, including those require spatial WM, such as the RM (Daniel et al, 1997; Fader et al, 1999) and a 2-choice WM task (O'Neal et al, 1996) and impairments in spatial reference memory tests, such as the MWM (Warren & Juraska, 1997). Estrogen replacement therapy (ERT) enhances spatial WM performance both on MWM and RM (Bimonte & Denenberg, 1999; Fader et al, 1999), confirming previous evidence that estrogen selectively improves performance on tasks depending on WM (Daniel et al, 1997; O'Neal et al, 1996). In fact, estrogen treatment improved WM performance during maze acquisition, without affecting reference memory performance; scopolamine treatment impaired WM, but not reference memory, while estrogen prevented the impairment of WM by scopolamine. A recent paper reported substantial sex differences in the effects of gonadectomy and hormone replacement on spatial working and reference memory in male and female rats (Gibbs & Jognson, 2008). An interesting direction of this field is the idea that estrogens may influence learning strategy, independent from memory.
Furthermore, ERT in both physiologically low and moderate doses improved the capability of ovariectomized rats to handle increasing amounts of WM information, when the demand on an animal's WM system was restricted to one to four elements of information (Bimonte & Denenberg, 1999). However, when the demand on the WM system was increased to six elements of information, ERT in physiologically moderate doses provided the maximum benefit, even beyond that of intact females.
Moreover, it was reported that estrogen can prevent deficits in spatial WM induced by neurotoxin treatments aimed to mimic the pathology of early AD (Hruska & Dohanich, 2007).
Cholinergic and HF systems are closely related to learning and memory processes (Hasselmo, 2006), and it can be predicted that estrogen has its most profound effect on HF-dependent cognitive functions such as learning and memory. In fact, estrogen enhances ACh function and the synthesis of ACh in basal forebrain and the Ach neurons projecting to the HF and cortex (Hasselmo, 2006), (Singh et al, 1994), and mediates dendritic spine density in the hippocampal CA1 region (Li et al, 2004; Wallace et al, 2007). The HF and adjacent anatomically related cortex play a crucial role in the explicit encoding and consolidation of verbal and nonverbal information into short-term memory, in humans (Squire, 2004). It has been speculated that estrogen activity in HF might underlie the effects of ERT on memory in postmenopausal women (Maki & Resnick, 2000; Maki, 2005). Estrogen receptors, as well as estradiol-concentrating neurons, were detected in the HF and entorhinal cortex of rodents (Prange-Kiel & Rune, 2006). Circulating estrogens have quantifiable effects on neurotransmitter activities in HF where, for example, a low estrogen state increases serotonin (5-HT) transporter activity in the HF, despite an apparent reduction in 5-HT transporter density (Bertrand, 2005); moreover, a regulation of NMDA and GABA receptors has also been reported (Jelks, 2007; Rudick & Woolley, 2001) Estradiol administration in OVX rats produces increased ChAT activity and high-affinity choline uptake in CA1 field (Singh et al, 1994). Even though research has mainly focused on the medial temporal lobe areas, they do not represent the only neuroanatomical regions involved in human memory. In fact, the PFC mediates a number of cognitive processes contributing to memory function, particularly WM which is strongly related to the PFC in both humans and nonhuman

primates. In humans, WM represents the basis for many cognitive functions, including reasoning, reading comprehension, and mental calculations (Baddeley, 1998). Both non verbal (Owen et al, 1996) and verbal (Petrides et al, 1993); stimuli were utilized in experimental tasks with a relevant WM component. The important role of the PFC in WM was demonstrated after lesion and electrophysiological techniques in monkeys (Funahashi et al, 1993; Petrides, 1995) functional neuroimaging techniques in healthy human volunteers (Jonides et al, 1993; Owen et al, 1996); and localized cortical excisions in human neurological patients (Owen et al, 1995). Taking into consideration that, by definition, WM tasks intrinsically involve both temporary retention of verbal or visual information and its active manipulation, some research have clarified that the requirement for active manipulation during WM tasks specifically recruits activity in dorsolateral PFC (Owen et al, 1995; Petrides, 1995; Postle et al, 1999). By contrast, passive storage processes seem to depend on more posterior brain areas, as evidenced by deficits in the immediate span for spatial or verbal information, in patients with lesion of parietal or perisylvian cortex (Milner, 1971) and by changes in functional cerebral activity in parietal and temporal regions of healthy volunteers, during performance of neuroimaging tasks that emphasize passive storage of information (Postle et al, 1999). Therefore, the dorsolateral PFC, as part of the WM system, plays a critical role in mediating the control processes required for the active manipulation, or selective utilization of items contained in WM.

Several lines of research raised the possibility of estrogen's modulating effect on the PFC (Joffe et al, 2006). In particular, analysis of human brain specimens has revealed that in PFC estradiol concentrations was approximately 2 times higher than in temporal cortex or 7 times higher than in HF, showing that the PFC is a principal target for estrogen in the adult female brain (Bixo et al, 1995). Animal studies reported that estrogen influences the activity of several neurotransmitter systems in the PFC. For example, a 56% reduction in ChAT and a 24% reduction in high affinity choline uptake in the frontal cortex of female rats at 28 weeks post-OVX were found; this effect was prevented or reversed in rats treated with ERT (Singh et al, 1994) Estrogen may also regulate neurotransmission in the PFC of nonhuman primates. Remarkable increases in axons immunoreaction for dopamine β-hydroxylase and 5-HT and reductions in the density of axons immunoreactive for ChAT and tyrosine hydroxylase were observed in the dorsolateral PFC of adult rhesus monkeys, following OVX (Kritzer & Kohama, 1998, 1999) In OVX monkeys treated with estrogen, the density of labeling was similar to hormonally intact controls, suggesting that estrogen plays a role in maintaining cholinergic, noradrenergic, serotonergic, and dopaminergic activity in the PFC. In addition, in humans, neuroimaging studies using positron emission tomography (PET) (Berman et al, 1997) or functional magnetic resonance imaging (fMRI) (Shaywitz et al, 1999) have evidenced systematic differences in patterns of task-induced brain activation in PFC, connected to differences in women's estrogen status (Roberts et al, 1997). A behavioral study conducted on rhesus monkeys showed that menopausal and postmenopausal females, compared to age-matched but premenopausal females, exhibited an impairment of performance on the WM delayed response task, which is commonly used to assess PFC dysfunction in nonhuman primates. Taken together, the neuroendocrine and behavioral data supply evidence to suggest that estrogen is active in the PFC. In such a case, estrogen could modulate cognitive functions mediated by the PFC in women.

Taking into account that the dorsolateral PFC is one of the areas of the frontal cortex where estrogen activity was demonstrated (Maki, 2005), this steroid hormone might contribute to WM function by modulating information processing in the PFC (Duff & Hampson, 2000). In order to verify the hypothesis that the WM system is responsive to estrogen in women, Maki et al. (Maki, 2005) designed a study evaluating, in a group of postmenopausal women, two measures, one verbal and one spatial, which strongly recruit the WM system (Digit Ordering, Spatial WM task). Their findings confirmed the hypothesis that estrogen is active within PFC and it can influence functions dependent on this region, like WM.

In agreement with the above findings, evidence exists showing the activation of PFC during the performance of WM tasks (Badre D, Wagner, 2007; Petrides et al, 1993) and decrease of WM with increasing age (Grady & Craik, 2000) . The integrity of both the PFC and its complex neural circuitry, which consolidates input from various modalities via cortical, subcortical, and limbic connections, are critical to intact executive functions, an amalgamation of cognitive processes that includes WM, besides directed attention, response inhibition, dual task coordination, cognitive set switching, and behavioral monitoring. Dopaminergic and serotonergic brain stem afferents to PFC (Jakob & Goldman-Rakic, 1998) modulate the excitability of prefrontal pyramidal neurons. Experimental reduction of prefrontal dopamine in rhesus monkeys and naturally occurring loss of dopaminergic neurons in Parkinson's disease are associated with deficits in WM (Gotham et al, 1988). The dopaminergic D2 receptor agonist bromocriptine improves WM (Luciana et al, 1991) while D2 antagonist raclopride had a minor inhibitory effect (Williams & Goldman-Rakic, 1995). Ovarian steroids are powerful modulators of the dopaminergic neurotransmission. In monkeys ovariectomy reduces, while subsequent estrogen and progesterone replacement restores, the density of axons immunoreactive for tyrosine hydroxylase in the dorsolateral PFC (Kritzer & Kohama, 1998) . Ovariectomy also decreases the density of axons immunoreactive for ChAT and increases the density of fibers immunoreactive for dopamine β–hydroxylase. ERT alone attenuates these effects (Kritzer & Kohama, 1999) estradiol also decreases monoamine oxidase (MAO), involved in the degradation of dopamine (McEwen, 2002).

3.1.1.1 Working memory for emotional facial expressions across the menstrual cycle in young women.

Facial expressions represent non-verbal communicative displays that are critical in social cognition, allowing quick transmission of valence information to cospecifics concerning objects or environments (Blair et al, 1999). In particular, humans and non-human primates use facial expressions to communicate their emotional state. This communication can be reflexive, as situations may induce emotions that are spontaneously expressed on the face. In other cases, particularly in humans, facial expressions may consist in volitional signals with the aim of communicating, and not reflecting, the real emotional state of the subject (Ekman, 1993) . Six basic emotions - happiness, sadness, anger, fear, disgust and surprise - and their corresponding facial expressions are recognized across different cultures (Ekman & Friesen, 1971). Imaging studies showed that different cerebral areas are activated during the processing of different, distinct emotions (Blair et al, 1999). It was also reported that not only subcortical areas, such as amygdala or basal ganglia, but also cortical areas, mainly PFC, cingulate cortex, and temporal cortices, are essential in emotion processing (Blair et al, 1999; Northoff et al, 2000). Many studies on emotion perception in faces have been focused on the identification of the cerebral regions, whose damage causes emotion perception deficits (Adolphs, 2002) . This facial emotion recognition deficit appears to be, at least in part, related to a more general problem in cognitive functions including the categorisation, discrimination and identification of facial stimuli, as well as deficits in other cognitive

processes, such as WM, which are impaired in the psychiatric and neurological damages (Addington & Addington, 1998; Kee et al, 1998).
Physiological fluctuations in ovarian hormones across the menstrual cycle allow for non-invasive studies of the effects of estrogen on cognition in young women and underlie a reliable pattern of cognitive change across the menstrual cycle (Maki et al, 2002).
The cognitive performance in a WM task for emotional facial expressions, using the six basic emotions (Ekman &Friesen, 1971) as stimuli in the DMTS, was evaluated in young women in the different phases of the menstrual cycle, in order to point out possible differences related to the physiological hormonal fluctuations (Gasbarri et al, 2008, 2009). Our findings suggest that high levels of estradiol in the follicular phase could have a negative effect on delayed matching-to-sample WM task, using stimuli with emotional valence. Moreover, in the follicular phase, compared to the menstrual phase, the percent of errors was significantly higher for the emotional facial expressions of sadness and disgust (Gasbarri et al, 2008, 2009) The evaluation of the response times (time employed to answer) for each facial expression with emotional valence showed a significant difference between follicular and luteal in reference to the emotional facial expression of sadness (Gasbarri et al, 2008, 2009). Our results show that high levels of estradiol in the follicular phase could impair the performance of WM. However, this effect is specific to selective facial expressions suggesting that, across the phases of the menstrual cycle, in which conception risk is high, women could give less importance to the recognition of the emotional facial expressions of sadness and disgust. This study is in agreement with research conducted on non-human primates, showing that fluctuations of ovarian hormones across the menstrual cycle influence a variety of social and cognitive behaviors. For example, female rhesus monkeys exhibit heightened interest for males and enhanced agonistic interactions with other females during periods of high estrogen level (Lacreuse et al, 2007).
Moreover, our data could also represent a useful tool for investigating emotional disturbances linked to menstrual cycle phases and menopause in women.

3.1.1.2 Working memory for emotional facial expressions in capuchin monkeys

Non-human primates represent important and relevant models for the study of emotional face processing, because they share several cognitive and physiological characteristics with humans. The behavioral evidence includes similarities in innate action patterns such as body movements and communication signals, as well as highly flexible behavioral tactics and clever problem-solving strategies (Preuschoft, 2000) . The capuchin monkey (*Cebus apella*) has been the focus of various researches due to its behavioral similarities with apes. Moreover, capuchins exhibit a rich repertoire of facial expressions and body postures, which convey an array of messages to co-specifics about their internal state (Fragaszy et al, 2004); furthermore, they display tool-using capacities, and can readily solve the WM tasks, such as DNMS and concurrent discrimination learning task (Resende et al, 2003; Tavares & Tomaz, 2002).
Capuchin monkeys have well-developed facial musculature mobility, which allows considerable expressive variability, and they also have excellent visual acuity for discerning signals by others. However, most of the visual signals of capuchin monkeys are accompanied by vocalizations and associated context. In general, movement and body expression are important to understand emotional valence.
In a previous study we developed a pool of 384 pictures of capuchin monkey (*Cebus apella*) faces, classified according to emotional valence (positive/ pleasant, negative/unpleasant and neutral/indifferent), to examine whether WM can benefit from the emotional content of visual stimuli in a delayed non-matching to sample task (DNMTS) (Abreu et al, 2006).

Seven adult capuchin monkeys were tested with a computer system and touch screen. Geometric figures (control) and the co-specific faces pictures were used as stimuli. The subjects obtained a similar performance to positive, negative and neutral pictures. However, the monkeys performed above the upper confidence limits around chance to all kinds of stimulus showing that they are able to learn the tests using emotional faces. Furthermore, the capuchin monkeys had much better performance when using geometric figures compared with the co-specific pictures.

On a whole, our results show that capuchin monkeys were able to perform this new WM task, thus indicating the possible usefulness of applying the paradigm utilized in this study to investigate emotional memory in non-human primates (Abreu et al, 2006).

4. Estrogen and the aging brain

One of the most interesting research fields in women's health of the last decade includes the growing appreciation that estrogen plays relevant neurotrophic and neuroprotective roles during adulthood. This amplifies the relevance of the potential impact of the prolonged post-menopausal hypoestrogenic state on learning and memory processes and the potential increased vulnerability of ageing women to brain injury and neurodegenerative diseases. The longer female life expectancy has implied that nowadays women live one-third of their lives beyond ending of their ovarian function, increasing the need for new therapeutic strategies to facilitate successful aging (defined as low probability of disease), high cognitive and physical abilities, and active engagement in life. Taking into account that changes in the ageing nervous system are subtle, they could be reversed and cognitive performance may be improved by pharmacological treatments.

The ematic concentration of estrogens decreases with age and the post-menopause low values of estrogens are often followed by an acceleration of the age effects on cognition. Cognitive decline during aging affect memory abilities, attention, and speed of information processing (Sherwin & Henry, 2008).

Even though several cognitive functions seem to be unaltered in normal aging, age-related impairments are mainly evident in tasks implying free or cued recall or WM (Small et al, 1999). Although verbal memory has been reported to be the cognitive function most deeply affected with increasing age (Marquis et al, 2002; Rabbitt & Lowe, 2000) other cognitive domains such as attention (Stankov, 1988) visual perception, and verbal fluency (Ashman, 1999) are also influenced. Thus, the attempt to delay or prevent the cognitive impairment occurring with normal aging is an important goal to protect the quality of life for women during the latter one third of their lifespan. Because ERs are present in both the HF and frontal lobes which subserve verbal memory, WM and retrieval, we can hypothesize that estrogen might play an important protective role against the decline in these cognitive functions, occurring with normal aging. Therefore, researchers have tried to verify if the estrogen administration to women at the beginning or during menopause would protect against cognitive impairments that normally take place with increasing age.

During the past few decades, data from basic neuroscience and from animal and human studies have suggested that ERT given to postmenopausal women might protect against specific cognitive declines occurring with normal aging. On the other hand, the numerous inconsistencies in this body of evidence point to the possibility that there are contingencies which modify the supposed neuroprotective effects of ERT on cognitive aging (Sherwin & Henry, 2008).

Even though an extensive literature on the putative neuroprotective effects of estrogen on cognitive functions in postmenopausal women is available, many discrepancies still exist. The critical period hypothesis, introduced many years ago, attempts to account for the inconsistencies in this literature by positing that ERT can have a protective effect on some aspects of cognition in older women, only when it is initiated soon after the menopause. Indeed, data from basic neuroscience and from the animal and human studies provides compelling support for the critical period hypothesis (Sherwin & Henry, 2008). Although it is not completely clarified why estrogen does not protect cognitive functions and may even cause harm when administered to women over the age of 65 years, it is possible that the typical modifications of brain aging, such as a reduction of brain volume, neuronal size, number of dendritic spines, and alterations in neurotransmitter systems form an adverse background preventing the neuroprotective effects of exogenous estrogen. Other factors that have likely contributed to the inconsistencies of the estrogen–cognition literature include differences in the estrogen agonist utilized, their route of administration, cyclic versus continuous regimens, and the concomitant administration of progestins. In conclusion, there is considerable evidence supporting the use of estrogen during the menopause and postmenopausal periods for the prevention and treatment of AD and other neurologic disorders. Nevertheless, the efficacy of estrogen requires that we take into account the most recent data on hormone neurobiology, in order to administer the hormone at the right time, with the right formulation, and to the appropriate population of women (Gleason, 2005; Simpkins & Meharvan, 2008).

5. Conclusions

Besides the mechanisms concerning the neuroprotective role of estrogen in dependence of the age of its administration, further studies are necessary to completely clarify the relative efficacy of cyclic versus continuous hormone regimens, the accessibility to the brain of various estrogen compounds, and their different routes of administration. Moreover, there are no dose response results related to estrogen and cognitive functioning in women, in spite of the increasing clinical trend for administering low doses of estrogen to postmenopausal women. The finding of a prominent dose-dependent effect of estradiol on the density of hippocampal CA1 pyramidal spine synapse in OVX rats (MacLusky et al, 2005) emphasizes the relevance of obtaining such data for women. When the optimal neurobiological and pharmacological parameters of the estrogen–cognition relationship are known, these data could be used clinically to attenuate or to prevent cognitive decline in older women, which represent the fastest growing section of the population in industrialized countries.

6. References

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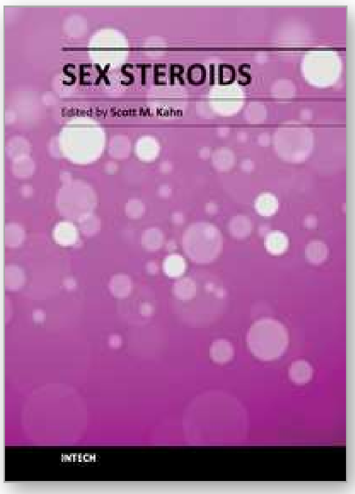

Sex Steroids

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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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