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Estradiol-mediated modulation of memory and of the underlying dendritic spine plasticity through the life span

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Summary. The morphophysiology of the nervous system changes and adapts in response to external environmental inputs and the experiences of individuals throughout their lives. Other changes in the organisms internal environment can also contribute to nervous system restructuring in the form of plastic changes that underlie its capacity to adapt to emerging psycho-physiological conditions. These adaptive processes lead to subtle modifications of the organisms internal homeostasis which is closely related with the activity of chemical messengers, such as neurotransmitters and hormones.

Hormones reach the brain through the bloodstream, where they activate specific receptors through which certain biochemical, physiological, and morphological changes take place in numerous regions. Fetal development, infancy, puberty, and adulthood are all periods of substantial hormone-mediated brain remodeling in both males and females. Adulthood, specifically, is associated with a broad range of life events, including reproductive cycles in both sexes, and pregnancy and menopause in women. Events of this kind occur concomitantly with eventual modifications in behavioral performance and, especially, in cognitive abilities like learning and memory that underlie, at least in part, plastic changes in the dendritic spines of the neuronal cells in cerebral areas involved in processing cognitive information.

Estrogens form a family that consists of three molecules [17β-estradiol (E2), estrone, estriol] which are deeply involved in regulating numerous bodily functions in different stages of the life-cycle, including the modulation of cognitive performance. This review addresses the effects of E2 on the dendritic spine-mediated synaptic organization of cognitive performance throughout the life span.

Key words: Estrogens, Estradiol, Modulation, Plasticity, Dendritic spines, Memory

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Steroids and the brain

Steroid hormones are among the fundamental components of the endocrine system. Their importance can be inferred from their wide distribution in numerous tissues of vertebrate organisms. Cholesterol is the precursor of steroid hormones. The cells of organs with steroidogenic function, such as the adrenal cortex, placenta, testes, and ovaries, dispose of cholesterol by incorporating it from circulating lipoproteins in the blood and storing it in the form of esters in the lipid inclusions of the cytoplasm and *de novo* synthesis from acetate. In particular, steroidogenic cells in the ovary obtain cholesterol from circulating lipoproteins (Solod et al., 1966; Strauss III et al., 1981; Gwynne and Strauss 3rd, 1982; Veldhuis et al., 1982; Rajendran et al., 1983).

The brain is an important target for circulating steroid hormones that originate from peripheral tissues or local production. They can interact with certain subunits of glutamate and GABA receptors to modify neuronal excitability (Beyer and González-Mariscal, 1991; González-Mariscal, 1993; Jennes and Langub, 2000). E2 exerts its effects on brain function by binding to two types of receptors located in the cell membrane: ERα (also known as ESR1 or NR3A1) and ERβ (also known as ESR2 or NR3A2), or to classical nuclear receptors. The estrogen receptor linked to the G protein-coupled ER1 receptor (GPER), formerly known as the GPR 30 orphan receptor (Funakoshi et al., 2006), abounds in the hippocampus and prefrontal cortex (Hutson et al., 2019). Treatment of rodents with the GPER agonist, G-1, or a selective antagonist, G-15,

enhances or impairs, respectively, several forms of memory and spinogenesis (Gabor et al., 2015; Kim et al., 2016, 2019). Nuclear steroid receptors are hormone-activated transcription factors that influence gene expression in a wide variety of CNS neurons. They exert profound influences on the brain throughout an individual's lifespan, beginning in early development and extending into adulthood. These hormones affect the morphology of neurons, cell survival, neurochemical phenotype, and neuronal connectivity (Jennes and Langub, 2000).

It is pertinent to distinguish between *neuroactive* steroids that are synthesized in peripheral tissues and the ones that are synthesized in the brain cells themselves, known as *neurosteroids*. This implies that the brain is equipped with all the enzymes required for the local synthesis of E2. Neurons are capable of synthesizing sex steroids *de novo* from cholesterol. Locally synthesized E2 and testosterone maintain synaptic transmission and synaptic connectivity. E2 is synthesized in the brain from testosterone through the catalytic action of aromatase. Systemic inhibition of aromatase in female mice impairs LTP, and is followed by dephosphorylation of the cytoskeleton-associated protein cofilin – related to the stabilization of mushroom spines (Sala and Segal, 2014) and their consequent long-term cognitive efficiency (Nabavi et al., 2014) – and a reduction in the number of both spines and synapses with spines (Vierk et al., 2014). Brain-derived E2 is more effective in females than males in sustaining spine-mediated cognitive performance (Vierk et al., 2012, 2014), where testosterone seems to play a key role (Leranth et al., 2004). Aromatase inhibition in healthy older men improves spatial memory (Cherrier et al., 2005). In accordance with this finding, the inhibition of aromatase in the hippocampus improves spatial learning in the Morris water maze (Moradpour et al., 2006), as well as the egocentric working memory in male rats, which might be mediated by the increase in cerebral testosterone levels that results from inhibition of E2 synthesis (Alejandre-Gomez et al., 2007).

Organizational and activational effects of steroids

The hormones secreted by the ovaries and testes produce a wide variety of effects on the structure and functions of the CNS, many of them permanent, others transient. Gonadal hormones (estrogens, progestagens, androgens) have a significant influence on the formation and development of numerous regions of the CNS and spinal cord through permanent *organizational actions* that regulate the differentiation and survival of specific types of neurons and glial cells. This is closely related to neuronal plasticity (Barón-Mendoza et al., 2023) and to the establishment and characteristics of synaptic connectivity among the components of neuronal circuits. Under normal conditions, and depending on the sex of the individuals, E2 or testosterone actions (or lack of same) during critical periods of brain development result in differential organization of neural circuitry (García-Segura, 2009) in specific cerebral regions. This is the case of the sexually dimorphic nuclei of the hypothalamus, the nuclei of the medial preoptic region, the anteroventral periventricular nucleus, the nuclei of the bed of the stria terminalis, the medial amygdaloid nucleus, the hippocampus, and the prefrontal cortex, among others. In fact, all these regions are involved in establishing different secretion patterns in the hypothalamic-pituitary-gonadal axis in men and women, and in various patterns of sexual behavior, affiliative behaviors, emotional states, and cognitive functions, among others, during adult life (Velázquez-Zamora et al., 2014; Cervantes-Alfaro et al., 2015).

Gonadal hormones can also participate in carrying out various brain functions through transitory *activational actions* on neuronal substrates of the CNS previously organized in a different way according to the sex of individuals and their organizational actions (Young et al., 1964; Simerly, 1998; Eichenbaum, 2004; Sisk and Zehr, 2005; McCarthy, 2008; García-Segura, 2009; De Vries and Södersten, 2009; Velázquez-Zamora et al., 2014). Under these conditions, it would be expected that during critical periods of gestation, the postnatal stage, childhood, and adolescence, gonadal steroids will exert their activational effects on the structural organization of some neuronal circuits, and that in these stages of development these steroids will play a role in determining differences in the brain function of males and females, including in the areas of learning and memory performance.

During critical periods of gestation, the brain is exposed to E2 from maternal circulation, the placenta, the gonads, and that which is synthesized locally in the brain through the aromatization of testosterone secreted by the fetal testes. This has led to the suggestion that the main action of E2 consists in masculinizing the fetal or neonatal brain to generate optimal conditions for male reproductive physiology and sexual behavior. It should be noted that during brain development, both the concentration and the activity of the enzyme aromatase that converts testosterone into E2, and the number of estrogen receptors, are higher in brain regions related to the expression of male sexual behavior (preoptic area), and to the integration of other behavioral patterns and cognitive functions. Evidence suggests that the configuration of these structures depends, at least in part, on the activational actions of E2 at critical stages of brain maturation (Morse et al., 1986; DonCarlos and Handa, 1994; Lephart, 1996; McEwen et al., 1997; Eichenbaum, 2004; McCarthy, 2008).

Feminization of the brain, in contrast, occurs in the absence of estrogenic actions due to the presence of high concentrations of α-fetoprotein, an E2-trapping protein that prevents its diffusion to the brain. Thus, in the absence of gonadal secretion of testosterone, exposure of the brain to masculinizing concentrations of E2 is avoided. Under these conditions, the female brain is configured in such a way that, under the cyclical

influence of E2 and progesterone during the stage of sexual maturity, the brain mechanisms of behavior (as well as the characteristics of the reproductive organs) become compatible with the potential to develop female reproductive activity, which is concomitantly associated with characteristic expressions in social behavior, emotions, and cognition (Phoenix et al., 1959; Naftolin et al., 1975; McCarthy, 2009).

Synaptic plasticity modulated by E2

Learning and memory are essential for individuals to adapt to their environment. These adaptive processes are activated by signals that may be either internal or external. Internal signals arise from a genetic base of some 30,000 genes that synchronously encode to direct the development of neural circuits whose synaptic connections are ruled by the so-called plasticity genes (Barros-Núñez et al., 2015). External signals are closely related to experience. From a neurophysiological point of view, learning and memory processes represent the means to access new information that will be acquired, encoded, integrated, and stored in specific neural circuits (mnemonic traces) (González-Burgos, 2015). These events require multiple changes at various neuropsychobiological levels, from molecular to behavioral, through the activation of the ERα and Erβ in several forebrain regions – amygdala, hippocampal formation, cerebral cortex – that are significantly related to cognitive functions (García-Segura, 2009; González-Flores et al., 2014).

Dendritic spines as mediators of the transmission of cognition-related information

Most excitatory synaptic information is mediated by glutamate. The information associated specifically with cognitive functions is processed by neurons that possess dendritic spines, the major sites for glutamate-mediated excitatory synaptic contacts in spiny neurons. E2-mediated plastic changes in dendritic spines are closely related to the synaptic modulation of synaptic activity and cognitive performance (González-Burgos, 2009, 2012, 2022; González-Burgos and Vázquez-Hernández, 2023).

Dendritic spines are cytoplasmic protrusions measuring 0.1-2µm in length that emerge perpendicularly from neuronal parent dendrites. They constitute 80% of excitatory synaptic contact sites (Harris and Stevens, 1989). Dendritic spines translate synaptic inputs. Their synaptic-related functioning is modulated by several extrasynaptic compounds, including steroid hormones that may induce various kinds of plastic changes (Luine and Frankfurt, 2023) including spine neoformation, pruning, and conformational changes among the different types of spines: thin, mushroom, stubby, wide, branched, and double (González-Burgos, 2022; González-Burgos and Velázquez-Zamora, 2023).

Based on their geometric structure, typical spines are characterized by the presence of two regions: the head and neck (Harris and Stevens, 1989) that confer distinct functional properties to these spines (Gulledge, 2023). The upper region of the spine head and the area below the cell membrane contain terminals where intracellular transmembrane proteins that act as receptors are inserted in an organized way, together with proteins associated with the actin cytoskeleton and various biomolecules (González-Tapia and Flores-Soto, 2023) that are related to the signaling pathways of presynaptic stimuli (Zagrebelsky, 2023). Plastic changes in the latter lead to differential translation of cognition-related synaptic inputs (González-Tapia et al., 2015, 2020; González-Burgos, 2022).

Estrogens and cognitive performance during development

Fetal development

From this genetic basis, the normal and atypical modulation of cognitive processes mediated by estrogens is manifested through various effects during the development of both males and females from the early stages of childhood to old age (Hodes and Epperson, 2019). Male and female embryos and young fetuses are virtually identical. The two sexes become completely differentiated only a few months before birth, as fetuses with XY chromosomes clearly develop male internal and external sex organs, while the precursor structures of female genitalia that were present in the young fetus with XX chromosomes disappear and internal and external organs corresponding to the female sex form. However, from early childhood to the pre-puberty period, sexual orientation is poorly differentiated until this quasi-bisexuality is gradually replaced by heterosexual monosexuality, whether male or female (Ågmo, 2007).

Ontogenic development of memory

Homeostatic actions of E2 in the brain contribute to the regulation of many neural functions, including cognitive processes like the ability to learn and remember. E2, in fact, regulates changes in cognition over the lifespan in both sexes (Arevalo et al., 2015).

Childhood

Pre- and postnatal brain development advances through distinct stages characterized by critical periods. These imply the end-and-onset of certain morpho-physiological events on a *continuum* that involves, among other aspects, the competitive development of nerve fibers and the consequent establishment of efficient synaptic contacts, with the resultant retraction of less effective axons. The dendritic spines associated with the excitatory synaptic contacts also exhibit a developmental pattern: neckless spines (wide, stubby)

represent the earliest stage of development, followed by thin spines and then the mushroom type, in a more-or-less unidirectional sequence (Velázquez-Zamora et al., 2011; González-Burgos, 2022). These successive events involve the appearance of a wide variety of psychoneural qualities, including memory and the ability to learn.

Memory also goes through different stages during postnatal development. In babies and infants of both sexes sensory memory stands out. Later, episodic memory processing appears, followed by semantic memory, until the adult stage is reached, when all cognitive qualities are fully expressed, reflecting an increase in the spectrum of memory systems as age advances (González-Burgos, 2022). The development of memory in children is strongly influenced by the processes of individual development of the capacities for attention and motivation, which are colored by the psychobiological state of infants and by transitory states due to physiological factors such as fatigue, or emotions like stress (Solís-Cámara Resendiz et al., 2015). The attention process highly conditions both learning and the consequent memorization. In infants aged 0-24 months, increasing attention to stimuli develops, and continues during school age and into adolescence (Matute et al., 2009). Motivation, meanwhile, covers both the needs and purposes of individuals. In infants, motives are limited to the so-called basic or primary needs (Mussen et al., 1973). During the second year of life, language development is particularly important, and we can consider that the development of memory progresses parallel to the acquisition of language. The efficiency of the memory's capacity to encode and store what it learns is facilitated by enriching language and knowing and assigning more words to objects and events (Solís-Cámara Resendiz et al., 2015). The developmental processes of attention, motivation, language, and eventual memorization in children can, however, be impeded by stressful and anxiogenic environmental variables (Matute et al., 2009).

Implicit memory (see González-Burgos, 2015) begins early in life and continues unchanged throughout it (Russo et al., 1995). In the ontogenic frame of reference, the highly hippocampal-dependent sensory, episodic, and autobiographical semantic memories play important roles. Sensory memory begins at approximately 2 years of age, episodic memory can endure for up to a few months before disappearing, while autobiographic semantic memory covers the person's life history, though it is absent before 3 years of age. It is currently believed that its development must be preceded by that of the cognitive self, which occurs precisely from that age onwards (Siegler, 1998). In this regard, it is important to recall that the hippocampus is an archicortical region that is related, especially, to long-term memory by virtue of the early establishment of stable, permanent synapses that occurs there.

In the preschool stage, around 3 years of age, both the speed and efficiency of cognitive processes continue to improve. Due to the development of attention, especially selective attention and language, both boys and girls may now be able to use recognition or their growing ability to identify previously known stimuli and to recall or reproduce information from memory. However, at this age they are still not able to use specific strategies to remember information. Therefore, although the information management process improves substantially from the age of two-to-three years, preschool infants continue to be sensitive to their primary needs. Much more complex factors are added in this stage, framed by the socialization process in which parents and other adults are the fundamental agents of the transmission of culture (Fivush et al., 2003). During the preschool stage and the first years of elementary school (6-7 years of age) the memories of previous events are usually very brief and involve only outstanding events for the infant's perception. In contrast, the ability to remember and carry out activities subsequent to the present moment (Papalia et al., 2005) – known as prospective memory – develops. The evolution of memory after childhood is associated with the development of information processing strategies (Papalia et al., 2005). For example, the strategy of "external aid" arises between the ages of 5 and 6 years, that of the "review" between 6 and 7 years; and that of "organization" after around the age of 10. The strategy of "elaboration" emerges years later.

Adolescence

The transition from childhood to adulthood involves a progressive maturation of the gonadal function that commences before puberty, understood as the onset of adolescence. This stage ends when the characteristics of the fully adult body are attained. One specific indicator of this occurs when the prefrontal cortex has matured entirely with the establishment of inhibitory synaptic contacts (Fuster, 2002). This transition can be divided into three periods: prepubertal maturation, puberty, and adolescence. The functional reorganization of the endocrine glands and the nervous system through prepubertal-puberty-adolescence involves interrelated processes that mutually influence each other during development and maturation (García-Segura, 2009) with far-reaching impacts on mood, arousal, motivation, sleeping patterns, personality, social interaction, affection, behavior, and cognition (Spear, 2000; Steinberg, 2005; Blakemore, 2008). These effects are associated with a high degree of plastic structural remodeling that underlies nonlinear modifications in brain growth during prepuberty-puberty-adolescence that continue into adulthood, including a reorganization of synaptic connectivity, a decrease in the number of dendritic spines, and the pruning of dendrites, all of which contribute to the refining of neural circuits that may be associated with new behavioral patterns (García-Segura, 2009).

The increase in the pulsatile release of the gonadotropin releasing hormone (GnRH) from

hypothalamic GnRH neurons is closely related to the initiation of puberty (Nass et al., 1984; Urbanski and Ojeda, 1987; Plant et al., 1989). Experimental studies have shown that the establishment of glutamate-mediated excitatory neuronal inputs to the GnRH neurons may play an important role in this process (Urbanski and Ojeda, 1990). The GnRH neurons of both prepuberal male and female rats have more numerous small (stubby) than large (thin) and giant (mushroom) spines, but these proportions are inverted in adulthood (Li et al., 2016). This suggests that the GnRH neurons of adult rats receive more, and larger, excitatory inputs than those of juveniles (Arellano et al., 2007; Bourne and Harris, 2008), a factor that may underlie the transitional process of sexual maturation from childhood to adulthood. Accordingly, the number of spinophilin-immunoreactive spines in CA1 decreases in postpubertal female rats compared to younger ones in a developmental process that seems to be independent of peripheral E2 and may be related more to altered hippocampal plasticity and synaptic consolidation during this stage of maturation (Yildirim et al., 2008).

E2 modulates not only the dendritic spines but also the birth and survival of new neurons. The process of neurogenesis involves a number of steps that lead, eventually, to mature neurons. E2 can influence neurogenesis, resulting in either a net increase or a net decrease in the levels of new mature neurons. Experimental studies conducted to date in males suggest that E2 does not influence the survival of new neurons in the hippocampus, but that both testosterone and dihydrotestosterone favor the survival of new neurons (Spritzer and Galea, 2007; Hatanaka et al., 2015) via interactions with the androgen receptor (Hamson et al., 2013). Thus, we know that E2 can have effects that promote survival in females at specific moments of the maturation of new neurons, but the rules of spine formation on new neurons in specific brain regions at this stage of life are little known and, therefore, merit additional research (Sheppard et al., 2019).

Reproductive age

In general, brain development progresses with upward and downward variations of different parameters related to the structure of the gray and white matter that affect the synaptic connectivity of various regions involved in the organization of cognitive processes (Rehbein et al., 2021). In particular, the interaction of gonadal hormones – especially E2 – with the brain structures involved in the integration of cognitive functions after puberty seems to be of great importance, since the cyclical variations in the plasmatic concentrations of ovarian hormones that remain exposed to the brain during menstrual cycles in women can influence the efficiency of various cognitive functions, unlike what occurs in men, where cognitive performance is not influenced by such fluctuations.

In adult males, memory performance is stable, but efficiency in the different activities that involve variations in behavioral performance is closely related to variations in the proportional density of the different spine types. A predominance of mushroom spines, for instance, has been reported in the prefrontal cortex and nucleus accumbens as a result of sexual experience, suggesting the consolidation of cognitive information underlying the refinement of directed motor actions inherent to mating (Hernández-González et al., 2023).

Likewise, cyclic variations in spine density and the proportion of spine types have been described in the receptivity-related ventromedial nucleus of the hypothalamus of virgin female rats (González-Burgos et al., 2015). Similar cognition-related findings are reported for women, as the variation in the results of certain cognitive function tests during the normal menstrual cycle may be associated with changes in the cortical volume of both gray and white matter during puberty (Herting et al., 2015). Those tests included a wide range of neural information processing phenomena involved in psychomotor skills, pattern recognition, attention, language, learning and memory, problem-solving, abstract reasoning, and other activities considered higher neural activities (imagination, creativity, logical reasoning, etc.).

Based on the results of these studies, the execution of tests of cognitive functions that involve verbal fluency, perception speed, fine motor skills, verbal memory, or working memory, is better in the middle of the follicular phase of the cycle, when plasma E2 concentrations reach their normal values, compared to the other stages of the cycle. These data support the notion that the plastic phenomena which appear to be associated with learning and memory processes may occur and change within a matter of days. However, it is important to note that even though variations in plasma ovarian hormone concentrations during the cycle are associated with changes in the efficiency of specific cognitive functions, those of any stage of the cycle appear to be sufficient to maintain adequate cognitive performance, which is thought to be associated with plastic changes that occur in specific brain structures within hours in experimental animals (González-Burgos et al., 2005).

Pioneering studies have reported a fluctuation in the number of dendritic spines (Woolley et al., 1990) and synaptic contacts (Woolley et al., 1996) in neurons of the CA1 field of the rat hippocampus during the estrous cycle, as well as variations in the proportion of thin and mushroom spines during proestrus and estrus (González-Burgos et al., 2005) that are crucially related to high and low E2 levels, respectively (Woolley, 1999). This clearly corresponds to what is observed in women of reproductive age (Hampson, 1990; Hampson and Kimura, 1992; Phillips and Sherwin, 1992; Bimonte and Deneberg, 1999; Janowski et al., 2000; Maki et al., 2002; Rosenberg and Park, 2002; Sherwin, 2003; Colzato et al., 2012). In addition, the execution of visual memory tests is better in the middle of the luteal phase

compared to results on the same test during the menstrual phase. These findings have been related to the maximum concentrations of progesterone in that stage of the cycle, not to plasma E2 concentrations. However, it has been proposed that other changes in cognitive functions related to the menstrual cycle are associated with cyclical changes in E2, not progesterone, in young women. This would be the case of poor performance on spatial ability tests and better performance on motor skills and verbal fluency tests during the mid-luteal phase compared to performance of the same tests during the follicular phase (Cervantes-Alfaro et al., 2015).

Variations in plasma E2 concentrations during the menstrual cycle have also been associated with better or poorer performance on certain cognitive function tests that men characteristically perform better than women. In contrast, the execution of tests on which women usually obtain better results than men tends to improve in the phases of the menstrual cycle when plasma E2 concentrations are high, compared to the phases when they are low. Finally, women's performance on tests in which males tend to outperform them improves in the phases of the menstrual cycle when E2 concentrations are low compared to those in which they are high. It should be noted that the magnitude of these differences in performance on cognitive functions tests during the menstrual cycle only reaches levels of significance between the phases in which plasma E2 concentrations are at their maximum (pre-ovulatory or mid-luteal phase) or minimum levels (menstrual phase) (Cervantes-Alfaro et al., 2015).

Pregnancy. Significant changes in cognitive functions under the influence of changes in the hormonal environment of the brain attributable to estrogens and progestagens have been reported during pregnancy and the immediate postpartum period. In pregnant women, especially during the last trimester, lower efficiency has been observed on tests of verbal memory, working memory, verbal fluency, incidental learning, visuo-spatial memory, and speed of information processing, compared to non-pregnant women (Sharp et al., 1993; Janes et al., 1999; de Groot et al., 2003; Henry and Rendell, 2007; Glynn, 2010; Henry and Sherwin, 2011), This could be related to more recent findings which show a reduction in the volume of telencephalic gray matter (Hoekzema et al., 2017) that has been interpreted as an adaptive mechanism to prepare for raising the newborn (Schurz et al., 2014), though these psychoneural events are reversed at some moment post-delivery (Kim et al., 2010).

An apparently paradoxical finding at the cellular level, however, is that the density of dendritic spines in the hippocampal CA1 field increases at a constant rate in late pregnancy and early lactation periods compared to virgin rats even in proestrus, though no changes in the proportional density of the different spine types was observed. However, the close association between pregnancy-related hormones and stable dendritic spine fluctuations in the hippocampus that impact maternal behavior (Kinsley et al., 2006) may well be related to subsequent non-maternal behaviors, such as learning and memory, especially spatial memory (Kinsley et al., 1999; Tomizawa et al., 2003) and environmental reactivity (Wartella et al., 2003), two aspects on which the female depends when caring for her newborn. In addition, complex fluctuations in spine density occur in several subcomponents of the medial nucleus of the amygdala of multiparous females, suggesting subtle plastic mechanisms for sensory information processing and the neural modulation of neuroendocrine, mnemonic, and behavioral aspects that are fundamentally important for social adaptation and reproduction (Rasia-Filho et al., 2004). Evidence supports the notion that the neuroendocrine activity and behavioral repertoire of females during maternity differ from those of females in other periods of the reproductive cycle, and that motherhood induces complex hormonal and behavioral modifications partially mediated by plastic changes in the dendritic spines that induce and allow proper postnatal care.

Menopause. Abrupt suppression (surgical removal of the ovaries) of estrogenic actions on the nervous system can lead to impaired cognitive functions (Rodriguez and Shoupe, 2015). At the same time, the endocrine characteristics of the hypothalamic-pituitary-ovarian axis change progressively towards the end of the reproductive stage in women, during a period identified as the transition to menopause. This initial phase has been defined as the period prior to the last menstruation when there is great variability in the duration of the menstrual cycles (<25 days or >35 days). In the late phase, this transition is characterized by the absence of menstruation for 3 to 11 months, which is indicative of the onset of menopause. Under these conditions, the subtle – though progressive – changes that can occur in the brain associated with the aging process may be accentuated by the endocrine changes that mark the transition stage and the onset of menopause, especially in relation to attention span, the speed of acquisition (learning), and information retrieval (memory) (Cervantes-Alfaro et al., 2015).

Observations show that certain memory systems (González-Burgos, 2015), such as working (Luine et al., 1998), episodic (Spencer et al., 2008), and semantic (Georgakis et al., 2019) memory, including operant conditioning (passive avoidance) (Cai et al., 2013), are negatively affected by the suspension of E2 activity. These impairments partially underlie a decrease in the density, and an imbalance in the proportions, of the different types of spines (González-Burgos and Velázquez-Zamora, 2023; Luine and Frankfurt, 2023).

Although several cognitive functions do not seem to be pathologically altered during the normal or successful aging process (González-Ramírez et al., 2014), the deterioration of these functions associated with age has been revealed through tests on which correct

performance entails retrieving information such that the action of working memory leads to successful problem-solving or decision-making in specific situations (Vázquez-Hernández et al., 2021). Likewise, it has been reported that women of menopausal age, and those approaching old age, are more prone than men to develop forms of dementia, such as Alzheimer's disease, though this can potentially be prevented by physical exercise and cognitive background activities, two strategies that directly impact "hippocampal health" (Torromino et al., 2021).

Various studies have analyzed women's subjective perceptions of changes in mood, anxiety, vasomotor disorders, and deterioration of cognitive functions during the transition to menopause and its early (<5 years) and late (>5 years) stages. Self-reported cognitive decline in peri- and postmenopausal women involves episodic memory, semantic memory, verbal memory, working memory, verbal fluency, visuospatial skills, and fine motor skills; as well as difficulty in focusing attention on situations that involve the learning and successful recall of new tasks. Those studies set out to confirm the accuracy of self-reported cognitive impairment using tests designed to assess specific cognitive deficits, and to establish possible correlations with other symptoms that characterize the comprehensive clinical situation and with some aspects of the endocrine profile of menopausal women. In most cases, results support differences in the direction of the progressive deterioration of performance efficiency on tests of the various modalities of the cognitive processes of four groups of women: (i) in the reproductive stage; (ii) in the transition stage to menopause; (iii) in the immediate postmenopausal stage; and (iv) in the late post-menopausal stage (Elsabagh et al., 2007; Weber and Mapstone, 2009; Schaafsma et al., 2010; Tuomisto et al., 2012; Berent-Spilson et al., 2012; Weber et al., 2012, 2013).

Although in most cases it is believed that the deficiency or absence of E2 secretion by the ovaries, and the consequent reduction of plasma concentrations, is predominantly involved in the deterioration of cognition in post-menopausal women, it has not always been possible to identify differences in the cognitive abilities of pre-menopausal, peri-menopausal, and post-menopausal women in terms of verbal memory, episodic memory, verbal fluency, execution of visuo-spatial tests, and recognition of people. Given these conditions, the status of E2 deficiencies as the sole cause of cognitive impairment in postmenopausal women with plasma E2 concentrations as a reference has been questioned (Herlitz et al., 2007). The fact this and other studies failed to produce conclusive data on the deterioration of cognitive functions (specifically episodic memory) during perimenopause and post-menopause has led to the suggestion that the brain can maintain its ability to synthesize E2 (neurosteroid), and under these conditions E2 action is exerted on brain structures that have estrogen receptors and are involved in various modalities of learning and memory processes (Kretz et al., 2004; Alejandre-Gómez et al., 2007; Hojo et al., 2008). Another possibility that has been considered is that deficiencies in certain cognitive functions during perimenopause and menopause may result from alterations in brain function associated with vasomotor disorders, mood changes –specifically depressive symptoms– and sleep disorders that occur often, though with marked interindividual variation in magnitude, in these stages of women's lives (Devi et al., 2005; Greendale et al., 2010).

Hormone replacement therapy. Since estrogen receptors are present in the hippocampal formation and the frontal cortex, both of which are involved in the processes of acquisition, encoding, and retrieval of information corresponding to several cognitive modalities, such as verbal and working memory, the termination of E2-secreting activity by the ovaries after menopause, and the co-occurrence of this phenomenon with the deterioration of cognitive functions, raises the possibility of reversing cognitive deterioration through estrogen replacement therapy. In this regard, data from studies in experimental animals suggest that administering E2-based hormonal replacement therapy after ovariectomy may protect against the deterioration of specific cognitive functions attributable to the absence of E2 actions (Tang et al., 2004; Hao et al., 2007; Nissen et al., 2012; Velázquez-Zamora et al., 2012; Young et al., 2013). However, an important factor to be considered here is that the older the subject, the longer it will take for the beneficial effects of this therapy to appear (Sager et al., 2018).

During the processes of coding and retrieving verbal or visual information in reproductive-age women, plasma E2 concentrations show a correlation with increased metabolic activity and oxygen demand in the left inferior frontal gyrus. Likewise, during the processing of verbal or visual memory in post-menopausal women under E2 replacement therapy, greater activation of the parahippocampal, precuneal, inferior parietal, and prefrontal regions has been identified, together with associated visual, anterior thalamic, and hypothalamic areas, compared to postmenopausal women without replacement therapy. This appears to show a relation between the activation of the frontal lobes and the highest degree of difficulty on visual work tests performed by postmenopausal women treated with E2, compared to untreated postmenopausal women. Even administration of different estrogen replacement therapies (equine conjugated estrogens, E2 with or without progestin), and the use of distinct routes of administration (oral, transdermal, vaginal) produces differences in the activation of the brain regions involved in integrating cognitive functions. Better conditions of metabolic activation have been attributed to the E2 formulation.

These estrogenic actions may be highly selective, depending on the stage of the cognitive test being

performed, as shown by decreased activation of the left parahippocampal gyrus and increased activation of the superior frontal gyrus in postmenopausal women receiving Raloxifene – a selective estrogen receptor modulator (SERM) – during the encoding of visual information, but not during visual information retrieval, compared to postmenopausal women who did not receive SERM (Resnick et al., 1998; Neele et al., 2001; Sherwin, 2003; Joffe et al., 2006; Craig et al., 2008; Kaya et al., 2008; Berent-Spillson et al., 2010; Dumas et al., 2010; Silverman et al., 2011). In support of this, recent experimental studies have shown that replacement therapy with the SERMs Tamoxifen and Raloxifene reverses both allocentric working memory impairment and dendritic spine density reduction in the prefrontal cortex of ovariectomized rats, similar to the effect observed with E2 (Velázquez-Zamora et al., 2012). Likewise, a Prolame-induced recovery in the density of dendritic spines in the hippocampal pyramidal neurons of ovariectomized female rats has been observed (Nissen et al., 2012). Various studies have shown that estrogen replacement therapy based mainly on administering equine conjugated estrogens, or the transdermal administration of E2, generally leads to better performance on tests that evaluate specific cognitive processes, such as verbal or working memory, in postmenopausal women (Duff and Hampson, 2000; Keenan et al., 2001; Genazzani et al., 2007; Dumas et al., 2008; Maki and Sundermann, 2009; Berent-Spillson et al., 2010; Silverman et al., 2011; Wroolie et al., 2011).

Estrogen replacement therapy, however, has not always produced substantial beneficial effects on cognitive impairment in postmenopausal women. In fact, a worsening of cognitive deterioration has been observed when replacement therapy based only on E2, or the combination of estrogens and progestagens, begins in women several years after the onset of menopause (Henderson, 2009; Resnick et al., 2009; Rocca et al., 2011; Sherwin, 2011). Several studies have highlighted that the efficiency of replacement therapy on cognitive impairment depends on whether it begins in the transition stage to menopause or within 5 years of onset. This is the case of the beneficial effects of 10-year E2 therapy from the age of 50 on working memory in postmenopausal women, compared to untreated postmenopausal women. This proposal has been extended to a reduced risk of cognitive function deterioration and the development of Alzheimer's disease. It has been suggested, however, that the use of estrogens (especially conjugated equine estrogens) as replacement therapy initiated in postmenopausal women aged 65 years or older may increase the risk of dementia. In contrast, transdermal administration of E2 for 3 months in postmenopausal women averaging 74-78 years of age with mild-to-moderate Alzheimer's disease has been shown to improve various modalities of cognitive functions, such as visual and semantic memory (Asthana et al., 1999; Rossouw et al., 2002; Espeland et al., 2004).

Based on the analysis of these findings, a hypothesis has been proposed that postulates the existence of a critical period in which the initiation (and maintenance) of E2 replacement therapy has positive neuroprotective effects against the deterioration of some aspects of cognitive functions in women, only when it begins during perimenopause or immediately after menopause. However, the issue of why E2 does not protect against the deterioration of cognitive functions, and may even be detrimental when administration begins in women after the age of 65, has not been clarified. It may be that changes in the brain associated with aging and a prolonged period of deprivation of E2 actions that may alter certain characteristics of the neural substrate (in terms of neuronal cytoarchitecture, dendritic arborizations, the number and type of dendritic spines, estrogen receptors, and alterations of neurotransmission systems) are not compatible with estrogenic actions that aid in preserving cognition. Another suggestion is that the use of different estrogen receptor agonists, different routes of administration, cyclical (intermittent) or continuous treatment schemes, and the co-administration of progestins may be factors that contribute to the failure of these therapies to preserve cognitive performance in postmenopausal women. Thus, it is important to consider information on the fundamental aspects of hormonal neurobiology in order to administer E2 at the appropriate time and formulation, based on the specific characteristics of each individual postmenopausal woman, as this may favor the efficacy of estrogen replacement therapy. Here, it is important to note that the justification of this type of therapy is that it aims not only to improve alterations in cognitive functions, but also to enhance cardiovascular and metabolic alterations associated with the onset of menopause (Genezzani et al., 2007; Sherwin and Henry, 2008; Simpkins and Meharvan, 2008; Maki and Sundermann, 2009; Rocca et al., 2011; Sherwin, 2011; Gasbarri and Tomaz, 2012).

Conclusions and perspectives

E2 is an estrogenic molecule closely associated with normal brain development. From its organizational effects in infancy to the cessation of ovarian production during menopause, E2 differentially modulates cognitive performance during childhood, adolescence, adulthood, and aging.

Current evidence suggests several basic principles that can help develop a unitary vision of how hormones act in the brain to generate and regulate plastic changes in neurons. These principles may eventually translate into changes in the processing of synaptic information related to cognition and its behavioral expression from childhood to adulthood (García-Segura, 2009). These principles can be summarized as follows:

a) Hormones regulate brain plasticity.

b) A single hormone (like E2) may regulate distinct forms of brain plasticity.

c) Hormones exert divergent plastic actions on distinct

brain structures.
d) Multiple hormones can carry out convergent plastic actions.
e) Hormones can carry out coordinated actions in different brain regions to generate a final functional response.

In addition to hormone replacement strategies for the brain structures involved in the deterioration of cognitive functions during the cessation of E2 activity, research into the changes in the secretion and activity of other hormones that are part of the profile of endocrine changes should be included to help prevent, delay, or reverse the deterioration of various learning and memory modalities that can occur, especially, after menopause.

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