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Role of 17 β -Estradiol in Learning and Memory

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Abstract

Ovarian hormones regulate a wide variety of non-reproductive functions in the central nervous system by interacting with several molecular and cellular processes. Estrogens are steroid hormones that are synthesized in the gonads [peripherally-synthesized or "neuroactive steroids"] as well as in various tissues throughout the body, including the brain [brain-synthetized or "neurosteroids"]. 17β-Estradiol [E2] is the most potent and predominant form of estrogen. E2 has a number of effects on cognition and brain function. The effects on memory depend on hormone levels and on binding to different estrogen receptors within neural circuits.

The purpose of this review is to highlight the complex relationship between E2 and cognitive functioning, analyzing the difference of effects described by observational studies compared to randomized controlled large-scale clinical trials. We review how E2 signaling affects memory processes: it starts from neurons and reaches superior learning and memory function through the effect on synapses and on the neuronal network.

Keywords: 17β-Estradiol; Memory; Ltp; Epigenetic

Introduction

Memory is a complex process involving different brain structures, hippocampus, amygdala and the adjacent para hippocampal gyrus usually defined as medial temporal lobe structure [MTL].

The processes of memory formation are quite complex and can be subdivided into memory encoding, consolidation, storage and retrieval. These processes are sequential, and fully inter-connected. The perception of sensory inputs triggers the encoding process. MTL structures are responsible for the transformation sensations into a memory representation which is first stored and consolidated in the MTL then allocated to other areas of the cortex committed for long-term storage. Attention such as association with positive and negative emotions may affect episodic memory performance: emotional response to an event is usually remembered more easily than neutral information and a negative context seems to narrow attention to central information at the expense of more peripheral details.

Encoding memory undergoes consolidation, a process by which a fragile short-term memory is transferred into stable long-term memory through neocortical areas. Emotionally arisen experiences are better remembered than other information.

After the process of consolidation, memories are represented by networks of neurons distributed across the neocortex, bound together for rapid storage and later retrieval by MTL structures.

Morphological and functional sex dimorphism in brain is present also in brain regions that are not directly associated with reproductive success but are important for learning, memory, mood like the hippocampus, the amygdala, the striatum and the neocortex, both in animals and in humans [for a review see Gillies and McArthur, 2010, [1]. All these brain regions display a sex-specific organization in neural network and on a cellular level, for example, in the number and branching of the dendrites of hippocampal CA1 and CA3 pyramidal cells, as well as in the number of glial cells present in these two hippocampal regions [1].

In addition, evidences in human and experimental animals have also documented that the sex differences in specific cognitive and behavioral tasks depend on the type of the task: males generally outperform females in visuo-spatial, and quantitative tasks and in targeted motor skills; females excel in perceptual tasks, and in verbal and fine motor skills [2]. Adult brain dimorphism arises from the organizational effect that sex steroid hormones exert during critical developmental windows by spanning from gestation to puberty in humans, followed by a correct hormonal activation at puberty/adulthood.

There are three potential sources for the estrogens that act within the brain: circulating estrogens produced outside the Central Nervous System [CNS]; estrogens produced through the conversion of the androgen precursor locally circulating; local estrogen synthetized directly from cholesterol sources It should be noted that to initiate rapid molecular and cellular responses a nanomolar concentration of E2 is required and it is not a concentration reached by the peripherally circulating hormone. At the current state of art experimental evidences do not allow us to identify with certainty the source of estrogens that underlies modulation of cognition.

Estrogen Effect on Cognitive Outcomes

The majority of women experience some symptoms of menopause of varying severity, such as hot flushes, vaginal symptoms, night sweats and insomnia. For ameliorating menopausal symptoms Hormone Therapy [HT] is the most effective options. The early observational studies reported supplementary health gains with HT, such as decreased risk of cardiovascular disease and hip fracture [3]. Sex hormones influence cognition [4-6] and numerous clinical research studies have examined memory and cognitive function in women whose levels of E2 have been altered either through ovariectomy or menopause. In general, the results of these studies show a decrease of cognitive function [increased memory deterioration and dementia] in women following the surgical removal of their ovaries or menopause. The level of estrogens and in particular, E2 exerts a definite beneficial influence on learning and memory process [7,8] and on cognitive decline during

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physiological aging and in neurodegenerative diseases. Cognitive impairment occurs when E2 concentrations are above or below an optimal level [9]. This inverted U-shaped dose-response of the estrogen effect on cognition may reflect the optimal level of estrogen receptors activation (Figure 1) [10].

It has interestingly been suggested that endogenous sex hormone fluctuations associated with the menstrual cycle can also have cognitive effects [11,12]. The menstrual cycle is characterized by changes in ovarian sex hormones, including neuroactive steroids E2 and progesterone. During the midluteal phase of the menstrual cycle, characterized by high levels of E2 and progesterone relative to the early follicular phase, memory in multiple mnemonic domains is enhanced and superior performance has been shown on tasks of conceptual implicit memory [13], visual memory [14], and verbal memory [15]. Conversely, when ovarian sex hormones are decreased during the early follicular phase better spatial memory performance has been described [16,17].

The HT effect on cognition gives inconsistency in findings. Actually, observational studies in midlife and aging women suggested that HT might also benefit cognitive function, but randomized clinical trials have produced mixed findings in terms of cognitive outcomes.

Observational studies describing the effects of HT on cognition suggest that individuals undergoing estrogenic treatment performed significantly better on tests of verbal memory [18], working memory [19-21], and visual memory [22] in comparison to non-HT users. Furthermore, observational studies suggested that HT offered a 50% reduction in Alzheimer's disease [AD] and protection against risk of dementia [23-25].

The neuroprotective effect of estrogen replacement therapy [ERT] was questioned some years ago by the results of the two randomized controlled large-scale clinical trials: the Women's Health Initiative [WHI] and the Women's Health Initiative Memory Study [WHIMS] [26-28]. Contrary to expectation, WHI and WHIMS showed increased dementia risk and poorer cognitive outcomes in older postmenopausal women randomized to HT versus placebo with prolonged administration of estrogens, leading to trial withdrawal.

Subsequent studies have demonstrated that HT has a positive effect on cognitive performance, only if the therapy is initiated immediately after the ovarian hormone loss [29] and therefore it is strictly linked to women's physiological status at the time of the initiation of treatment. Therefore, a window of opportunity may exist shortly after menopause during which estrogen treatments are most effective as suggested by the "critical window hypothesis" [30]. This observation is confirmed by the results of more recent studies that show that increase in cognitive performances of HT are minimal in women older than 65 [31,32].

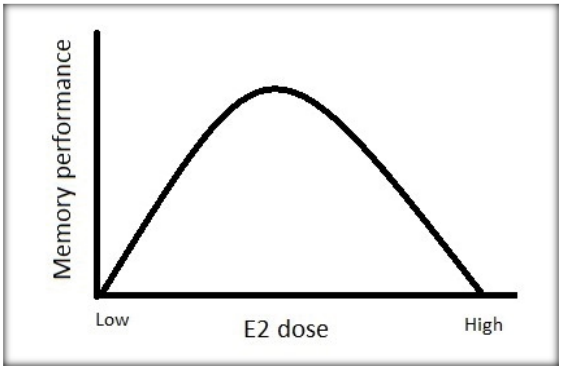

Figure 1: Relationship between 17β-estradiol (E2) level and memory performance is described by an inverted U function.

In rodents, the ability of E2 to improve performance on spatial memory learning tasks is highly dependent on the age of animal in ovariectomized rodents, the estrogen dose, and the time window between the estrogen decline and the initiation of E2 treatment [33,34]. Studies in rodents have demonstrated the ability of estrogens to improve the cognitive performance of several types of hippocampal-dependent memories, including spatial memory [35,36], novel object recognition, social recognition, inhibitory avoidance memory [37,38]. This effect depends on many factors: sex and age of animals, treatment and duration dose, the length of hormone withdrawal before treatment, the type of memory tested, the time window between treatment and testing [39].

These findings apparently mirror HT clinical observation in women and strongly suggest that the underlying mechanisms that account for the effectiveness of HT to improve memory performances in women are likely to be multifactorial. Therefore, the inconsistency of findings about the HT effect on cognition could be explain by possible variables known to influence cognitive abilities such as age, education and socio economic status, and by factors linked to HT therapy like types, doses and duration of hormones administered [including cyclic versus continuous administration], route of treatment delivery, and the time of the initiation of treatment compare to proximity relative to menopause.

Recently, it has been published the randomized large scale trial Women's Health Initiative Memory Study-Younger [WHIMS-Y] [40], an ancillary study to the [WHI], to test whether an average of 5.4 years of HT during early menopause has longer term protective effects on global cognitive function and if these effects vary by regimen, time between menopause and study initiation, and prior use of HT. Furthermore, the KEEPS Cognitive and Study Affective [KEEPS-Cog] [41] demonstrate that HT did not improve cognition when initiated in healthy recently postmenopausal women compared to placebo. For mood outcomes, HT up to 4 years was associated with statistically significant improvements in symptoms of anxiety and depression, mood symptoms commonly seen in recently postmenopausal women. It is notable that in both these randomized large scale studies the hormone therapy does not alter cognition. In other words, these results did not indicate adverse or beneficial cognitive effects associated with HT.

In addition, it is emerging evidence that potential adverse effects of HT on cognition are most pronounced in women who have other health risks, such as lower global cognition or diabetes [30]. In agreement with this hypothesis, in observational studies, women who opted to use HT were inclined to be healthier overall.

It is now apparent that in women's therapy with transdermal estrogen coupled with micronized progesterone at the time of menopause is associated with cognitive and affective benefits [32,35].

Interestingly, the nasal route is an effective and well-established route for E2 delivery [42]. 300 μg intranasal E2 produces a pulsed profile of plasma E2, with systemic plasma levels rising, reaching the peak concentration in about 30 minutes and returning to baseline level within 12 hrs. Nasal administration of E2 induces a significant vasodilatatory effects on cerebrovascular and ocular circulation [43]. It is supposed that E2 may reach the brain via trans-ethmoidal absorption

through areas not protected by the Blood Brain Barrier [BBB], reaching the olfactory lobe and the base of the brain [43].

Genomic and Non-Genomic Estrogen Action in the Brain

Classically, a steroid function has been described to occur via the regulation of a gene transcription, a process that typically takes hours to days to manifest a so called "genomic response". Critically, it is now emerging that steroids can also elicit cellular actions that occur as fast as seconds to minutes. The rapid actions of steroids has been described as "non-genomic" [Figure 2].

The slow genomic response involves the two classic nuclear estrogen receptors [ERalpha and ERbeta], while rapid onset response involves cytoplasmic estrogen receptors [mERalpha and mERbeta]. Typically, mERs activation is involved in synaptic plasticity, required for memory coding and retrieval, while nuclear ERs are associated with neuroprotection and long-term maintenance of cognitive functions [39].

ERalpha and ERbeta activation can bind to classical estrogen responsive elements [ERE] on DNA, or interact with other DNA-bound transcription factors, as CREB or FOS/Jun regulating gene transcription.

Microarray DNA studies describe different batteries of genes up and down regulated upon single or chronic estrogen administration in young or middle-aged rats [38,44,45]. Among proteins, the expression of which is modulated by estrogens there are proteins involved in neurotrophism and neuroprotection [e.g., BDNF-, IGF2 and its binding protein], in neuronal plasticity [Enpp2], in protein folding activation [Hsp70], in cytoskeletal modifications and protein trafficking [actin, beta-tubulin]. Estrogens also modulate the expression of some enzymes involved in DNA methylation and histone remodeling [see chapter 5 on epigenetic effect].

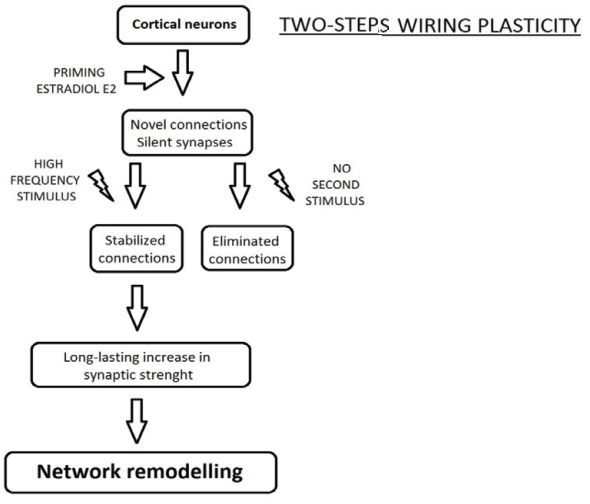

Figure 2: The "Two-steps wiring plasticity" hypothesis (see Srivastava et al. 2013). Treatment with E2 primes the formation of novel spines within 30 minutes. These "silent" synapses containing only NMDA receptors can undergo two different destinies. In the presence of high frequency stimulation the novel connections will be stabilized causing a long-lasting increase in synaptic strength and in network remodelling. In the absence of a second stimulus the new spines will be eliminated and the network returns to control level.

Rapid non-genomic response is mediated through mERalpha and mERbeta, including GPER1 G-protein coupled receptor and the interaction of mERalpha and mERbeta with metabotropic receptors. Investigations using receptor specific agonists suggest that all of the three receptors rapidly activate signaling cascades involving Ca^{2+}, adenylcyclase, phospholipase C, and specific kinase-signaling [IP3K, Src, PKA, PKC, ERK, AKT etc.,] which in turn can rapidly influence neurons activity or the phosphorylation state of transcription factors such as CREB or ERalpha [46-49]. Kinase activity within a few minutes' rises and declines and activation curve exhibits an inverted U function, with inhibition at low and higher doses [50].

To add a further level of complexity to this mechanism of action, studies on neuronal cells have demonstrated that kinase activation phosphorilates nuclear ERs, enhancing their transcriptional activity [51]. What is emerging in the overall mechanism of action of estrogens is a cross-talk between the rapid non-genomic signaling and the activation of transcriptional/translational machinery, and this cooperation promote long-term changes in synaptic plasticity. During aging, loss of ERs, disruption of the hormone cycle, or uncoupling of the hormone/receptor system could contribute to a decline in these pathways.

The relative levels of nuclear ERalpha and ERbeta, mERs and GPER1 varies across brain regions [52,53]. Estrogen receptors are present in all the areas involved in the processing of learning and memory: amygdala, cerebral cortex and hippocampal formation. The maintenance of hippocampal functions depends on a balance between estrogen levels and relative expression of the two ER subtypes within the structure. In addition ERalpha is basic for the maintenance of cognitive processes while ERbeta seems to play a minor role: when estrogen levels decline with aging, the ippocampal expression of ERalpha relative to ERbeta is reduced, by decreasing the ability of estrogens to preserve cognition. ERbeta could compensate ERalpha decline but only if the estrogen levels increase [54].

In agreement with this hypothesis, it has been demonstrated that albeit a common decrease of hippocampal ER expression with aging, the decline of ERalpha is more pronounced, causing a shift in the relative expression and a parallel reduction of estrogen-driven neuroprotection, synaptogenesis and synaptic plasticity [55,56].

Estrogen Effect on Long-Term Potentiation

Very rapid and presumably non-genomic effects are triggered by estrogen. Brief infusions of E2 in rat hippocampal slices result in an almost immediate enhancement of fast excitatory postsynaptic potentials [EPSPs] in CA1 neurons [57]. E2 increases synaptic excitability in part by enhancing the magnitude of α-amino-3-hydroxy-5-methyl-4-isoxazoleproprianate [AMPA] receptor-mediated responses probably through a postsynaptic effect. This facilitation reverses quickly upon washout.

A second acute physiological action related to memory encoding is the generation of long-term potentiation [LTP] or depression [LTD]. This involves both a reduced threshold for inducing LTP and the enhancement of both AMPA and NMDA-mediated responses [57].

In area CA1 of hippocampus, LTP requires NMDA receptor activation for its induction, and an increase in AMPA receptor function for its expression and maintenance. The ability of estrogens to modulate the activity of the two ionotropic glutamate receptors demonstrates the important role of these hormones on LTP. Manipulations that promote LTP are reported to improve memory in animal models [for a review

see Lynch et al. 2008, 58]. The ability of estrogens to enhance memory consolidation occurs also via the physical interaction of mERS with metabotropic glutamate receptor [mGluR1] and the activation of a common signal transduction pathway [59].

In vitro and *in vivo* studies demonstrate that estrogens rapidly influence LTD, a necessary step for a complete memory processing, both in males [60] and females [61]. The use of selective ER agonists reveals that, as opposed to LTP, mERalpha, but not mERbeta, participate to LTD [60].

Estrogen and Synaptic Remodeling

The expression of a large number of postsynaptic proteins is regulated by steroids, whereas presynaptic proteins appear to be less sensitive to steroid regulation. The change in the profile of post-synaptic proteins affected by estrogens involves PSD-95, a scaffolding protein involved in the organization of glutamate receptors, and spinophilin, a dendritic actin-binding protein present primarily in excitatory neurons [62]. The effect might be due to a redistribution from cytosolic regions to nascent dendritic spines.

One of the main post-synaptic morphological changes induced by estrogens is the fast formation of dendritic spines. Dendritic spines exhibit both transient and enduring morphological modifications. Novel dendritic spines are highly dynamic structures that can be either stabilized or eliminated. A single estrogen administration [63] rapidly increases the number of thin, philopodia-like spines, able to make synaptic connections, and the spine density returns to pretreatment levels within an hour unless further stimulated [64].

Cellular and molecular studies indicate that E2 can rapidly "prime" neurons to respond with greater efficacy to subsequent synaptic stimulation [50]. This "two-steps wiring plasticity" begins with the transient formation of new dendritic spines and generates new connections with silent synapses containing NMDA but not AMPA receptors. The addition of a subsequent activity-dependent stimulus shortly after, is followed by the appearance of AMPAR in both new and pre-existing synapses. The combined treatment of E2 and an activity-dependent stimulus result in a long-term increase in connectivity in neurons that lasts for at least 24 hrs. Without this second stimulus, the new synapses are eliminated and the neurons return to a "resting state" [50]. This "two-step wiring plasticity" [Figure 2] mechanism might be responsible for the enhanced cognitive performance in rapid learning paradigms observed in female rats treated with low estrogen doses [65,66].

For the consolidation of the altered synaptic configuration and the AMPAR transfer to the synaptic membrane [leading to a stable LTP] a re-organization of sub-synaptic actin cytoskeleton is required.

Estrogen activates synaptic TrkB receptors for Brain Derived Neurotrophic Factor [BDNF], and synaptic integrins, modulate actin assembly and stabilization [67,68].

Role of Estrogen in the Epigenetic Mechanism of Memory

Studies exploring the role of epigenetics mechanism in learning and memory [69,70] have focused primarily on the hippocampus. However, recent data support the importance of epigenetic modifications for memory processes in other brain regions including the amygdala and the prefrontal cortex [71,72]. Epigenetic modifications of chromatin consist in post-translational modifications of nuclear proteins and in covalent modification of DNA. Epigenetic modifications of chromatin result in potent regulation of gene readout. Two basic molecular epigenetic mechanisms currently studied are post-translational histone modifications and DNA methylation.

Histone acetylation is involved in ERE-sequences mediated gene transcription, since ER needs to recruit as coactivators, histone acetyltransferases [HATs or interact with HATs], or as corepressors histone deacetylase [HDAC] activity [73,74].

Furthermore, estrogens may exert epigenetic effects through membrane receptors. In this case, mER activates cell signaling pathways and in particular, the mitogen-activated protein kinase [MAPK] and the extracellular signal-regulated kinase 1/2 [ERK1/2]] that, among the various neuronal responses, initiate also processes like histone acetylation [75,76].

DNA metylation seems also to be involved in some of the mnemonic effects of estrogens. Infused E2 significantly increases both the mRNA level of DNA [cytosine-5-]-methyltransferase 3a [DNMT3A] and DNA [cytosine-5-]-methyltransferase 3b [DNMT3B] at dorsal hippocampus [77]. These findings suggest that DNA methylation is necessary in the E2 induced memory enhancement and that E2 enhances memory, at least in part, by DNA methylation.

In conclusion, histone H3 acetylation and DNA methylation play a pivotal role in regulating the beneficial effects of E2 on memory. A possible interplay between histone acetylation and DNA methylation in the modulation of memory has also been suggested [78].

Epigenetic treatments [e.g., HDAC inhibitors] might provide menopausal women with the cognitive benefits of HRT without the harmful side effects [e.g., cancer, heart disease, and stroke] common to such therapy. However, even if histone deacetylase inhibitors are generally well tolerated [79] the lack of specificity of the compound currently available might make their use rather problematic in post-menopause.

Conclusions

This review provides an overview of the current literature concerning the effect of E2 on cognitive function. We review the relationship between hormone therapy and cognitive functioning, highlighting the difference of effects described by observational studies compared to randomized controlled large-scale clinical trials. The effectiveness of HT to improve memory performances in women is likely to be multifactorial. The "critical window hypothesis" [for a review see Maki 2013, [80] posits that early treatment in younger postmenopausal women, closer to the menopausal transition, might be more beneficial to cognition. In addition, the potential adverse effects of HT on cognition are most pronounced in not-healthy women with lower global cognition or diabetes.

In summary, investigations of HT in menopausal women have produced many inconsistent findings. The lack of cognitive benefit described in WHIMS-Y and KEEP-Cog trials and the absence of short- and long-term harm to cognitive function should reassure healthy women who choose to use HT for treatment of menopausal symptoms.

The mechanisms of learning and memory encoding, consolidation, storage and retrieval are not completely clarified. Neuronal activity changes in a dynamic way to handle different types of information in the network and creating new memories. In this first step of memory encoding the mechanisms involved in formation and modulation of synaptic connectivity are crucial. Change in synaptic strength and LTP are the main processes involved. The formation *de novo* of synapse

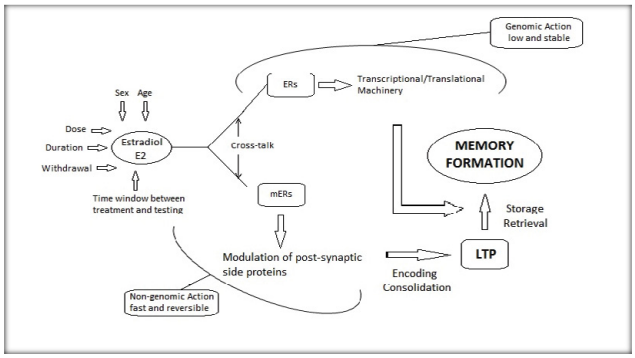

Figure 3: A cartoon summarizes the main mechanism linking E2 with memory.

or the remodeling of pre-existing dendritic spines is the sequential event aimed at stabilizing new memories for storage and retrieval. The transduction of synaptic event into intracellular signaling leads to the induction of gene expression and protein synthesis critical for a stable memory formation. The most potent and predominant form of estrogen, E2 might modulate the series of events leading to memory formation and storage, through slow genomic and fast non-genomic effects. Non genomic, rapid, transient effects are extremely active in modulating memory mechanisms. E2 appears to enhance memory through epigenetic modifications, DNA methylation and histone acetylation, processes that are both critical for the basic memory formation.

A cartoon summarizes the main mechanism linking E2 with memory [Figure 3].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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