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Estrogen-mediated effects on cognition and synaptic plasticity: what do estrogen receptor knockout models tell us?

Hyun Jin Kim¹ and Gemma Casadesus^{1,*}

¹ Department of Neurosciences, Case Western Reserve University, 2109 Adelbert Road, Cleveland, OH 44106, USA

Abstract

A plethora of evidence supports a beneficial role of estrogen in the brain. However, while these effects are hypothesized to be driven via the two main forms of estrogen receptors (ER α and ER β), the mechanism through which these receptors mediate estrogen's effects on cognition and plasticity remain unclear. Estrogen receptors are heterogeneously expressed in many cognition sensitive regions of the brain, have the ability to dimerize and heterodimerize, and are localized to both neurons and glia. In addition, while many of the known actions of estrogen through their receptor are mediated via the classical genomic regulatory mechanism of gene transcription, rapid non-genomic action of estrogens are also gaining relevance. These complex events make the mechanistic understanding of estrogen effects challenging. The development of transgenic estrogen receptor knockout mouse models has provided some much needed insight on the role of these receptors in mediating estrogen effects on cognition and synaptic plasticity. This review provides an overview of estrogen receptors in the brain and an update of knowledge gained from transgenic knockout models on cognition and synaptic plasticity.

Keywords

Estrogen; Cognition; Synaptic plasticity; Estrogen receptors (ER α and ER β) ER knockout models; CNS

Introduction

For many years it was thought that only a single form of the nuclear estrogen receptor, ER α existed [1]. However, with the later discovery of ER β [2] and of estrogen binding receptor proteins, whose role remains unclear [3], the complexity of estrogen receptor signaling in addition to it study has greatly increased during the last 50 years..

ER α and ER β belong to the superfamily of nuclear receptors, specifically to the family of steroid receptors that act as ligand-regulated transcription factors. Each receptor is encoded by a separate gene (ESR1 and ESR2 respectively) which dimerize, and are also hypothesized to form homodimers or heterodimers [4,5]. Both receptors show significant overall sequence homology, and are composed of seven domains. However, they have differences in their

*Corresponding author: Gemma Casadesus, Ph.D., Case Western Reserve University, Department of Neurosciences, 2109 Adelbert Road, E729, Cleveland OH, 44106, Tel.: +1 216 368 8503, Fax: +1 216 368 4650., gxc40@case.edu.

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binding affinities for ligands and are expressed differentially in various body regions. For example, ER β is highly expressed in central nervous system, the cardiovascular system, the immune system, the urogenital tract, the gastrointestinal tract, the kidneys and the lungs [6–12]. ER α , on the other hand, is more highly expressed in the uterus. In the brain, both ER α and ER β are expressed, and a long standing question in the field is the significance of each of these receptors on synaptic plasticity and modulation of learning and memory.

The study of estrogen receptor function in the body and particularly in the brain has presented some challenges, particularly regarding which receptor is primarily responsible for the effects of estrogen on the central nervous system (CNS) function [13–14]. One invaluable tool to study the biological function and effects of estrogen on synaptic plasticity in the nervous system has been the creation of ER α and ER β knockout mice. This article will address the significance of each receptor type on these important central processes.

The role of estrogen on synaptic plasticity and cognition

Over the last 30 years intense pre-clinical and clinical study of the role of estrogen (E2) on neuroprotection and cognition has been undertaken to elucidate the brain-estrogen connection. E2 can act as a neuroprotective agent [15], promoting synaptic plasticity and growth of nerve processes [16–19] and modulates various synaptic markers that are associated with cognition [20,21]. For example, E2 can act as a neuroprotective agent by lowering brain levels of amyloid beta (A β) [15], ameliorating the nerve cell injury caused by A β [22], and promoting synaptic plasticity and neurite outgrowth [16]. As such, the influence of E2 on synaptic plasticity and remodeling in the hippocampus has been known for quite some time.

Early studies show that ovariectomy (OVX) reduces synaptic remodeling via the reduction in spine density in the CA1 region, and that this effect can be rescued by E2 replacement in rodents [23–25] and in primates [25–26]. Furthermore, synaptic remodeling has been shown to occur in coordination with the phasic nature of E2 [25] as well as after local administration of E2 in various brain regions. This is supported by evidence demonstrating a dramatic increase in the density of CA1 area spine synapses [28–29]. Likewise, various synaptic markers are upregulated after systemic E2 application [17], namely, synaptophysin, a member of the transmitter vesicle membrane localized in pre-synaptic boutons [30] and synaptophilin, a cytoskeleton-associated protein, found in post-synaptic spines [31–32]. Changes in synaptic plasticity associated with OVX are improved by estrogen replacement have been tightly correlated with cognitive improvement in Rodents [33–34]. Importantly, at a clinical level, the role of E2 on cognition and Alzheimer's disease (AD) has risen to prominence based on various epidemiological and small clinical trials indicating that E2 deficiency, by natural or surgical menopause, contributes to both benign cognitive decline [35] as well as the etiology of AD [36]. Epidemiological and observational studies indicating that estrogen replacement therapy (ERT) lessen the risk of AD in post-menopausal women [37–38] and improve cognition in several domains [39–40] have granted further support to preclinical findings.

Estrogen receptor distribution in the brain

ER α and ER β show largely non-overlapping brain distributions [41]. This suggests different roles of these receptors on neuronal function and behavior [42]. Specifically, while the presence of ER α and ER β mRNA is observed throughout the rostral-caudal extent of the brain, ER β mRNA but not ER α is found in olfactory bulb, supraoptic, paraventricular, suprachiasmatic, and tuberal hypothalamic nuclei, zona incerta, ventral tegmental area, cerebellum Purkinje cells of the cerebellum, and pineal gland. In contrast, only ER α but not ER β expression has been observed in the ventromedial hypothalamic nucleus and subfornical organ. Furthermore, other regions such as stria terminalis, medial and cortical amygdaloid nuclei, preoptic area, lateral habenula, periaqueductal gray, parabrachial nucleus, locus ceruleus, nucleus of the

solitary tract contain both forms of ER mRNA [41,43–44]. Importantly, areas associated with cognition such as the cerebral cortex and hippocampus contain both ER mRNAs. However, ER α mRNA expression has been reported to be weak compared with ER β mRNA [41]. Protein expression of ERs follows a similar pattern. Receptor protein expression has been suggested to primarily localize to interneurons rather than pyramidal or granule cell neurons, particularly in the hippocampus [45]. Furthermore, ER α and ER β in this region and others are differentially expressed throughout the rodent brain both in a cytosolic and nuclear fashion. ER α is observed in nuclei of interneurons in CA1 and CA3, stratum radiatum, and in the pyramidal cell layer, as well as the hilus, the dentate gyrus, granule cell layer. By contrast, ER β is highly expressed in the nuclei of CA3 stratum lucidum, CA1 stratum radiatum, and dentate gyrus, and is also expressed in axons, dendrites, and dendritic spines, which suggests local synapse modulation. Nevertheless, both receptors are also localized to glia of CA1, CA2, CA3, and in the hilus of the dentate gyrus of male and female rats and are shown to be upregulated in response to injury suggesting an acute neuroprotective role of estrogen [46].

The importance of estrogen in the brain and particularly synaptic function and cognition is clear based on the wide localization of these receptors, both with regard to region and cellular type. However, the diverse regional expression of these receptors together with intricate receptor dynamics (i.e. homodimerization or heterodimerization) [4–5] have made the understanding of the individual contribution of these receptors difficult. The development of ERKO mice has made some strides towards uncovering their individual contribution as well as their inter-relationship as it pertains to synaptic plasticity and cognition.

Cognition and synaptic plasticity changes in ER knockout models *ER α* *Knockout mice*

The ER α knockout mice (ER α KO) lack functional ER α during development and adulthood. ER α is essential in females for normal regulation of the hypothalamic–pituitary gonadal axis as shown by altered plasma levels of estradiol (E2), testosterone, and luteinizing hormone [50]. ER α KO male and female mice, are unable to respond to many of the actions of estradiol in adulthood [47]. ER α KO males show reduced sexual behaviors [49] such as mounting and sexual attraction toward wild-type females [48]. ER α KO females do not show female-typical behavior or display masculine behavior under the appropriate hormone and testing conditions [49–50]. Interestingly, ER α KO females are often attacked by the male, likely due to increased levels of testosterone in ER α KO females.

The significance of the ER α on cognition has gained strength by studies demonstrating that ER α polymorphisms are associated with age-related memory deficits and an increased incidence of Alzheimer's disease among women [51–52]. As such, the ER α KO mouse provides a useful dissection tool to help elucidate the mechanism through which estrogen acts to influence spatial learning. In this regard, an early study demonstrated that ER α KO mice were able to learn the Morris water maze task, a task commonly used to study hippocampal spatial memory function [53]. The fact that ER α KO mice (OVX with and without E2 treatment) can learn MWM task, indicates that ER α is likely not involved in the learning aspect of this task. However, the fact that estrogen administration impaired cognitive function in WT mice but did not in ER α KO mice suggests that negative effects of E2 on spatial learning may be mediated via the ER α receptor. Interestingly, while female OVX ER α KO mice appear to learn Morris water maze, ER α KO mice are unable to perform the inhibitory avoidance task [54]; a deficit that is reversed by the supplementation with estrogen and was not blocked by tamoxifen, suggesting that estrogen modulation of memory in this task is not driven by known genomic receptor mechanisms.

There is also evidence for ER α dependent synaptic plasticity changes. In this regard, an early study demonstrated that application of estrogen to normal hippocampal slices produces a rapid increase in synaptic transmission that is muted in hippocampal slices prepared from male and female ER α KO mice [55]. However, because ER α is critical during development [56] the early ER α knockout mouse cannot be used to separate adult versus developmental effects of ER α . An important recent study in which lentiviral delivery of the gene encoding ER α was delivered to the hippocampus of adult ER- α -knockout (ER α KO) has separated developmental from ER α specific effects on synaptic function and behavior [57]. Specifically, this work demonstrates that such delivery in adult ER α KO mice is not only able to restore cognitive function but also synaptic responses that are induced by estrogen. Therefore, ER α seems to be important in achieving a global effect on hippocampal synaptic function that is likely to be associated with estrogen's activation of rapid signaling pathways.

ER β Knockout mice

ER β is the predominant estrogen receptor in the prostate, lung, bladder, gastrointestinal tract, salivary gland, and developing pituitary [58]. The ER β knockout mouse (ER β KO) shows normal sexual behavior. Moreover, both ER β knockout male and female mice are reproductively competent; although ER β KO female mice exhibit reduced fertility. In addition, unlike the ER α KO mouse, circulating gonadal steroid levels in these animals appear within the normal range observed in gonad-intact individuals of both sexes [60].

In the brain, the high expression levels of ER β compared to ER α in the hippocampus suggests that at least some of the effects of estradiol are likely to be mediated by ER β [42]. As such, learning ability in ovariectomized ER β KO females was impaired compared to wild-type ovariectomized females. In addition, ER β KO females given the low dose of E2 showed delayed learning acquisition, and when administered a higher dose failed to learn the task completely. These data indicate that ER β is required for optimal spatial learning [60]. Further support stems from the fact that ER β KO mice show memory impairment in the hippocampus-dependent contextual fear conditioning task and deficits in hippocampal neuronal activity, at the level of synaptic input-output curves and their LTP in the CA1 [61]. Given that previous work with higher dose of E2 than used in this study showed that water maze learning was impaired in WT but not in ER α KO females [53]. Together, these data suggest that the inhibitory effect of E2 on learning is ER α dependent and the lack of ER β increases sensitivity to the negative consequences of E2 on spatial learning and memory.

Of note, a recent study combining pharmacological, genetic, and behavioral approaches demonstrates the impact of ER β receptors in mediating the effects of estrogen on synaptic plasticity and hippocampus-dependent spatial memory. First, WAY-200070, a specific ER β agonist increased a range of synaptic proteins in vivo, including PSD-95, synaptophysin and the AMPA-receptor subunit GluR1 and ERbeta activation enhanced long-term potentiation in slices. Importantly, these were correlated with enrichment of neuronal architecture and spine number. These effects were absent in ERbeta knockout mice. Furthermore, An ERbeta agonist, but not an ERalpha agonist, improved performance in hippocampus-dependent memory tasks [62]. Interestingly, Rissman and colleagues [59] demonstrated that ER β KO mice showed downregulation of ER α in the hippocampus and other regions. As such, on potential explanation discussed by the authors, is that the presence of ER β may protect ER α protein from E2 dependent downregulation. Downregulation of ER α then can influence learning associated mechanisms [63] that lead to cognitive dysfunction.

Nevertheless, what is clear is that the estrogen-dependent effects through ER β and ER α on cognitive abilities appears dependent on the specific task as demonstrated by the fact that inhibitory avoidance was not impaired in ER β KO mice relative to wild type whereas ER α KO mice exhibited impaired performances on the same test [55].

Conclusions

The role of estrogen on cognition and synaptic plasticity is supported by 30+ years of research demonstrating the undisputable impact of this hormone in these CNS processes. However, what is also evident is that the mechanism through which estrogen produces its effects is undoubtedly complex. Studies aimed at understanding estrogen effects on hippocampal processes are complicated by the fact that estrogen can act through classic genomic nuclear mechanisms as well as rapid non-genomic membrane-mediated ones to alter synaptic plasticity and ultimately the behavior associated with these changes. For example, two recent studies show that estradiol improves cognitive function in the OVX model via signaling pathways involving ERK phosphorylation that are independent of ERs genomic activation [64] and that involve epigenetic alterations such as DNA methylation and acetylation [65]. Additionally, this task is further complicated by the fact that key structures on cognition such as the hippocampus, express both types of receptors (ER α and ER β) and that these receptors are shown to homodimerize and heterodimerize. In this regard, it is almost certain that the pattern of dimerization of these receptors will impact their function and modulatory effects on neuronal function and behavior. Furthermore, both, ER alpha and ER beta, have been implicated in neuroplasticity processes such as hippocampal neurogenesis [66], dendritic spine increases [67,68], aspects profoundly influence cognition and that are, at least partially, driven via the classical genomic pathways [69].

The development of ERKO mice has allowed the field to dig deeper into the mechanistic understanding of these receptors as mediators of estrogen effects on cognition and synaptic plasticity. However, several caveats such as changing hormone levels or the inability to dissect developmental effects of ERs from those specific to cognition, in addition to different doses of estradiol and behavioral tasks has added ambiguity to the mechanistic profile of these receptors

To date, studies remain contradictory on both sides of the aisle. Whether both receptors have a direct impact on synaptic plasticity and cognition or whether the effects observed by downregulation of one receptor are secondary to the impact of this downregulation on the other receptor remains to be further clarified. In this regard, more, advanced genetic tools such as inducible transgenic models and the development of selective modulators of these receptors are likely to deliver a long awaited dissection of the role of ER α and ER β and their mode of action.

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