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Role of estrogen receptor α in membrane-initiated signaling in neural cells: Interaction with IGF-1 receptor☆

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ABSTRACT

The mechanisms of action of estradiol in the nervous system involve nuclear-initiated steroid signaling and membrane-initiated steroid signaling. Estrogen receptors (ERs) are involved in both mechanisms. ERα interacts with the signaling of IGF-1 receptor in neural cells: ERα transcriptional activity is regulated by IGF-1 receptor signaling and estradiol regulates IGF-1 receptor signaling. The interaction between ERα and the IGF-1 receptor in the brain may occur at the plasma membrane of neurons and glial cells. Caveolin-1 may provide the scaffolding for the interaction of different membrane-associated molecules, including voltage-dependent anion channel, ERα and IGF-I receptor.

1. Introduction

The ovarian hormone estradiol, a key regulator of reproductive physiology, acts in different regions of the central nervous system to control neuroendocrine secretions, reproductive behaviors and non-reproductive events, modulating synaptic function and synaptic plasticity and affecting mood and cognition [1–3]. In addition, estradiol is a neuroprotective factor that promotes neuronal survival and tissue integrity in different experimental models of neurodegeneration [1,4,5]. As in other tissues, the actions of estradiol in the nervous system involve estrogen receptors (ERs) α and β [6,7] and two different but interrelated mechanisms: (i) the transcriptional regulation of target genes, by nuclear-initiated steroid signaling, and (ii) rapid membrane and cytoplasmic actions, by membrane-initiated steroid signaling, which in turn may also finally result in the regulation of transcription [8–10]. ERs mediate nuclear-initiated estradiol signaling, acting as transcription factors that are activated after ligand binding to regulate the transcriptional activity of target genes. In addition, ERs are also involved in membrane-initiated steroid signaling [10,11] and numerous actions of estradiol in the nervous system involve cross-talk between ERs and the membrane/cytoplasmic signaling of growth factor/neurotrophin receptors [12,13].

Estradiol may directly interact with growth factors at different levels of the intracellular signaling pathways in neurons and glial cells, including the regulation of G proteins [14–18], the modulation of intracellular calcium levels [19–27], the activation of calcium-calmodulin-dependent protein kinase II [28], the activation of the src tyrosine kinase [18,29,30], the activation of extracellular signal-related protein kinase (ERK)/mitogen-activated protein kinase (MAPK) cascade [12,18,21,29,31–37], the activation of the phosphatidylinositol 3-kinase (PI3K) pathway [32,33,37–41], the activation of c-jun-kinase [42,43] and/or the phosphorylation of the cAMP response element binding protein (CREB) [44–50]. The colocalization of ERs with growth factor receptors in the same neural cells provides a cellular substrate for cross-coupling between these signaling pathways. For instance ERs colocalize with p75, the low-affinity NGF receptors, in cholinergic neurons of the basal forebrain [51]. In addition, there is a widespread colocalization of estrogen and neurotrophin receptors within estrogen and neurotrophin targets, including neurons of the cerebral cortex, sensory ganglia and PC12 cells [12,52–55]. Immunohistochemical analyses have also shown an abundant colocalization of ERs and insulin-like growth factor-1 (IGF-1) receptor in different neuronal and glial populations in the rat central nervous system [56–58].

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2. Interactions between estrogen receptor α and IGF-1 receptor in the brain

The interaction of ERs and growth factor receptors in the same neural cells not only allows the regulation of membrane-initiated growth factor signaling by estradiol but also the regulation of nuclear-initiated ER signaling by growth factors. There are now good evidences indicating that in addition to classical activation of ERs by estradiol binding, ER mediated transcriptional activity can be regulated by ligand-independent mechanisms. Estrogen independent ER activation in the brain is suggested by studies on a transgenic strain of mouse with a luciferase transgene driven by a promoter containing estrogen response elements. ER-dependent transgene expression is observed in the brain of these animals when plasma estrogen levels are low and when brain aromatase is inhibited, suggesting that ERs can be activated by estrogen-independent mechanisms [59]. Intracellular kinase signaling pathways, activated by extracellular growth factors, regulate the ability of ERs to promote changes in gene expression. Epidermal growth factor, fibroblast growth factor and IGF-1 are among the extracellular regulators of these kinase pathways that have been shown to promote ER receptor dependent transcription. Regulation of ERα transcriptional activity by growth factors has been extensively studied in non-neuronal tissues and cell lines [60,61]. These studies have shown that, by phosphorylating ERα and some transcriptional cofactors, the intracellular kinases regulated by growth factors positively regulate ER mediated gene expression [60,62]. The role of IGF-1 receptor as regulator of ERα transcriptional activity has also been characterized in neuronal cells. Maggi and co-workers have determined that insulin/IGF-1 signaling can activate the unliganded ERα in neuronal cells via the ras/MAPK pathway [63,64] and that this activation involved the N-terminal activation function 1 (AF-1) domain of the receptor [65]. More recent studies have shown that although IGF-1 promotes ligand-independent ER transcriptional activity, it has a different effect in the presence of estradiol. In the absence of the hormone, IGF-1 increases ERα activity in N2a cells, as in other neuroblastoma cells. In contrast, IGF-1 negatively regulates, through activation of the PI3K pathway, estradiol-induced activation of ERα transcriptional activity in this cell type [66]. The inhibition of ERα transcriptional activity by IGF-1 in N2a cells depends on its ability to regulate the activities of glycogen synthase kinase 3β (GSK3β) and β-catenin through the PI3K pathway. By opposite, MAPK blockade has no effect in the regulation by IGF-1 of estradiol-induced transcriptional activity of ERα [66]. Thus, by using different components of its signaling system, IGF-1 may regulate ligand-independent and dependent ER transcriptional activity in neuronal cells and by this mechanism regulates hormonal actions of estradiol via ERα.

The functional significance of the regulation of ERα transcriptional activity by IGF-1 is suggested by the fact that the blockade of ER activity prevents effects of IGF-1 on the survival and differentiation of developing neurons [67–69] and on adult neurogenesis in the dentate gyrus [70]. ER inhibition also blocks neuroprotective effects of IGF-1 in the rat hippocampus [71]. On the other hand, IGF-1 receptor activation is essential for several actions of estradiol in the brain, including the hormonal regulation of the survival and differentiation of developing neurons [57,68,71], the estrogenic regulation of synaptic plasticity in the hypothalamus [72–74], the hypothalamic control of gonadotropins, estrous cyclicity and sexual receptivity [75–77] and neuroprotective effects in the hippocampus and substantia nigra [57,78].

Immunoprecipitation studies, showing the interaction between ERα and the IGF-1 receptor in the brain, have provided some clues on the possible mechanisms involved in the cross-talk between IGF-1 and estradiol. Estradiol administration to adult ovariectomized rats results in a transient increase in the association between IGF-1 receptor and ERα in the brain [79]. The interaction is coincident in time with the increase in tyrosine phosphorylation of IGF-1 receptor, suggesting a possible causal relationship. Estradiol also increases the interaction between p85 and IRS-1, one of the first events in the signal transduction of the IGF-1 receptor. In addition, the interaction between estrogen and IGF-1 systems seems to be reciprocal, since the intracerebroventricular administration of IGF-1 also increases the levels of association between ERα and IGF-1 receptor [79].

The administration of estradiol to ovariectomized rats also results in the association of ERα with components of the PI3K/Akt signaling pathway in the brain and in the regulation of the activity of Akt and its downstream kinase GSK3β [80,81]. In addition, immunoprecipitation studies suggest that in the hippocampus GSK3β forms a macromolecular complex with Tau, β-catenin and the p85 subunit of the PI3K and another complex with ERα and β-catenin. Estradiol increases the amount of phosphorylated GSK3β associated to the first complex and reduces the amount of β-catenin associated to the second complex [80–83]. The regulation of these interactions of GSK3β with other molecular components may be involved in the neuroplastic and neuroprotective effects of estradiol [82–85].

3. Membrane localization of estrogen receptor α in neural cells

An important question is the subcellular localization in which the interactions of ERα with IGF-1 receptor and the components of the IGF-1 receptor-associated signaling complex occur. Although IGF-1 receptor immunoreactivity has been detected in neuronal and glial cell nuclei [86] there is little evidence that other components of the IGF-1 receptor signaling system may reach a nuclear localization. In contrast, several studies have demonstrated localization of ERα, or ERs subtypes structurally close to classical ERα, in the cytoplasm and plasma membrane of neurons and glial cells [87–89]. Experimental evidence accumulated over the years in different cell types strongly supports the idea that the membrane and nuclear ERα share a common transcriptional origin [90,91]. In particular in neurons, membrane ERα has been shown to have the same expected molecular weight than its nuclear counterpart (67 kDa), although other forms migrating at higher molecular weight seem to be also recognized by specific antibodies against canonical ERα (reviewed in [92,93]). In murine septal SN56 and hippocampal HT22 immortalized neurons, as well as in the cortex, septum and hippocampus of mouse and human, an ERα-like protein with an apparent molecular weight of 80 kDa has been identified [94,95]. Our studies revealed that this 80 kDa protein was not the result of ERα glycosylation that may confer a higher molecular weight [95], although we cannot discard that it may be the target of small ubiquitin-like modifier (SUMO) as previously described in COS-1 cells [96]. Other data from different laboratories have revealed the presence of extranuclear, still not characterized, ERs with high molecular weight (80–112 kDa) in human and murine neurons [92] which may be obtained by different susceptibility to proteolysis. Alternatively, these ERs may be the product of different splicing of ER genes, as evidenced in non-neuronal systems, where an 80 kDa ER was identified as the result of duplication of exons 6 and 7 in ERα gene [97]. Aside from classical ERα, a novel membrane ER, the G-protein-coupled transmembrane receptor (GPR30), has been found to be expressed in different brain areas [98,99], associated with a modulation of hypothalamic and nociceptive activity [100–102]. Furthermore, a membrane ER-like (ERX) which shares some homologies with G-protein coupled receptors has been found in hippocampus and neocortex, related to estrogen neuroprotective functions [88,92], and more recently, in myelin and oligodendrocytes [103].

Even though it is generally accepted that ER present at the plasma membrane shares high homology with classical ERα, a protein lacking transmembrane domains, the mechanisms acting at the neuronal plasma membrane in order to allow its integration into a highly hydrophobic environment remain unclear. Some recent studies in non-neuronal models have demonstrated that palmitoylation of ERα is crucial for plasma membrane location and function of the receptor [104,105]. Palmitoylation can influence targeting and recruitment of the modified proteins to membrane microdomains, caveolae and lipid rafts, and may enable the palmitoylated proteins to efficient signaling transduction [106,107]. Thus, one of the plausible explanations for the presence of ERα at the plasma membrane of neurons is that it may be part of caveolar microstructures, specialized microdomains which have a particular lipid composition and a high density of lipid-anchored proteins [108]. Interestingly, caveolae are known to assemble specific pools of proteins that participate in signaling events, facilitating the interaction of receptors and signaling proteins [109]. Best described in non-neuronal systems, caveolins (1–3) are structural proteins essential for the formation of caveolae [110]. Related to breast cancer cells, caveolins are known to play a pivotal role in the trafficking of ERs to the plasma membrane, acting as anchoring factors to provide additional stability for the integration and functionality of the receptor [111,112]. Furthermore, an essential step for either ERα and ERβ localization to caveolae or the induction of estrogen effects in cancer proliferation is the palmitoylation of the receptor at cysteine 447 (for human), which is required to caveolin-1 binding of the receptor [105,113,114]. However, the physiological relevance of caveolin proteins in the mechanisms of membrane ERs signaling in the nervous system is not well known. Different reports have demonstrated the expression of all three caveolin isoforms in neurons and, in particular, caveolins 1 and 3. These proteins seem to be responsible of functional segregation of different intracellular pathways related to modulation of estrogen responses in neurons (reviewed in [115]). In this regard, it is of interest that caveolins regulate a variety of key signaling elements involved in different mechanisms of estrogen action relevant for brain function, including IGF-1 receptor, nerve growth factor receptors, Src tyrosine kinases, some components of PI3K and MAPK pathways, and metabotropic glutamate receptor (mGluR) signaling [116–119]. In addition, caveolae and caveolins appear to be implicated in modulation of amyloid precursor protein (APP) [120,121] and the production of β-amyloid peptide [122], suggesting an involvement of these proteins in the control of β-amyloid pathology [123]. Furthermore, CavKO mice deficient in caveolin-1 expression appeared to show a central cholinergic dysfunction and altered spatial memory [124]. Altogether, these data make conceivable that membrane ERs activities may be related to caveolae through the association with these anchoring proteins, thus allowing the interaction of the receptors with other modulators that may participate in alternative estrogen mechanisms to regulate neural function and promote neuroprotection. In line with this, ERX was found to be located in caveolar fractions of murine neocortex where it was shown to be upregulated after ischemic injury [98], and ERα localized in caveolae-enriched membranes has been shown to mediate calcium intracellular mobilization in a hypothalamic cell line [125]. However, very little is known about the potential molecules that may interact with the receptor in this domain to control physiological changes in neurons. As mentioned before, one of the best studied candidates for these interactions is IGF-1 receptor. Although still little explored in neurons, it is noteworthy that IGF-1 receptor also appears to localize to caveolin-rich subcellular fractions of pheochromocytoma PC12 cells [126], and in SN56 and HT22 cells (unpublished results), thus suggesting that caveolae may have a pivotal role in ER-IGF-1 receptor interactions to coordinate their interdependent mechanisms in the nervous system. Furthermore, in caveolar fractions of SN56 and HT22 neurons, we have previously demonstrated the accumulation of a membrane ERα known to be crucial for neuronal preservation against β-amyloid-induced toxicity [36,127]. These evidences have been reproduced in microsomal fractions of murine cortical, septal and hippocampal areas [128] as well as in the caveolar extracts from human cortex (manuscript in preparation). In an attempt to find putative targets of membrane ERα able to modulate the neuroprotective effects, we identified a voltage-dependent anion channel (VDAC) that was found to associate with the receptor in caveolar fractions of human and mouse brain areas. In support of these results, other evidences had demonstrated a direct modulation of the channel by estrogens and other ER modulators [129]. Whereas VDAC has been traditionally characterized as a porin localized at mitochondrial membranes, where it participates in the transport of different metabolites [130] and in the modulation of apoptosis [131], some few data also found VDAC at the plasma membrane of some different cell types [132,133]. Though the functional relevance of this channel at the plasma membrane is unclear, some evidences have suggested a role for plasma membrane VDAC in neuronal apoptosis induced by toxic stimuli [134]. In agreement with these observations, we provided the first evidence that VDAC can modulate the toxic effect provoked by β-amyloid exposure [127]. Together with VDAC, caveolin-1 also appeared to take part in this molecular complex in which ERα is incorporated [127,128], probably supplying additional stability of the molecular associations in these membrane microstructures. Since the mechanisms to explain neuronal caveolar integration of VDAC and ERα are still unexplored, a plausible possibility may be through their binding to caveolar scaffolding domain (CSD) of caveolin-1, known to be the binding site of different signaling proteins [117,135]. Using bioinformatics tools [136,137], a consensus motif $\phi X \phi XXXXH^{y}$ (ϕ, aromatic amino acid; H^{y}, bulky hydrophobic aminoacid) conserved in murine and human molecules and susceptible of binding to CSD was identified in the ER ligand binding domain as well as in the second N-terminal intracellular loop of VDAC [128]. This paradigm is compatible with the required linkage of palmitate to ER Cys447 residue essential for the receptor association with caveolin-1 demonstrated in non-neuronal cells [113]. Apart from VDAC, other candidates may be part of the complex with ERα at the plasma membrane and may participate in different mechanisms of estrogen actions in neurons. Among them, IGF-1 receptor not only physically interacts with ERα as previously mentioned, but it also induces caveolin-1 phosphorylation and translocation to the plasma membrane [138]. Moreover, preliminary data has also shown a co-precipitation of VDAC with IGF-1 receptor in lipid rafts and microsomal fractions of human cortex and hippocampus (unpublished results), that may be an indicative of the association of these two proteins. Overall, these findings bring new data about the mechanisms developed by neural cells to integrate and maintain the stability of ERs at the plasma membrane to modulate membrane-initiated effects of estradiol in the nervous system.

4. Concluding remarks

From the information reviewed in this paper we may propose that the plasma membrane is a plausible site for the interaction of ERα and IGF-1 receptor in neural cells. The interaction may occur in specialized membrane domains in which caveolin-1 may provide the scaffolding for the interaction of different membrane-associated molecules, including VDAC, ERα and IGF-I receptor. In addition, the macromolecular complex formed by ERα and IGF-1 receptor is associated to components of IGF-1 receptor signaling, including IRS-1, p85, Akt, GSK3β and β-catenin (Fig. 1). This macromolecular complex may be differentially activated by estradiol and IGF-1 and may then operate as a coincidence signal detector to

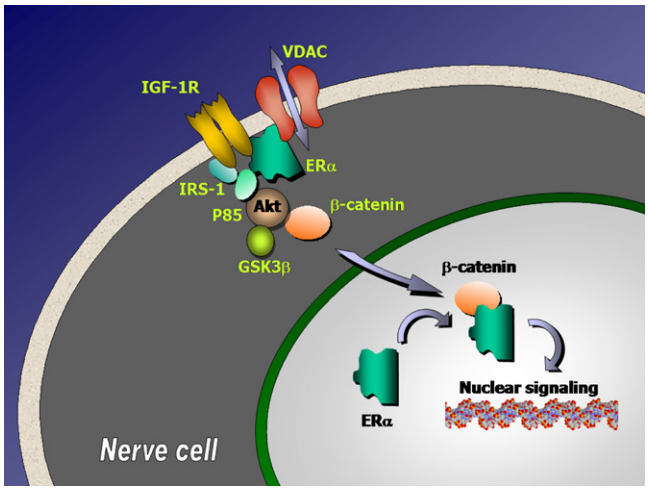

Fig. 1. Proposed model for the interaction of ERα and IGF-1 receptor in neural cells. ERα and IGF-1 receptor may interact in the plasma membrane, where caveolin-1 may provide the scaffolding for the interaction of different membrane-associated molecules, including VDAC. The macromolecular complex formed by ERα and IGF-1 receptor is associated to components of IGF-1 receptor signaling, including IRS-1, p85, Akt, GSK3β and β-catenin. Some components of this complex, such as ERα and β-catenin are also targeted to the nucleus, where they regulate gene transcription.

adapt the intracellular homeostatic responses of nerve cells to the changing extracellular levels of estradiol and IGF-1.

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