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Review

Molecular mechanisms involved in the regulation of neuritogenesis by estradiol: Recent advances

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ABSTRACT

This review analyzes the signaling mechanisms activated by estradiol to regulate neuritogenesis in several neuronal populations. Estradiol regulates axogenesis by the activation of the mitogen activated protein kinase (MAPK) cascade through estrogen receptor α located in the plasma membrane. In addition, estradiol regulates MAPK signaling via the activation of protein kinase C and by increasing the expression of brain derived neurotrophic factor and tyrosine kinase receptor B. Estradiol also interacts with the signaling of insulin-like growth factor-I receptor through estrogen receptor α, modulating the phosphoinositide-3 kinase signaling pathway, which contributes to the stabilization of microtubules. Finally, estradiol modulates dendritogenesis by the inhibition of Notch signaling, by a mechanism that, at least in hippocampal neurons, is mediated by G-protein coupled receptor 30.

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Contents

1. Introduction

Estradiol regulates the differentiation of neurons and glial cells in the central nervous system. The developmental actions of estradiol have been well characterized in the hypothalamus [1–4], where the hormone generates sex differences in neuronal circuits controlling neuroendocrine events, feeding, growth and reproduction. However, the regulation of neuronal development by estradiol is not restricted to the hypothalamus, since it has also been detected in other brain regions such as the midbrain [5] the cerebellum [6,7], the hippocampus [8] and the neocortex [9]. Estradiol also affects axonal growth in primary sensory neurons in the dorsal root ganglia [10]. These developmental actions of estradiol do not always correspond to a hormonal effect, since estradiol locally synthesized by neurons or astrocytes also participates in the regulation of neuronal development by paracrine or autocrine mechanisms [9,11–15].

In addition to regulate the survival of developing neurons, estradiol regulates at least other four aspects of neuronal development:

Abbreviations: BDNF, brain-derived neurotrophic factor; CREB, cAMP-response element-binding protein; ER, estrogen receptor; ERE, estrogen responsive element; ERK, extracellular signal-regulated kinases; GPR30, G-protein-coupled-receptor 30; GSK3β, glycogen synthase kinase 3; IGF-I, insulin-like growth factor-I; MAPK, mitogen activated protein kinase; Ngn3, neurogenin 3; PI3K, phosphoinositide-3 kinase; PKC, protein kinase C; TrkB, tyrosine kinase receptor B.

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(i) the growth of axons; (ii) the growth of dendrites; (iii) the growth of dendritic spines and (iv) the formation of synapses. Different mechanisms may be implicated in each one of these four developmental actions of estradiol and it is also possible that the mechanisms differ depending on the neuronal type or the brain region considered.

Estradiol may potentially affect neuronal differentiation by a variety of integrated and convergent mechanisms. These may involve classical estrogen receptors (ERs), which include nuclear-initiated ER signaling and membrane/cytoplasm-initiated ER signaling. The nuclear-initiated ER signaling by classical ERs (ERα and ERβ) is the best characterized mode of action of estradiol and involves transcriptional actions at estrogen responsive element (ERE) sequences in the genome [16]. In addition, classical ERs may act as transcriptional partners at non-ERE sites, such as AP-1 sites, interacting with other DNA-binding elements [17]. Membrane/cytoplasm-initiated ER signaling involves the interaction of classical ERs in the membrane or the cytoplasm with G-proteins, glutamate receptors, signaling kinases and phosphatases [18–21] as well as actions on the mitochondria [21]. Finally, estradiol may signal through ER-dependent mechanisms by non-classical ERs, such as those mediated by G-protein-coupled-receptor 30 (GPR30), a putative membrane ER [22–24].

The implication and interaction of these potential mechanisms on the developmental effects of estradiol on neurons are still not well understood. In this review, we will focus on recent advances in the understanding of the mechanisms involved in the regulation of neuritogenesis (axogenesis and dendritogenesis) by estradiol.

2. The mitogen activated protein kinase (MAPK) cascade plays a central role in the neuritogenic actions of estradiol

Estradiol is known to increase ERK phosphorylation in developing neurons. Toran-Allerand and her collaborators [25] showed that estradiol phosphorylates c-Src in explants form postnatal mice cerebral cortex. The phosphorylation of c-Src in cortical explants is associated with the phosphorylation of Shc in tyrosine and with an increased association of Shc with Grb2 and the induction of Ras activation. Since Ras is the initial signaling kinase of the MAPK cascade, estradiol may activate ERK signaling via the phosphorylation of c-Src.

These findings suggest that estradiol may regulate neural development by the activation of c-Src/Ras/ERK signaling (Fig. 1). Indeed, direct evidence of the involvement of ERK on neuritogenesis was obtained by Dominguez et al. [26] on cholinergic neurons from the basal forebrain in culture and by Carrer and collaborators [27,28] in primary hypothalamic neurons. More recently, the involvement of c-Src/Ras/ERK signaling pathway on the neuritogenic effects of estradiol has been demonstrated in cerebellar granule cell cultures [29]. The activation of ERK signaling by estradiol in primary cerebellar granule cells, primary hypothalamic neurons, primary hippocampal neurons and in dorsal root ganglion neurons in culture is associated with the activation of the transcription factor cAMP-response element-binding protein (CREB) [29–32]. There is also evidence that an increase in intracellular Ca++ concentration participates in the regulation of c-Src/Ras/ERK cascade and in the activation of CREB in hippocampal and hypothalamic neurons by estradiol [30,31]. Furthermore, activation of protein kinase C by estradiol is also involved in the activation of ERK in hypothalamic neurons [31].

3. Interaction of estradiol with BDNF signaling in the regulation of neuritogenesis

In the previous section we have seen that estradiol promotes neuritogenesis through the regulation of the MAPK cascade. Other factors that regulate neuritogenesis, such as brain derived neurotrophic factor (BDNF) and insulin-like growth factor-I (IGF-I) also activate MAPK and may therefore interact with estradiol on developing neurons (Fig. 1).

Estradiol is known to interact with BDNF in the nervous system [33–35]. BDNF regulates neuronal development and may therefore participate in the developmental actions of estradiol on neurons. For instance, estradiol increases the expression of BDNF in the developing cerebellum and this may participate in the estrogenic effects on dendritogenesis, spinogenesis and synaptogenesis of Purkinje neurons [13]. Estradiol also promotes synaptogenesis in the hippocampus by increasing BDNF release by granule cells of the dentate gyrus [36]. Furthermore, estradiol increases the expression of tyrosine kinase receptor B (TrkB) in male-derived hypothalamic neurons in culture [37] and an antisense oligonucleotide against TrkB prevents the axogenic action of estradiol in these cells [27,38]. Therefore, estradiol may regulate neuronal development by modulating the levels of both BDNF and its receptor TrkB. Since TrkB, in turn, regulates the activity of MAPK signaling cascade, BDNF and estradiol may potentially interact in the regulation of neuritogenesis at the level of MAPK signaling. However, this possibility remains unexplored.

4. Interaction of estradiol with insulin/IGF-I signaling in the regulation of neuritogenesis

IGF-I, which is highly expressed in the developing CNS, is one of the factors that regulate neuritogenesis [39–42]. IGF-I signals through the IGF-I receptor, a tyrosine kinase receptor that activates the MAPK and the phosphoinositide-3 kinase (PI3K) cascades. Both signaling pathways, which are also regulated by estradiol [43], participate in the neuritogenic actions of IGF-I [39–41].

Both estradiol and IGF-I regulate the dendritic arbour of embryonic hypothalamic neurons in culture. The dendritogenic action of IGF-I on hypothalamic neurons is blocked when the cultures are incubated with antisense oligonucleotides that block ERα expression or when the cultures are incubated with an ERα antagonist (ICI 182,780) that block ERα mediated transcription. In turn, the dendritogenic action of estradiol is blocked when the cultures are incubated with an antisense oligonucleotide that blocks IGF-I synthesis [44]. A similar interaction between estradiol and IGF-I has been detected in PC12 cells. The ER receptor antagonist ICI 182,780 blocks the neuritogenic effect of IGF-I on PC12 cells and the IGF-I receptor antagonist JB1 blocks the neuritogenic effect of estradiol on PC12 cells [45]. Furthermore, estradiol induces an increase in axonal growth and in the expression of IGF-I receptors in ventromedial hypothalamic neurons from male rats, when neurons are cultured in the presence of conditioned media from glial cells removed from the target region. In contrast, estradiol does not affect the expression of IGF-I receptors and axonal growth when neurons are not incubated with conditioned media from glial cells [37]. All these findings suggest that estradiol interacts with IGF-I receptor signaling to induce neuritogenesis and that factors released by glia may regulate this interaction.

5. Interaction of estradiol with Notch signaling in the regulation of neuritogenesis

Notch signaling, which is activated by Notch receptor ligands Delta and Jagged, regulates neurogenesis and neuronal differentiation in vertebrates [46]. Activation of Notch inhibits neurite outgrowth, while the inhibition of notch signaling promotes neurite extension [47–49]. Notch signaling inhibits the expression of neurogenin 3 (*Ngn3*) a proneural gene that is involved in the control of dendrite morphology and synaptic connectivity of

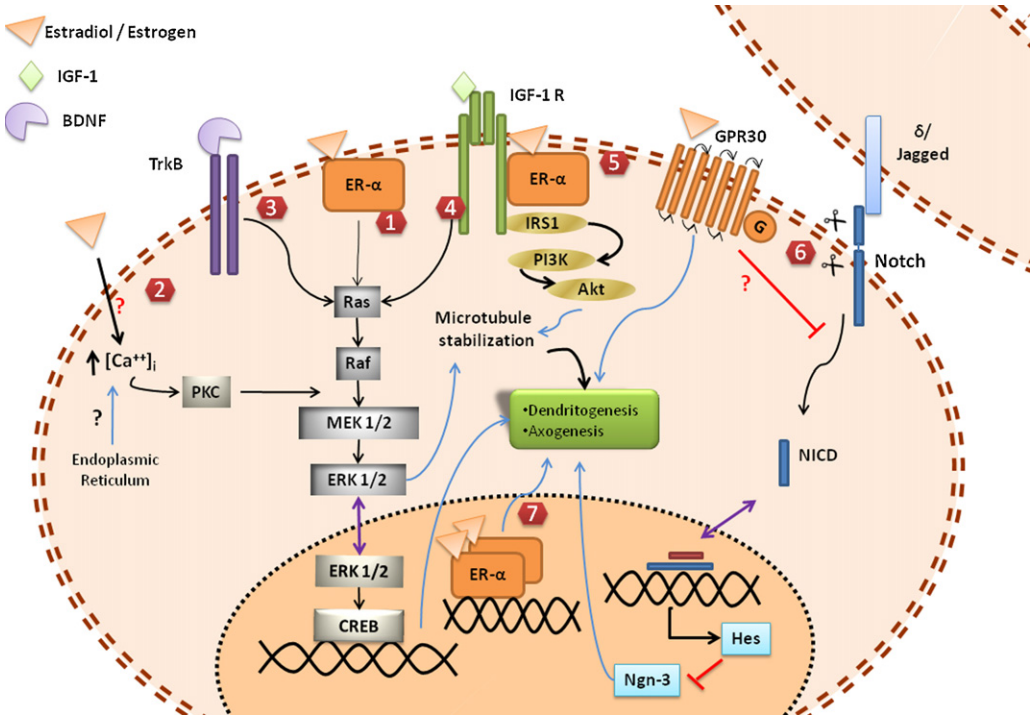

Fig. 1. Schematic representation of the signaling pathways involved in the regulation of neuritogenesis by estradiol. Activation of ERK signaling by estradiol (triangle), via ERα located in the plasma membrane, plays a central role in the neuritogenic actions of the hormone (1). Regulation of intracellular Ca++ concentration by estradiol, via the activation of PKC, contributes to the regulation of neuritogenesis, through the MAPK pathway (2). Signaling elicited by TrkB (3) and IGF-I receptor (IGF-1R) (4) may interact with estradiol in the regulation of ERK signaling and neuritoegenesis. ERα also interacts with IGF-I receptor (5) and with components of the PI3K signaling pathway, contributing to the stabilization of microtubules. Actions of estradiol on GPR30 may also contribute to neuritogenesis by the inhibition of Notch signaling (6) by mechanisms that remain unknown. Classical genomic actions of estradiol (7) via the activation of ER mediated transcription at ERE sites in the genome probably contribute as well to dendritogenesis and axogenesis.

hippocampal neurons [49–51]. Recent studies have shown that estradiol inhibits Notch signaling in developing hippocampal neurons [52,53], increasing the expression of *Ngn3* and the growth of dendrites [53]. In addition, the downregulation of *Ngn3* with specific siRNAs blocks the neuritogenic action of estradiol [53]. Therefore, these findings indicate that estradiol regulates dendritogenesis in developing hippocampal neurons by the modulation of Notch signaling (Fig. 1).

6. How neuritogenic estradiol signaling is initiated?

Although the studies previously mentioned clearly indicate that estradiol regulates neuritogenesis in several neuronal types trough the activation of c-Src/Ras/ERK/CREB signaling and by interaction with BDNF, IGF-I and Notch signaling, a still unresolved question is the role of ERs in the initiation of this mechanism. In cortical explants, the mechanism of activation of Src/Ras/ERK/CREB by estradiol seems to be independent of ERα, since estradiol elicits the phosphorylation of c-Src from both ERαKO and wild type mice [25]. However, a recent study has shown that estradiol induces the recruitment of beta-arrestin-1, a G-protein-coupled receptor adaptor protein and c-Src to ERα in cortical neuronal cultures [54], suggesting that ERα may be involved in the activation of c-Src. In addition, the neuritogenic effect of estradiol in hypothalamic and midbrain neurons is imitated by a membrane impermeable estradiol construct (E2-BSA), supporting the possible implication of a membrane-associated ER in ERK activation and neuritogenesis [5,27,28]. Indeed, ERα has been localized in the plasma membrane of embryonic hypothalamic neurons and an ERα agonist activates ERK in these neurons [55]. ERα localized in the plasma membrane has also been proposed to participate in the activation of ERK and in the induction of neuritogenesis in cerebellar granule cells [29].

The interaction of estradiol and IGF-I on neuritogenesis may also be mediated by ERα (Fig. 1), which interacts with IGF-I receptor in different cell types including neurons [20,43]. ERα also interacts with other components of the insulin/IGF-I receptor signaling, such as insulin receptor substrate-1, PI3K, Akt, glycogen synthase kinase (GSK) 3β and β-catenin [43,56,57]. ERα, via this signaling pathway [56] inhibits the activity of GSK3β in neural cells [56–59] and this may be involved in the neuritogenic action of the hormone, since GSK3β is crucial for neuronal polarization and axonal growth [60]. On the other hand, recent findings indicate that G1, an agonist of GPR30, which is known to regulate microtubule stability [61], imitates the effect of estradiol on developing hippocampal neurons, promoting dendritogenesis by the inhibition of Notch signaling [53]. This suggests that estradiol may in part regulate neuritogenesis acting on GPR30 or on other G1 targets (Fig. 1).

7. Concluding remarks and future perspectives

Knowledge about cellular and molecular mechanisms that participate in the neuritogenic actions of estradiol have significantly advanced over the past decade. Far from being simple, these mechanisms involve multiple signaling cascades that are activated through classical and non-classical ERs, depending on the neuronal type and the brain region considered. Moreover, the existence of cross-talk with neurotrophic factors and their receptors increase the complexity of interactions by estradiol in the brain during different development stages. We have reviewed here the best characterized signaling pathways and extracellular factors involved in the regulation of neuritogenesis by estradiol. However, it is important to consider that other endocrine, paracrine and autocrine factors may interact with the hormone to coordinate neuritogenesis. Thus, extracellular signals such as nitric oxide,

apolipoprotein E and angiotensin II are involved in the neuritogenic actions of the hormone in some neuronal types [62–64]. Probably, future studies will clarify the interaction of estradiol with the signaling mechanisms of other major modulators of neuritogenesis under physiological and pathological conditions. Additional studies will be also necessary to assign specific functions to the proteins and signaling pathways involved in neuronal outgrowth. Because microtubule assembly and membrane expansion are the two key events involved in neurite elongation, it is necessary to evaluate how the estradiol-activated cascades affect cytoskeletal and membrane dynamics in growing dendrites and axons. In this regard, the recent identification of signaling cascades linking ERα, via WAVE 1 and moesin, to actin remodeling and branching during the formation of dendritic spines [65] may be also relevant to understand the actions of the hormone on axonal and dendritic growth cones.

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