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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