REVIEW

Interdependence of oestrogen and insulin-like growth factor-I in the brain: potential for analysing neuroprotective mechanisms

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Abstract

The actions of oestradiol in the brain involve interaction with growth factors, such as insulin-like growth factor-I (IGF-I). Many cells in the brain co-express receptors for oestradiol and IGF-I and both factors interact to regulate neural function. The relationship of oestrogen receptor α with IGF-I receptor through the mitogen-activated protein kinase and the phosphoinositide 3-kinase signalling pathways may represent the point of convergence used by these two factors to cooperatively modulate neuritic growth, synaptic plasticity, neuroendocrine events, reproductive behaviour and neuronal survival. In addition, Akt and glycogen synthase kinase 3β are key molecular targets to explain the interaction of oestrogen and IGF-I receptor signalling in the promotion of neuroprotection.

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Introduction

The nervous system is a target for the ovarian hormone oestradiol. This hormone regulates brain development and function, acting on neurons, synapses and glial cells (Chowen *et al.* 2000, McEwen 2002). For many years it was considered that the actions of oestradiol in the brain were restricted to areas involved in neuroendocrine regulation and the control of sex behaviour. Today it has become evident that oestradiol exerts a broad spectrum of actions, including neuroprotective effects, in many brain areas that are not directly related to reproduction (Chowen *et al.* 2000, Garcia-Segura *et al.* 2001, Stein 2001, Wise *et al.* 2001, McEwen 2002). One of the main mechanisms of action of oestradiol in the brain, as in other organs, is the activation of nuclear oestrogen receptors. These receptors belong to the steroid/thyroid nuclear receptor superfamily, and once activated homo- or heterodimerize, interact with DNA and recruit a cohort of transcriptional cofactors to the regulatory regions of target genes. The two mammalian oestrogen receptors cloned to date, α and β, are widely distributed through the central nervous system. In addition oestradiol exerts rapid membrane effects on neural cells, modulating ion channels, neurotransmitter transporters, levels of intracellular calcium and other second messengers and phosphorylation of different kinases (Chowen *et al.* 2000, Cardona-Gomez *et al.* 2001, Stein 2001, Wise *et al.* 2001, McEwen 2002).

In this review we focus on one of the mechanisms of action of oestradiol in the brain: the interaction with the signalling of insulin-like growth factor-I (IGF-I). First, we present several lines of evidence of crosstalk between oestradiol and IGF-I in the brain. Then we analyse the implications of this crosstalk for neuroprotection. Finally we discuss the molecular mechanisms involved in the interaction of oestrogen receptors and IGF-I receptors in the brain and their potential implications for neuroprotection.

Crosstalk between oestradiol and IGF-I in the brain

In several cellular systems there is a crosstalk between the signalling of oestradiol and IGF-I (Ghahary *et al.* 1990, Klotz *et al.* 2002, Sato *et al.* 2002). Among the most studied examples are breast cancer cells: both factors play a role in the development and proliferation of breast cancer cells and show synergistic interactions in the activation of cell-cycle components, resulting in increased proliferation rates (Dupont & Le Roith 2001, Hamelers *et al.* 2002, Martin & Stoica 2002, Hamelers & Steenbergh 2003, Song *et al.* 2004, Thordarson *et al.* 2004). Interactions

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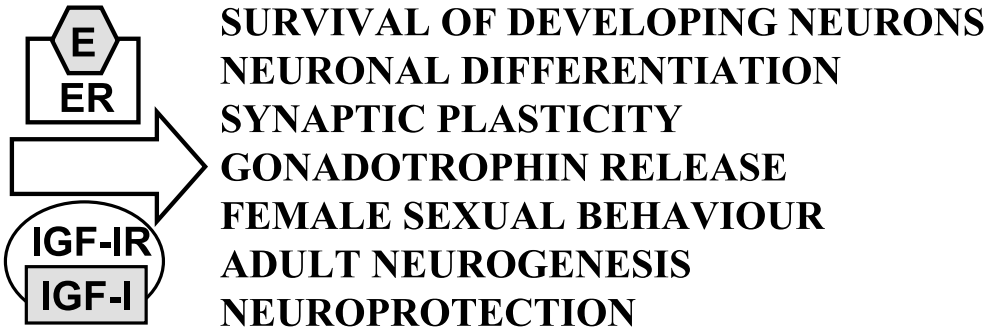

Figure 1 Neural events where interactions between oestradiol (E) and IGF-I, or between oestrogen receptors (ER) and IGF-I receptors (IGF-IR), have been documented.

between IGF-I and oestradiol have been detected in the nervous system as well. As an endocrine signal, IGF-I represents a link between the growth and reproductive axes and the interaction between IGF-I and oestradiol in the brain may be of particular physiological relevance for the regulation of growth, sexual maturation and adult neuroendocrine function.

Analysis of the distribution of IGF-I receptor and of the two known forms of oestrogen receptors (α and β) in the rat brain reveals that many brain cells express both types of receptor and that most neural cells expressing IGF-I receptor also express oestrogen receptors (Cardona-Gomez *et al.* 2000*a*, Garcia-Segura *et al.* 2000). This suggests that oestrogen and IGF-I may interact in different brain regions to regulate neural function. Such interactions have been reported in brain areas involved in neuroendocrine control (Fig. 1). For instance, there is an interdependence of oestrogen receptors and IGF-I receptor in the promotion of the survival and differentiation of developing hypothalamic neurons (Toran-Allerand *et al.* 1988, Dueñas *et al.* 1996, Cambiasso *et al.* 2000, Carrer & Cambiasso 2002). Both factors interact as well in the control of synaptic plasticity in the arcuate nucleus, a key centre for neuroendocrine regulation of the growth and reproductive axes. Oestradiol increases IGF-I accumulation in the arcuate nucleus during the oestrous cycle (Garcia-Segura *et al.* 1994) and both oestrogen receptors and IGF-I receptor are involved in the induction of synaptic and glial plastic modifications in this brain area (Fernandez-Galaz *et al.* 1997, 1999, Cardona-Gomez *et al.* 2000*b*). Furthermore, oestradiol and IGF-I interact in the control of luteinizing hormone secretion at the hypothalamic level (Hiney *et al.* 2004), and blockade of IGF-I receptor during oestrogen priming blocks oestrogen-induced luteinizing hormone release and partially inhibits hormone-dependent reproductive behaviour (Quesada & Etgen 2002, Etgen 2003, Etgen & Acosta-Martinez 2003).

Another functional outcome of the interaction of IGF-I with oestrogen in the brain is the regulation of adult neurogenesis. Neural precursors located in the subgranular zone of the dentate gyrus of the hippocampus proliferate in adult rodents. The newly generated neurons are functional, integrate in hippocampal circuits and may be involved in certain forms of hippocampal-dependent learning. IGF-I and oestradiol are among the molecules that have been identified as modulators of adult neurogenesis (Tanapat *et al.* 1999, Trejo *et al.* 2001). The intracerebroventricular administration of the oestrogen receptor antagonist ICI 182 780 blocks IGF-I-induced neurogenesis in adult ovariectomized rats (Perez-Martin *et al.* 2003), suggesting that oestrogen receptors are involved in the action of IGF-I on adult hippocampal neurogenesis. This interaction of IGF-I with oestrogen receptors may directly occur in the proliferating cells, since they express receptors for both IGF-I and oestrogen (Perez-Martin *et al.* 2003).

Interaction of oestradiol and IGF-I on neuroprotection

IGF-I and oestradiol have neuroprotective properties and prevent neuronal cell death in different experimental models of neurodegenerative diseases (Garcia-Segura *et al.* 2001, Carro *et al.* 2003). The interaction of IGF-I and oestradiol in neuroprotection has been assessed in ovariectomized rats, using systemic administration of kainic acid to induce degeneration of hippocampal hilar neurons (Azcoitia *et al.* 1999), an experimental model of excitotoxic cell death. Both the systemic administration of oestradiol and the intracerebroventricular infusion of IGF-I prevent hilar neuronal loss induced by kainic acid. The neuroprotective effect of oestradiol is blocked by the intracerebroventricular infusion of the IGF-I receptor antagonist JB-1, while the neuroprotective effect of IGF-I is blocked by the intracerebroventricular infusion of the oestrogen receptor antagonist ICI 182 780 (Azcoitia *et al.* 1999). Similar results have been obtained after the unilateral infusion of 6-hydroxydopamine into the medial forebrain bundle to lesion the nigrostriatal dopaminergic pathway, a model of Parkinson's disease. Pretreatment with oestrogen or IGF-I significantly prevents the loss of

substantia nigra compacta neurons and the related motor disturbances. Blockage of IGF-I receptors by intracerebroventricular JB-1 attenuates the neuroprotective effects of both oestrogen and IGF-I (Quesada & Micevych 2004). These findings suggest that the neuroprotective actions of oestradiol and IGF-I after brain injury depend on the coactivation of both oestrogen receptors and IGF-I receptor.

It should be noted that the studies which up to now have assessed the interactions of oestrogen receptors and IGF-I receptors in the brain *in vivo* have been conducted on ovariectomized females. We may assume that similar interactions will occur in the brains of intact females and in the brains of males. However, the outcome of these interactions may be different in males than in females. Although it is known that oestrogen and IGF-I may exert neuroprotective actions in male rodents (Carro *et al.* 2003, Garcia-Segura *et al.* 2001, 2003), there are several reports of sex differences in the response to brain injury and in the neuroprotective actions of oestradiol (Roof & Hall 2000, Garcia-Segura *et al.* 2001, Galanopoulou *et al.* 2003, Hilton *et al.* 2003). Furthermore, the potential effects of androgens on the interaction of oestrogen receptors and IGF-I receptors in the brain have not been explored.

Mechanisms of crosstalk between oestradiol and IGF-I in the brain

The abundant coexpression of oestrogen receptors with IGF-I receptor in neurons and glia in the brain (Cardona-Gomez *et al.* 2000*a*, Garcia-Segura *et al.* 2000) indicates that interactions of the intracellular signalling pathways of IGF-I receptor and oestrogen receptors are possible in many brain cells. In different cell lines, including neuroblastoma cells (Ma *et al.* 1994), IGF-I may activate oestrogen receptors in the absence of oestradiol. Whether or not this is also valid for the brain *in vivo* is unknown. However, both *in vitro* and *in vivo* studies have shown that oestradiol regulates the expression of IGF-I receptors in neural tissue (Cardona-Gomez *et al.* 2001, El-Bakri *et al.* 2004) and activates the two main signal transduction cascades coupled to the IGF-I receptor: the mitogen-activated protein kinase (MAPK) and the phosphoinositide 3-kinase (PI3K) signalling pathways.

Estradiol induces a rapid activation of extracellular-signal-regulated kinase (ERK) in primary cultures of astroglia (Ivanova *et al.* 2001) and in explants of cerebral cortex (Toran-Allerand *et al.* 1999, Singh *et al.* 2000, Setalo *et al.* 2002). In addition, the oestradiol-induced activation of ERK may be detected *in vivo* after systemic administration of the hormone (Cardona-Gomez *et al.* 2003). ERK activation may be involved in the induction of neurite arborization of cholinergic neurons by oestradiol (Dominguez *et al.* 2004) and in the neuroprotective effects of the hormone (Singer *et al.* 1999, Garcia-Segura *et al.* 2000, Kuroki *et al.* 2001). Oestradiol also induces the phosphorylation of protein kinase B, also known as the kinase Akt, in primary neuronal cultures, in cerebral cortical explants and in the adult rat brain *in vivo* (Singh 2001, Cardona-Gomez *et al.* 2002, Ivanova *et al.* 2002, Wilson *et al.* 2002, Znamensky *et al.* 2003). Furthermore, IGF-I and estradiol act synergistically to increase Akt activity, but not ERK, in the rat brain (Cardona-Gomez *et al.* 2002). Activation of Akt may regulate oestradiol-induced synaptic plasticity (Znamensky *et al.* 2003) and may also be involved in the neuroprotective effects of oestradiol (Garcia-Segura *et al.* 2000, Honda *et al.* 2000, Zhang *et al.* 2001, Yu *et al.* 2004).

Glycogen synthase kinase 3β (GSK3β), downstream of Akt, may also be a point of interaction of oestrogen and IGF-I signalling. Physiological phosphorylation of microtubule-associated proteins by GSK3β may be involved in the regulation of microtubule dynamics, neuritic growth, synaptogenesis and synaptic plasticity (Hall *et al.* 2000). However, under pathological conditions, GSK3β may be responsible for the hyperphosphorylation of Tau in Alzheimer's disease (Lovestone *et al.* 1994) and its inhibition is associated with the activation of survival pathways in neurons (Cross *et al.* 1995). Interestingly, oestradiol regulates the activity of GSK3β and decreases the phosphorylation of Tau in the rat hippocampus *in vivo* (Cardona-Gomez *et al.* 2004). Furthermore, oestradiol increases the association of Tau with phosphorylated GSK3β, with the p85 subunit of the PI3K and with β-catenin, another substrate of GSK3β (Cardona-Gomez *et al.* 2004). These observations are coherent with results showing that systemic administration of oestradiol to adult ovariectomized rats results in a transient increase in tyrosine phosphorylation of the IGF-I receptor, in a transient interaction of the IGF-I receptor with the oestrogen receptor α, but not β, and in an enhanced interaction of oestrogen receptor α with the p85 subunit of the PI3K in the brain (Mendez *et al.* 2003). All these findings suggest that oestrogen receptor α may affect IGF-I actions in the brain by an interaction with some of the components of IGF-I signalling, such as the IGF-I receptor, PI3K and GSK3β. A hypothetical model for these interactions is presented in Figure 2.

The interaction of oestrogen receptor α with the signalling pathways of IGF-I receptor in the brain may explain the interdependence of oestradiol and IGF-I in the regulation of different neural events. ERK and Akt may be involved in the interaction of IGF-I and oestradiol in the regulation of neuronal differentiation, synaptic function, synaptic remodelling, neuroprotection and sexual behaviour. The synergistic interaction of IGF-I and oestradiol in the phosphorylation of Akt may be critical for neuroprotective actions. Akt regulates several transcription factors that may be involved in the control of neuronal survival, such as cAMP-response-element-binding protein (CREB; Pugazhenthi *et al.* 2000), nuclear factor κ

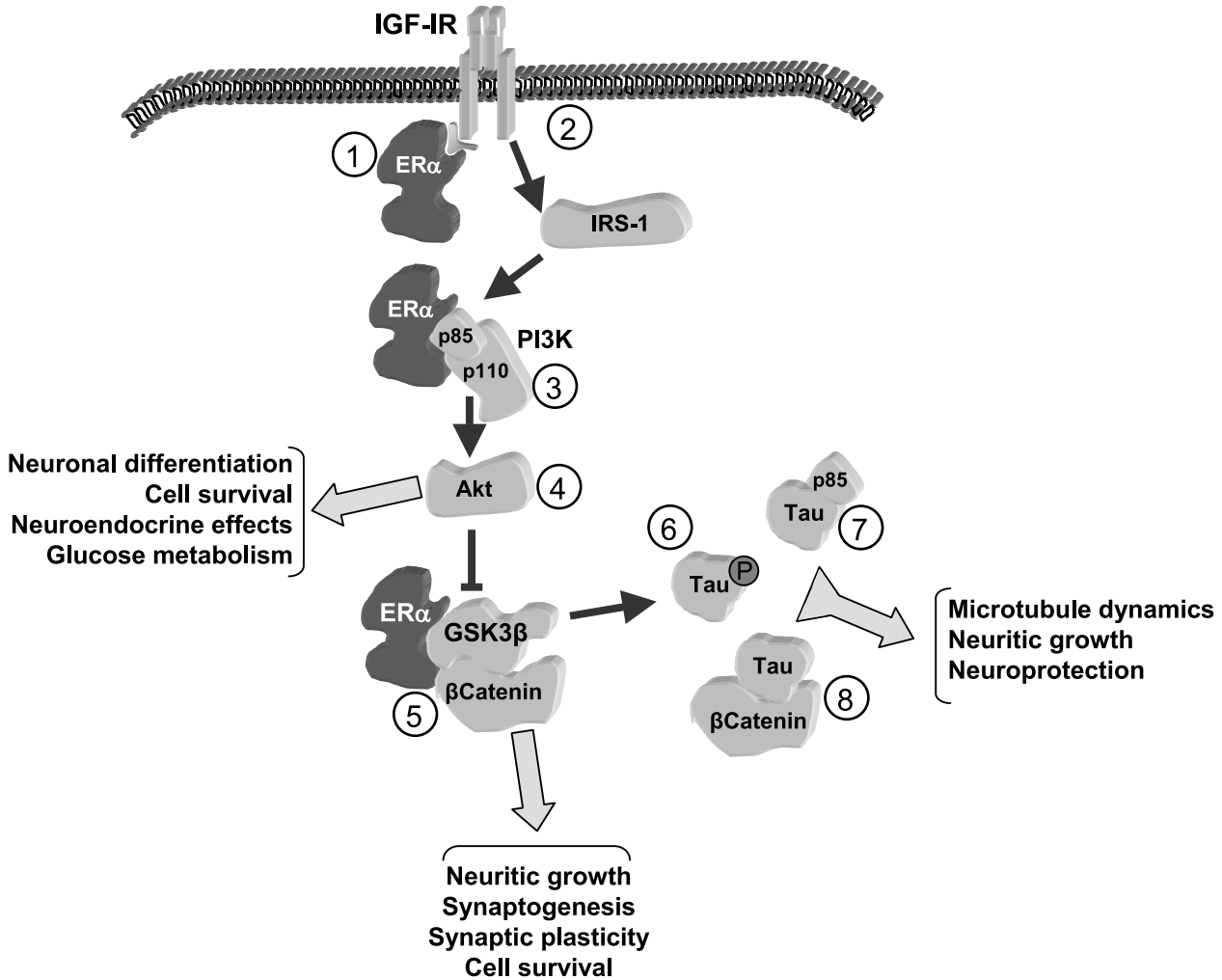

Figure 2 Proposed model for the interaction of oestradiol and IGF-I in the brain. Oestradiol interacts with IGF-I at different levels, regulating the activity and association of different proteins involved in the cellular response to IGF-I. (1) Oestradiol induces the association of oestrogen receptor α (ERα) with IGF-I receptor (IGF-IR), probably through an adapter protein. (2) Oestradiol increases IGF-I receptor phosphorylation.(3) Oestradiol treatment modulates the interaction between oestrogen receptor α and p85. (4) Oestradiol regulates the activity of protein kinases, increasing Akt phosphorylation. (5) Oestrogen receptor α interacts with GSK3β and β-catenin, and oestradiol decreases GSK3β activity, which in turn (6) decreases Tau phosphorylation. (7, 8) The associations of p85 and β-catenin with Tau are also increased upon oestradiol treatment in the brain. Some potential functional outcomes of these interactions are indicated in the figure. IRS-1: insulin receptor substrate-1.

(NF-κB; Kane *et al.* 1999) and several members of the Forkhead family (Brunet *et al.* 1999, Kops *et al.* 1999, Tang *et al.* 1999). In addition, activation of Akt results in the phosphorylation of the Bcl-2 family member Bad and this may suppress Bad-induced cell death (Datta *et al.* 1997, del Peso *et al.* 1997). Furthermore, Akt activation enhances Bcl-2 promoter activity (Pugazhenthi *et al.* 2000) and both IGF-I and oestrogen induce Bcl-2 expression in neurons. Interestingly, IGF-I receptor activation is necessary for the induction of Bcl-2 by estradiol in the adult brain (Cardona-Gomez *et al.* 2003). Also downstream of Akt, IGF-I and oestradiol may interact on the regulation of microtubule dynamics, neuritic growth, synaptogenesis, synaptic plasticity and neuronal survival, acting on GSK3β and on its substrates, β-catenin and Tau (Cardona-Gomez *et al.* 2004).

Conclusions

The studies reviewed in this paper indicate that the mechanisms of intracellular signalling of IGF-I and oestradiol are intimately associated in the nervous system. Oestrogen receptor α appears to be part of the signalling

mechanism of IGF-I in the brain. In turn, oestradiol activates IGF-I receptor signalling in neurons and glia. This interaction between IGF-I and oestradiol appears to be relevant for the neuroprotective effects of both factors.

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