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BRAIN RESEARCH REVIEWS

Review

Estrogen receptor beta in the brain: From form to function

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ABSTRACT

Estrogens have numerous effects on the brain, both in adulthood and during development. These actions of estrogen are mediated by two distinct estrogen receptor (ER) systems, ER alpha (ERα) and ER beta (ERβ). In brain, ERα plays a critical role in regulating reproductive neuroendocrine function and behavior, however, a definitive role for ERβ in any neurobiological function has been slow in forthcoming. Clues to the function of ERβ in the central nervous system can be gleaned from the neuroanatomical distribution of ERβ and the phenotypes of neurons that express ERβ. ERβ immunoreactivity has been found in populations of GnRH, CRH, vasopressin, oxytocin and prolactin containing neurons in the hypothalamus. Utilizing subtype-selective estrogen receptor agonists can help determine the roles for ERβ in non-reproductive behaviors in rat models. ERβ-selective agonists exert potent anxiolytic activity when animals were tested in a number of behavioral paradigms. Consistent with this, ERβ-selective agonists also inhibited the ACTH and corticosterone response to stress. In contrast, ERα selective agonists were found to be anxiogenic and correspondingly increased the hormonal stress response. Taken together, our studies implicate ERβ as an important modulator of some non-reproductive neurobiological systems. The molecular and neuroanatomical targets of estrogen that are mediated by ERβ remain to be determined. A number of splice variants of ERβ mRNA have been reported in brain tissue. Imaging of eGFP labeled chimeric receptor proteins transfected into cell lines shows that ERβ splice variation can alter trafficking patterns and function. The originally described ERβ (herein termed ERβ1) is characterized by possessing a high affinity for estradiol. Similar to ERα, it is localized in the nucleus and is trafficked to nuclear sites termed "hyperspeckles" following ligand binding. In contrast, ERβ2 contains an 18 amino acid insert within the ligand-binding domain and as a result can be best described as a low affinity form of ERβ. A delta3 (δ3) variant of ERβ has a deletion of the 3rd exon (coding for the

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Abbreviations: 3β-diol, 5α-androstane-3β,17β-diol; αERKO, estrogen receptor alpha knockout; βERKO, estrogen receptor beta knockout; AA, amino acid; ACTH, adrenocorticotropin hormone; AP-1, activator protein complex-1; AR, androgen receptor; AVP, arginine vasopressin; BNST, bed nucleus of the stria terminalis; CBP, cAMP response element binding protein; CORT, corticosterone; CRH, corticotropin-releasing hormone; CTX, cortex; DEX, dexamethasone; DHT, dihydrotestosterone; DPN, diarylpropionitrile; DRN, dorsal raphe nucleus; eGFP, enhanced green fluorescent protein; EPM, elevated plus maze; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; ERE, estrogen response element; FSL, flinders sensitive line; FST, forced swim test; GnRH, gonadotropin-releasing hormone; GRIP-1, glucocorticoid receptor interacting protein-1; HPA, hypothalamic–pituitary–adrenal axis; HSD, hydroxysteroid dehydrogenase; IR, immunoreactivity; LH, luetinizing hormone; LS, lateral septum; MA, medial amygdala; MDD, major depressive dissorder; OXY, oxytocin; POA, preoptic area; PPT, propylpyrazoletriol; PRL, prolactin; PVN, paraventricular nucleus; RBA, relative binding affinity; SCN, suprachiasmatic nucleus; SERT, serotonin transporter; SON, supraoptic nucleus; TPH, tryptophan hydroxylase; VMH, ventromedial hypothalamic nucleus

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second half of the DNA-binding domain) and as a result does not bind an estrogen response element in DNA. δ3 variants are trafficked to a unique low abundance and larger nuclear site following ligand binding. A delta4 (δ4) variant lacks exon 4 and as a result is localized to the cytoplasm. The amount of individual splice variant mRNAs varies depending upon brain region. Examination of neuropeptide promoter regulation by ERβ splice variants demonstrates that ERβ functions as a constitutively active transcription factor. Moreover, it appears that splice variation of ERβ alters its ability to regulate transcription in a promoter-dependent and ligand-dependent fashion.

Contents

1. Expression and function of estrogen receptors

The genomic actions of estrogen are mediated by two distinct intracellular receptors that function as ligand-activated transcription factors. These have been termed estrogen receptor alpha (ERα) and beta (ERβ) (Green et al., 1986; Kuiper et al., 1996). For both forms of ER, the binding of estrogen results in receptor dimerization, binding to specific DNA sites in gene promoter regions known as estrogen response elements (ERE) and subsequent modulation of gene transcription (Tsai and O'Malley, 1994). ERα and ERβ share similar DNA-binding domains (96% homology) and similar ligand-binding domains (56% homology) and bind to the same hormone response element on DNA (Fig. 1) (Kuiper et al., 1996).

ERα and ERβ are expressed throughout the rostral–caudal extent of the brain and spinal cord. The receptors have been shown to have overlapping expression patterns with a few exceptions where either ERα or ERβ is not expressed, or one of the receptors is expressed at significantly higher levels compared to the other. Brain regions, including the bed nucleus of the stria terminalis (BNST), medial and cortical amygdaloid nuclei, preoptic area (POA), lateral habenula, periaqueductal gray, parabrachial nucleus, locus ceruleus, nucleus of the solitary tract, spinal trigeminal nucleus and superficial laminae of the spinal cord, express both forms of ER. However there are also striking differences in the expression pattern in certain brain areas. Only ERα is found in the ventromedial hypothalamic nucleus (VMH) and subfornical organ. In contrast, neurons of the olfactory bulb, supraoptic (SON), paraventricular (PVN), suprachiasmatic (SCN), and tuberal hypothalamic nuclei, zona incerta, ventral tegmental area, cerebellum, laminae III–V, VIII, and IX of the spinal cord, and pineal gland contain exclusively ERβ. Although both receptors are expressed by neurons in the arcuate nucleus and hippocampus, ERα is more abundant in the arcuate nucleus, and ERβ is more prevalent in the hippocampus (Shughrue et al., 1996; Chu and Fuller, 1997; Kuiper et al., 1997; Shughrue et al., 1997; Laflamme et al., 1998; Hileman et al., 1999; Mitra et al., 2003). Recent studies have also demonstrated that glia can also express ERα and ERβ (Santagati et al., 1994; Azcoitia et al., 1999; Platania et al., 2003; Zhang et al., 2004; Mhyre and Dorsa, 2006), although the function of glial ERs is not known.

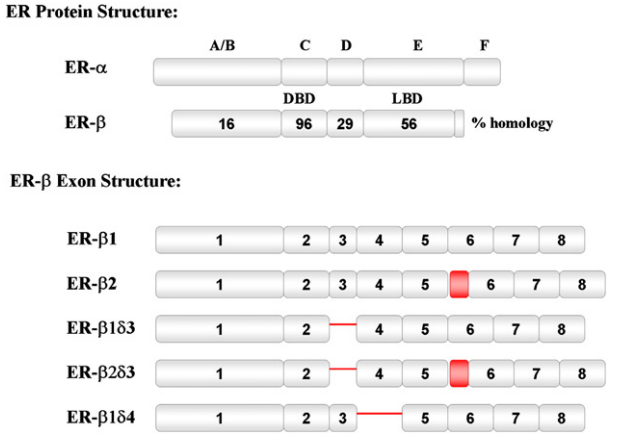

Fig. 1 – Schematic representation of ERα and ERβ protein structure and relative homology and ERβ splice variant exon structure. Deletions are indicated by a single line, and insertions are indicated by a shaded box. DBD = DNA-binding domain, LBD = ligand-binding domain.