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Frontiers in Neuroendocrinology 27 (2006) 217–232
Frontiers in Neuroendocrinology
www.elsevier.com/locate/yfrne

Review

New roles for estrogen receptor β in behavior and neuroendocrinology ☆

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Available online 17 April 2006

Abstract

In this review we critically examine the data on functions of the estrogen receptor β (ERβ) in both behavior and neuroendocrinology. The influence of estradiol via the ERβ has been assessed using several methods: estrogen receptor knockout mice, specific ERβ selective agonists, and phytoestrogens which preferentially bind to ERβ rather than ERα. The behavior for which a solid database and consensus is forming is anxiety; activation of ERβ reduces anxiety on a number of tasks and in several species. Moreover, the relationship between ERβ and serotonin may be critical for the regulation of this behavior by estradiol. There have been very few studies on learning and memory but the little we know suggests that ERβ is involved in visuospatial learning; in its absence learning is inhibited. Recent work has suggested a unique function for ERβ in sexual differentiation; its activation in male neonates may promote defeminization of sexual behavior. Several neurotransmitter-containing neurons in the rat paraventricular nucleus coexpress ERβ including; vasopressin, oxytocin, prolactin, and to a lesser extent corticotrophin releasing hormone. Given the potential for ERβ to interact with these important neurotransmitters and its co-expression in gonadotropin releasing hormone neurons it is surprising how normal the hypothalamic–pituitary–adrenal and –gonadal axes appear to be in ERβ knockout mice. Either this represents a species difference (the neuroanatomy has been conducted in the rat) or compensatory actions of ERα or other mechanisms. Exciting avenues for future research include; in vivo interactions between ERα and ERβ, actions of non-estrogenic ligands with ERβ, and the role of ERβ in sexual differentiation.

Keywords: Sex differences, Hypothalamic–pituitary–gonadal axis; Hypothalamic–pituitary–adrenal axis; Sexual differentiation; Serotonin; Depression; Anxiety; Reproduction

1. The two estrogen receptors; α and β

The effects of steroid hormones are mediated by specific intracellular receptors in the target tissue, with the steroid–receptor complexes playing a central role in the recruitment of the cellular machinery necessary for the activation of gene transcription [20,40]. The first member of what is now known as the steroid and thyroid hormone receptor superfamily was a protein isolated from the rat uterus exhibiting specificity for 17β-estradiol [191]. Although many other members of the family were identified in subsequent years (reviewed in [102]), this protein remained the only estrogen receptor (ER) known in animal tissues, until 1996 when a second ER subtype was isolated from the rat prostrate and ovary [88]. Subsequently the novel estrogen receptor was described in mice [196] and humans [123]. Because it is coded by a gene located on a different chromosome than the ERα gene [38,196], the two ERs are not true isoforms. Instead they are the products of two independent genes that share an important degree of homology due to the identity of their common endogenous ligand.

Both ERs exhibit the typical six functional domains (A–F) that are characteristic of the members of the superfamily [40]. The C and E domains correspond to the DNA- and ligand-binding regions, respectively [153] and domain D possesses the signals for nuclear localization [38]. Sequence identity between the two receptors is 97% for the DNA-binding domain, but drops to only 60% for the ligand-binding domain. This feature likely accounts for

☆ This work was supported by NIH Grants R01 MH57759 and K02 MH01349 (E.F.R.).
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doi:10.1016/j.yfrne.2006.02.004

some variations in the binding specificity to different ligands [87]. Some functional domains resulting from the tertiary structure adopted by the mature peptide have been defined for the estrogen receptors, and of these, the critical residues involved in the function of the AF-2 domain are highly conserved [197]. The functional ability to recruit transcriptional coactivators when interacting with an estrogen response element (ERE) has also been assayed in vitro and is similar for both estrogen receptors [196]. On the other hand, the other main functional domain (AF-1) located on the N-terminus portion of the receptor is very dissimilar between ERα and ERβ [46]. Receptor subtype dictates important differences in the transactivational activity of estrogen agonists and antagonists assayed in vitro along with DNA-bound AP-1 transcription factors [139]. Moreover, even the ability to interact with ERE-containing promoters can vary between the ER subtypes in presence of estrogenic ligands other than 17β-estradiol [54]. Finally, the two ERs exhibit different responses to the synthetic antiestrogens tamoxifen and raloxifene: whereas both compounds exhibited a partial agonist activity when interacting with ERα, only antagonism was observed for ERβ [4]. Furthermore, the potency of raloxifene in antagonizing estradiol-induced gene expression in an in vitro reporter system was fifteen times higher with ERα compared with ERβ [4]. Considered together, these data strongly suggest that ERβ has specific roles in the transduction of hormonal signals that are independent from ERα.

Supporting this assertion, of novel functions for ERβ, its distribution pattern differs from that of ERα in several areas. ERβ is the predominant ER in the prostate, lung, bladder, gastrointestinal tract, salivary gland, and developing pituitary [87,104,124,199]. Even in those organs where both estrogen receptors are present, the identity of the cells expressing each subtype appears to be different: for example in the ovary, the granulosa cells express mainly ERβ, whereas ERα is restricted to the surrounding thecal cells [62]. Similarly, the stroma of the prostate expresses mostly ERα and the epithelium contains ERβ [88] and the presence of ERβ in the uterus, in contrast with ERα, is confined to the glandular epithelium [62].

2. The estrogen receptor β knockout mouse

Shortly after the original description of the novel estrogen receptor [88], Krege et al. [82] generated a mouse with a disrupted and presumably dysfunctional ERβ gene. Because specific antagonists for this receptor are only now becoming available, estrogen receptor β knockout mice (ERβKO) have been a valuable tool to characterize roles for ERβ in vivo, most of what is known about its specific functions has been derived from the study of the ERβKO phenotype.

In contrast to female ERαKO mice, ERβKO mice exhibit a normal uterus, capable of responding to ovarian steroid stimulation [82], and the general morphology of their mammary glands is indistinguishable from that of age-matched wild-type littermates [60]. Moreover, both males and females are reproductively competent, although a reduction in fertility has been described in the females, attributed to a deficit in their ability to ovulate [82]. Finally, circulating gonadal steroid levels appear to be within the normal range in gonad-intact individuals of both sexes [19]. These early observations led to the hypothesis that ERβ is not directly responsible for the regulation of reproductive physiology in rodents, but may mediate some of the many effects of estrogens that are not directly associated with reproduction. Among these, the central nervous system has a prominent position as a target for estrogen action [108], with effects described on locomotor activity [7,129] arousal and fear responses [122], anxiety [22,79], drug addiction [14,67,148,164], and learning and memory processes [23].

Although the levels of expression of ERα are high in the areas of the rodent brain associated with reproduction, such as the hypothalamus [170], many of the non-reproductive actions of estradiol in the brain have been more difficult to trace since the neural structures normally linked to these behaviors have extremely low to undetectable levels of ERα protein [108]. The discovery of a second estrogen receptor offered therefore a new avenue for investigation. The hypothesis that ERβ had actions on non-reproductive processes was further enhanced by the distribution pattern of ERβ in the brain [89]. Although ERβ is coexpressed with ERα in certain regions such as the preoptic area, bed nucleus of the stria terminalis (BNST), ventromedial nucleus (VMN), and medial amygdala [89,170], ERβ appears to be the main, if not the only, estrogen receptor subtype to be expressed in areas such as the cerebral cortex, the hippocampus, the anterior olfactory nucleus, the cerebellum, the dorsal raphe, the substantia nigra and ventral tegmental area of the midbrain, and several brainstem nuclei [21,171,172]. These regions include important sources of serotonergic and dopaminergic innervations which have been in turn shown to be regulated at different levels by estradiol [6,7,10,29,141]. There is also a fair amount of evidence on ERβ expression by several neuropeptidergic subpopulations of neurons known to be important components in the interaction between the endocrine and nervous systems (see Table 1).

Here we will focus on reviewing data collected on the involvement of ERβ in several aspects of the development and functioning of the central nervous system in mammals. In particular we focus on the roles it may play in the regulation of neuroendocrine and behavioral responses by gonadal steroids.

3. Estrogen receptor β and behavior

3.1. Learning and memory

Changes in memory ability and performance in visuospatial tasks vary along the menstrual cycle in women [56,152], and the decline experienced by post-menopausal women can, in some cases, be successfully counteracted by estrogen replacement therapy [101]. The same effect has been reported repeatedly in animals when tested in a