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Frontiers in Neuroendocrinology 26 (2005) 65–84
Frontiers in Neuroendocrinology
www.elsevier.com/locate/yfrne

Diversity of ovarian steroid signaling in the hypothalamus

Oline K. Rønnekleiv [a,b,*], Martin J. Kelly [a]

[a] Department of Physiology and Pharmacology, Oregon Health and Science University, Portland, OR 97239, USA
[b] Division of Neuroscience, Oregon Regional Primate Research Center, Oregon Health and Science University, Beaverton, OR 97006, USA

Available online 11 July 2005

Abstract

It is well known that many of the actions of gonadal steroids in hypothalamic neurons are mediated via intracellular receptor/transcription factors that interact with steroid response elements on target genes. Since the cloning of the intracellular steroid receptors/transcription factors, it has been assumed that most if not all of the actions of the gonadal steroids are mediated via these intracellular receptors. However, there now exist compelling evidence for membrane (G-protein-coupled) steroid receptors for estrogen and progesterone in hypothalamic and other brain neurons. But, it is not well understood how steroids signal via membrane receptors, and how these signals impact not only membrane excitability but also gene transcription in hypothalamic neurons. Indeed, it has been known for sometime that gonadal steroids can rapidly alter hypothalamic neuronal activity within seconds, indicating that some cellular effects can occur via membrane delimited events. In addition, gonadal steroids can affect second messenger systems, including calcium and various kinases to prompt and/or alter cell signaling. Therefore, this chapter will consider our current knowledge of rapid (i.e., seconds to minutes) membrane-initiated and intracellular signaling as well as classical nuclear receptor signaling by gonadal steroids in hypothalamic neurons, the nature of these receptors and how they contribute to homeostatic functions.

Keywords: Estrogen; Progesterone; Membrane actions; Genomic actions; Cross talk

1. Hypothalamus and the role of estrogen and progesterone

1.1. Diverse actions of E_2 on hypothalamic neurons

The archetypical role of estrogen in the mammalian central nervous system (CNS) is its negative and positive feedback actions on the hypothalamic–pituitary axis to regulate the reproductive cycle. In all mammalian species, disruption of feedback loops by ovariectomy results in rising levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) within one or two days. Restoring the feedback loop with doses of exogenous E_2 that mimic the follicular concentrations of E_2, results in a rapid (<20–30 min) decline in plasma gonadotropin levels. Following this initial inhibition, high levels of E_2 induces a LH surge in the ovariectomized female the specific nature of which varies across species [84,100,137,238,245]. These multifaceted aspects of E_2 action are time and dose-dependent. The effects of estrogen on the hypothalamus and anterior pituitary act in concert with its effects on other tissues (ovary, uterus, etc.) to ensure a single ovulatory event that is precisely timed.

In addition to its role in the control of reproduction, estrogen is involved in the regulation of appetite, energy expenditure, body weight, adipose tissue deposition, and distribution in females [70,157,186]. Ovariectomy induces an increase in food intake and decreases ambulatory and wheel running activities in rodents, which is reversed with estrogen replacement [4,10,42,211]. In fact, hypo-estrogenic states are associated with decreased activity and an increase in body

* Corresponding author. Fax: +1 503 494 4352.
E-mail address: ronnekle@ohsu.edu (O.K. Rønnekleiv).

0091-3022/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.yfrne.2005.05.001

weight in females [10,30,50,51,97,152]. The anorectic effects of estrogen are thought to be mediated through CNS actions based on the findings that direct injections of E_2 into the paraventricular nucleus of the hypothalamus (PVH) or arcuate/ventromedial nucleus are effective to reduce food intake, body weight, and increase wheel running activity in females [4,30,42]. It is evident that neurons in these hypothalamic nuclei regulate energy homeostasis and are affected by E_2. For example, estrogen up-regulates the expression of β-endorphin protein in proopiomelanocortin (POMC) neurons in ovariectomized female guinea pigs [18,241]. Furthermore, there is a decrease in hypothalamic β-endorphin levels in the hypothalamus of postmenopausal women who are not on hormone replacement, which correlates with their weight gain [133]. In contrast, E_2 reverses the ovariectomy-induced increase in arcuate neuropeptide Y (NPY) mRNA expression in animal models [210]. Therefore, it appears that the arcuate nucleus and specifically NPY and POMC neurons are a major target for the anorectic actions of estrogen, which emphasize their importance in energy homeostasis.

Beyond its role in reproduction and energy homeostasis, observations in human as well as in animal models have suggested that estrogen affects anxiety and mood. Numerous symptoms including increased irritability, mood swings, severe depression, and anxiety are associated with estrogen fluctuations during the menstrual cycle of vulnerable women [77]. Similarly, reduced estrogen levels at the time of menopause may be associated with depression, anxiety (nervousness), agitation, insomnia, and inability to concentrate [230]. These symptoms are often improved by estrogen or estrogen combined with progesterone replacement therapy. In animal models, estrogen treatment has been found to have both anxiolytic and anxiogenic actions [161,162,196]. It appears that the anxiolytic actions of estrogen in rodents are mediated through estrogen receptor β (ERβ) [142,196]. At least in rodents ERβ is expressed in the PVH, a brain area that is involved in stress responses and anxious behavior [37,91,94,142, 213,214,234]. Recent studies have attempted to elucidate the role of ERβ in modulating stress responses. These studies have revealed that adrenalectomy reduces ERβ mRNA expression in the PVH, an effect which is reversed by corticosteroid replacement. Moreover, dexamethasone treatment increases immunoreactive ERβ in the PVH, whereas estradiol benzoate (EB) reduces the expression of ERβ in this and other brain areas [234]. Interestingly, microinjection of the antiestrogen ICI 182,780 into the PVH during diestrus (low endogenous estrogen levels) but not during proestrus (high endogenous estrogen levels) inhibits stress-induced corticosterone release [94]. Therefore, ERβ in the PVH has the capacity to modify the hypothalamic–pituitary–adrenal (HPA) axis during stressful situations in an estrous cycle-dependent manner. However, the signaling cascades coupled to ERβ have not been elucidated.

1.2. Role of progesterone feedback in hypothalamic function

The ovaries are the main source of circulating progesterone, although progesterone can also be synthesized in the adrenals [204]. Adrenocorticotropic hormone (ACTH) stimulates both the synthesis and secretion of progesterone [194]. Therefore, adrenal progesterone production is sensitive to stress. Plasma progesterone is increased during diestrus and in late proestrus in rodents [11,205]. The elevation in plasma progesterone during diestrus, in contrast to the proestrous surge of progesterone, is eliminated following adrenalectomy, confirming its adrenal origin [11]. In primates (and guinea pig, unpublished), plasma progesterone is elevated during the luteal phase of the cycle, following the LH surge and ovulation (for review see) [205].

Progesterone exerts biphasic effects on LH release and ovulation in estrogen-primed animals, i.e., it can be inhibitory or stimulatory depending on the timing and sequence of estrogen and progesterone injections [32,239,265]. In the ovariectomized rat, estrogen alone can induce daily surges of LH [134]. These daily surges are blocked by progesterone [65]. It is, therefore, believed that one of the functions of the increased secretion of progesterone on proestrus is to eliminate daily LH surges [65]. In addition, treatment with progesterone following estrogen priming activates female sexual behavior (for review see [20]). Thus during the estrous cycle of rats, the sequential secretion of estradiol and progesterone from the ovaries results in a period of sexual behavior that is linked to the timing of ovulation [20]. During copulatory mounts, the female rat displays lordosis, a steroid dependent behavior that can be quantified [182]. Therefore, lordosis behavior is frequently used to assess the physiological consequence of estrogen and progesterone signaling in the brain. For example, sexual behavior, specifically lordosis, is eliminated in ovariectomized animals and restored by replacement with estradiol and progesterone [20]. A major effect of estrogen in reproductive tissues and the hypothalamus is to promote progesterone receptor (PR) synthesis via an ERE-dependent mechanism [121,154]. Progesterone is also necessary for the initiation and maintenance of pregnancy. Following ovulation, follicles are converted into corpora lutea, which secrete high levels of progesterone. During pregnancy the secretion of high levels of progesterone from the luteal cells blocks the GnRH/LH surge [204].