A Review on Effect of Estrogen on Neural Growth and Sexual Dimorphism in the Brain

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Abstract

In addition to the usual classic views of estrogen's actions in the brain as regulator of ovulation and reproductive behavior in the female; estrogens also play important roles in the male brain as well, where they can be generated from circulating testosterone by local aromatase enzymes or can also be synthesized de novo by neurons and glia and have profound effects on volumetric differences in different brain regions, promotion and inhibition of neurite growth, regulation of synaptic patterning, organizational and activational process of brain sex differentiation. Estrogen has opposite as well as similar effects in male and female brains. These differences include sex dimorphisms in the ability of estrogen to influence synaptic plasticity, neurotransmission, neurodegeneration, and cognition. A large part of sex differences is due to the organization of the underlying circuitry.

Key words: Estrogen, brain, neuron, hypothalamus, sex dimorphism

1. Introduction

Many years back estrogen, produced by the ovaries, was identified as "the woman's hormone," leading to its use as hormone replacement therapy (HRT) for menopausal/ post menopausal symptoms [1]. Other than the female reproductive tract, the brain, is important target for estrogen's action, it has expanded role in the male as it can be synthesized locally from steroid precursors, including circulating testosterone, by aromatase enzymes in many tissues [2, 3].

The profound effects and multiple mechanisms of action of estrogen provide mounting support for the views that estrogen is neurotrophic, neuroprotective, and psychoprotective [4] and it is classically associated with proliferation and survival, usually favoring mitosis and reducing apoptosis in both normal and pathological tissues [5].

Estrogen also plays an active role in mediating many of the effects of testosterone in target tissues in males, where aromatase enzymes, encoded by the *CYP19* gene, are responsible for the local synthesis of estrogens from circulating androgens [2] .Circulating testosterone therefore acts as a precursor for estrogens, in tissues expressing aromatase in the brain [3].

In the adult brain, the highest levels of aromatase activity are found in the hypothalamus of all species studied, especially the POA and ventromedial nucleus (VMN), where the enzyme is regulated by gonadal steroids and found at higher levels in males than in females [6]. Significant levels of aromatase are also found in other brain regions, including the amygdala, hippocampus, midbrain, and cortical regions in rodents, nonhuman primates, and humans, where its expression is steroid-independent and not significantly different in males and females [7].

2. Estrogen receptors

2.1. Distribution of estrogen receptors in CNS

ERα shows a characteristic distribution in the nervous system, with high levels in the pituitary, hypothalamus, the hypothalamic preoptic area and amygdala and much lower levels, and a more scattered distribution, in other brain regions [8]. Nuclear ERα immunoreactivity is the predominant subtype in the hippocampus, preoptic area, and most of the hypothalamus, whereas it is sparse or absent from the cerebral cortex and cerebellum [9].

ERβ immunoreactivity is primarily localized to cell nuclei within select regions of the brain including the olfactory bulb, cerebral cortex, septum, preoptic area, bed nucleus of the striaterminalis, amygdala, paraventricular hypothalamic nucleus, thalamus, ventral tegmental area, substantia nigra, dorsal raphe, locus coeruleus, and cerebellum [9].

2.2. Nuclear estrogen receptors

NERs are members of a superfamily of nuclear transcription factors, which are characterized by the presence of a central DNA-binding domain that targets the receptor to a hormone responsive element (HRE). For ER, the

DNA binding site contains two palindromic hexanucleotide repeats that bind an ER homodimer [10]. The estrogen receptors, α and β, are encoded by a separate genes (*ESR1* and *ESR2*, respectively) [11].

2.3. Non-nuclear or membrane estrogen receptors

Estrogen is able to initiate rapid signaling via actions at the cell membrane in many brain regions. Classic "nuclear" ERα and ERβ, and other receptors (such as GPR30), can be localized at the cell membrane to effect rapid activation of intracellular brain signaling pathways and modulatory proteins within seconds to minutes of exposure to steroids [12, 13].

The variety of nongenomic estrogen effects include:

a. Rapid actions on excitability of neuronal and pituitary cells;

b. The activation by estrogens of cyclic AMP and mitogen-activated protein kinase pathways that affect activity of such targets as insulin-like growth factor-1 (IGF-1) receptor;

c. Modulation of G protein coupling and affect calcium currents GnRH release;

d. Effects on calcium channels and calcium ion entry and;

e. Protection of neurons from damage by excitotoxins and free radicals [13, 14].

3. Effect of estrogen on brain development

Many aspects of the brain are bipotential until secondarily differentiated into a male versus female phenotype in response to gonadal phenotype. This is true in brain regions which are directly involved in reproductive functions. The default phenotype is feminine and thereby it supports female associated endpoints [15].

The developing brain is exquisitely sensitive to gonadal steroid exposure during a critical window beginning embryonically and extending postnatally [16]. Structurally, sex differences in the brain can be categorized as volumetric, signifying a brain region is larger in one sex versus the other, or connective, meaning the type or amount of synapses or size of a particular projection differs between males versus females. Physiologically, a sex difference in the brain refers to those related to the amount of neurochemicals or neurotransmitters, or the intrinsic excitability of particular classes of neurons [17].

In rodents involved in sexual behavior, such as the sexually-dimorphic nucleus of the preoptic area (SDN-POA) and the bed nucleus of the striaterminalis (BNST), are affected, [18]. Testicular derived testosterone diffuses into the male brain where it is locally aromatized to estrogen; estrogen then initiates the process of masculinization [17]. α- Fetoprotein protects female fetuses from behavioral masculinization and infertility caused by maternal estrogens [19]. Testosterone administration of female pups increased E_2 content exclusively in the preoptic area, suggesting local variation in aromatase activity and/or substrate availability [20].

4. Manifold effect of estrogen on different brain areas

4.1. Estrogen driven volumetric sex difference in hypothalamus

Sex differences have been observed morphologically in medial POA and VMH, including differences in volume of nuclei and number of neurons. The volume of the sexually dimorphic nucleus of the preoptic area (SDN-POA) and VMH in the rat hypothalamus is larger, with greater numbers of cells present in the nuclei in males than females. The anteroventral periventricular nucleus (AVPV) of the rat preoptic area is sexually dimorphic with greater numbers of dopaminergic neurons in the female rat compared with males. Perinatal androgen or estrogen decreases the nuclear volume of AVPV-POA in female rats through enhanced apoptosis, whereas testosterone increases the nuclear volume of SDN-POA in females through suppressed apoptosis [21].

Estrogen modulation of naturally occurring cell death in the developing brain is limited to very specific regions and can possibly have opposite effects, sometimes promoting cell survival, and sometimes orchestrating a cell's demise [17].

4.1.1. Estrogen induced volumetric differences in the preoptic area

In rats, the SDN is the poster child for sex differences in the brain. It is five to seven times larger in males than females situated in the male-sex-behavior-central, i.e. the preoptic area [22]**.** The density of cells does not differ in males and females, but the number and the area occupied does. Males and females start out with the same number of neurons destined to become part of the SDN, but beginning about postnatal day 3 and peaking on postnatal day 7, cells in the female die at a prolific rate [23]**.**

4.1.2. Estrogen induced volumetric differences in anteroventral periventricular nucleus The anteroventral periventricular nucleus is in contrast to the SDN, this nucleus is larger in females, and this is due to the ability of estrogen to kill off cells [24]**.** The AVPV controls the surge of gonadotropin secretion required for ovulation. Moreover, the AVPV is part of a well-defined sexually dimorphic circuit. A substantial portion of the neurons in the AVPV are dopaminergic, and it is their survival that is primarily undermined by estrogen [25].

4.2. Estrogen promotes neurite growth

Estrogen stimulates a massive increment in secretion of GnRH from GnRH neurons in the mPOA to induce ovulation in the female mammal, but it has no comparable effect in males. In males orchidectomized at birth, an LH surge can be induced by estrogen treatment in adulthood [21]. The neurite growth promoting effects of estrogen is found in the neural circuitry regulating sexually differentiated gonadotropin secretion. There are sexually dimorphic projections from the bed nuclei of the stria terminalis BSTp, with a greater galanin projection to the AVPV in males and a greater substance P projection to the preoptic area in females [26].

Changes in circulating steroid levels in adults have no impact on the dimorphism in innervations, providing proof of principle of the organizational impact of steroids during development [17]. Estrogen also promotes axon growth of fetal neurons derived from the VMN of the hypothalamus and cultured in vitro. The embryonic day on which the neurons are cultured impacts on the magnitude of the effect, the younger the neurons when plated, the more responsive [27].

Focal adhesion kinase (FAK) and paxillin are negative regulators of neurite growth and branching. During the perinatal sensitive period for sexual differentiation, estrogen down-regulates both FAK and paxillin and this appears to be an important component of the increase in dendritic branching observed in response to estrogen in this brain region [28].

4.3. Estrogen regulates synaptic patterning

Complex behavioral and physiological responses, such as those associated with reproduction, require neural networks capable of coordinating diverse amounts of information, both external and internal. Essential data include olfactory profiles of conspecifics, time of day, internal endocrine milieu, and reproductive state. Estrogen is a potent modulator of the formation of dendritic spines, the major site of excitatory glutamatergic synapses. Depending on the brain region, estrogen can either increase or decrease the density and/ number of dendritic spines [17]. In ovariectomized rats, 48 hours of estrogen treatment increases levels of the pre synaptic proteins synaptophysin and syntaxin, and postsynaptic proteins spinophilin and postsynaptic density 95 (PSD-95), in the CA1 region [29].

4.3.1. Synaptic patterning in the arcuate nucleus induced by estrogen

The arcuate nucleus contains dopaminergic, enkephalinergic, and GABAergic neurons, many of this neurons co-express releasing peptides for instance corticotrophin releasing hormone (CRH), growth hormone releasing hormone (GHRH), and thyrotropin releasing hormone (TRH). The neurons of the arcuate exert regulatory control over the anterior pituitary as well as other hypothalamic nuclei and thereby play a central role in reproduction, feeding, and stress responding [17].

Males have two to three fold more axosomatic synapses than females, the pattern is reversed in males castrated as neonates or females treated with testosterone. Axodendritic spines are the major site of excitatory glutamatergic synapses, whereas axosomatic synapses tend to be inhibitory GABAergic synapses. Thus a sex difference in the relative amount of axosomatic versus axodendritic synapses has impact on the excitability and potential source of afferent input to arcuate neurons in males versus females [30]. Estrogen down-regulates dendritic spines on the neurons by physical barrier to spine formation created by the highly stellate male astrocytes [17].

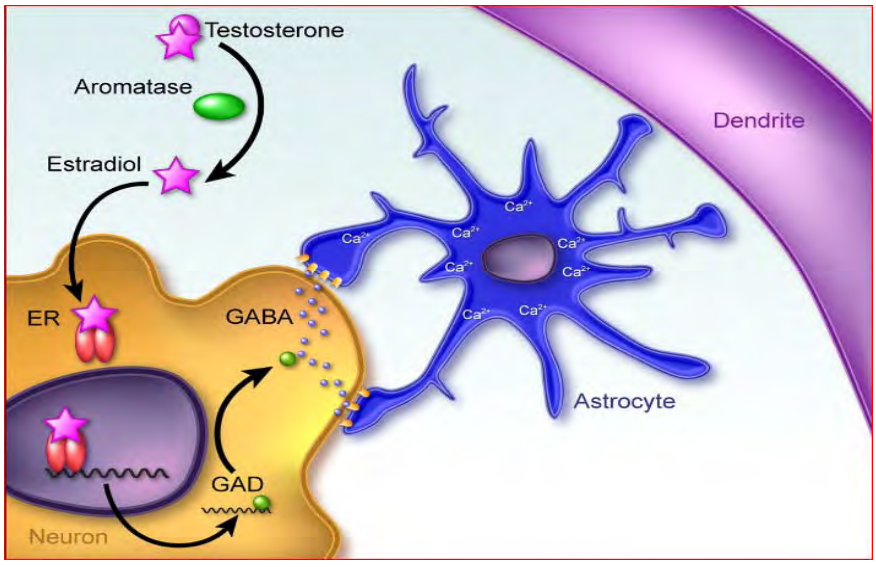

Figure1. Estrogen Action Establishing Sexually Dimorphic Astrocyte Morphology and Synaptic Patterning in the Arcuate Nucleus [31].

4.3.2. Synaptic patterning in the preoptic area induced by estrogen

The medial preoptic area is the major brain site controlling adult male sexual behavior and female maternal behavior and is a site of major sex differences in morphometry. The SDN has a sex differrence in dendritic spine synapses, with males having two- to three fold higher level than females [32].

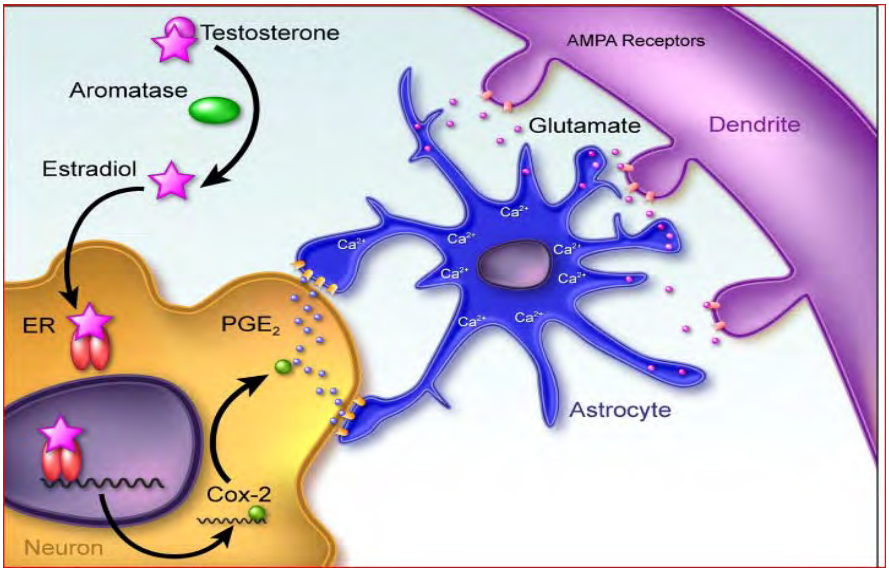

Figure 2. Mechanism of Estrogen Action Establishing Sexually Dimorphic Synaptic Patterning in the Preoptic Area [33]

4.3.3. Synaptic patterning in the VMN of the hypothalamus induced by estrogen

What the POA is to male sex behavior, the VMN is to female sex behavior. In this nucleus, estrogen has no effect on dendritic spine density but does increase the number of dendritic spines per neurite [32]. A lesion of this hypothalamic nucleus eliminates lordosis responding in the female rat, and implanting estrogen directly into the VMN induces the behavior. Neurons in the ventrolateral subdivision express high levels of ER and project to the midbrain central gray forming an essential link in the neural circuitry controlling female sex behavior [17].

Cellular mechanisms of estrogen action in this nucleus differ fundamentally from those in the POA and arcuate nucleus. Both PGE_2 and GABA have been ruled out as critical mediators of estrogen induction of spines in the VMN. Furthermore, unlike the POA and arcuate, astrocytes are not part of the cell-to-cell communication required for estrogen induction of spines in the VMN, but there is a central role for glutamate. Moreover, the mechanism of estrogen action is trans-synaptic, involving enhanced glutamate release from presynaptic terminals acting on postsynaptic NMDA and AMPA receptors to activate MAP kinase and increase levels of the protein spinophilin [32].

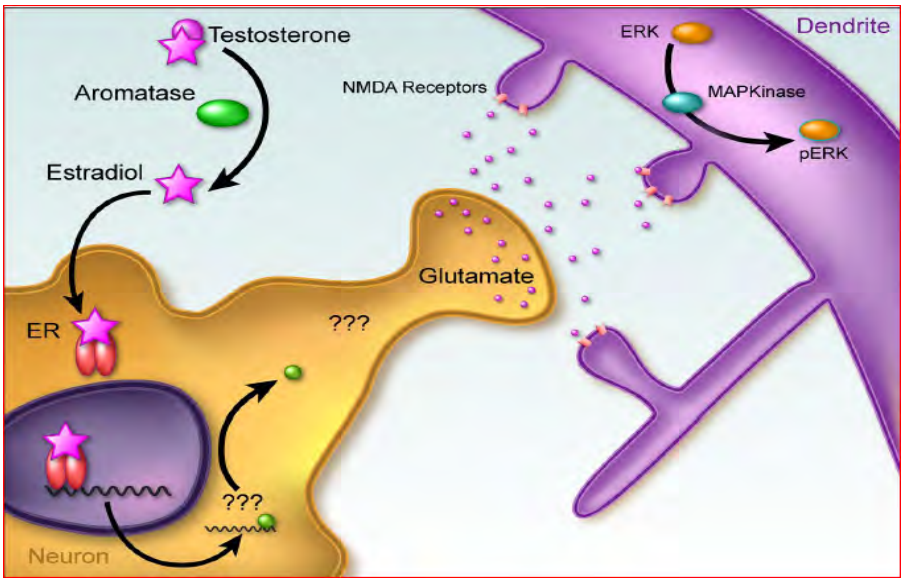

Figure 3. Mechanism of Estrogen Action Establishing Sexually Dimorphic Dendritic Morphology in the Ventro- Medial Nucleus (VMN) Of the Hypothalamus [34].

Dendrites on neurons in this nucleus branch more frequently in males, and also have an overall greater number of spine synapses. This sex difference is established during the perinatal sensitive period and is a function of estrogen action in the male brain. The fundamental effect of estrogen is to promote the release of glutamate from nerve terminals. Unlike the arcuate nucleus and the POA, no definitive role for astrocytes has been established in this system. However, since the primary effect of estrogen is presynaptic, there is a requirement for cell-to-cell communication to permanently organize this brain region into the masculine phenotype **[**32**].**

5. Mechanism by which estrogen influence developing brain regions

The cellular mechanisms by which estrogen masculinizes the brain are highly region specific. In the preoptic area, estrogen increases the level of the COX-2 enzyme and its product, prostaglandin E2 which promotes dendritic spine synaptogenesis. In the ventromedial nucleus of the hypothalamus, estrogen promotes glutamate release from synaptic terminals, activating NMDA receptors and the MAP Kinase pathway. In the arcuate nucleus, estrogen increases GABA synthesis, altering the morphology of neighboring astrocytes and reducing formation of dendritic spines synapses. Glutamate, GABA and the importance of neuronal-astrocytic cross talk are common aspects of masculinization [17].

5.1. Behavioral differences induced by estrogen

Steroid hormones of gonadal origin act on the neonatal brain, particularly the hypothalamus, to produce sex differences that underlie copulatory behavior. Sex differences in distinct hypothalamic regions can be organized by the same steroid hormone, but the direction of sex difference is often specific to one region or cell type, illustrating the wide range of effects that steroid hormones have on the developing brain [35].

5.2. The organizational / activational process of brain sex differentiation

Organization of the brain refers to specific patterns of synaptic connectivity, differential cell death and determination of neurochemical phenotype. This organization allows for activation of the brain later in life by circulating hormones to invoke the appropriate sex-typic response, be it behavior or control of gonadal function [36]. Sex differences in behaviour are the direct descent of sex differences in the brain [10].

Organizational effects are such that the developmental hormonal milieu both potentiates as well as limits the brain's subsequent response to adult hormone exposure. In this way a brain organized as male during development has a greatly reduced ability to produce female sexual behavior in adult- hood, even when receiving female-typical hormone replacement. Thus, the organizational effects of hormones ensure that the brain of an animal is appropriately matched to the hormonal signals it will receive in adulthood [35].

In the rodent, the organizing hormonal signal is the perinatal androgen surge from the testes, which begins prenatally (at approximately embryonic day 18), peaks on the day of birth and rapidly declines within hours [37].

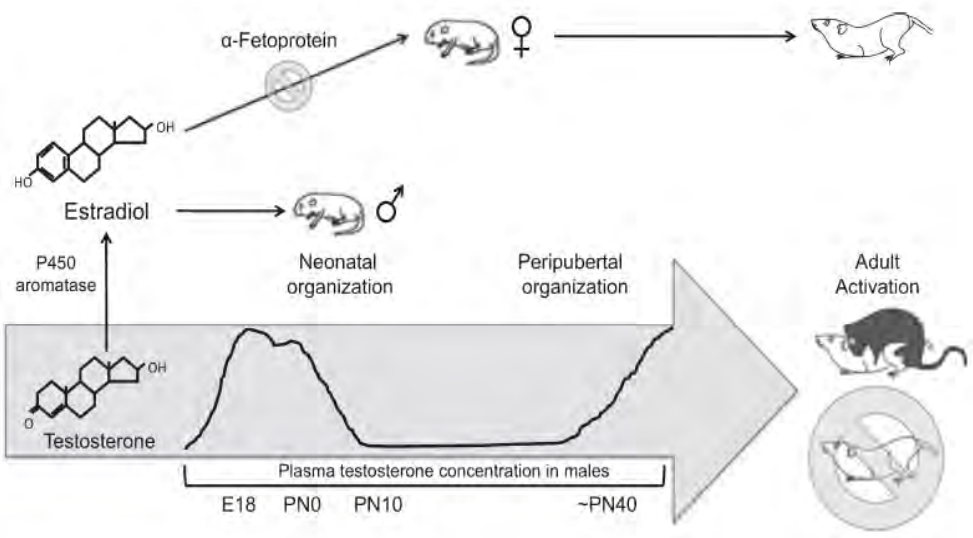

Fig 4.The Sensitive Period for the Organizational Effects of Steroids on the Brain [35]

5.3. Masculinization, defeminization and feminization

Sexual differentiation of the brain involves three processes: masculinization, defeminization and feminization. Masculinization and defeminization are active but distinct processes in the male brain, both of which rely on gonadal hormone action during the perinatal period. Masculinization is the process through which the brain

becomes capable of producing male sexual behavior, which includes sexual motivation and the copulatory behavior itself, consisting of mounting, erection, intromitting and ejaculating in rodents [19].

Defeminization is the process through which the brain loses the ability to produce female-typical sex behavior [17]. Feminization is a default program that proceeds in the absence of organizing steroid hormone action, but is nonetheless an active process. Feminization results in a brain that mediates female sexual responding, which in the rodent consists of a combination of proceptive solicitous behavior and the receptive posture called lordosis [19].

6. Conclusion and future perspectives

Estrogen modulates the activity of all types of neural cells through a multiplicity of mechanisms i.e. by binding to two cognate receptors ERα and ERβ, may also interact with selected promoters to commence the synthesis of target proteins in the selected cell or the hormone receptor complex may also interfere with intracellular signaling at both cytoplasmic and nuclear levels.

Estrogen in the brain has significant differences as well as similarities in males as well as females of humans and animals. Studies in the hypothalamus showed sexually dimorphic effects of estrogen on synaptic remodeling, glial plasticity, neuronal activity (including GABAergic interneurons and glutamatergic, cholinergic, and dopaminergic populations), estrogen receptors expression, and intra- cellular signaling pathways which are related to the neuroendocrine control of reproduction and sex-specific reproductive behaviors. Similar sexually dimorphic responses to estrogen are present in brain regions that are not directly associated with reproductive processes, understanding the cellular and molecular basis of sex differences in brain physiology and responses to estrogen is therefore important and it should be fully exploited in future studies to the in-depth analysis of the mechanisms underlying this sex differences and the molecular basis of these differences in order to know and treat male and female patients accordingly.

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