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REVIEW PAPER

Non-reproductive Functions of Aromatase in the Central Nervous System Under Physiological and Pathological Conditions

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Abstract
The modulation of brain function and behavior by steroid hormones was classically associated with their secretion by peripheral endocrine glands. The discovery that the brain expresses the enzyme aromatase, which produces estradiol from testosterone, expanded this traditional concept. One of the best-studied roles of brain estradiol synthesis is the control of reproductive behavior. In addition, there is increasing evidence that estradiol from neural origin is also involved in a variety of non-reproductive functions. These include the regulation of neurogenesis, neuronal development, synaptic transmission, and plasticity in brain regions not directly related with the control of reproduction. Central aromatase is also involved in the modulation of cognition, mood, and non-reproductive behaviors. Furthermore, under pathological conditions aromatase is upregulated in the central nervous system. This upregulation represents a neuroprotective and likely also a reparative response by increasing local estradiol levels in order to maintain the homeostasis of the neural tissue. In this paper, we review the non-reproductive functions of neural aromatase and neural-derived estradiol under physiological and pathological conditions. We also consider the existence of sex differences in the role of the enzyme in both contexts.

Keywords Astrocytes · Neuroinflammation · Neuroprotection · Radial glia · Sex differences · Synapses

Introduction

Almost five decades have elapsed since Naftolin et al (Naftolin et al. 1971, 1972) discovered that the brain is a steroidogenic organ by the detection of aromatase (i.e., estrogen synthase) activity in human fetal diencephalic and limbic tissues and in the hypothalamus of male and female rats. These findings revealed that brain estrogens do not necessarily derive from peripheral sources, such as the gonads, but can also be the result of local synthesis by the nervous tissue (Naftolin et al. 1971, 1972; Simpson et al. 1999; Barakat et al. 2016). Thus, estradiol is synthesized in the brain from its precursor testosterone by the steroidogenic and microsomal enzyme, cytochrome P450 aromatase, the product of the cyp19a gene (CYP19A in humans).

Estradiol produced by the brain acts and is metabolized locally. Therefore, the levels of estradiol in a given brain structure will depend not only on the plasma levels of the steroid, but also on its local synthesis and degradation (Konkle and McCarthy 2011). Indeed, in some brain regions the levels of estradiol may be highly dependent on its local synthesis. For instance, studies by Hojo et al. (2009) have shown that the levels of 17 β-estradiol in the hippocampus of male rats are six-fold higher than in plasma. However, hippocampal levels of estradiol fluctuate following the changes of estradiol in plasma in female rats (Kato et al. 2013).

The expression of aromatase in cognitive brain regions, such as the hippocampus, extends the role of neural-derived estradiol beyond the regulation of reproduction (Garcia-Segura 2008). Thus, neural estradiol synthesis is involved in the regulation of neurogenesis, neuronal development, synaptic function, synaptic plasticity, pain processing, learning, memory, and mood (Garcia-Segura 2008; Bowers et al. 2010; Saldanha et al. 2011; Ghorbanpoor et al. 2014; Fester and Rune 2015; Tuscher et al. 2016; Bailey et al. 2017;

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Fester et al. 2017; Bender et al. 2017; Azcoitia et al. 2018). This homeostatic action is exerted in both male and female animals and in all central nervous system (CNS) regions, including those involved in cognition and affection. Furthermore, brain estradiol synthesis is also involved in the activation of neuroprotective signaling mechanisms under pathological conditions (Azcoitia et al. 2003; Garcia-Segura 2008; Arevalo et al. 2015).

The function of neural-derived estradiol has been explored by the intracerebral administration of aromatase inhibitors or aromatase antisense oligonucleotides, or by the inhibition of aromatase activity in neural cultures. Such studies have shown that aromatase activity is necessary to maintain synapses and to induce LTP in the hippocampus (Kretz et al. 2004; Vierk et al. 2012) and in the basolateral amygdala (BLA) of females rats (Bender et al. 2017). Moreover, the inhibition of aromatase activity results in hippocampus-related memory deficits in women and female rodents (Bayer et al. 2015; Tuscher et al. 2016). These studies have shown that the neural-derived estradiol regulates cognition and behavior in male and female animals (Moradpour et al. 2006; Saldanha et al. 2011; Bailey et al. 2013, 2017; Tuscher et al. 2016; Fester et al. 2017). Here, we will review the non-reproductive functions of neural aromatase and neural-derived estradiol under physiological and pathological conditions.

Non-reproductive Functions of CNS Aromatase Under Physiological Conditions

CNS aromatase expression and distribution have been assessed in a wide number of vertebrate species, ranging from fish, amphibians, reptiles, to birds and mammals, including monkeys and humans (Roselli et al. 1985; Balthazart et al. 1990, 1991; Naftolin et al. 1996a, b; Abdelgadir et al. 1997; Garcia-Segura et al. 1999; Stoffel-Wagner et al. 1999; Iwabuchi et al. 2007; Diotel et al. 2010; Azcoitia et al. 2011; Coumailleau and Kah 2014; Biegon 2016; Moraga-Amaro et al. 2018). In the CNS of teleost fish, aromatase is expressed by neurons (Gelinas and Callard 1997) and by radial glial cells, both during development and in adult life (Forlano et al. 2001; Pellegrini et al. 2007; Mouriec et al. 2009; Le Page et al. 2010; Coumailleau et al. 2015). In contrast to teleost fish, in the amphibian brain aromatase is expressed only in post-mitotic neurons and not in radial glial cells (Coumailleau and Kah 2014) (Fig. 1).

Aromatase expression in radial glia of fish is involved in neurogenesis during development and adulthood (Mouriec et al. 2008; Strobl-Mazzulla et al. 2010; Coumailleau and Kah 2014). The CNS of teleost fish is in a continuous growth during adult life and radial glia cells act as progenitor cells. It should be noted that in mammals, radial glial cells act as

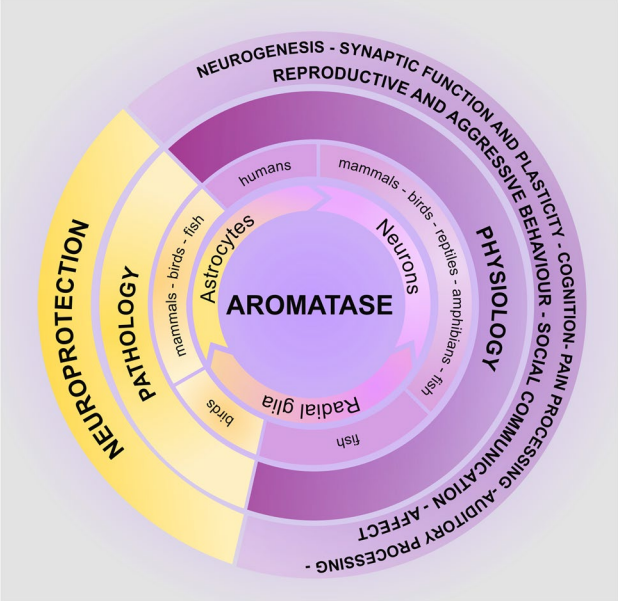

Fig. 1 Cell types expressing aromatase and homeostatic effects of the enzyme under physiological and pathological conditions in different vertebrate groups

progenitors during embryonic development, but disappear at the end of the embryonic period in which they become astrocytes or the so-called B cells (Kriegstein and Alvarez-Buylla 2009). Interestingly, in the cerebral cortex of developing mice, aromatase has also been detected in progenitor cells (Martínez-Cerdeño et al. 2006). In addition, developing neurons express aromatase and estrogen receptors (ERs) in many brain regions. Local estradiol synthesis and the consequent activation of ERs are involved in neuronal differentiation, notably by influencing cell migration, survival, death, dendritic growth and axogenesis, synaptogenesis, and synaptic plasticity (Beyer 1999; Hoffman et al. 2016; Ruiz-Palmero et al. 2016; Cambiasso et al. 2017).

In the CNS of adult birds and mammals, aromatase is mainly expressed in diencephalic and limbic neurons (Naftolin and MacLusky 1982; Roselli and Resko 1987; Balthazart et al. 1990; Prange-Kiel et al. 2003; Evrard et al. 2004; Hojo et al. 2004; Azcoitia et al. 2011; Stanić et al. 2014). In the human brain, aromatase expression has been observed in the inferior olive, cerebellum, thalamus, hypothalamus, hippocampus, amygdala, putamen, nucleus basalis of Meynert, and neocortex (Sasano et al. 1998; Ishunina et al. 2005; Yague et al. 2006, 2010; Biegon et al. 2010; Azcoitia et al. 2011). Therefore, in the human brain, aromatase is expressed in several regions that are not related with the neuroendocrine control of reproduction or in the regulation of sex behavior.

Immunohistochemical studies have detected aromatase immunoreactivity in the hippocampus and temporal cortex

of monkeys and humans (Yague et al. 2006, 2008). Most aromatase immunoreactive cells in these structures are pyramidal neurons. However, there is also a subpopulation of interneurons. Aromatase expression in interneurons has been also detected in the Zebra finch brain and in pain-processing regions of the medulla and the spinal cord (Tran et al. 2017; Ikeda et al. 2017), suggesting a role of local estradiol synthesis in the control of inhibition. In addition, a subpopulation of aromatase immunoreactive astrocytes was detected in the human temporal cortex (Yague et al. 2006).

In neurons, aromatase immunoreactivity has been localized in the perikarya, dendrites, axonal processes, and synaptic buttons in the brain of birds and mammals (Naftolin et al. 1996a, b; Evrard et al. 2004; Peterson et al. 2005; Rohmann et al. 2007). The presynaptic localization of aromatases (Naftolin et al. 1996a, b; Hojo et al. 2004; Peterson et al. 2005), together with the localization of ERs in synapses has suggested that local estradiol synthesis in synapses may be involved in synaptic transmission (Kretz et al. 2004; Balthazart and Ball 2006; Mukai et al. 2006; Saldanha et al. 2011; Bian et al. 2012; Tanaka and Sokabe 2012; Liu et al. 2015; Bailey et al. 2017; Zhao et al. 2017). Recent studies have shown that aromatase is associated with ERs (ERα and G-protein coupled estrogen receptor-1) in the plasma membrane in the central nervous system (Liu et al. 2017; Storman et al. 2018), suggesting a possible mechanism for rapid actions of locally synthesized estradiol on ERs. In addition, synaptic activity and neurotransmitters, such as glutamate and dopamine, exert a regulation of aromatase activity (Balthazart et al. 2002; Remage-Healey et al. 2008; Rudolph et al. 2016; Di Mauro et al. 2017; de Bournonville et al. 2017), further suggesting a role for local brain synthesis in neurotransmission. Indeed, there is evidence that aromatase activity is involved in the regulation of synaptic transmission in specific types of synapses, such as the synapse between the parallel fibers and the dendritic spines of cerebellar Purkinje cells (Dieni et al. 2018; Hedges et al. 2018). In addition, aromatase activity regulates structural and functional synaptic plasticity (Leranth et al. 2004; Hajszan et al. 2004; Grassi et al. 2009, 2011; Zhou et al. 2010; Scarduzio et al. 2013; Tozzi et al. 2015; Azcoitia et al. 2018), the expression of synaptic proteins (Liu et al. 2015), and the levels of neurotransmitters (Kokras et al. 2018) in different brain regions, including the hippocampus, the amygdala, and the vestibular nuclei.

Neural-derived estradiol has been also shown to be involved in the regulation of the processing of information by neurons. This is the case for processing of auditory information in the brain of birds (De Groof et al. 2017; Vahaba and Remage-Healey 2018; Van der Linden and Balthazart 2018) or pain information processing in birds and mammals (Ghorbanpoor et al. 2014; Gao et al. 2017). Brain aromatase activity is also involved in song production by songbirds (Alward et al. 2016) and hippocampal memory in female mice (Tuscher et al. 2016; Frick et al. 2018) and male Zebra finches (Bailey et al. 2017). Regulation of aggressive behavior in male and female rodents is another well-characterized function of brain-derived estradiol (Unger et al. 2015). Furthermore, aromatization of testosterone in the hippocampus has antidepressive effects in male rats (Carrier et al. 2015).

Aromatase in the CNS Under Pathological Conditions

Although in rodents, the enzyme aromatase is not expressed by glial cells under normal circumstances, stressful conditions, such as serum deprivation, induce aromatase expression in cultured astrocytes (Azcoitia et al. 2003). In addition, acute brain lesions induce the expression of aromatase in astrocytes of rodents (Garcia-Segura et al. 1999; Azcoitia et al. 2003; Carswell et al. 2005) and in radial glia of birds (Peterson et al. 2001, 2004; Duncan and Saldanha 2011) (Fig. 1). In this context, the upregulation of aromatase expression in cells of the astroglial lineage is observed in all injured brain areas of rodents, including the cortex, corpus callosum, striatum, hippocampus, thalamus, and hypothalamus (Garcia-Segura et al. 1999). The increase in aromatase expression after brain injury is associated with an increase in aromatase activity (Garcia-Segura et al. 1999) and brain estradiol levels (Mehos et al. 2016).

Not all neurodegenerative conditions induce the expression of aromatase in astrocytes. Thus, in spontaneously hypertensive rats (SHR), a chronic hypertension animal model, neurodegenerative changes were accompanied by increased aromatase expression in neurons, but not astrocytes (Pietranera et al. 2011). In a model of sciatic nerve chronic constriction injury, aromatase expression is induced in dorsal ganglion neurons but not in glial cells (Schaeffer et al. 2010). This suggests that aromatase expression in astrocytes is induced by acute insults. However, aromatase expression in astrocytes has been also reported in the prefrontal cortex of Alzheimer's disease patients (Luchetti et al. 2011) and in the ventral horn of the spinal cord of a mouse model of familial amyotrophic lateral sclerosis (Sun et al. 2017), which presents chronic degeneration of motoneurons. Interestingly, in this latter model, aromatase expression in ventral horn astrocytes increases in parallel to the decrease of aromatase in motoneurons, suggesting that the induction of aromatase in astrocytes is a compensatory mechanism to maintain local estradiol levels.

Studies in Zebra finches have shown that the cyclooxygenase, prostaglandin E2, and neuroinflammation induce the expression of aromatase in glial cells (Pedersen and Saldanha 2017; Pedersen et al. 2018). In turn, local estradiol synthesis in the injured brain reduces neuroinflammation

(Pedersen et al. 2018). Indeed, aromatase expression by astrocytes and radial glia after brain injury would be part of the mechanisms supporting brain repairs after lesion. Studies in mammals demonstrate increased neurodegeneration after injury following central administration of aromatase inhibitors (Azcoitia et al. 2003) or aromatase antisense oligonucleotides (Zhang et al. 2014) and in aromatase-knockouts relative to controls (Azcoitia et al. 2001). Furthermore, peripheral administration of estradiol or aromatizable androgens decreases injury size in rats (Garcia-Segura et al. 2003). These results suggest a critical role for glial aromatization in limiting degeneration following the insult. One of the mechanisms induced by brain-derived estradiol, which reduces neurodegeneration, is the inhibition of apoptotic signaling pathways (Saldanha et al. 2005). Thus, inhibition of aromatase activity with letrozole decreases Bcl-2 expression and increases cell apoptosis in the rodent brain (Fester et al. 2006; Zhang et al. 2017).

Sex Differences in the Non-reproductive Actions of Brain Aromatase

It is known that sex differences in the expression and activity of aromatase by neurons during specific periods of development are involved in the generation of structural and functional sex differences in CNS regions associated with reproduction (Foidart and Balthazart 1995; Roselli et al. 1997; Hutchison 1997; Wade 2001; Balthazart et al. 2003; Stanić et al. 2014; Cisternas et al. 2015; Cambiasso et al. 2017). Recent studies suggest that brain estradiol synthesis may be also involved in the generation of sex differences in brain regions unrelated to reproductive control, modifying synaptogenesis, synaptic plasticity, and non-reproductive behaviors and exerting neuroprotection.

Aromatase inhibition has been shown to result in different outcomes in males and females. For instance, aromatase inhibition has different effects in the neuritogenesis and synaptogenesis of male and female hippocampal neurons (Brandt et al. 2013; Ruiz-Palmero et al. 2016). Thus, aromatase inhibition reduces neuritogenesis and synaptogenesis in female neurons only. Alterations in aromatase activity during development may have different consequences for males and females. For instance, it has been shown that the disruption of aromatase activity during a critical developmental period by inflammation has permanent effects in Purkinje cells and in social behavior, but only in males (Hoffman et al. 2016). Furthermore, neonatal aromatase inhibition in rats results in a decreased hippocampal neurogenesis in males but not in females (Bowers et al. 2010).

Aromatase activity may also be involved in sex differences in synaptic plasticity. Sex differences in the effect of aromatase inhibition on the number and synapses and the induction of LTP have been observed in the rat hippocampus and basolateral amygdala. Aromatase inhibition decreases the number and synapses and impairs LTP, but only in females (Vierk et al. 2012; Fester et al. 2017; Bender et al. 2017).

Aromatase activity is also involved in the regulation of non-reproductive behaviors, with different effects on anxiety and cognitive behavioral tests in males and females. Thus, it has been reported that the inhibition of aromatase activity with letrozole in middle age rats induces anxiety in males but not in females (Borbélyová et al. 2017). In addition, Graham and Milad (2014), have shown that aromatase inhibition by fadrozole impairs fear extinction in male rats. Moreover, enhanced aromatase expression in the prefrontal cortex of female rats, compared to males, has been shown to exert a protective effect against the detrimental effect of repeated stress on cognition on females (Yuen et al. 2016). Furthermore, 6-month-old male but not female aromatase KO (ArKO) mice develop compulsive behavior (Hill et al. 2007) and male but not female ArKO mice develop age-dependent reduction in prepulse inhibition (van den Buuse et al. 2003). In contrast, female ArKO mice exhibit depressive-like behavior (Dalla et al. 2004) but not male ArKO mice (Dalla et al. 2005).

Aromatase activity is also necessary to prevent cell death of specific brain neuronal populations, and this is also different in males and females. Studies in ArKO mice have shown that aromatase deficiency causes apoptosis of dopaminergic neurons in the arcuate nucleus and the medial preoptic nucleus of 1-year-old male mice, but not in female mice (Hill et al. 2004). In contrast, 1-year-old female ArKO mice show apoptosis of pyramidal cells in the frontal cortex and this was not detected in male mice (Hill et al. 2009).

Furthermore, there are gender differences in the upregulation of aromatase associated with chronic neurodegenerative disorders such as multiple sclerosis (MS). Studies in MS patients have shown an increase in aromatase expression in MS lesions only in male patients (Luchetti et al. 2014); whereas in some pathological environments, as it has been described in the Streptozotocin-induced diabetes model, the compensatory neuroprotective mechanisms are more efficient in female rats showing an increase of aromatase expression levels in the hippocampus and sciatic nerve at 12 weeks of diabetes (Burul-Bozkurt et al. 2010). Moreover, aromatase expression has been also described as an important modulator of female cerebrovascular function (Zuloaga et al. 2014). In this case, female mice have enhanced cerebrovascular aromatase expression associated with an increased cerebrovascular endothelial function compared with male mice and the inhibition of aromatase or gene deletion eliminates the sex difference observed in endothelial function.

Aromatase activity is also protective for astrocytes. In primary rat cortical astrocyte cultures, female cells express higher aromatase levels and higher aromatase activity than male cells and are more protected than male cells against oxygen-glucose deprivation and oxidant cell death (Liu et al. 2007). Female mouse astrocytes are also more resistant than male mouse astrocytes to oxygen-glucose deprivation in vitro. However, this sex difference disappears in ArKO astrocytes (Liu et al. 2008). These findings suggest that aromatase activity confers a different protection to male and female astrocytes against neurodegenerative insults. Sex differences in estradiol synthesis have been also observed in astrocytes after a brain injury in Zebra finches. Aromatase expression in astrocytes and brain estradiol levels are increased early in females after brain injury than in males (Pedersen et al. 2018). This sex difference in the astrocyte aromatase expression after brain injury may be involved in the different neuroinflammatory responses observed in the injured brain of male and female animals (Pedersen et al. 2018).

Concluding Remarks and Perspectives

In summary, neural-derived estradiol participates in the regulation of the development and function of different CNS regions that are not directly involved in the control of reproductive functions and behaviors. In addition, estradiol synthesized in the CNS exerts neuroprotective actions after neural injury. Therefore, the endogenous modulation of the expression and activity of aromatase in the CNS contribute to the regulation of different non-reproductive functions. Furthermore, the local production of estradiol in the CNS contributes to the generation of sex differences in synaptic plasticity, behavior, and the endogenous neuroprotective response to neural injury.

Changes in aromatase activity in the CNS not only affect the local levels of estradiol but also the local levels of the estradiol precursor testosterone. Therefore, changes in aromatase activity may impact on the signaling on androgen receptor and ERs (Ruiz-Palmero et al. 2016). Since both testosterone and estradiol from the periphery can cross the blood–brain barrier, the final concentration of these steroids in a given structure of the CNS will depend on their local synthesis and metabolism and on their uptake from plasma. It is unknown how estradiol synthesis in the CNS is coordinated with the changes in peripheral estradiol and the expression of androgen receptor and ERs by neurons and glial cells. Peripheral estradiol may impact on brain estradiol synthesis, since it has been shown that circulating estradiol increases aromatase activity in the hypothalamus (Storman et al. 2018). In addition, the enhancement of cognition in ovariectomized female rats by the systemic administration of estradiol depends on an increase in brain estradiol synthesis induced by circulating estradiol by a mechanism mediated by GnRH receptor in the hippocampus (Nelson et al. 2016). Furthermore, in vivo and in vitro studies suggest that brain estradiol synthesis is necessary for the actions of peripheral estradiol on synaptic plasticity and neuroprotection (Chamniansawat and Chongthammakun 2012; Li et al. 2013). On the other hand, recent studies suggest that the brain may contribute, as an endocrine organ, to circulating estrogens. The presence of a subpopulation of hypothalamic neurons expressing aromatase that project their axons outside the blood–brain barrier suggests that at least a portion of hypothalamic estrogens can be secreted and released into the circulation (Storman et al. 2018). Further studies are necessary to clarify the interaction between estradiol from peripheral and central sources.

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Compliance with Ethical Standards

Conflict of interest The authors report no conflict of interest.

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