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Studies on The Regulation of Aromatase For Brain Derived Estrogen: A Systematic Review

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ABSTRACT

Despite being traditionally recognised as an ovarian endocrine signal, 17β-estradiol (E2) is also a neurosteroid that is generated in the brains of several animals by neurones and astrocytes. The location, regulation, sex variations, and physiological/pathological significance of brain-derived E2 (BDE2) are all well covered in this review. Studies employing particular inhibitors of the E2 production enzyme, aromatase, and the subsequent creation of conditional forebrain neuron-specific and astrocyte-specific aromatase knockout animal models have provided a large portion of our knowledge about the physiological roles of BDE2. According to the data from these investigations, neuron-derived E2 (NDE2) plays a crucial part in the control of memory, synaptic plasticity, sexual differentiation, reproduction, injury-induced reactive gliosis, neuroprotection, and sociosexual behavior.

Key words: Brain, Estrogen, Aromatase, neurons, astrocytes, neurosteroids.

Introduction

The cytochrome P450 enzyme aromatase is responsible for converting androgen precursors into estrogens [Figure 1] [1]. Three molecules of NADPH and oxygen are used in the hydroxylation of androgen precursors in the aromatase-driven catalysis process to yield one molecule of estrogen. The human chromosome 15's 21.2 region contains the sole gene CYP19, which encodes aromatase [2]. The gonads, bone, breast, adipose, vascular tissue, skin, placenta, and brain are among the tissues that express this 123 kb gene. The alternate usage of multiple promoter-specific first exons results in tissue-specific transcripts of aromatase [3].

Several distinct aromatase transcripts are produced when the untranslated first exons are spliced into the coding exons 2 through 10, yet each transcript codes for the same protein [4]. According to conventional wisdom, the brain-specific variation is Exon 1.f. Nonetheless, the brains of rats and humans also express the ovarian-specific exon PII as well as the adipose-specific exons 1.3 and 1.4. It should be noted that the two aromatase isoforms that teleost fish possess—CYP19a, which encodes aromatase A, and CYP19b, which encodes aromatase B—make them special. The brain and gonads both express CYP19b, whereas the gonads express CYP19a [5-7].

Despite their structural differences, these two genes have similar enzymatic activity and more than 20 regulatory sites in the promoter, such as transcription factors that control neurogenesis and response elements for sex steroid receptors [8].

Aromatase activation produces estrogens, which are steroid hormones that can interact with estrogen receptors in the brain and other bodily tissues. estrone (E 1) and estriol (E 3) are regarded as weak estrogens, but 17β-estradiol (E 2)

is the most powerful and extensively researched estrogen [9-10]. Numerous physiological and pathological processes, such as reproduction, sexual differentiation and behaviour, cancer biology, bone physiology, synaptic plasticity, cognitive function, anti-inflammatory effects, and neuroprotection, have been linked to E II control [11-13].

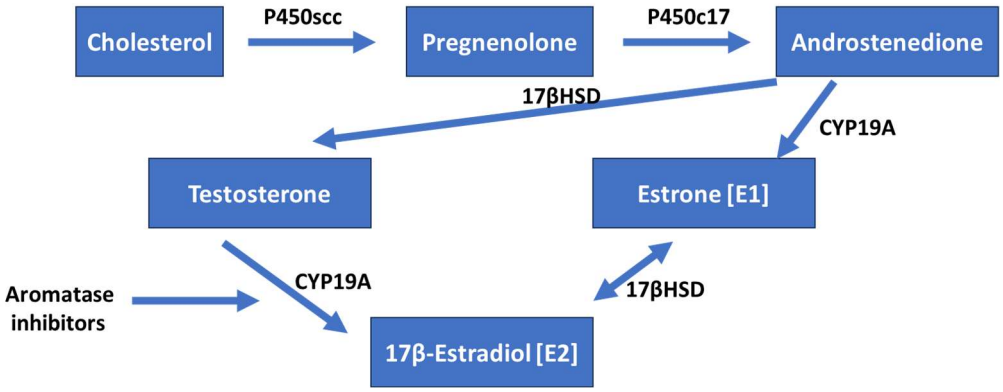

Figure 1: Simplified estrogen Biosynthesis Pathway.

The roles and functions of brain-derived E 2 (BDE 2) have been less well investigated and are just now starting to be completely understood, whereas the role of gonadal-derived E 2 has been well examined [14]. Therefore, the location, regulation, and roles of BDE 2 in the brain will be the main topics of this review. The majority of the research in this field has been done on songbirds and rodents. On the other hand, we will present and discuss discoveries in non-human primates and humans, if accessible [15]. Studies with pharmacological aromatase inhibitors have provided a large portion of our knowledge on the roles and activities of BDE 2 in the brain (Figure 2).

Determining the precise function of neuron-derived E 2 2 vs astrocyte-derived E 2 (ADE 2 (NDE 2)) in the brain is difficult using such a cell-non-specific pharmacological method, though, because both neurones and astrocytes may make E [16]. E 2 is implicated in anti-inflammatory, synaptic plasticity and cognition, and neuroprotection against neurodegenerative diseases, according to whole body global aromatase knockout mice [17, 18].

The function and precise contributions of aromatase/E 2 generated from the brain versus the gonadal glands to these effects, however, cannot be clearly distinguished by these research [19]. Our team's recent research, which used animal models with brain cell-specific aromatase deletion, has addressed this problem and provided crucial information about the roles and functions of NDE 2 and ADE 2 in the brain in both healthy and diseased conditions. In addition to reviewing this new study, we will talk about current debates and possible future paths for knowledge development in this crucial field [20,21].

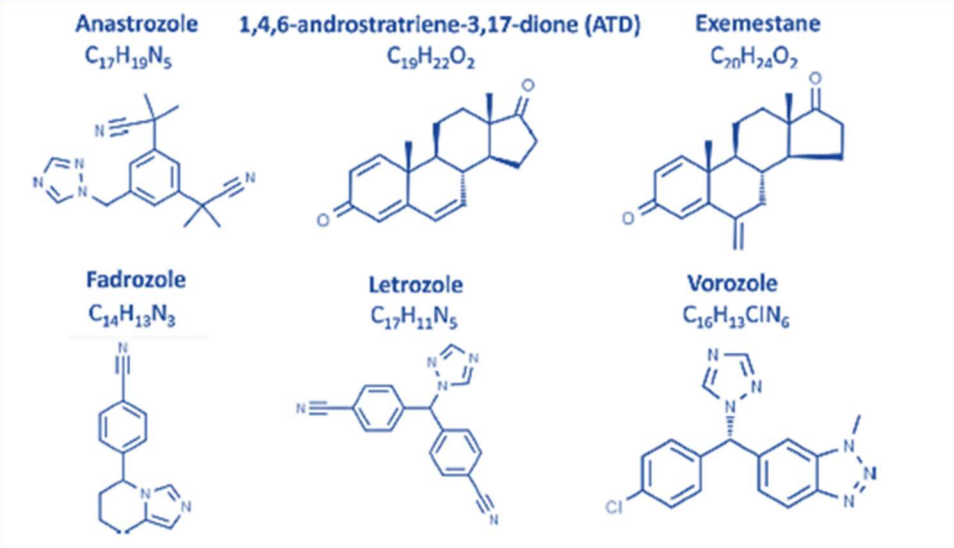

Figure 2: Inhibitors of aromatase are used to inhibit the humans & animals brain aromatase activity.

2. Localization of aromatase in human brain:

A overview of aromatase's brain location across animals is provided in Table 1. Below is a detailed explanation of each species' aromatase localization [22]. Using human foetal brain homogenates, Naftolin and colleagues measured the conversion of radiolabeled androgen precursors to estrogens and showed that the human foetal diencephalon and limbic system possess significant aromatase activity. This was the first report of aromatase activity in the brain. The hypothalamus, amygdala, pons, thalamus, hippocampus, temporal cortex, and frontal cortex were shown to have the greatest aromatase mRNA expression in subsequent investigations employing RT-PCR of adult human brain tissues [23, 24].

Further research revealed no sex differences in aromatase expression in the human hippocampus, temporal cortex, or frontal cortex, and verified high expression of aromatase mRNA in these brain areas. Additionally, the widespread localisation of aromatase in the human brain was confirmed by positron emission tomography (PET) imaging using radiolabeled aromatase inhibitors [25]. The thalamus and amygdala had the highest concentrations, followed by the preoptic area (POA), hippocampus, cortex, putamen, cerebellum, and white matter [26]. With the exception of higher levels in the male left hypothalamus, PET imaging further shown that there are no discernible sex variations in aromatase levels in the human brain. Additionally, regional brain absorption of the radiolabeled aromatase inhibitor 11 C-vorozole did not change during the menstrual cycle in premenopausal women, according to PET imaging [27].

3. Localization of aromatase in non-human primates brain:

In order to investigate the cellular and subcellular localisation of aromatase, immunohistochemical studies revealed that aromatase expression was widely distributed in the granule cells of the dentate gyrus, pyramidal neurones in the human temporal cortex and CA1-CA3 regions of the hippocampus, a small number of astrocytes, and certain interneurons in both normal and epileptic human brains [28]. Ultrastructural investigations using light and electron microscopy in the human brain also showed aromatase immunoreactivity in many boutons with synaptic vesicles and throughout the neuronal cell body, including dendrites and axonal processes [29]. Furthermore, it was shown that axon terminals may create synapses with both immuno-positive and immuno-negative dendrites and neuronal cell bodies. Aromatase's synaptic location points to a potential neuromodulatory or neurotransmitter function for estrogen generated from neurones, which will be covered in more detail in the next section [30-31]. Significant aromatase immunoreactive protein localisation was verified at the protein level by immunohistochemistry investigations in the hippocampus CA1-3 pyramidal neurones, dentate gyrus granule neurones, monkey temporal cortex, and certain interneurons. Further research revealed that aromatase localisation took place in boutons that held synaptic vesicles

as well as throughout the neuronal cell body, including dendrites and axons [32, 33].

4. Localization of aromatase in rat brain:

The hypothalamus was the focus of the initial investigations to identify aromatase's location in the rat brain using activity tests. The POA, mediobasal hypothalamus, and male and female hypothalamus all showed strong activity in these investigations. The amygdala, POA, and hippocampus of the female rat brain exhibited the highest levels of aromatase activity and E 2 in subsequent investigations that employed a microsomal-based aromatase activity assay and high-performance liquid chromatography (HPLC) measurement of E [34]. These investigations conducted a more thorough examination of the brain. In the adult male and female rat brains, RT-PCR investigations also revealed that aromatase mRNA was highly expressed in the amygdala, bed nucleus of the stria terminalis, and POA, followed by the hippocampus and cingulate cortex. The brainstem and cerebellum showed modest amounts of aromatase mRNA [35-37].

Given that the hippocampus is a site of E production, the rat hippocampus showed significant mRNA expression for the steroidogenic enzymes required for E 2 α 2 synthesis, such as aromatase, P450 side chain cleavage (P450scc), P450 17 hydroxylase (P45017 α), 17β-hydroxy steroid dehydrogenase (17β-HSD), and 3β-hydroxysteroid dehydrogenase (3β-HSD) [38]. Significantly higher than the blood concentration, the basal concentration of E 2 was found to vary between 1 and 8 nM in the male rat hippocampal region and between 0.5 and 2 nM in the female rat hippocampal region. It has been shown that E 2 in the hippocampus is extremely stable and does not undergo considerable conversion to other metabolites. Additional research on the rat hippocampal region showed that aromatase is found in basal neurons [39].

For example, immunohistochemistry investigations showed that aromatase was significantly localised in granule neurones in the dentate gyrus and pyramidal neurones in the adult male and female rat hippocampus CA1-CA3 areas [40]. Aromatase enzymatic activity in neurones was further validated by in vitro investigations; astrocytes and oligodendrocytes showed no activity. Further research showed that aromatase was found at the synapse and in presynaptic terminals in cultured rat cortical neurones, as well as in pre- and post-synaptic compartments and the endoplasmic reticulum in the rat hippocampal region. Aromatase's neuronal and synaptic localisation is comparable to findings in humans, non-human primates, mice, and birds, as will be covered in more detail below [41].

5. Localization of aromatase in mouse brain:

Although there are less studies on mice, they are broadly in agreement with the location of aromatase in the rat brain. For example, RT-PCR and immunohistochemistry have shown that aromatase is significantly localised in the mouse cerebral cortex, hippocampus, amygdala, and hypothalamus. Similar to research on rats, aromatase was exclusively found in mouse hippocampal neurones; no localisation was found in basal astrocytes [42]. Only neurones, not astrocytes, expressed aromatase, according to in vitro tests of cultured mouse neurones and astrocytes. Widespread aromatase expression was seen in the brains of mice designed to express enhanced green fluorescent protein (EGFP) upon aromatase activation [43]. The amygdala, hypothalamus, and bed nucleus of the stria terminalis had the largest levels of EGFP-positive cell bodies and fibres. EGFP-positive cells co-expressed the androgen receptor or estrogen receptor-β (ERβ) and estrogen receptor-α (ERα) in several mouse brain regions [44]. Together, these investigations demonstrate that aromatase is extensively distributed in neurones at synaptic sites in the rat and mouse brains, which is consistent with findings in humans and monkeys. This implies that BDE 2 and aromatase may control brain synaptic activity. As will be covered in a later section, there is, in fact, mounting evidence that BDE 2 plays a synaptic function [45].

5. Localization of aromatase in birds brain:

A research that showed a high level of aromatase activity in the avian forebrain was among the first to describe the location of aromatase in the bird brain. It's interesting to note that this study also verified a comparable significant level of aromatase activity in the forebrain of opossums, teleosts, snakes, sea turtles, and skates. Significant aromatase

protein localisation was found in the Japanese quail's medial preoptic nucleus, septal region, ventromedial, and tuberal hypothalamus, according to immunohistochemical investigations [46]. Aromatase and estrogen receptor were colocalized in several of these areas. Electron microscope research showed that aromatase was present in synaptic boutons in the brain of Japanese quails, and aromatase activity was detected in synaptosomes [47]. Additional research revealed that aromatase is expressed in the POA of several bird species, including as ringbills, canaries, house sparrows, and zebra finches.

It is noteworthy that the quail has strong aromatase expression that is mostly restricted to the hypothalamus, but the songbird telencephalon expresses aromatase considerably more broadly and with much higher activity. The songbird has therefore been very helpful in identifying the function of BDE 2 and aromatase in neuroplasticity, memory, and behaviour [48]. The POA, hypothalamus, hippocampus, and neostriatum showed the greatest aromatase localisation in the adult zebra finch brain, according to in situ hybridisation. Later research showed that aromatase was found in pre-synaptic boutons in the brain regions of the zebra finch's high vocal centre and hippocampal regions, and that males had more aromatase-containing synaptic profiles than females [49].

Table 1: Aromatase for brain localization

Techniques Description	Localized brain area	Species
Aromatase activity assay, 1971	Fetal diencephalon	Human [50]
Immunohistochemistry, 1991	High in medial & tuberal HYP	Mouse [51]
RT-PCR, IHC, HPLC, 2003 and 2004	Pyramidal neuron HPC in male rat. Aromatase localization in presynaptic and postsynaptic site in male rats	Rat [52]
IHC, WB, ELISA, 2020	Aromatase expression in HPC and cortex	Human [53]
IHC, WB, ELISA, 2024	Astrocyte aromatase & E2 increased HPC	Mouse [54]

7. Phosphorylation for Regulation of aromatase in brain

A wide range of intrinsic and extrinsic variables, as well as transcriptional and post-transcriptional processes, can control the levels of aromatase and BDE 2 in the brain. We will go over the main processes and elements that regulate the brain's generation of E 2 and aromatase expression and activity in this part [55].

Phosphorylation is a crucial method for quickly controlling aromatase activity, as demonstrated by early research in quail, which demonstrated that Ca-dependent phosphorylation of aromatase immediately reduced brain aromatase activity in hypothalamic homogenates and explants. Subsequent research showed that there are 15 consensus phosphorylation sites predicted for quail aromatase, and that protein kinase C and A play a role in the phosphorylation regulation of aromatase function [56]. According to Hayasi and Harada, aromatase in human JEG-3 cells is phosphorylated by calcium/calmodulin-dependent protein kinase II (CaMKII) and dephosphorylated by calcineurin, resulting in reversible regulation of catalytic activity. Further research showed that acid phosphatase prevents Ca-dependent phosphorylation from reducing quail aromatase activity. Additionally, it was demonstrated that sexual contact reduces aromatase [57].

The authors hypothesised that the effect's quickness points to a nongenomic mechanism that may include glutamate signalling and Ca2+-dependent aromatase phosphorylation. Glutamate is, in fact, elevated in the male quail's medial

POA during sexual contact, and when the glutamate agonist kainate was injected into the male quail's medial preoptic nucleus, aromatase activity was significantly reduced. Similar to what was shown in quail, the male and female zebra finch hypothalamus, hippocampus, and caudomedial nidopallium (NCM) all showed a sharp decline in 2+ aromatase activity due to Ca 2+-dependent phosphorylation [58].

Depletion of Ca stores in zebra finch forebrain and rat hippocampus neurones in culture led to increased release of E 2+ 2 and dephosphorylation of aromatase, further supporting a function for Ca in regulating brain aromatase. Remarkably, E 2 administration raised aromatase protein levels and phosphorylation in rat hippocampal neurones, indicating that E 2 can control aromatase in the rat hippocampus [59].

Later research identified the phosphorylation sites in human aromatase using tandem mass spectrometry analysis and liquid chromatography. According to the study, there are up to 19 phosphorylation sites in human aromatase, with T 462 and Y 361 462, T162, and H 475 / S 478 being the most significant and consistently detectable. Highly similar phosphorylation sites T, S118, and S 478 are found in humans, monkeys, rats, zebra finches, mice, and chickens. Rats and mice do not have phosphorylation site Y 361, but humans, monkeys, zebra finches, chickens, and quail have [60].

It's interesting that phosphorylating Y 361 and S 478 was shown to increase aromatase activity. It was also suggested that the active site access channel was important because S 478 was previously linked to catalysis. It's crucial to keep in mind that phosphorylating and dephosphorylating circumstances probably cooperate to control aromatase activity. Research employing brain homogenates from zebra finches suggests that under low to moderate phosphorylating settings, acid phosphatase boosts aromatase activity, but under high phosphorylating conditions, the reverse impact is seen [61].

Glutamate:

Although there are species- and brain region-specific variations, glutamate, the primary excitatory amino acid transmitter in the brain, has been demonstrated to quickly control neural aromatase activity and BDE 2 levels. For instance, in quail hypothalamus explants, glutamate agonists quickly reduced aromatase activity. Effectiveness was ranked as follows: kainate > AMPA > NMDA. Similarly, it was demonstrated that glutamate retrodialysis significantly reduced local E 2 levels in the zebra finch's NCM. Aromatase and NMDA receptors have been demonstrated to colocalize in zebra finch hippocampus neurons [62], which suggests that NMDAR may mediate the impact. However, the glutamate receptor that mediates the effect was not investigated. Glutamate, the brain's main excitatory amino acid transmitter, has been shown to swiftly regulate cerebral aromatase activity and BDE 2 levels, despite species- and brain region-specific variances. For example, glutamate agonists rapidly decreased aromatase activity in quail hypothalamus explants [63]. The following is a ranking of effectiveness: AMPA > NMDA > Kainate. Likewise, glutamate retrodialysis was shown to dramatically lower local E 2 levels in the NCM of zebra finches. In zebra finch hippocampal neurones, aromatase and NMDA receptors have been shown to colocalize, indicating that NMDAR may mediate the effect. Nevertheless, no research was done on the glutamate receptor that causes the impact [64].

Hormones:

There is mounting evidence that both peptide and steroid hormones control brain aromatase. In the POA of castrate male Japanese quail, castrate male and female rat POA, periventricular magnocellular nucleus, and posterior medial hypothalamic nucleus, as well as in the song system nuclei of the castrate male zebra finch and the suprachiasmatic, paraventricular, ventromedial, and lateral hypothalamic nuclei of the castrate male monkey, it was demonstrated that testosterone, a substrate for the production of estrogen, increased aromatase activity. Since testosterone has been shown to raise aromatase mRNA levels in the brains of several species, it appears that testosterone regulates aromatase activity in the brain at the transcriptional level [65].

E 2 has also been shown to control brain aromatase expression in addition to testosterone. It was demonstrated that ER E 2 interacts with the 1.f promoter using a mouse hypothalamus neuronal cell line. Treatment elevated aromatase mRNA, which was reversed by ER knockdown or an ER antagonist. In the ovariectomised female rat amygdala, E 2

also raised the levels of aromatase mRNA. Similarly, it was discovered that tonic E 2 therapy increased the expression of aromatase in the hippocampus of female mice, whereas phasic E 2 treatment was actually inhibitory [66].

Drugs:

The regulation of brain aromatase has been linked to both recreational and pharmaceutical substances. For example, research from a variety of animals, including humans, indicates that nicotine may lower the amount of the enzyme aromatase in the brain. Nicotine treatment dramatically reduced forebrain aromatase activity, according to studies conducted in foetal and neonatal rats and mice. Similarly, nicotine injection dose-dependently reduced 11C-vorozole absorption in the brain of female baboons, with the amygdala and POA exhibiting the biggest reductions, according to PET imaging [67]. This suggests that nicotine lowers aromatase levels in the brain of non-human primates. Although this has not yet been confirmed, the results suggest that smoking may reduce brain aromatase and BDE2 levels since the nicotine dosages employed in the study generated plasma levels comparable to those reported in smokers [68].

Brain injury and inflammations:

As was previously indicated, aromatase is often only basally expressed in neurones, with little to no expression seen in astrocytes. However, after a penetrating brain injury or injection of the excitotoxin kainic acid, Garcia-Segura's laboratory was the first to show in 1999 that aromatase may be substantially activated in astrocytes in numerous parts of the male and female rat and mouse brain [69]. All brain areas with severe neuronal loss, including the hippocampus, pyriform and entorhinal cortex, amygdala, and bed nucleus of the stria terminalis, showed aromatase-positive astrocytes in mice injected with kainic acid. It's interesting to note that kainic acid infusion had no effect on neuronal aromatase expression. Additionally, aromatase-positive astrocytes were seen in the striatum, corpus callosum, cortex, hippocampus, hypothalamus, and thalamus in the penetrating injury model. These results suggest that after excitotoxic or penetrating brain damage, aromatase is activated in astrocytes in the majority of brain regions. Additionally, aromatase activity significantly increased in response to penetrating brain damage, suggesting enhanced local E2 generation. Later research on the zebra finch showed that aromatase was elevated in astrocytes in the lesion site 24–48 hours after penetrating brain damage, and that local E2 was also raised in parallel [70].

Conclusion:

Although 17β-estradiol (E2) is often identified as an ovarian endocrine signal, it is really a neurosteroid that is produced by astrocytes and neurones in the brains of several animals. This paper thoroughly discusses the location, regulation, sex differences, and physiological/pathological relevance of brain-derived E2 (BDE2). Much of what we know about the physiological functions of BDE2 has come from studies using selective inhibitors of the E2 synthesis enzyme, aromatase, and the subsequent development of conditional forebrain neuron-specific and astrocyte-specific aromatase knockout animal models. The findings of these studies indicate that neuron-derived E2 (NDE2) is essential for the regulation of memory, synaptic plasticity, sexual differentiation, reproduction, reactive gliosis brought on by injury, neuroprotection, and sociosexual behaviour.

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