Abstract

The sexual dimorphism of human central nervous system (CNS) is a fact confirmed in many imaging and functional studies. The action of sex hormones in fetal and postnatal life seems to be main factor determining the brains’ gender. Recent studies revealed that estrogens are potent modulators of CNS function also in adults and they pose many non-reproductive activities. It was also proven that estrogens could be synthesized in brain and act directly in there. The action occurs not only through slow acting genomic effects, dependent on nuclear receptors, but also by rapid non-genomic pathway. Many brain structures were found to be estrogen-sensitive and they can be recognized as specific neural systems disseminated in whole CNS. It was found that the cholinergic, serotoninergic and dopaminergic systems are under strong influence of estrogens. In general, animal and human studies indicates that estrogens have a stimulatory and neuroprotective functions in these systems. It brings opportunity that these sex steroids can be of significance for pathology and treatment of neurodegenerative diseases, psychiatric traits and substance addiction.

Key words: estrogens, central nervous system, Alzheimer disease, Parkinson disease, neuroprotection

Introduction

There are many differences in central nervous system (CNS) function found between males and females, and those were described in healthy as well as in pathological state. The „sex of the brain“ has a deep background in CNS biology, including its anatomy, which differs between sexes [1-5]. Also susceptibility to some neurological disorders is gender dependent. The sex hormones, especially estrogens and progesterone, are believed to be the key factors determining differences in CNS physiology and pathology between males and females. Role of sex steroids in neurodevelopment and neurobiology is under intense investigation for more than 30 years now, and even though a huge progress has been made since then, still there are more questions than answers. One of the points of interest is how the exogenous hormones, delivered as estrogen or hormonal replacement therapy (ERT or HRT) can influence the brain function in peri- and postmenopausal women. The aim of this review is to shortly characterize and summarize the most important conclusions from studies concerning relationship between estrogens and CNS function.

Estrogens and CNS function in adult women

Estrogens are able to easily cross the blood-brain barrier so hormones produced by ovaries in reproductive-age women or exogenous hormones administered orally or parenterally are main sources of estrogens for brain. On the other hand, some neurons (as glutaminergic in hippocampus) are able to synthesize estrogens in CNS itself [1]. Those steroids, in the same manner as in other tissues, can exert their function in two ways: (1) nongenomic – rapid pathway dependent on membrane receptors and (2) genomic – slow pathway mediated by nuclear receptors.

The best-known relationship between estrogens, progesterone and brain is their involvement in feedback regulation of reproductive functions. It is mediated in CNS by kiss-neurons and gonadotropin-releasing hormone (GnRH) neurons in hypothalamus, and partially by pituitary gonadotrophs. The role of estrogens in hypothalamo-pituitary-ovarian axis is well-known and is out of scope of this article, however insights from those earliest studies were stimuli for further research regarding interaction between sex steroids and neurons. Currently, it is known that estrogens play a role in variety of CNS functions. From those, the best recognized are: impact on verbal skills, coping with spatial tasks, verbal and nonverbal memory and communication, motor skills and mood and emotional processes [1-3, 6].

Estrogen-sensitive CNS structures

Estrogen receptors α and β has been detected in different brain areas, including amygdala, hippocampus, neocortex, nucleus coeruleus, raphe nuclei, median grey area and cerebellum [2, 4-6]. The density of estrogen...
receptors in most of those areas, excluding amygdala and hippocampus, is significantly lower than in hypothalamus, but they play an important role in regulation of non-reproductive functions of CNS [4]. Not only neurons are receptive for estrogens, but also surrounding glial cells, which are responsible for regulation of neuroglial response. Due to vasodilatory action of estrogens, they are believed to be involved also in regulation in whole-brain blood flow [5].

As mentioned above, estrogens play a role in memory [4, 5]. This phenomenon seems to be related to their action in hippocampus and basal forebrain, especially cholinergic and serotonergic neurons. The link to motor skills is mediated mainly by such brain structures as: tegmentum, the nucleus accumbens, substantia nigra, tectum [4, 5]. The influence of estrogens on emotional functions, mood and affect is linked to their activity in brain cortex and limbic system. The spatial specific estrogen activity in brain is reviewed in details in [4]. Below we present another point of view, which focuses on interplay between hormones and specific neural systems, instead of anatomical structures. This neuroendocrine approach reflects better the nature of brain function, its physiology and pathology.

**Estrogens and cholinergic system**

Acetylcholine is widely spread neurotransmitter in human brain, it acts through 2 types of receptors: muscarinic and nicotinic [6]. Cholinergic system is functionally responsible for act of conscious thinking and thoughts, cognitive processes, memory. It is also involved in activation of reward system, excitement and arousal [6, 10, 11]. According to those modalities, acetylcholine insufficiency in CNS is found in neurodegenerative diseases and dementia. Pathology of acetylcholine neurotransmission is also involved in mechanisms of substance addiction [6, 10, 11].

The relationship between estrogens and cholinergic system was in some matter discovered in animal studies. It was shown, that long-lasting estradiol deficiency leads to decreased choline uptake and decreased choline acetyltransferase activity. Lower availability of acetylcholine results in decreased activity of cholinergic system. Exogenous estrogens, in animals after oophorectomy has a opposite effect with increased activity of main enzymes of cholinergic system (choline acetyltransferase and cholinesterase) [6]. Estrogens are also able to increase acetylcholine release in neurons in the presence of depolarization [7]. It is proven also, that estrogen deficiency is related to generalized hypotrophy of cholinergic neurons of prefrontal cortex, and this process can be prevented by ERT [8]. In vivo animal studies, confirms conclusions from in vitro experiments. Vojtko et al. [7] showed lower scores in visuo-spatial memory’s tests in macaques after oophorectomy, and ERT restored those deficits. To clarify whether the improvement was related to direct effect on the cholinergic system scopolamine, which is a muscarinic receptor antagonist, was administered to animals. ERT reduced the impediment effect of scopolamine, indicating a close relationship between ERT and secretion of acetylcholine [7]. Subsequent experiments on primates undergoing ovariectomy helped to confirm these results [8, 9]. The results of anatomical and functional imaging indicate that estrogens modulate the cholinergic system and pharmacological studies have shown that modulation affects mainly muscarinic receptors [9].

**Hormone replacement therapy and the cholinergic system in humans**

Recently some interesting experiments has been carried out on humans, which seems to confirm the stimulatory effect of estrogen on this neurotransmitter system.

The first experiment showed a clear relationship between ERT and the cholinergic system in humans and confirmed the observations made on animals. ERT abrogated the negative effect of scopolamine in the tests evaluating concentration and speed while coping with the tasks [10]. Norbury et al. [11] using single-photon emission tomography (SPET), showed that with age the number of muscarinic receptors decreases, but in women after surgical menopause undergoing HRT, the density of these receptors was greater than in untreated women. A statistically significant difference was shown in the left striatum, hippocampus, frontal cortex and the side of the thalamus. Interestingly, a receptor density in the parietal cortex and the hippocampus was correlated with the concentration of estradiol in the plasma.

**Estrogens and serotonergic system**

The projection signals from serotonergic neurons of the raphe nucleus arise to many regions of the brain – the thalamus, the hypothalamus, basal ganglia, nucleus accumbens, cingulate gyrus and the neocortex [15, 16]. Therefore, serotonin-secreting neurons are involved in the regulation of mood, cognition, sleep and reproductive functions. It is also known that abnormalities of this system play a major role in the pathogenesis of depression, obsessive-compulsive disease and other
mental disorders, since serotonin reuptake inhibitors have become the main agents in the fight against these disorders [16-18].

Serotonergic neurons in primates were shown to express both subtypes of estrogen receptor and estrogens seems to positively affects the function of the serotonergic system [12-15]. Estrogens exerts their activity through several mechanisms: (1) the stimulating effect on the activity of tryptophan hydroxylase – a key enzyme in serotonin synthesis pathway; (2) increased transport and serotonin transporter binding capacity; (3) reduction of the expression of the serotonin receptor (5HT) 1A, and its affinity for the serotonin (Gi-protein interaction); (4) reducing the gene expression of the monoamine A oxidase, the enzyme responsible for the degradation of serotonin in the CNS; (5) inhibition of apoptosis of serotonergic neurons and reducing their sensitivity to damaging factors [12-14]. Furthermore, administration of estrogen increases 2A receptor expression in the amygdala, hippocampus, nucleus accumbens and some regions of cortex [15].

The whole effect of these changes is well illustrated by behavioral changes that occur in animals after administration of estrogen. It was shown, that estrogens are able to reverse the inhibitory effects of serotonin at the hyperphagia and mating behavior in rats. In contrast, an animal model of depression, restoring the correct expression of estrogen receptors of serotonin [12-15].

**Estrogens and serotonergic system in humans**

In humans, serotonin system is also under strong influence of sex hormones. Kugaya et al. [16] using a receptor – specific imaging technique of positron emission tomography (PET) showed that ERT up-regulates the expression of cortical 5HT2A serotonin receptors in postmenopausal women. This effect was observed in the frontal and prefrontal cortex, cingulate gyrus, and what is more, in some regions of the brain (frontal ventral gyrus) receptor density was directly correlated with serum estradiol levels. The authors also observed that women undergoing treatment, performed better in tests of verbal fluency and determining the path, but did not achieve significantly better results in tests assessing mood. Other researchers have also confirmed these results, and this fact clearly shows that the experimental results on non-human primates are likely to be transferred to the human body [17]. In those studies, duration of ERT was quite short, as it does not exceed 6 months. In 2008, a group of researchers led by Compton [18] repeated analogous study, with the exception that HRT duration was longer (14 ± 8 years). The results were surprising. Binding affinity of cortical 5HT2A receptors did not differ significantly between the HRT group and the controls. Revealed differences, even though not statistically significant, also were not in line with those of previous studies. It has been found, for example that in the cingulate gyrus signal was stronger in the treated group, whereas in cortex the response was weaker in intervention group [18]. The significant difference in receptors density has been shown only for hippocampus: women taking HRT had a lower number of serotonin receptors. Further analysis showed correlation between the reduced number of receptors in this region and improved verbal memory. Interestingly, it was shown that women during HRT have a lower concentration [18].

Results summarized above differ from animal studies and research done on short-term HRT. However, in conclusion we can hypothesize about the full impact of estrogenotherapy on serotonergic neural system. HRT causes a general stimulation of serotonergic activity – both in receptor-dependent mechanism, and through interaction with serotonin synthesis and breakdown. This stimulation results in a down-regulation of the number of postsynaptic receptors, which results in better performance in memory tasks. According to the cited study, reduced concentration may be related to the increased activity of GABAergic neurons or reduced levels of testosterone [18].

**Estrogens and the dopaminergic system**

Dopaminergic neurons are located mainly in three regions of the brain: the compact part of the substantia nigra, the ventral part of tegmentum and in the hypothalamus, and their projections are organized in four main ways: two of the midbrain of the tegmentum: (1) mesocortical – to the cortex and (2) the mesolimbic – to the limbic system and prefrontal cortex; (3) nigrostriatal – between the substantia nigra and the striatum and (4) tuberoinfundibular – from the arcuate nucleus to the infundibulum. These connections imply the involvement of these neurons in: (1) and (2) the emotional and motivational processes, feeling of satisfaction; (3) – motor function; (4) – the secretion of prolactin. Disorders of the dopamine-dependent signaling were confirmed in Parkinson’s disease, other dyskinesias, psychosis, addiction and Alzheimer’s disease [19, 20-24].

In animal studies, estrogen and progesterone induced both pro- and antydopaminergic effect, depending on the dose, and time of administration [19].
ERT/HRT in postmenopausal women seems to increase dopaminergic activity. This thesis is supported mainly by studies of Parkinson’s disease and schizophrenia, although there are scant data about the effects of estrogens in healthy women. Craig et al. [20] using apomorphine stimulation test (measuring growth hormone response rate) showed that postmenopausal women undergoing long-term HRT presents increased dopaminergic activity. In contrast, a Gardner group [21] showed that 4 weekly HRT increases the availability of dopamine transporter in the midbrain in SPET imaging.

In the pathogenesis of schizophrenia undoubtedly one of the main roles is played by impaired secretion of dopamine, primarily through mesocortical pathway. However, also other abnormalities are of great importance, including glutamatergic and serotonergic, neurotransmitter systems. For more than a decade clinical trials began analyzing the ERT use as a drug decreasing the symptoms of schizophrenia. In several of them it was shown that short-term use reduces the symptoms of schizophrenia [22, 23, 43, 44]. Bergermann et al. [24-26, 45-47] evaluated the usefulness of ERT in schizophrenia in different ways to yield positive results for reducing the symptoms of metaphorical speech. However, there was no improvement in alloorientation, nor in reducing the likelihood of disease relapse.

Summary

Despite numerous controversies arising from research analyzing the links between estrogen use and function of the brain, those studies bring a new quality in our understanding of processes occurring in the CNS. In the last three decades huge progress occurred in this field. The brain was identified not only as a target of estrogen action, but also as a estrogens source. The whole new branch of knowledge is arising after discovering non-genomic mechanisms of estrogens action and a number of new features is under scope which was not known them so far. Thanks to the latest advances in medical research and neuroendocrine imaging, more and more observations made on animals can be confirmed also in humans. These studies shows what potential lies in discovering the role of estrogens in CNS, especially for diseases that until recently seemed to have no relation to the reproductive system.

The knowledge about physiological and pathological phenomena related to estrogens action in the brain provides an opportunity to develop new therapeutic approaches. Previously gained experience with HRT learned us, how a great option gives selective modulation of sex steroid receptors. Just as developed selective estrogen receptor modulators (SERMs) in the treatment of breast cancer (tamoxifen) or osteoporosis (bazedoxifen) we can expect new pharmaceuticals – NeuroSERMs. These drugs with adapted profile of activities can contribute to new quality for the treatment of neurodegenerative diseases and psychiatric disorders.

References


