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Review

Estrogens are neuroprotective factors for hypertensive encephalopathy

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ABSTRACT

Estrogens are neuroprotective factors for brain diseases, including hypertensive encephalopathy. In particular, the hippocampus is highly damaged by high blood pressure, with several hippocampus functions being altered in humans and animal models of hypertension. Working with a genetic model of primary hypertension, the spontaneously hypertensive rat (SHR), we have shown that SHR present decreased dentate gyrus neurogenesis, astrogliosis, low expression of brain derived neurotrophic factor (BDNF), decreased number of neurons in the hilus of the dentate gyrus, increased basal levels of the estrogen-synthesizing enzyme aromatase, and atrophic dendritic arbor with low spine density in the CA1 region compared to normotensive Wistar Kyoto (WKY) ratsl. Changes also occur in the hypothalamus of SHR, with increased expression of the hypertensinogenic peptide arginine vasopressin (AVP) and its V1b receptor. Following chronic estradiol treatment, SHR show decreased blood pressure, enhanced hippocampus neurogenesis, decreased the reactive astrogliosis, increased BDNF mRNA and protein expression in the dentate gyrus, increased neuronal number in the hilus of the dentate gyrus, further increased the hyper-expression of aromatase and replaced spine number with remodeling of the dendritic arbor of the CA1 region. We have detected by qPCR the estradiol receptors ERα and ERβ in hippocampus from both SHR and WKY rats, suggesting direct effects of estradiol on brain cells. We hypothesize that a combination of exogenously given estrogens plus those locally synthesized by estradiol-stimulated aromatase may better alleviate the hippocampal and hypothalamic encephalopathy of SHR.

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1. The hippocampus in human and experimental hypertension

Hypertension is referred to as the "silent killer", because it gives no warning signs or symptoms of the incoming pathology. According to statistics from the World Health Organization, raised blood pressure causes 7.5 million deaths per year worldwide, about 12.8% of the total of all deaths. High blood pressure places a strong stress on target organs including the brain. Within the different brain structures, the hippocampus is highly vulnerable to the effects of hypertension. Patients suffering from chronic essential hypertension present atrophy of hippocampus and temporal lobe, with morphological evidence of remodeling of the microvascular wall, ischemia, cytotoxic edema, demyelination, micro infarcts, beta-amyloid deposits and tau pathology. These changes may be accompanied by cognitive decline [1–7]. Hippocampal dysfunction is frequent in elderly hypertensive subjects, leading to high incidence of small hippocampus volume and increased risk of dementia [8].

Animal models become valuable tools to study brain changes of hypertension. The spontaneously hypertensive rat (SHR), originally developed in 1960s by Okamoto and colleagues in Japan, is by far the most widely used rat model of primary hypertension. Sabbatini and coworkers [9,10] were pioneers in describing regressive changes and astroglial reaction in the hippocampus from SHR, similar to those occurring in neurodegenerative disorders with cognitive impairment. These authors have pointed out that SHR represent an animal model of vascular dementia and Alzheimer's disease, considering their flourished hippocampus pathology. Studies in the brain of SHR disclosed a range of disturbances, such as hydrocephalus, increased expression of the astrocytic marker glial fibrillary acidic protein (GFAP), blood–brain barrier disruption, cytoskeletal breakdown, decreased growth factor expression, decreased forebrain white matter volume, abnormal neurogenesis and hyperstimulation of the vasopressinergic and angiotensinergic systems [11–15]. Changes in learning and memory displayed by SHR made them also models of dementia and the attention-deficit hyperactivity syndrome [7]. Taking into consideration the high incidence of abnormalities in humans and rodents, the expression "hypertensive encephalopathy" has been coined as far back as 1928 to describe the brain damage caused by a persistent elevation of blood pressure [16].

Gender differences in the development of cardiovascular diseases and hypertension have suggested that female steroids exert a protective function in humans and rodent models. For example, it is widely recognized that during menopause transition, declining estrogen levels in women constitutes a risk factor for hypertension [17,18]. Female SHR suffer from alterations of the reproductive axis, including defects of ovarian development, decreased steroidogenesis and poor responsiveness to gonadotropins [19]. In fact, loss of gonadal hormones due to ovariectomy aggravates the hypertension of SHR [20]. Several reports have given proof that treatment with natural or synthetic estrogens decrease blood pressure and show protective effects on the brain and the cardiovascular system of SHR [21–24]. In women, however, the situation is less clear and conflicting results have been reported. The Women Health Initiative trial employing estrogen alone has shown increased risk of dementia and cerebrovascular disease [25]. However, these data have been reinterpreted based on the selection of patient cohort and the timing of estrogen replacement therapy after cessation of menses. Recent reports have accentuated that early initiation of steroid treatment after loss of ovarian hormones may prove beneficial, suggesting the existence of a window of opportunity for estrogen neuroprotection [26–28].

In this review we describe our contributions to unravel 17β-estradiol effects in the brain of SHR, emphasizing the pharmacological relevance of estrogens for the prevention of hypertensive encephalopathy. To avoid the confounding issue of ovarian cyclicity, we routinely used male normotensive Wistar Kyoto rats and male SHR. Our experiments demonstrated that hypertensive – but not normotensive – rats were highly sensitive to estrogen treatment, supporting that tissue microenvironment plays an important role for steroid responsiveness and for neuroprotection.

2. Neuroprotective effects of estrogens in the hippocampus

Estrogen modulation of hippocampus functions has strong implications for the management of inflammation, trauma, ischemia, neurodegeneration and changes of higher cognitive functions caused by aging and neurological disorders. There is unanimous support for the view that estrogens qualify as hippocampus "neuroprotectans". The pleiotropic effects of 17β-estradiol in the hippocampus involves the prevention of excitotoxicity, inflammation and oxidant injury, the inhibition of apoptosis with stimulation of the anti-apoptotic gene Bcl_2, increased neuronal survival, the regulation of dendritic remodeling, synaptogenesis and spinogenesis and the regulation of a plethora of neurotransmitters: acetylcholine, dopamine, serotonine, catecholamines, glutamate and GABA [28–34]. Although these effects may be genomically-mediated, extranuclear sites of estrogen action involving membrane, synaptic and mitochondrial sites are also likely players in neuroprotection. In molecular terms, estrogen actions via activation of nuclear or extranuclear binding sites regulate the phosphatydylinositol 3-kinase, a Ca^{2+} independent protein kinase C isoform, Src kinase, mitogen-activated kinase, phosphorylation of AKT, the LIM kinase and also regulate Ca^{2+} influx and the ERK 1/2 pathways [35]. In response to 17β-estradiol, mitochondrial sequestration of Ca^2 play an important role for ion homeostasis and cell survival [27,28]. Estrogens also increase dendritic spine formation and synaptic density in CA1 pyramidal cells, an effect probably mediated by estrogen receptors (ER). Gould et al. [36] and Herrick et al. [37] have detected extranuclear ERβ immunoreactivity in doublecortin (DCX) positive, newly born cells of the dentate gyrus.

Further information on estrogen neuroprotection has been provided by culture studies. In hippocampal neurons in culture, estrogens protect against glutamate toxicity, glucose deprivation, FeSO toxicity and amyloid-peptide toxicity, the hallmark of Alzheimer's disease [30]. According to Azcoitia et al. [26] and Garcia Segura et al. [38], 17β-Estradiol interaction with IGF1 is an important neuroprotective mechanism. Some of the estrogen effects could be genomically mediated, after interaction of ligand with ER. Estrogen binding has been reported in the hippocampal pyramidal cells and the hilus of the dentate gyrus. Of the two isoforms of the estrogen receptor, ERα and ERβ the β isoform is abundantly expressed in hippocampus, whereas ERα is found in CA1 interneurons and a subset of pyramidal and granule cells [35,39].

Besides the classical concept that ERα and ERβ are the predominant nuclear receptors involved in many effects of estrogen, modulation of cell-signaling pathways also occurs via membrane estrogen receptors, such as the G protein coupled receptor (GPER). This receptor participates in the control of several hippocampal functions, including neuritogenesis [40]. It is also known that ligand-bound GPER regulates vasomotor tone, delays development of hypertension [41], and plays a protective function in the cardiovascular system of SHR [42]. Therefore, a relevant endeavor would be to establish a link between nuclear and extranuclear sites with the estrogen positive stimulation of neurochemical parameters in hypertensive encephalopathy.