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Review article

Menopause and Parkinson's disease. Interaction between estrogens and brain renin-angiotensin system in dopaminergic degeneration

Jose L. Labandeira-Garcia *, Ana I. Rodriguez-Perez, Rita Valenzuela, Maria A. Costa-Besada, Maria J. Guerra

Laboratory of Neuroanatomy and Experimental Neurology, Dept. of Morphological Sciences, CIMUS, University of Santiago de Compostela, Santiago de Compostela, Spain
Networking Research Center on Neurodegenerative Diseases (CIBERNED), Spain

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ABSTRACT

The neuroprotective effects of menopausal hormonal therapy in Parkinson's disease (PD) have not yet been clarified, and it is controversial whether there is a critical period for neuroprotection. Studies in animal models and clinical and epidemiological studies indicate that estrogens induce dopaminergic neuroprotection. Recent studies suggest that inhibition of the brain renin-angiotensin system (RAS) mediates the effects of estrogens in PD models. In the substantia nigra, ovariectomy induces a decrease in levels of estrogen receptor-α (ER-α) and increases angiotensin activity, NADPH-oxidase activity and expression of neuroinflammatory markers, which are regulated by estrogen replacement therapy. There is a critical period for the neuroprotective effect of estrogen replacement therapy, and local ER-α and RAS play a major role. Astrocytes play a major role in ER-α-induced regulation of local RAS, but neurons and microglia are also involved. Interestingly, treatment with angiotensin receptor antagonists after the critical period induced neuroprotection.

Contents

Abbreviations: 6-OHDA, 6-hydroxydopamine; ACE, angiotensin converting enzyme; ACEIs, ACE inhibitors; AII, angiotensin II; AT1, AII type 1 receptor; AT2, AII type 2 receptor; CNS, central nervous system; DA, dopamine; DPN, 2,3-Bis-4-hydroxyphenyl-propionitrile, ER-β agonist; E2, 17-β-estradiol; ER-α, estrogen receptor-α; ER, estrogen receptor; ERT, estrogen replacement therapy; GPER1, GPR30, G protein-coupled estrogen receptor 1; HRT, hormonal replacement therapy; IL-1β, interleukin-1β; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; OS, oxidative stress; ovx, ovariectomized; PD, Parkinson's disease; PPAR-γ, peroxisome proliferator-activated receptor gamma; PPT, 1,3,5-Tris-4-hydroxyphenyl-4-propyl-1H-pyrazole, ER-α agonist; RAS, renin-angiotensin system; RNS, reactive nitrogen species; ROCK, Rho kinase; ROS, reactive oxygen species; SNc, substantia nigra compacta; VTA, ventral tegmental area; WHI, Women's Health Initiative.

* Corresponding author at: Dept. of Morphological Sciences, Faculty of Medicine, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain.
E-mail address: joseluis.labandeira@usc.es (J.L. Labandeira-Garcia).

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease, and is characterized by progressive degeneration of dopaminergic neurons. There are sex differences in dopaminergic degeneration, as observed in animal models and in clinical and epidemiological reports on PD. It is also known that the incidence and prevalence of PD is higher in postmenopausal than in premenopausal women of similar age. This is consistent with numerous studies that showed that sex hormones exert trophic actions on neurons and glial cells, promote neuron survival and have a neuroprotective role in several models of neurological diseases. After hormonal depletion in menopausal women, hormonal replacement therapy (HRT) is a logical choice. The initial indication for HRT was to alleviate uncomfortable symptoms of menopause. However, numerous observational studies have supported the concept that HRT in postmenopausal women protects against aging-related diseases such as cardiovascular diseases, stroke and neurodegeneration, including PD. As detailed below, this was not confirmed in several randomized controlled trials, which reported null or even detrimental effects, and many women are being denied the use of HRT because the data on the benefits and risks of HRT are controversial and confusing.

Clarification of mechanisms involved in effects, particularly the neuroprotective effects, of estrogens and HRT is crucial. On the other hand, non-hormonal management of menopausal effects before clarification of HRT consequences has also been suggested, at least for women who cannot or do not wish to take HRT. Regarding neuroprotection of the dopaminergic system, we have shown an important interaction between the brain renin-angiotensin system (RAS) and effects of 17-β-estradiol in models of PD, which suggests that manipulation of brain RAS may be an efficient approach for the prevention or coadjuvant treatment of PD in estrogen-deficient women not suitable for HRT.

2. Parkinson's disease

2.1. Major neuropathological and clinical aspects

PD is a neurodegenerative disease characterized by progressive degeneration of dopamine-containing neurons in the substantia nigra compacta (SNc) and by the presence of intraneuronal proteinaceous cytoplasmic inclusions known as Lewy bodies. This leads to a marked deficiency in striatal dopamine (DA), which causes the major clinical symptoms of PD (Fig. 1A–D). The neurotransmitter dopamine is synthesized by mesencephalic neurons in the SNc and ventral tegmental area (VTA), and by some other groups of neurons such as hypothalamic neurons in the arcuate and periventricular nuclei (Carlsson et al., 1962). SNc neurons innervate the striatum through the nigrostriatal pathway. Dopamine acts as a neuromodulator that controls important physiological functions such as voluntary movements, motivated behavior, learning and hormone production. In PD, clinical signs are usually detected when approximately 50% of nigral neurons and 80% of striatal dopamine are lost. It is known, however, that other areas of the brain may be affected in PD, and that lesions also occur outside the central nervous system (CNS) such as in the enteric nervous system (Lebouvier et al., 2009). Clinically, PD is predominantly a movement disorder that is characterized by bradykinesia, rigidity, tremor at rest, gait disturbances and other motor problems. Non-motor symptoms are also associated with PD, such as anxiety, depression, insomnia, autonomic dysfunction, constipation, and different levels of dementia.

2.2. Pathogenic mechanisms

The clinical phenotype of PD is relatively homogeneous. However, the pathogenic mechanism appears to be multifactorial. It has been shown that several genes are mutated or deleted in familial PD (see for review Verstraeten et al., 2015). However, the etiology of sporadic, idiopathic PD, which accounts for most cases of PD, is still unclear. A number of mechanisms have been involved in dopaminergic neuron degeneration in PD, including mitochondrial dysfunction, oxidative stress, neuroinflammation, and impairment of the ubiquitin-proteasome system (Olanow, 2007; Vilchez et al., 2014). These pathogenic factors are not mutually exclusive, and one of the key aims of current PD research is to discover the mechanisms involved in possible interactions between these pathways, which result in dopaminergic neuron degeneration. Several studies have provided evidence that oxidative stress (OS) plays a major role in all forms of PD (Andersen, 2004; Berg et al., 2004), and there has been some discussion as to whether OS is a primary event or a consequence of other pathogenic factors. However, dopaminergic degeneration is unquestionably mediated by overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS are generated as a result of normal metabolism. OS occurs when ROS or RNS are produced in excess or are insufficiently degraded and overwhelm the protective defense mechanisms of a cell, leading to functional impairment and finally cell death (Berg et al., 2004). The dopaminergic nigrostriatal neurons appear particularly vulnerable to OS-derived cell death (Olanow, 1990; Fahn and Cohen, 1992). Different factors have been involved in increased vulnerability of dopaminergic neurons (Brichta and Greengard, 2014), including oxidation of cytosolic dopamine and its metabolites that leads to the production of cytotoxic free radicals (Greenamyre and Hastings, 2004), high terminal density and axonal arborization of dopaminergic terminals (Brichta and Greengard, 2014), elevated mitochondrial bioenergetics (Pacelli et al., 2015), presence of dopamine transporters that also introduce neurotoxic substances (Dauer and Przedborski, 2003), elevated Ca^{++} concentration that leads to alpha-synuclein aggregation

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