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Review

Signaling pathways mediating the neuroprotective effects of sex steroids and SERMs in Parkinson's disease

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ABSTRACT

Studies with the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) animal model of Parkinson's disease have shown the ability of 17β-estradiol to protect the nigrostriatal dopaminergic system. This paper reviews the signaling pathways mediating the neuroprotective effect of 17β-estradiol against MPTP-induced toxicity. The mechanisms of 17β-estradiol action implicate activation of signaling pathways such as the phosphatidylinositol-3 kinase/Akt and the mitogen-activated protein kinase pathways. 17β-estradiol signaling is complex and integrates multiple interactions with signaling molecules that act to potentiate a protective effect. 17β-estradiol signaling is mediated via estrogen receptors, including GPER1, but others receptors, such as the IGF-1 receptor, are implicated in the neuroprotective effect. Glial and neuronal crosstalk is a critical factor in the maintenance of dopamine neuronal survival and in the neuroprotective action of 17β-estradiol. Compounds that stimulate GPER1 such as selective estrogen receptor modulators and phytoestrogens show neuroprotective activity and are alternatives to 17β-estradiol.

1. Parkinson's disease and estrogens

Selective and progressive death of dopamine (DA) neuronal cell bodies in substantia nigra characterizes Parkinson's disease (PD). As a result, an imbalance in the control of movement by the basal ganglia appears, leading to manifestation of clinical symptoms such as resting tremor, rigidity and bradykinesia [88]. Several aspects including susceptibility to develop the disease, age at onset and symptoms support the existence of a sex difference in PD. These differences benefit women, as a higher predisposition of the disease is reported in men (with at least 1.5-fold greater risk) [129,131] and the age at onset occurs about 2 years later in women [47,128]. Different profiles of motor symptoms have also been described. Women present a PD phenotype with greater instability scores while men have worsened rigidity [8]. Although motor scores do not show sex differences in early PD, women have better scores than men in advanced PD (disease duration more than 5 years) [73]. Furthermore, at symptom onset, higher levels of striatal [^{123}I]FP-CIT binding to DA transporter (DAT) are observed in women, suggesting that the development of symptomatic PD may be delayed by higher endogenous striatal DA levels and that the phenotype of PD in women is more benign [47].

Various studies have been conducted to investigate how endogenous estrogen exposure and how the use of estrogens therapy could exert a positive effect on PD risk (reviewed in [71]). A longer fertile lifespan [104,112] and the use of estrogen therapy [24,97] are associated with a reduced risk of PD in most of the studies, suggesting a beneficial effect of estrogen with regard to PD risk. In addition to the beneficial effect of estrogens exposure on PD risk, data from clinical reports show that endogenous and exogenous estrogens can modulate PD symptoms. A worsening of PD symptoms in menstrual women was reported in pre-menstrual and menstrual periods, when estrogen and progesterone levels are low [55,127]. Several women with PD report a deterioration of their symptoms and the extensive variations in estrogen levels during and after pregnancy were suggested to be implicated in worsening of PD symptoms [107,109]. Lower symptom severity scores were reported in women with early PD taking estrogen therapy, but not yet taking levodopa [113]; an effect that was not observed at later stages of the disease [122]. Thus, clinical and epidemiological studies support the conjecture that endogenous and exogenous estrogen exposure exerts a beneficial effect upon the risk of PD. Moreover, these studies also suggest that estrogens can act as a neuromodulator of the DA system with the result being a diminution in PD symptoms. The neuromodulatory effects of estrogens may or may not share the same mechanisms as that of

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the neuroprotective effects. Since the focus of this review is on the neuroprotective effect of estrogen, we refer readers to a recent review on the neuromodulatory effect of estrogen on DA neurotransmission for more details on this aspect of estrogen action [110].

2. The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) animal model of PD

Discovered as by-product of an analog of the narcotic meperidine, MPTP produces an irreversible parkinsonian syndrome in humans that mimics the main characteristics of PD including rigidity, tremor, bradykinesia, postural instability and freezing [29,64]. After crossing the blood brain barrier, MPTP is converted into its active metabolite 1-methyl-4-phenyl pyridinium (MPP^+) in glial cells by monoamine oxidase B. MPP^+ then enters the neuron through the DAT [28]. Inside the DA neurons, MPP^+ concentrates within mitochondria where it impairs mitochondrial respiration by inhibiting complex I of the electron transport chain, leading to an increased production of free radicals, which causes oxidative stress and activation of cell death pathways [28].

In mice, MPTP impairs the nigrostriatal DA system by decreasing DA concentrations as well as DAT and vesicular monoamine transporter 2 (VMAT2) densities [54], effects similar to that observed in PD [50]. The DAT and VMAT2 are both important modulators of DA neurotransmission and localize in striatal DA terminals and DA cell bodies in the substantia nigra. The DAT controls synaptic and extrasynaptic DA levels by re-uptake of released neurotransmitter from the presynaptic neuronal terminals [121], while the role of the cytoplasmic VMAT2 is to sequester DA within vesicles [46]. Thus, DAT and VMAT2 play crucial roles in the maintenance of DA homeostasis and DA, DAT and VMAT2 are valuable markers to evaluate integrity of DA terminals and cell bodies. With a moderate MPTP lesion, DA markers in substantia nigra are less intoxicated than that observed in striatum [54], suggesting that DA neuronal cell bodies in the substantia nigra are less affected than their terminals in striatum. Low doses of neurotoxins cause a loss of tyrosine hydroxylase positive terminals whereas high doses of neurotoxins are required to damage DA cell bodies, suggesting that damage to DA terminals is an early indicator of degeneration [17].

Studies in MPTP-treated mice have shown a greater neurotoxic effect in males as observed by more extensive striatal DA reduction [81]. Thus, the MPTP mouse model faithfully mimics the sex difference of PD. Moreover, this sex difference to MPTP suggests that endogenous estrogen levels appear to influence the vulnerability to MPTP toxicity and support a beneficial role of estrogen against nigrostriatal DA neurodegeneration (as described in Section 4). Given this protective potential of estrogen in the MPTP model and the clinical evidence supporting a beneficial effect of estrogen, particularly in the early stages of PD, these early stages of neurodegeneration, where substantia nigra DA neurons are injured but not yet dead, may represent an appropriate time to evaluate this capacity for neuroprotection by steroids.

3. Estrogen receptors

Estrogens produce their effects by binding to estrogen receptors (ER), ERα and ERβ, both belonging to the nuclear receptor family [76]. 17β-estradiol mediates its effect through two mechanisms. A genomic mechanism of ER action involves gene transcription mediated by activation of ERs, and requires hours to days to exert their effects (reviewed in [76]). ER-direct DNA association is mediated through an estrogen responsive element (ERE) and an ER-indirect DNA association could also result by interaction with the nuclear factor κB (NFκB), specificity protein 1 (SP1), the cAMP-response element binding protein (CREB) and/or by interaction with fos/jun transcription factors thereby regulating gene transcription via the activator protein-1 (AP-1) site. A non-genomic mechanism of estrogen action is also present and is defined as a rapid effect (within minutes even seconds) initiated by interaction with plasma membrane-associated ER and/or G protein-coupled estrogen receptor 1 (GPER1), leading to activation of signaling pathways. The activation of signaling pathways by 17β-estradiol could also result in transcriptional activity. Thus, genomic and non-genomic actions could converge to potentiate transcriptional activity.

Both ERα and ERβ are found in the striatum and substantia nigra while a difference in their distribution is described for these brain regions. The immunoreactivity of ERα in the striatum seems to be higher than ERβ whereas superior immunoreactivity of ERβ relative to ERα is reported in the substantia nigra [82]. Furthermore, ERβ and tyrosine hydroxylase positive substantia nigra pars compacta neurons were found to project to the striatum [23]. Striatal ERα has been shown to be primarily associated with the membrane versus the nuclear fraction of the neuron [115].

In addition to the classic ERα and ERβ, a high binding affinity of 17β-estradiol for an orphan receptor of the 7-transmembrane receptor family was described in 2005 [106,126]. This receptor, first known as GPR30 and now called GPER1, is expressed in the brain including the striatum and the substantia nigra [15,48]. Plasma membrane expression of GPER1 as well as Golgi apparatus and reticulum endoplasmic localization for this receptor have been found [38,77] and GPER1 levels have been detected in astrocytes [59]. GPER1 is able to mediate both rapid and transcriptional effects in response to 17β-estradiol in the brain and peripheral tissues [99].

GPER1 has been the subject of some controversies related to its role as an estrogen receptor due to its inability to mediate estrogenic responses in reproductive organs [89,90]. Nevertheless, it has been shown that the GPER1 agonist, G1, can reproduce many estrogen effects [99]. Additional discussions on the role of GPER1 as an estrogen receptor also come from data showing the lack of estrogenic responses by GPER1 in the absence of both ERα and ERβ as well as the absence of any changes in 17β-estradiol effects when GPER1 was not present [93]. But these data could also be interpreted to suggest that GPER1 acts as a collaborator of ERs and that the presence of ERs in some tissues is required to induce a GPER1 effect [68]. It was reported that GPER1 could change ERα phosphorylation signals in the mouse uterus [39] and that ERα can directly interact and activate G proteins to mediate estradiol signaling [58], supporting the potential collaboration of ER and GPER1. In addition to a potential collaboration of GPER1 and ERs, some 17β-estradiol effects in the brain are observed even when both ERα and ERβ are blocked [92,120], suggesting another mechanism of 17β-estradiol action through an alternative receptor, perhaps via GPER1. Experiments using the GPER1 agonist G1 have shown that GPER1 activation mediates many estrogen effects in various tissues (reviewed in [99]) and that G1 is as potent as 17β-estradiol in mediating neuroprotection following ischemia [65]. The mechanisms of 17β-estradiol signaling are complex, tissue specific and could include independent as well as co-dependent effects through ERα, ERβ and GPER1 [99]. Thus, further research is required to determine the contribution of GPER1, and its potential role as an ERs collaborator, in mediating estradiol effects in the brain.

4. Neuroprotective effects of estradiol against MPTP

Findings from several studies have shown that 17β-estradiol treatment is protective against MPTP toxicity in both female and male mice (reviewed in [12]). Beneficial effects of 17β-estradiol