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REVIEW ARTICLE

ESTROGEN ROLE IN PARKINSON DISEASE: UNLOCKING NEW PATHWAYS AND THERAPEUTIC POTENTIALS

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ABSTRACT

Parkinson's disease (PD) is a common neurodegenerative condition marked by both motor and nonmotor impairments. According to recent data, estrogen may have a major impact on PD, and its neuroprotective properties may open up new avenues for treatment. Female gonadal hormones, especially estradiol, have been implicated in regulating the risk and symptoms of PD, as evidenced by epidemiological studies that have revealed sex variations in the disease's incidence and course. The biology of estrogen receptors (ERα, ERβ, and GPER) and their location in the nervous system are examined in this overview, with an emphasis on their potential for neuroprotection. This review delves into estrogen's neuroprotective effects, focusing on its interaction with estrogen receptors and its activation of critical molecular pathways. The cAMP-PKA-CREB pathway promotes neuronal survival, while the MAPK and NF-κB pathways reduce neuroinflammation. Furthermore, the PI3K-Akt pathway enhances anti-apoptotic signaling, and the IP3-DAG pathway supports calcium-mediated neuronal processes. Collectively, these mechanisms reveal how estrogen mitigates neuronal damage and influences PD pathophysiology. By elucidating the molecular mechanisms underlying estrogen's effects, this review underscores its potential as a therapeutic target for PD. Future research on estrogen receptor modulation and signaling may unlock novel interventions to address both motor and nonmotor symptoms of PD.

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INTRODUCTION

PD is the second most frequent age-related neurodegenerative disorder. PD is characterized by motor and nonmotor (cognitive and limbic) deficits. The motor signs of PD include hypokinetic signs such as akinesia/bradykinesia, rigidity and loss of normal postural reflexes, and hyperkinetic signs such as tremor (1). The pathological hallmarks of PD are loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and accumulation of misfolded alpha-synuclein, which is found in intra-cytoplasmic inclusions called Lewy bodies (LBs**)** (2). Despite decades of research and an increased understanding of the pathophysiology of PD, there are many aspects of the disease that remain challenging and difficult to manage in daily clinical practice (3). Despite several decades of advances in medications and neurosurgical approaches, there remains an unmet need for symptomatic motor control. Better control of tremor, gait and balance, posture, dexterity, and communication skills are major challenges for better therapeutics of the PD movement disorder. Non-motor symptoms (NMS), which often precede motor impairments, add complexity to the burden of PD and its management (4).

The prevalence of PD is roughly 2:1 higher in males than in women, indicating that sex plays a significant role in its development (5). Men are twice as likely as women to get Parkinson's disease (PD), although women die from the condition more frequently and it advances more quickly. Additionally, men and women have different disease risk factors, treatment responses, and motor and nonmotor symptoms (6). Female gonadal hormones, especially circulating estradiol, may have a neuroprotective effect on the dopaminergic system, according to epidemiological evidence of sex differences in Parkinson's disease. As a result, a number of observational studies have looked into the connection between PD risk and estrogen intake. Women who are exposed to more estrogen overall in their lifetime are far less likely to get PD (7).

Estrogen Receptors (ERα, ERβ, and GPER): Estrogens are a group of gonadal sex hormones that exist naturally in three different forms in humans. 17β-estradiol (E2) is the most dominant biological form, followed by Estrone (E1) the intermediate form, and Estriol (E3) (8). Estrogen receptors (ERs) are a group of protein found within a cell, which gets activated in response to estrogen and its agonists.

There are three different ERs; Estrogen receptor alpha (ERα) and Estrogen receptor beta (ERβ), which are nuclear receptors, G protein-coupled estrogen receptor 1 (GPER1), which is a membrane-bound receptor (9). ERα and ERβ exist in many tissues in both rodents and humans but with distinct distribution patterns. Estrogen receptor **(**ERs) were recognized in brain regions like the hippocampus, cerebral cortex, midbrain, and brainstem (10). GPER is a membrane-associated estrogen receptor (ER) associated with rapid estrogen-mediated effects. Over recent years GPER emerged has a potential therapeutic target to induce neuroprotection. On nervous system, GPER is similarly expressed throughout the CNS and peripheral nervous system (PNS) of male and female rodents. GPER is observed in the forebrain (Cortex, hypothalamus, hippocampus, hypothalamic-pituitary axis and striatum brainstem (The pontine nuclei locus coeruleus, brainstem autonomic nuclei, cerebellum Purkinje layer, spinal cord and autonomic and sensory ganglia). In addition, GPER is present in brain vasculature. The levels of GPER expression are heterogeneous with GPER presenting high expression in hypothalamic-pituitary axis, hippocampus, cortex and thalamus. The hippocampus and frontal cortex present higher GPER mRNA levels than the septum and striatum (11).

Neuroprotective effect of Estrogen

Activation of cAMP-PKA-CREB pathway: The cAMP-PKA pathway is a well described signal transduction pathway in which increased adenylate cyclase activity results in increased cAMP concentrations and downstream activation of protein kinase A (PKA). E2 increases cAMP accumulation in brain and has cellular effects in neurons consistent with increased cAMP levels including increased phosphorylation of cAMP response element binding protein (CREB). Activation of the cAMP signalling and increased CREB phosphorylation could contribute to the neuroprotective effects of estradiol, as activation of the cAMP pathway is associated with decreased susceptibility of neuronal cell to apoptotic signals (12). Activation of the cAMP-PKA-CREB pathway may enhance neuronal survival by increased expression of the anti-apoptotic protein bcl-2 (13). The cAMP response element-binding protein (CREB) is believed to play a pivotal role in dopamine (DA) receptor-mediated nuclear signaling and Neuroplasticity (14).

Anti-Inflammatory Effects

Activation of the MAPK signal transduction pathway: MAPK signalling pathways are associated with E2 activity in the brain. ERs relay MAPK signals through sequential activation of Ras, B-raf, MAPK / ERK kinase (MERK 1 / 2) and MAPK (ERK 1 / 2) to finally induce various transcriptional factors that promote neuronal survival (15). The MAP kinase pathway is activated upstream of ERK phosphorylation, and most likely, activation of b-raf is cardinal (16). E2 regulation of Bcl-2 transcription occurs through a non-genomic mechanism mediated by MAPK signaling, a genomic action mediated by ER binding to ERE sites in the coding region of the Bcl-2 and Bcl-x gene (17) (18). Thus, E2 promotes the expression of Bcl-2 and Bcl-x by different mechanisms and there is convergence of genomic and non-genomic actions of E2 to potentiate transcription of target genes implicated in cell survival (19).

NF-κB Pathway: Many studies have shown that altered levels of NF-κB expression and its nuclear translocation are associated with degeneration of DA neurons in PD (20). Centrally, the effects of estrogen are transduced through the activation of ERK and CREB in the hypothalamus and hippocampus, activation of Akt signalling pathways in the striatum or mediating anti-inflammatory effects through inhibition of NF-κB [21] [22] Physiological levels of estrogen may promote female longevity through the upregulation of antioxidant signals through survival signalling (MAPK, ERK) or anti-inflammatory signalling (NF-κB) cascade both centrally and peripherally (23). Estrogen has been shown to downregulate inflammatory cytokines in the CNS, which has a neuroprotective role against neurodenerative diseases. E2 has been shown to inhibit NF-κB, thereby reducing transcription of NF-κB target genes (9).

Anti-apoptic pathway

PI3K-Akt pathway: Estrogen activated PI3K/Akt and decreased MAPK/ERK signaling in the SN. Decreased PI3K/Akt signaling associated with cell death has been demonstrated in drosophila models of PD. Additionally, by promoting the expression of anti-apoptotic signals, the PI3K/Akt pathway may also inhibit proapoptotic gene expression. For instance, Akt phosphorylates and inactivates the caspase-9 and proapoptotic protein BAD. Because caspase-9 is a major activator of the downstream effector caspase-3, reduced activity of the latter might account for the neuroprotection mediated by Akt. Recent in vitro research has shown that dopamine transporter (DAT) expression and function are reduced when the PI3K/Akt and MAPK/ERK pathways are inhibited. The expression and functionality of this tranporter are restored when DAT is phosphorylated via the Akt and MAPK pathways (24). Phosphatidylinositol-3-kinase (PI3K) is activated by E2 via a plasma membrane-associated ER (25), which then activates Ca2+ independent PKC (26). The L-type Ca2+channel is phosphorylated by a Ca2+ independent PKC isoform, which is followed by Ca2+ influx (27). The intracellular Ca^{2+} rise activates conventional Ca^{2+} dependent PKCs (28), which then phosphorylate and activate Src kinase (29, 30). Src then activates the MEK/ERK1/2 pathway (31, 32) followed by translocation of activated ERK into the nucleus. Subsequent to CREB activation by activated ERK phosphorylation. Activation of CREB is also required for E2 induction of the antiapoptotic genes, Bcl-2 and Bcl-xl (33, 34). In parallel, PI3K also activates Akt (35, 36), which can phosphorylate the proapoptotic protein BAD, preventing heterodimerization with and inactivation of Bcl-2.

IP3 DAG pathway: Estrogen binds to its putative membrane receptor and stimulates inositoltriphosphate (IP3) formation which, in turn, causes a rapid release of calcium from intracellular stores. Second, calcium-dependent kinases appear to target the adenylate cyclase by stimulating cyclic adenosinemonophosphate (cAMP) formation and protein kinase A (PKA) activation. Finally, the nuclear transcription factor CREB is phosphorylated (pCREB), and it is suggested that pCREB mediates estrogen effects on the differentiation of midbrain dopaminergic neurons (37). E2 binds to the Gq-mER and activates G□q, a G-protein subunit. G□q dissociates from the membrane and activates phospholipase C (PLC) and initiates the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2).

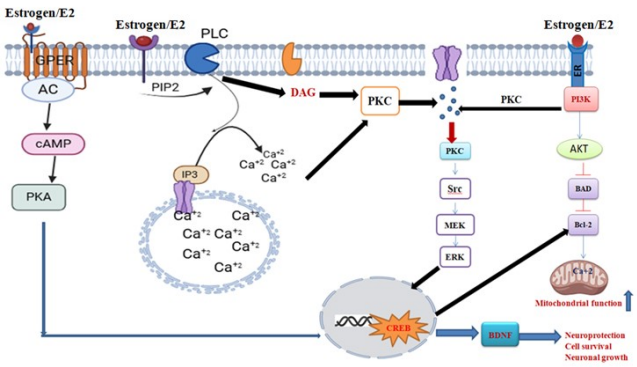

Figure 1. Schematic of Estrogen-activated signaling Pathways involved in treatment of Parkinson's disease

PLC then hydrolyzes PIP2 into diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3). DAG actives protein kinase C (PKC), which activates adenylate cyclase VII, which increases cAMP production and stimulates protein kinase A (PKA). Activation of PKA also phosphorylates cAMP-responsive element binding protein and control gene expression through the CREB response element. IP3 activates Ca^{2+} release from the endoplasmic reticulum that can activate calcium-dependent signaling. E2 also has been found to bind to the nuclear receptors and activate estrogen response element dependent transcription (38).

CONCLUSION

PD poses significant challenges, with current therapies often falling short in addressing both motor and nonmotor symptoms. Estrogen emerges as a key neuroprotective factor, with its actions mediated through receptors such as ERα, ERβ, and GPER and pathways including cAMP-PKA-CREB, MAPK, NF-κB, and PI3K-Akt, IP3/DAG. These mechanisms promote neuronal survival, mitigate inflammation, and reduce apoptosis, offering a compelling case for estrogen-based therapeutic strategies. Sex differences in PD further emphasize the importance of estrogen in disease modulation. Harnessing its multifaceted potential could lead to innovative approaches that not only target symptoms but also slow disease progression, improving outcomes for PD patients. Future research into estrogen's pathways is essential for unlocking these therapeutic possibilities.

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