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Review

Sex differences in Parkinson's disease and other movement disorders

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ABSTRACT

Movement disorders including Parkinson's disease (PD), Huntington's disease (HD), chorea, tics, and Tourette's syndrome (TS) display sex differences in disease susceptibility, disease pathogenesis, and clinical presentation. PD is more common in males than in females. Epidemiologic studies suggest that exposure to endogenous and exogenous estrogen contributes to these sex differences. There is extensive evidence that estrogen prevents dopaminergic neuron depletion induced by neurotoxins in PD animal models and therefore is neuroprotective. Estrogen may also decrease the efficacy of other neuroprotective substances such as caffeine in females but not males. Sex chromosomes can exert effects independent of sex steroid hormones on the development and maintenance of the dopamine system. As a result of hormone, chromosome and other unknown effects, there are sexual dimorphisms in the basal ganglia, and at the molecular levels in dopaminergic neurons that may lead to distinct mechanisms of pathogenesis in males and females. In this review, we summarize the evidence that estrogen and selective estrogen receptor modulators are neuroprotective in PD and discuss potential mechanisms of action. We also briefly review how sex differences in basal ganglia function and dopaminergic pathways may impact HD, chorea, and tics/Tourette's syndrome. Further understanding of these sex differences may lead to novel therapeutic strategies for prevention and treatment of these diseases.

Contents

Abbreviations: PD, Parkinson's disease; HD, Huntington's disease; TS, Tourette's syndrome; SNpc and SNpr, substantia nigra pars compacta and pars reticulata; DA, dopamine; HRT, hormone replacement therapy; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MA, methamphetamine; 6-OHDA, 6-hydroxydopamine; DA, dopamine; DOPAC, dihydroxyphenylacetic acid; HVA, homovanillic acid; DAT, dopamine transporter; VMAT2, vesicular monoamine transferase 2; TH, tyrosine hydroxylase; PPT, propyl-pyrazole-triol; DPN, diarylpropionitrile; SERM, selective estrogen receptor modulator; KO, knock out; PSP, progressive supranuclear palsy; MAO, monoamine oxidase inhibitor.

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Introduction

Movement disorders are a diverse group of neurologic conditions that can be grouped broadly into hyperkinetic and hypokinetic disorders. There are significant sex differences in the pathophysiology, epidemiology and clinical manifestations of many of these diseases. The unifying pathophysiology of these various diseases relates to dysfunction of the basal ganglia and interconnected pathways. The basal ganglia are compromised of the caudate and putamen, also known together as the striatum, the globus pallidus, the subthalamic nucleus, and the substantia nigra pars compacta and pars reticulata (SNpc and SNpr), which contain dopaminergic neurons. Dopamine (DA) is one of the major regulatory neurostransmitters of the basal ganglia, and dopaminergic system dysfunction can manifest in highly divergent clinical presentations.

The most common disease of dopamine dysfunction is Parkinson's disease (PD). There are sex disparities in PD, with a higher incidence and prevalence of PD in men. Sexual dimorphisms in non-diseased basal ganglia and substantia nigra may partly explain this sex-specific risk (Beyer et al., 1991). Estrogen may also account for some of these differences, and we will review the evidence that estrogen is neuroprotective to the dopaminergic system. In addition, chromosome differences may contribute to the sex differences noted in PD, with interplay between chromosomal factors and gonadal hormone factors. We will review the evidence available that implicates the male Y chromosome in increased risk of PD in men. Tourette's syndrome (TS) and tics, both hyperkinetic movement disorders, are also much more common in men than women. Conversely, the genetic movement disorder of dopa responsive dystonia occurs more often in women due to higher penetrance, and chorea associated with pregnancy occurs exclusively in women. We will also briefly review the limited literature that describes potential mechanisms by which sex may impact disease susceptibility, disease pathogenesis, and clinical presentation of these other movement disorders.

Parkinson's disease risk in clinical studies

PD occurs more often in men than in women, with a meta-analysis reporting an increased relative risk of 1.5 (Wooten et al., 2004). PD incidence rates are twice as high in men compared to women at all ages in an Italian population, and 91% higher in men in the Kaiser Permanente Medical Care Program in Northern California (Baldereschi et al., 2000). Because estrogen is known to exert effects on dopamine synthesis and function, clinical studies have focused on the correlation between estrogen exposure and PD risk. Rocca and colleagues evaluated the risk of PD (or parkinsonism) in the Mayo Clinic Cohort Study of Oophorectomy and Aging, which included over 2000 patients and controls. In women who had undergone unilateral oophorectomy, the risk of PD was increased, but was only statistically significant if the surgery was performed before age 42. In women who underwent bilateral oophorectomy, there was a significantly increased risk of PD with a hazard ratio of 1.8 (Rocca et al., 2008). In a case-control study, PD was associated with a lower cumulative estrogen exposure during life, or shorter fertile lifespan (R S-P et al., 2009; Ragonese et al., 2004). Similarly, increased length of endogenous estrogen exposure was associated with older age of onset and less severe motor impairment in a cross-sectional study of women with PD (Cereda et al., 2013). Women with PD were less likely to have used HRT, and postmenopausal use of HRT correlated with lowered PD risk in another case-control study (Currie et al., 2004). However, this was not the case in a group of women studied by Marder and colleagues where the use of HRT did not decrease the risk of PD, but did decrease the risk of developing PD with dementia (Marder et al., 1998). Similarly, Simon and colleagues did not find an increased risk of PD associated with any endogenous or exogenous estrogen exposure marker in the Nurses' Health Study (Simon et al., 2009). Therefore, although both endogenous and exogenous estrogen can be potentially protective, it remains unclear to what degree estrogen exposure contributes to the risk of developing PD in the majority of women with this disease.

An epidemiologic phenomenon possibly related to both PD and estrogen exposure is pesticides. Exposure to various pesticides may increase the risk of PD (Brown et al., 2006). Moreover, many pesticides either mimic or block estrogen. While a causal relationship between pesticide exposure, estrogen and PD risk has not been established, the underlying mechanisms may be elucidated by studying the effect of pesticides on estrogen pathways and sex differences in exposure-related risk.

Estrogen may also affect the clinical presentation of women with PD. Estrogen has been shown to both improve and worsen symptoms. Much of the older literature in this field points to estrogen as an anti-dopaminergic agent (Koller et al., 1982; Quinn and Marsden, 1986). A case was reported in which PD symptoms improved with pharmacologically induced menopause (Session et al., 1994). On the other hand, there are more recent and numerous reports of estrogen improving the motor symptoms of PD. In a randomized placebo-controlled study of oral conjugated estrogen, patients receiving estrogen had significantly more “on” time and a clinically significant decrease in motor scores over 8 weeks of treatment (Tsang et al., 2000). In the POETRY study, a pilot study of HRT in postmenopausal women with PD, there was a trend toward improvement in motor scores, however this did not reach statistical significance and the study was limited by under-enrollment (Anon, 2011).

Animal studies of neuroprotection by estrogen and progesterone

Estrogen is likely a contributor to the sex differences observed in PD prevalence. As discussed above, longer estrogen exposure during a female's lifetime may decrease the risk of PD. Most women develop PD after menopause, which suggests that estrogen withdrawal may be related to the pathogenesis of the disease. Furthermore, estrogen appears to protect against dopaminergic neuron loss in both disease and non-disease states. It has been shown that dopaminergic neuron loss occurs after ovariectomy in rats and primates (Le Saux and Di Paolo, 2006) and this can be reversed with administration of estrogen compounds. A study in monkeys demonstrated that estradiol altered DA metabolism and transporter uptake in the brain after surgically induced menopause (Morissette and Di Paolo, 2009). Interestingly, this post-ovariectomy DA loss also manifests clinically as decreased spontaneous locomotor activity in rats, which can be reversed with administration of exogenous estrogen (Ohtani et al., 2001). Although the clinical manifestations of post-menopausal DA loss have not been studied in non-parkinsonian human females, a small pilot study showed that estrogen replacement therapy in non-parkinsonian women increased putamenal dopamine active transporter (DAT) as measured by TRODAT SPECT scan (Gardiner et al., 2004). With evidence pointing more consistently to estrogen as a pro-dopaminergic agent, as well as exciting implications for estrogen as a neuroprotective agent in ischemia and other neuropathologic processes, there has been a great deal of research into estrogen's potential neuroprotective effects on dopaminergic neurons. The majority of this research has utilized animal neurotoxin-mediated models of PD. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a by-product of meperidine synthesis that is well known to cause parkinsonism in humans, and is probably the most widely utilized animal model for PD. Male mice are more sensitive to MPTP, in terms of striatal dopaminergic neuron loss, than female mice (Dluzen et al., 1996). Methamphetamine (MA) also causes degeneration of striatal dopaminergic neurons in animals and humans, and has a greater negative effect on male mice compared to female mice (Miller et al., 1998). If estrogen accounts for this differential susceptibility, then exogenous estrogen administration should be able to further protect from DA neuron loss in these PD animal models. This hypothesis has been studied extensively and the results are summarized in Tables 1.1–1.4. Overall, certain formulations of estrogen