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Review

Neuroactive gonadal drugs for neuroprotection in male and female models of Parkinson's disease

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ABSTRACT

The existence of sex differences in Parkinson's disease (PD) incidence is well documented with greater prevalence and earlier age at onset in men than in women. These reported sex differences could be related to estrogen exposure. In PD animal models, estrogen is well documented to be neuroprotective against dopaminergic neuron loss induced by neurotoxins. Using the 1-methyl 4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) mouse model, we showed that several compounds are neuroprotective on dopaminergic neurons including estrogen, the selective estrogen receptor modulator raloxifene, progesterone, dehydroepiandrosterone, the estrogen receptor alpha (ERα) agonist PPT as well as the G protein-coupled membrane estrogen receptor (GPER1) specific agonist G1. Accumulating evidence suggests that GPER1 could be implicated in the neuroprotective effects of estrogen, raloxifene and G1 in collaboration with ERα. We recently reported that the 5α-reductase inhibitor Dutasteride is also neuroprotective and could bring an alternative to estrogens for therapy in male. Additional studies are needed to optimize therapies with these gonadal drugs into safe personalized treatments according to sex for treatment of PD.

Contents

1. Parkinson's disease: treatments and progression

Parkinson's disease (PD) is a multisystemic disorder characterized by motor symptoms consisting of a combination of rest tremor, rigidity, bradykinesia and postural abnormalities (Stacy, 2009). It is linked to the degeneration of dopamine (DA) neurons in the substantia nigra pars compacta (SN*pc*) (Lang, 2007). Besides these motor symptoms, non-motor symptoms include a variety of cognitive, neuropsychiatric, sleep, autonomic and sensory disturbances (Park and Stacy, 2009) and are related to the degeneration of other neuronal groups as serotoninergic neurons of the raphe nucleus, noradrenergic neurons of the locus coeruleus or cholinergic neurons of the nucleus basalis of Meynert (Lang, 2007). Although there are a number of treatments available for

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parkinsonian patients, they are symptomatic. Levodopa (L-dopa) therapy remains the most effective symptomatic therapy in the treatment of PD; it is co-administered with peripheral decarboxylase inhibitors. Catechol-O-methyl transferase and monoamine oxidase-B (MAO-B) inhibitors that inhibit the main pathways responsible for DA degradation are also used in order to extend DA plasma half-life (Hickey and Stacy, 2011). This strategy allows a L-dopa dose reduction as well as a more continuous delivery of L-dopa to the brain (Stocchi, 2005).

In the early stages of PD, parkinsonian symptoms are well controlled, as the DA neurons are still functional and able to store and release DA, thus avoiding fluctuations in plasma L-dopa concentration. Due to the progression of the disease and loss of DA neurons, striatal DA levels become dependent on the availability of peripherally administered L-dopa (Olanow et al., 2006). The L-dopa concentration is not well regulated resulting in abnormal pulsatile stimulation of striatal DA receptors that induce further disruption of motor control pathways (Sujith and Lane, 2009). The major limitation to the chronic use of L-dopa is associated with the development of motor complications (Stacy, 2009). These complications affect about 50% of L-dopa-treated patients who have been treated for more than 5 years (Fahn, 2000), in 80% of patients treated for 10 years (Schrag, 2000), and are more likely to occur in patients with young disease onset (Golbe, 1991). Long-term use of L-dopa is characterized by a change in response of the patients to the drugs. Duration of the antiparkinsonian effect of L-dopa becomes progressively shorter which leads to fluctuations in motor functions including end-of-dose deterioration, alternating between «on» and «off» responses and involuntary movement as dyskinesia and dystonia (Stacy and Galbreath, 2008). Although the etiology of motor complications is not fully understood, several studies suggest that they are related in part to abnormal pulsatile dopaminergic stimulation (Bastide et al., 2015). DA agonists offer an important alternative in the treatments of PD with long-term data supporting their efficacy and safety (Stacy and Galbreath, 2008). When DA therapies are compared in subjects initially treated with L-dopa, there is higher incidence of dopaminergic motor complications while DA agonists are associated with higher incidence of side effects such as hallucinations, edema, somnolence, and abnormal sexual behavior (Stacy and Galbreath, 2008) while motor fluctuations are less common with these agonists (Hauser et al., 2007; Investigators, 2009). Several clinical trials investigated whether antiparkinsonian therapies have an effect on progression of the disease (Fahn and the Parkinson Study Group, 2005; Morrish, 2003; Parkinson Study Group, 2000; Schapira et al., 2010; Whone et al., 2003). However, there was no proven neuroprotective nor disease-modifying activities associated with these therapies. It is worth noting that MAO-B inhibitors have aroused interest as possible disease-modifying drugs from their ability to slow striatal DA metabolism. The selective MAO-B inhibitors Selegiline and Rasagiline have been reported to exhibit neuroprotective effects *in vitro* and in *in vivo* studies (Jenner, 2004). The DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) study has initially showed that Selegiline could safely delay the introduction of the L-dopa therapy (Parkinson Study Group, 1993). However, this effect was due to symptomatic effects of Selegiline (Olanow and Calne, 1992). Furthermore, Selegiline metabolites could induce toxic effects (Okuda et al., 1992). Similarly, Rasagiline has been studied in clinical trials to assess its neuroprotective effect against PD. The results of the TEMPO (TVP-1012 in Early Monotherapy for Parkinson's Disease Outpatients) and ADAGIO (the Attenuation of Disease Progression with Azilect Given Once Daily) studies suggest a potential disease-modifying activity of early Rasagiline treatment compared to later introduction of the drug (Olanow et al., 2008; Parkinson Study Group, 2002). Given the accumulating evidence, a neuroprotective and disease-modifying effects of the selective MAO-B inhibitors should be considered.

Besides dopaminergic medications, anticholinergics and the N-methyl-D-aspartate receptor antagonist amantadine are used for treatment of PD (Connolly and Lang, 2014); these therapies are only symptomatic with no proven effect on disease progression.

The unmet need for neuroprotective therapeutics is more relevant than ever given the progression and disability of the disease.

2. Parkinson's disease and gonadal hormones

The existence of sex disparities in PD incidence is now well documented with both the prevalence and the incidence of the disease higher in men than in women (Baldereschi et al., 2000; Shulman and Bhat, 2006; Swerdlow et al., 2001; Taylor et al., 2007; Van Den Eeden et al., 2003; Wooten et al., 2004) (Table 1). In a recent review and meta-analysis, a significant difference in prevalence by sex was reported with a lower prevalence of the disease in women than in men in the 50–59-year age group (Pringsheim et al., 2014). These reported sex differences could be due to effects of the circulating neuroprotective hormone estradiol, which is associated with a lower susceptibility to develop PD (Popat et al., 2005; Ragonese et al., 2004; Saunders-Pullman et al., 1999).

To further investigate this hypothesis, several clinical reports have investigated the correlation between estrogen exposure and PD risk (Benedetti et al., 2001; Currie et al., 2004; Liu et al., 2014; Marder et al., 1998; Popat et al., 2005; Ragonese et al., 2004; Simon et al., 2009). Most but not all the studies reported a neuroprotective effect of endogenous or exogenous estrogen on the risk of PD and disease progression. Longer fertile lifespan and later age at menopause were associated with later age at onset of PD (Haaxma et al., 2007; Nitkowska et al., 2014; Ragonese et al., 2004) and less severe motor impairment in women with PD (Cereda et al., 2013). By contrast, when women undergo premature menopause *via* bilateral oophorectomy, consisting in removing the ovaries, there was a significantly increased risk of PD (Benedetti et al., 2001; Rocca et al., 2008). Hence, a relationship between the duration of endogenous estrogen exposure and the susceptibility to develop PD could exist in women. Currie et al. also suggest that postmenopausal estrogen replacement therapy may decrease the risk of developing PD in women only when given in the early stages of the disease (Currie et al., 2004). However, this was not the case in a group of women where the use of estrogen replacement therapy did not affect the risk of PD, but did show a protective effect for the development of PD with dementia (Marder et al., 1998). Similarly, preliminary findings in the Nurses' Health Study found no beneficial effect of endogenous or exogenous estrogens exposure on risk of PD (Simon et al., 2009). It remains unclear what level of estrogen exposure could affect the risk of developing PD in women. It is worth noting that all the studies assessed the possible neuroprotective effect of exogenous estrogens without differentiating formulation types. It is in this perspective that Lundin et al. analyzed the effect of different formulations of hormone therapy on the risk of PD (Lundin et al., 2014). Results of this study highlighted differences in risk of PD in women depending on the hormones therapy with increased risk of PD associated with esterified estrogen use in combination with synthetic progestin while no risk was associated with conjugated estrogen combined with progestin (Lundin et al., 2014). Rocca et al. suggested that the increased risk of PD associated with oophorectomy might partly be explained by a deficit in progesterone (P) and testosterone (T) rather than in estrogen although the possible neuroprotective effects of P and T on the risk of PD remain unexplored (Rocca et al., 2008). It has been clearly demonstrated in an animal model of PD that estrogen and natural P are