Frontiers in Neuroendocrinology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review

Sex differences in Parkinson's disease

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Sex differences
Parkinson's disease
Nigrostriatal dopaminergic pathways
Sex hormones
Neuroprotection

ABSTRACT

Parkinson's disease (PD) displays a greater prevalence and earlier age at onset in men. This review addresses the concept that sex differences in PD are determined, largely, by biological sex differences in the NSDA system which, in turn, arise from hormonal, genetic and environmental influences. Current therapies for PD rely on dopamine replacement strategies to treat symptoms, and there is an urgent, unmet need for disease modifying agents. As a significant degree of neuroprotection against the early stages of clinical or experimental PD is seen, respectively, in human and rodent females compared with males, a better understanding of brain sex dimorphisms in the intact and injured NSDA system will shed light on mechanisms which have the potential to delay, or even halt, the progression of PD. Available evidence suggests that sex-specific, hormone-based therapeutic agents hold particular promise for developing treatments with optimal efficacy in men and women.

1. Introduction

One's sex is increasingly recognised as a factor which influences the incidence and/or nature of all major complex diseases, including neurodegenerative and neuropsychiatric disorders. This, in turn, may be determined by biological sex differences in brain organisation, structure and function, which are determined genetically and epigenetically (Gabory et al., 2009; Kaminsky et al., 2006; McCarthy et al., 2009; Cahill, 2006). This review will consider these phenomena in relation to Parkinson's disease (PD), numerous aspects of which strongly support the urgent need for a better understanding of brain sex dimorphisms in the intact and injured brain, in order to design improved therapies with optimal efficacy in male and female patients alike.

2. Parkinson's disease: differences between men and women

2.1. Aetiology and pathology of PD

PD is the second most common neurodegenerative disorder, affecting approximately 0.3% of people in the developed world. This rises rapidly to 3% for individuals over the age of 65 years, to demonstrate that advanced age comprises a major risk factor (Dexter and Jenner, 2013). In addition, such figures highlight the increasing burden that treatment of PD place on health care systems worldwide, as the population life-expectancy increases in several countries. Clinically, PD is a movement disorder that is characterised by motor symptoms such as bradykinesia with rigidity, tremor at rest, gait disturbances and difficulty in swallowing and producing speech. Non-motor symptoms associated with the disorder include anxiety, depression, insomnia, dementia, autonomic dysfunction and constipation, which can often reduce patients' quality of life even more significantly than motor aspects (Weintraub et al., 2008; Jenner et al., 2013). A major pathological lesion associated with PD is the loss of midbrain dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNc) and the consequent loss of DA input to the caudate nucleus and putamen (the striatum). This nigrostriatal DA (NSDA) pathway plays a central role in regulating fine motor control, and its degeneration thus leads to the primary motor symptoms of PD. In up to approximately 10% of cases, rare familial genetic mutations have been identified as causing PD. However the vast majority of cases are of unknown cause and are termed idiopathic or sporadic (Klein and Schlossmacher, 2007). Yet, studies have begun to cast light on the cellular and molecular processes which may underlie the degeneration of the NSDA system. Putative pathological substrates include but are not limited to mitochondrial dysfunction (Vives-Bauza et al., 2010; Pienaar and Chinnery, 2013) accompanied by the excessive production of radical oxygen species (Mattson, 2006), the formation of protein aggregates, termed Lewy bodies(principally composing of α-synuclein and ubiquitin) within the surviving DAergic neurons and microglial inflammation (Halliday and Stevens, 2011). Collectively, these observations support the general concept that PD is a complex disease, representing a clinical syndrome with an aetiology that is likely to comprise of

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http://dx.doi.org/10.1016/j.yfrne.2014.02.002
0091-3022/

interactions between multiple genetic factors, the environment, the immune system and aging (Jenner et al., 2013; Klein and Schlossmacher, 2007).

2.2. Sex differences in PD

After aging, epidemiological studies have revealed the male sex as a prominent risk factor for developing PD at all ages and for all nationalities studied. Reports of male to female ratios for incidence rates vary from 1.37 to 3.7 (Baldereschi et al., 2000; Swerdlow et al., 2001; Van Den Eeden et al., 2003; Wooten et al., 2004; Shulman and Bhat, 2006; Taylor et al., 2007), with a large meta-analysis study suggesting that, in any specific time-frame, twice as many men than women suffer from PD (Elbaz et al., 2002).

2.2.1. Clinical profile of PD

In addition to differences in its prevalence in men and women, many studies have reported sex differences in the clinical profile of PD. For example, some studies report that the age of onset of PD is approximately 2 years later in women compared with men (Haaxma et al., 2007; Alves et al., 2009). Although earlier work contradicted this finding (Baba et al., 2005), such discrepancies can be explained, at least in part, by sex differences in disease presentation. For example, several studies suggest that females present with a milder PD phenotype, which is most notable in the early clinical stages, especially prior to the introduction of anti-parkinsonian medication (Shulman and Bhat, 2006; Haaxma et al., 2007; Miller and Cronin-Golomb, 2011). Compared to men, women are also reported to present more often with tremor, a symptom that correlates both with a later age of onset and a slower rate of decline of motor impairment (Haaxma et al., 2007). Other symptoms that were found to be more prevalent in women than in men include nervousness, sadness, depression and constipation, whereas men suffered more from daytime sleepiness, dribbling and sex-related symptoms (Martinez-Martin and Falup, 2012). Rigidity and rapid eye movement behaviour disorder occurs more frequently in men, whereas women are more likely to have dyskinesias and PD-associated depression than men (Martinez-Martin and Falup, 2012). A sex-specific pattern is also emerging for PD-associated cognitive changes, with deficits in verbal fluency and recognition of facial emotions being more prevalent in men, whilst a reduction in visuospatial cognition occur more frequently in women (Miller and Cronin-Golomb, 2011). Additionally, the efficacy, tolerability and pharmacokinetics of drugs used for treating PD appear to differ in men versus women (Shulman and Bhat, 2006).

In support of the notion that sex differences in disease susceptibility may be determined, at least in part, by biological sex differences in various affected brain regions, a number of differences in motor and sensory functions, which rely on the NSDA system have been noted in healthy men and women. For example, in tests of fine motor control and speech articulation, women generally outperform men (Jennings et al., 1998). The advent of real-time *in vivo* imaging techniques also provides direct evidence for innate differences in NSDA transmission in men and women. These include differences in basal striatal DAergic neuron dynamics (Pohjalainen et al., 1998; Lavalaye et al., 2000; Kaasinen et al., 2001; Mozley et al., 2001; Laakso et al., 2002), amphetamine-stimulated DA release (Munro et al., 2006) and sex-related differences in the functional relationship between regional DA release and motor performance, affect and cognitive function (Mozley et al., 2001; Riccardi et al., 2011). Sex differences in the healthy NSDA system are further corroborated by evidence discussed below from gene profiling studies (Section 2.2.2) and the discovery that the *SRY* gene (sex determining region on the Y sex chromosome) is expressed in SNc DA neurons in humans (Section 2.3.1) as well as rodents (Section 6.1).

2.2.2. Molecular pathology of PD

New technologies which enable dissection of the molecular pathology of PD are beginning to provide a more objective analysis of underlying sexual dimorphisms. For example, the SNc DAergic neurons are identifiable in post-mortem brains, due to their dark neuromelanin pigmentation. This uniquely enables single-cell laser capture micro-dissection of this neuronal population, and has been coupled with microarray analysis of DNA in order to investigate gene expression profiles obtained from post-mortem brains of control subjects with individuals who, in life, had been diagnosed with late-stage idiopathic PD (Simunovic et al., 2011; Cantuti-Castelvetri et al., 2007). In the normal brain, genes involved in signal transduction and neuronal maturation were up-regulated in women, whereas genes implicated in PD pathogenesis, when harbouring specific mutations (e.g. α-synuclein and PINK-1), were up-regulated in men. In the DAergic neurons surviving in PD-affected brains, changes in the expression of genes encoding for protein kinase activity and genes associated with proteolysis and Wnt signalling predominated in women, whereas predominant expressional changes for genes involved in protein- and copper-binding activities occurred in men (Simunovic et al., 2011; Cantuti-Castelvetri et al., 2007). These studies demonstrate that gene expression profiles in normal SNc DAergic neurons are sex-specific and suggest a bias in males which may underlie the predisposition to develop PD. They also indicate that adaptive processes in the surviving DAergic neurons proceed via different mechanisms in males and females, suggesting that the nature of the disease, and potentially the response to treatment, may be sex-specific.

Collectively, clinical and molecular studies clearly support the notion that women are relatively protected from PD compared with men. They also underscore the need for a better knowledge of the basis of sex differences in PD. Investigations into the pathophysiology underlying sex differences in the presentation, progression and treatment responses in PD are in their infancy, but offer considerable potential for improving clinical assessment and treatment of the disease.

2.3. Genetic and epigenetic factors contributing to sex bias in PD

The influence of genetic and epigenetic factors underlying disease is a vast subject, and this section will briefly focus only on areas of relevance to sex differences in PD. Environmental factors, which can alter the epigenetic signature, shall be considered, and in this context, sex and sex hormones, as well as stress and stress hormones, can be included as environmental factors since hormonal effects include DNA methylation and histone modifications, thereby altering epigenetic regulation of autosomal genes and potentially influencing differential susceptibility to complex diseases (Kaminsky et al., 2006).

2.3.1. Genes

The genetics of PD is a rapidly growing field. To-date, mutations in at least 17 different genes have been identified as the cause of the rare familial forms of the disease (Dexter and Jenner, 2013). These genes often encode proteins that are associated with molecular pathways that are affected in sporadic forms of the disease. For example, mutations in the gene encoding α-synuclein accounts for only a very small proportion of familial PD. Yet protein aggregations containing α-synuclein (Lewy bodies) comprise a diagnostic pathology related to the final stages of DA neuronal loss in idiopathic PD and indicate altered protein aggregation as a contributory cause. Other mutations causing familial variants of PD involve genes that protect against mitochondrial dysfunction (PINK-1) and oxidative stress (DJ-1), all of which are pathological processes that have been implicated in idiopathic PD. However,

Please cite this article in press as: Gillies, G.E., et al. Sex differences in Parkinson's disease. Front. Neuroendocrinol. (2014), http://dx.doi.org/10.1016/j.yfrne.2014.02.002