Environmental Toxicology and Pharmacology 78 (2020) 103412

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

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

Nigral and ventral tegmental area lesioning induces testicular and sperm morphological abnormalities in a rotenone model of Parkinson's disease

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ARTICLE INFO

Keywords:
Parkinson's disease
Testicular pathology
Nigrostriatal degeneration
Sperm abnormalities
Neural-hypothalamic-testicular circuit
Acetylcholinesterase

ABSTRACT

Although sexual health is affected by Parkinson's disease (PD), the effect on testicular health and/or sperm quality is not well discussed. After 21 days of rotenone lesioning, we observed dopaminergic neuronal degeneration in the substantia nigra and hypothalamus. There were minimal SPACA-1-expressing epididymal spermatozoa with morphological abnormalities, scanty luminal spermatozoa and reduced testicular spermatids and post-meiotic germ cells indicating hypospermatogenesis. Occludin-expressing sertoli cells were dispersed over a wide area indicating compromised blood-testes barrier. Activated caspase-3 expression was intense while immunoreactivity of spermatogenic-enhancing SRY and GADD45 g was weak. Although serum follicle stimulating hormone level was not affected, the lesion was associated with reduced serum testosterone level, testicular oxidative damage and inhibition of acetylcholinesterase activity, even when rotenone was not detected in the testes. Together, dopaminergic lesions may mediate testicular and sperm abnormalities via the brain-hypothalamic-testicular circuit independent of the pituitary, thereby establishing a causal link between Parkinsonism and reproductive dysfunction.

1. Introduction

Parkinson's disease (PD) is a widespread neurological condition that affects the capacity of the brain's nigrostriatal fibers to produce dopamine (DA) due to progressive degeneration (Kalia and Lang, 2015). PD, which infrequently affects women, manifests as behavioral deficits including trembling of extremities, muscle stiffness, impaired balance and slowness of movement that significantly reduce the quality of life (Ostrem and Galifianakis, 2010). Epidemiological reports have strongly implicated environmental toxicants, including rotenone-containing insecticides and herbicides in the etiology of PD (Tanner et al., 2011). Many aspects of life requiring motor functions, including sexual health, have also been reported to be hugely affected in PD (Kuhlman et al., 2019; Moore et al., 2002). For instance, sexual dysfunctions involving reduced libido, erectile dysfunction, premature or inability to ejaculate and/or reduced frequency of lovemaking are common issues reported by 70–80% of Parkinsonians (Bhattacharyya and Rosa-Grilo, 2017). Indeed, palliative management of PD involving enrichment of striatal DA and improvement of motor imbalance often results in hypersexuality (Weintraub et al., 2010). This suggests a cause-effect relationship between dopamine deficiency and sexual issues, apart from the direct contribution of psychosocial effect of the disease on individuals with PD. However, little is known of the relationship between PD and testicular/sperm health, a significant determinant of infertility.

Increased susceptibility of males to PD (Cantuti-Castelvetri et al., 2007; Carruth et al., 2002) and associated motor deficits have been linked to sex-dependent regulation of dopamine synthesis in nigrostriatal fibers by sex-determining region on Y chromosome (SRY) (Dewing et al., 2006). SRY colocalizes with DA neurons in the substantia nigral pars compacta (SNc), where it directs the transcription of a battery of genes involved in DA synthesis including tyrosine hydroxylase, monoamine oxidases, dopamine receptors and L-Dopa decarboxylase (Czech et al., 2012; Wu et al., 2009). SRY knockdown in a neurotoxin-induced male dopaminergic M-17 cells results in enhanced production of reactive oxygen species, apoptosis and cell injury whereas ectopic upregulation of SRY expression confers significant

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https://doi.org/10.1016/j.etap.2020.103412
Received 4 February 2020; Received in revised form 26 April 2020; Accepted 12 May 2020
Available online 18 May 2020
1382-6689/