Neuropharmacology 62 (2012) 115–124

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

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

Review

Anxiety in Parkinson's disease: A critical review of experimental and clinical studies

Rui D.S. Prediger[a,b,*], Filipe C. Matheus[a], Marcelo L. Schwarzbold[b], Marcelo M.S. Lima[c], Maria A.B.F. Vital[d]

[a] Departamento de Farmacologia, Centro de Ciências Biológicas, Universidade Federal de Santa Catarina (UFSC), 88049-900 Florianópolis, SC, Brazil
[b] Centro de Neurociências Aplicadas (CeNAp), Hospital Universitário, Universidade Federal de Santa Catarina (UFSC), 88040-900 Florianópolis, SC, Brazil
[c] Departamento de Fisiologia, Universidade Federal do Paraná (UFPR), 81531-990 Curitiba, PR, Brazil
[d] Departamento de Farmacologia, Universidade Federal do Paraná (UFPR), 81531-990 Curitiba, PR, Brazil

ARTICLE INFO

Article history:
Received 30 April 2011
Received in revised form
22 August 2011
Accepted 23 August 2011

Keywords:
Parkinson's disease
Anxiety
Clinical studies
Animal models
Review

ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting about 1% of the population older than 60 years. Classically, PD is considered as a movement disorder, and its diagnosis is based on the presence of a set of cardinal motor signs that are the consequence of a pronounced death of dopaminergic neurons in the substantia nigra pars compacta. There is now considerable evidence showing that the neurodegenerative processes leading to sporadic PD begin many years before the appearance of the characteristic motor symptoms, and that additional neuronal fields and neurotransmitter systems are also involved in PD, including olfactory structures, amygdala, caudal raphe nuclei, *locus coeruleus,* and hippocampus. Accordingly, adrenergic and serotonergic neurons are also lost, which seems to contribute to the anxiety in PD. Non-motor features of PD usually do not respond to dopaminergic medication and probably form the major current challenge in the clinical management of PD. Additionally, most studies performed with animal models of PD have investigated their ability to induce motor alterations associated with advanced phases of PD, and some studies begin to assess non-motor behavioral features of the disease. The present review attempts to examine results obtained from clinical and experimental studies to provide a comprehensive picture of the neurobiology and current and potential treatments for anxiety in PD. The data reviewed here indicate that, despite their high prevalence and impact on the quality of life, anxiety disorders are often under-diagnosed and under-treated in PD patients. Moreover, there are currently few clinical and pre-clinical studies underway to investigate new pharmacological agents for relieving these symptoms, and we hope that this article may inspire clinicians and researchers devote to the studies on anxiety in PD to change this scenario.

This article is part of a Special Issue entitled 'Anxiety and Depression'.

1. Introduction

The prevalence of Parkinson's disease (PD) is generally estimated at 0.3% of the entire population and at about 1% of people over 60 years of age (Mayeux, 2003). Since the incidence of the disease increases with age (the most important risk factor), it is likely that the number of people suffering from PD will rise steadily in the future. Overall, the annual economic impact of PD in the United States is estimated at $10.8 billion, 58% of which is related to direct medical costs (O'Brien et al., 2003).

Classically, PD is considered as a movement disorder, and its diagnosis is based on the presence of a set of cardinal motor signs (e.g. rigidity, bradykinesia, rest tremor, and postural reflex disturbance). These symptoms of PD mainly result from the progressive and profound loss of neuromelanin-containing dopaminergic neurons in the substantia nigra pars compacta (SNpc) with

Abbreviations: BLA, basolateral nucleus of the amygdala; BDZs, benzodiazepines; CNS, central nervous system; DSM, Diagnostic and Statistical Manual of Mental Disorders; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; EPM, elevated plus maze; GABA, gamma-aminobutyric acid; HVA, homovanillic acid; HPLC, high performance liquid chomatography; 6-OHDA, 6-hydroxydopamine; 5-HIAA, 5-hydroxyindoleacetic acid; ICDs, impulse control disorders; mGluRs, metabotropic glutamate receptors; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MFB, medial forebrain bundle; MAO-B, monoamine oxidase B; NMDA, N-methyl-d-aspartate receptor; NA, noradrenaline; NSRIs, noradrenaline and serotonin reuptake inhibitors; PD, Parkinson's disease; RCTs, randomized controlled trials; SSRIs, selective serotonin reuptake inhibitors; 5-HT, serotonin; 5-HT1A, serotonin receptor type 1A; 5-HT2A/2C, serotonin receptors types 2A and 2C; SN, substantia nigra; SNpc, substantia nigra pars compacta; TCAs, tricyclic antidepressants; TH, tyrosine hydroxylase; VTA, ventral tegmental area; VMAT-2, vesicular monoamine transporter-2.

* Corresponding author. Departamento de Farmacologia, Universidade Federal de Santa Catarina, Campus Trindade, 88049-900 Florianópolis, SC, Brazil. Tel.: +55 48 3721 9491; fax: +55 48 3337 5479.
E-mail address: ruidsp@hotmail.com (R.D.S. Prediger).

0028-3908/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropharm.2011.08.039

presence of eosinophillic, intracytoplasmic, proteinaceous inclusions termed as Lewy bodies and dystrophic Lewy neurites in surviving neurons (Hirsch et al., 1988).

Dopamine (DA)-replacement therapy has dominated the treatment of PD since the early 1960s and although the currently approved anti-parkinsonian agents offer effective relief of the motor deficits, especially in the early/moderate stages of the disease, they have not been found to alleviate the underlying dopaminergic neuron degeneration and drug efficacy is gradually lost (Allain et al., 2008). Moreover, the dopaminergic therapy in PD is based on the importance of nigral dopaminergic cell loss, the ensuing striatal DA depletion, and the onset of motor symptoms. However, there is now considerable evidence showing that the neurodegenerative processes leading to sporadic PD begin many years before the appearance of the characteristic motor symptoms, and additional neuronal fields and neurotransmitter systems are also involved in PD, including the anterior olfactory structures, amygdala, dorsal motor nucleus of vagus, caudal raphe nuclei, *locus coeruleus*, autonomic nervous system, hippocampus, and cerebral cortex (Braak et al., 2004). Accordingly, cholinergic, adrenergic and serotonergic neurons are also lost, which seems to contribute to the appearance of non-motor symptoms of PD encompassing olfactory and memory impairments, sleep abnormalities, anxiety and depression, as well as gastrointestinal disturbance, which in many cases precede the manifestation of motor symptoms (Chaudhuri et al., 2006).

Remarkably, systematic reviews have indicated non-motor symptoms (including depression and anxiety) as major factors in determining health-related quality of life, progression of disability, and nursing home placement in PD patients (Den Oudsten et al., 2007; Soh et al., 2011). Moreover, non-motor features of PD usually do not respond to dopaminergic medication and probably form the major current challenge faced in the clinical management of PD (Chaudhuri et al., 2006). As illustrated in Fig. 1, over the past 30 years (and particularly in the last decade) an increasing number of studies has been devoted to the investigation of anxiety in both PD patients and animal models of PD.

Theories related to the etiology of anxiety symptoms in PD argue that they are "reactive" and secondary to the psychosocial stress of a chronic disease and the associated disability. On the other hand, there is increasing evidence that psychological symptoms could be a result from neurochemical changes that occur due to the neurodegeneration even during early pre-motor phases of PD. In many cases, anxiety disorders may precede or be accompanied by depression and, in such cases, even when the depression is treated anxiety may remain (Marsh, 2000). However, despite their high prevalence, anxiety disorders are often under-diagnosed and under-treated in PD patients (Leentjens et al., 2011a).

Interventions for psychological symptoms in PD patients received not as much attention as that for motor symptoms in PD patients, and thus, much of the information and management strategies presented are based on observational studies, expert opinion, or clinical guidelines for a condition in patients without PD, but few have been studied extensively in randomized controlled trials (RCTs).

On the other hand, a valid animal model is helpful for screening potential drugs in pre-clinical study and for developing new therapeutic methods for PD. In this context, recent pre-clinical findings have indicated that, through the use of low doses or specific routes of

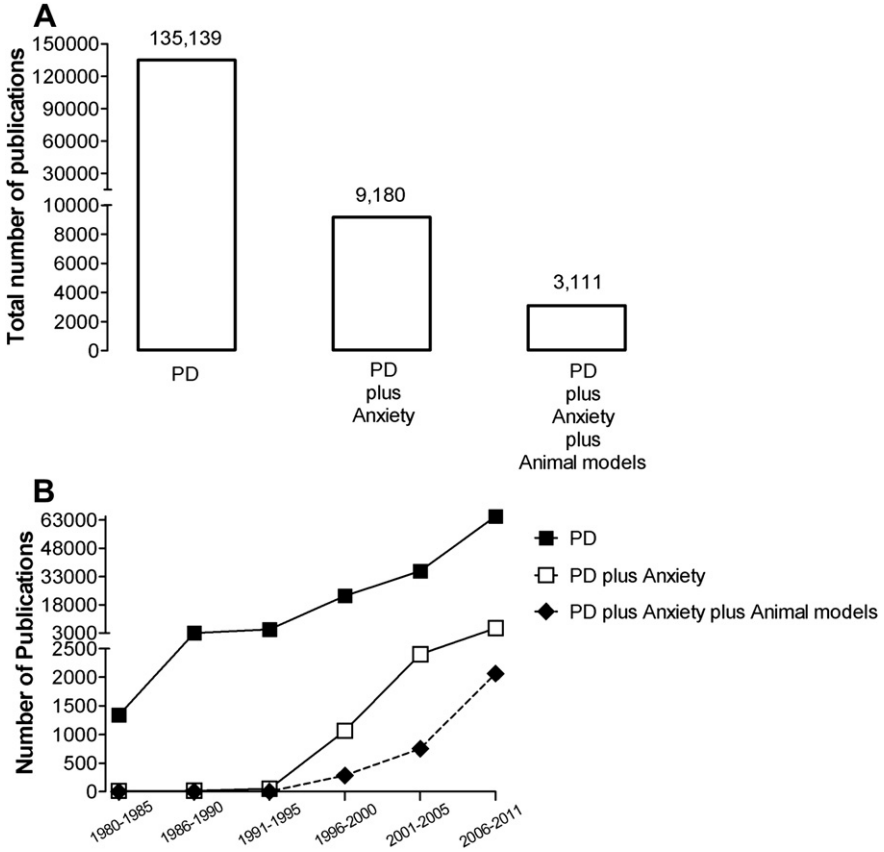

Fig. 1. Number of publications containing the keywords "Parkinson's disease" (PD), "PD plus Anxiety", and "PD plus Anxiety plus Animal Models" found in the SCOPUS databases. Panel A illustrates the total number of publications (time spam "all years") obtained for the queries. A time-line concerning the publications from year 1980 until July 15th of the year 2011 obtained from SCOPUS databases is shown in panel B.