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Review

Dyskinesias and impulse control disorders in Parkinson's disease: From pathogenesis to potential therapeutic approaches

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ABSTRACT

Dopaminergic treatment in Parkinson's disease (PD) reduces the severity of motor symptoms of the disease. However, its chronic use is associated with disabling motor and behavioral side effects, among which levodopa-induced dyskinesias (LID) and impulse control disorders (ICD) are the most common. The underlying mechanisms and pathological substrate of these dopaminergic complications are not fully understood. Recently, the refinement of imaging techniques and the study of the genetics and molecular bases of LID and ICD indicate that, although different, they could share some features. In addition, animal models of parkinsonism with LID have provided important knowledge about mechanisms underlying such complications. In contrast, animal models of parkinsonism and abnormal impulsivity, although useful regarding some aspects of human ICD, do not fully resemble the clinical phenotype of ICD in patients with PD, and until now have provided limited information. Studies on animal models of addiction could complement the previous models and provide some insights into the background of these behavioral complications given that ICD are regarded as behavioral addictions. Here we review the most relevant advances in relation to imaging, genetics, biochemistry and pharmacological interventions to treat LID and ICD in patients with PD and in animal models with a view to better understand the overlapping and unique maladaptations to dopaminergic therapy that are associated with LID and ICD.

Contents

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide, with a prevalence of 1.43% in people older than 60 years. Although it is clinically characterized by motor impairment, the cardinal signs of which are rigidity, resting tremor and bradykinesia, emotional and cognitive disturbances (i.e. apathy, depression, executive dysfunction, etc.) are also frequent (Rodriguez-Oroz et al., 2009). Several neuronal systems degenerate in PD, but it is the abnormal dopaminergic modulation of the basal ganglia (BG)–cortex networks, derived from the neuronal death in the substantia nigra *pars compacta* (SNc) and, to a lesser extent, in the ventral tegmental area (VTA), that leads to the emergence of these clinical features (Rodriguez-Oroz et al., 2009).

The BG structures are a group of interconnected subcortical nuclei (i.e. striatum, globus pallidum, subthalamic nucleus and substantia nigra) with a complex functional organization. They are anatomically and physiologically subdivided into interconnected areas which constitute the motor, oculo-motor, associative and limbic circuits according to their main cortical projection areas (Alexander et al., 1986; Parent and Hazrati, 1995; Haber, 2003; Obeso et al., 2008a,b, 2014; Tremblay et al., 2015). Within this organization, the dorsal region of each nucleus is connected to motor and premotor cortical areas (motor circuit), whereas the ventral areas are linked to the cingulate and orbital cortices in the limbic circuit. The medial regions of the BG are also connected with the orbitofrontal (OFC) and prefrontal cortex (PFC, associative circuit). Thus, the BG are not only involved in the control of movement, but also in associative functions such as learning and planning processes, and in the regulation of emotion and appetite.

The dopaminergic system plays a key role in the functional regulation of these cortical–BG–cortical circuits, acting through three main pathways. The nigrostriatal pathway, formed by projections from the SNc to the dorsal striatum, mainly to the putamen, is essential for the correct execution of movements in addition to participating in reward and learning (Wise, 2009; Haber, 2014). In the mesocortical and mesolimbic pathways, the dopaminergic neurons of the VTA project to different areas of the brain, in particular to the PFC and ventral regions of the striatum (i.e. nucleus accumbens, NAc), which are involved in the reinforcement of behaviors, reward-guided behaviors, working memory and attention and in motor execution (Amalric and Koob, 1993; Beninger, 1983; Nieoullon, 2002; Wise, 2004; Haber, 2014).

3,4-Dyhydroxyphenylalanine (levodopa), which is the precursor of dopamine (DA), is the most effective treatment to alleviate the motor symptoms of PD (Fabbrini et al., 2007). However, its chronic use leads to the induction of motor fluctuations and levodopa-induced dyskinesias (LID), with a prevalence of more than 80% after 10 years of treatment (Fabbrini et al., 2007). LID are involuntary, purposeless, irregular movements, which are mainly choreic and coincide with the anti-parkinsonian benefit of levodopa. The pathophysiology of LID is not well known, but the pulsatile stimulation of DA receptors invariably associated with multiple daily doses of levodopa (Olanow et al., 2006) is a critical factor.

In the past decades, new pharmacological strategies aimed at providing more continuous drug delivery, such as the long half-life dopaminergic agonists, have been shown to have a less dyskinesogenic profile (Rascol et al., 2000). In fact, almost all patients with PD are treated with levodopa within a few years of evolution, with most of them receiving a combination of levodopa and dopaminergic agonists afterward (Connolly and Lang, 2014; Jenner, 2015). However, it is now recognized that the chronic use of dopaminergic agonists can prompt the development of behavioral disorders. Impulse control disorders (ICD), such as pathological gambling (PG), hypersexuality, binge eating, and compulsive buying, are defined as the failure to resist an impulse, drive, or temptation to perform an act harmful to either the self or others according to the *Diagnostic and Statistical Manual of Mental Disorders (*DSM-IV) (American Psychiatric Association, 1994). Their prevalence according to these diagnostic criteria is about 14% of PD patients under DA replacement therapy (Weintraub et al., 2010a); however, according to the "Questionnaire for impulsive–compulsive disorders in Parkinson's disease" (QUIP) (Weintraub et al., 2009), prevalence rises to around 40% (Sharma et al., 2015, Garcia-Ruiz et al., 2014). Other impulsive–compulsive behaviors (ICB) such as punding (i.e. abnormal repetitive non-goal oriented behaviors), hobbyism (similar but oriented to higher activities such as internet use, playing of music, etc.), walkabout (excessive aimless wandering) and hoarding, along with dopamine dysregulation syndrome (DDS; compulsive PD medication overuse), are also increasingly recognized in PD patients under dopaminergic therapy (Voon and Fox, 2007; Weintraub et al., 2010a, 2015). It is not fully understood how these abnormal behaviors are similar to ICD in terms of their neural substrate. Dopaminergic agonists are mostly associated with ICD, although they can also be triggered by levodopa (Molina et al., 2000; Ballivet et al., 1973; Weintraub et al., 2010a). DDS occurs mainly with levodopa or short-acting, high-potency dopaminergic agonists such as subcutaneous apomorphine (O'Sullivan et al., 2009; Weintraub et al., 2015). No data are available regarding punding and other ICB and the type of dopaminergic treatment. Moreover, DDS has a prevalence of about 3–4% (Cilia et al., 2014), while conflicting or no information is available regarding other ICB (Weintraub et al., 2015).

Overall, ICD have been conceptualized as "behavioral addictions" as they overlap with substance use abuse with respect to risk factors, clinical features, cognitive changes, neurobiological substrates, diagnostic criteria, genetic variance, associated factors and treatment approaches (Dagher and Robbins, 2009; Holden, 2001; Potenza, 2008; Voon et al., 2011; Weintraub et al., 2015). PD patients with ICD repeat the execution of abnormal behavior time and again, in spite of negative consequences. Actually, ICD can lead to disastrous consequences such as loss of employment, financial ruin, divorce and other family problems, increase health risks (including suicide), etc (Voon et al., 2011; Bharmal et al., 2010). There is a definitive preoccupation for the procurement of the behavior as these patients lie to family members, therapists, or others and try to overcome any difficulty to perform the abnormal behavior. Lastly, it has been well described that, in contrast to patients who do not have ICD, cessation of treatment