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Review Article

Compensatory mechanisms in Parkinson's disease: Circuits adaptations and role in disease modification

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ABSTRACT

The motor features of Parkinson's disease (PD) are well known to manifest only when striatal dopaminergic deficit reaches 60–70%. Thus, PD has a long pre-symptomatic and pre-motor evolution during which compensatory mechanisms take place to delay the clinical onset of disabling manifestations. Classic compensatory mechanisms have been attributed to changes and adjustments in the nigro-striatal system, such as increased neuronal activity in the substantia nigra pars compacta and enhanced dopamine synthesis and release in the striatum. However, it is not so clear currently that such changes occur early enough to account for the pre-symptomatic period. Other possible mechanisms relate to changes in basal ganglia and motor cortical circuits including the cerebellum. However, data from early PD patients are difficult to obtain as most studies have been carried out once the diagnosis and treatments have been established. Likewise, putative compensatory mechanisms taking place throughout disease evolution are nearly impossible to distinguish by themselves. Here, we review the evidence for the role of the best known and other possible compensatory mechanisms in PD. We also discuss the possibility that, although beneficial in practical terms, compensation could also play a deleterious role in disease progression.

1. Introduction

Parkinson's disease (PD) is associated with slow progressive deterioration of motor performance classically associated with the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) and dopamine (DA) striatal depletion (Kalia and Lang, 2015). The cardinal features of PD become clinically obvious only after an extensive population of dopaminergic neurons is lost, usually around 50–60% (Fearnley and Lees, 1990) and striatal DA concentration falls below 70% approximately (Ehringer and Hornykiewicz, 1960). Thus, compensatory mechanisms must be operating in the early phase (pre-symptomatic) of PD to allow such marked depletion to take place without symptomatic manifestations (Bezard et al., 2003, 2009; Bezard and Gross, 1998; Zigmond et al., 1990). Furthermore, SNc cell loss and striatal denervation follow an exponential pattern with changes mainly occurring some ± 5 years around diagnosis (Kordower et al., 2013). However, motor deterioration continues to increase over many more years of evolution, so that "off" medication severity becomes higher over time. This poses the intriguing question whether compensatory mechanisms may be important not only in the early pre-symptomatic phase of disease evolution by delaying the clinical onset of PD but also by playing a role in the clinical progression of motor deficits. Accordingly, understanding compensatory mechanisms would appear to be an important factor to take into account when assessing the evolution of PD at different stages.

Despite all of the above, the pathophysiology of compensatory mechanisms in PD remains unclear, and indeed, has not been fully explored. These mechanisms may be dopaminergic and also non-dopaminergic, occur at the molecular or cellular level, and may also be related to adaptive circuit changes within the basal ganglia (BG) and their connections. It is also possible that compensatory mechanisms are implicated in the onset of other clinical manifestations associated with advanced PD, such as cognitive impairment, autonomic disturbances or disequilibrium (Schapira et al., 2017), but these are even less well-known and have not yet been ascertained. In this review, we concentrate on the main compensatory mechanisms related to motor control and discuss the evidence supporting their relative importance.

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2. Compensatory mechanisms in Parkinson's disease

Classically, the model most commonly used to explain the compensation that follows nigro-striatal lesions proposed that surviving DA neurons go through functional changes aimed at preserving DA availability in the striatum (Calne and Zigmond, 1991; Zigmond, 1997; Zigmond et al., 1990). It is understood that once the dopaminergic deficit surpasses a given threshold, the globus pallidum externa – subthalamic nucleus – globus pallidum interna (GPe-STN-GPi) network becomes hyperactive and loses its normal modulatory action, leading to dysfunctional and abnormal BG output activity (Obeso et al., 2008). Several nigro-striatal changes have been proposed to occur at molecular and synaptic levels as a consequence of DA depletion, mainly in the form of increased dopaminergic activity. These include increments in synthesis, release and turnover of DA and tyrosine hydroxylase (TH) activity (Barrio et al., 1990; de la Fuente-Fernandez et al., 2001, 2004; Kozina et al., 2014; Lee et al., 2000; Nakashima et al., 2013; Nandhagopal et al., 2011; Perez et al., 2008; Pifl and Hornykiewicz, 2006); DA receptor changes (Bezard et al., 2001); DA diffusion and passive stabilization (Bezard and Gross, 1998) or reduced DA transporter to enhance DA pre-synaptic uptake and compensate for the low terminal field remaining (Creese et al., 1977; Dickinson et al., 1999; Lee et al., 2000; Nandhagopal et al., 2009; Vezoli et al., 2014) (Fig. 1).

In addition, there are other changes that could either be compensatory or the consequence of striatal DA depletion. These include morphological modifications in type and sizes of medium spiny neurons (MSNs) spines (Smith et al., 2009; Villalba and Smith, 2017), plastic synaptic changes (Schirinzi et al., 2016), changes in the serotoninergic system (Wile et al., 2017), increment or appearance of striatal TH + neurons (Huot and Parent, 2007) and enhanced DA synthesis by alternative biochemical pathways (Kozina et al., 2017) (Fig. 2). Finally, adjustments in neuronal activity in the GPe-STN-GPi (Quiroga-Varela et al., 2013) motor cortical areas (Ko et al., 2013; Kojovic et al., 2015) and cerebellum (Wu and Hallett, 2013) could also be associated with compensation although they are difficult to separate from the pathophysiology of parkinsonism (Fig. 3).

2.1. Striatal mechanisms

2.1.1. Increased dopaminergic metabolism

Hornykiewicz et al. first demonstrated that the tissue concentrations of DA metabolites 3.4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were less affected that tissue concentrations of DA in PD patients with mild motor severity, resulting in increased ratios of these metabolites to DA content (Bernheimer and Hornykiewicz, 1965). This finding was later consistently found in all PD animal models. It was then hypothesized that such up-regulation of DA transmission could represent a possible pre-symptomatic compensatory

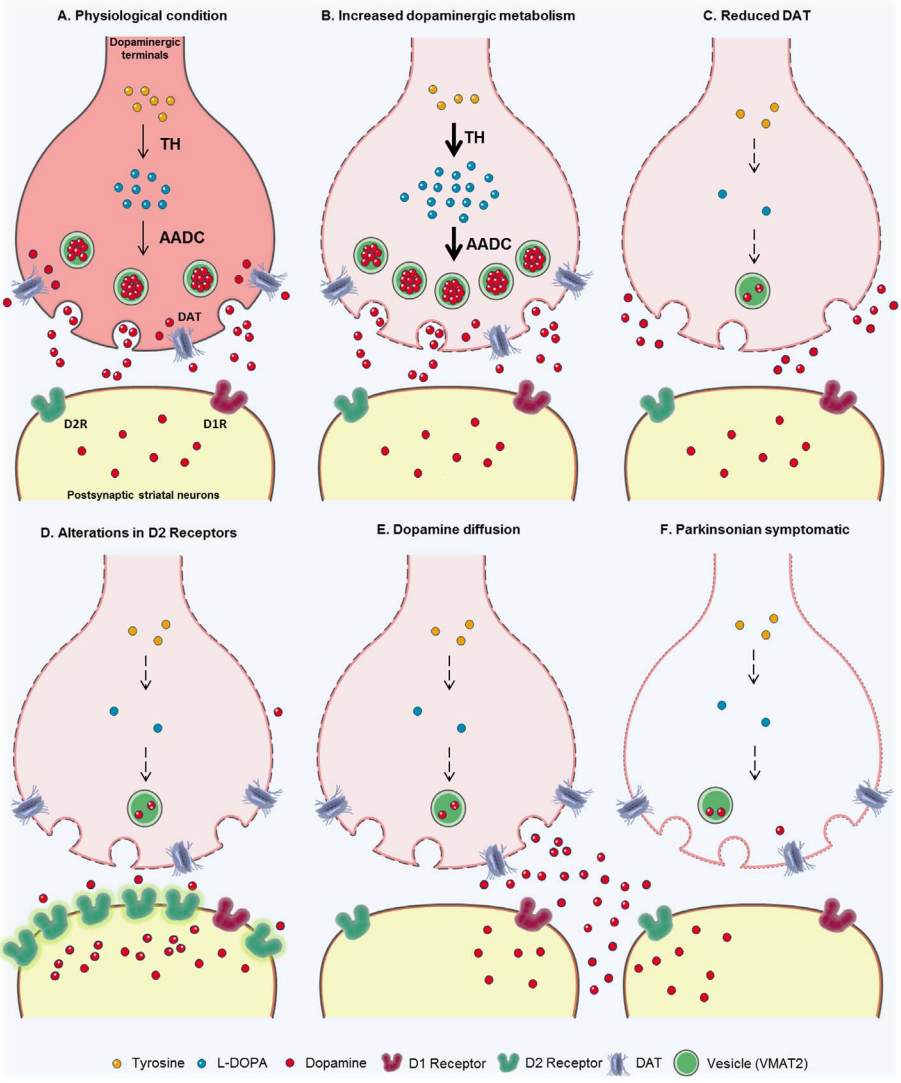

Fig. 1. Striatal mechanisms. Schematic summary of the best-recognized nigro-striatal compensatory mechanisms in Parkinson's disease. A. Synaptic terminals at physiological condition. B–E. Proposed compensatory mechanisms in the presymptomatic stage of disease. (B) Increased dopamine release and turnover (C) Reduced dopamine re-uptake by DAT. (D) Alterations in D2 receptors (E) Dopamine diffusion and passive stabilization. F. Synaptic terminals in the parkinsonian symptomatic state TH: tyrosine hydroxylase; L-DOPA: L-3,4-dihydroxyphenylalanine; AADC: Aromatic L-amino acid decarboxylase; DAT: dopamine transporter.