Parkinson's Disease

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Introduction to Parkinson's Disease

Parkinson's disease (PD), the second most common neurodegenerative disease after Alzheimer's disease, affects approximately 1 % of the population over 65 years of age. PD is primarily a sporadic disease and aging is the principal risk factor. Sporadic PD is a complex multifactorial disorder with variable contribution of genetic susceptibility and environmental factors. Several mechanisms are involved in the disease pathogenesis, such as mitochondrial dysfunctions, oxidative damage, autophagic alterations, proteasome impairment and protein aggregation [1]. There are also familial forms of PD, accounting for 5–10 % of all cases, associated with mutations in PARK genes. Interestingly, PARK genes encode for proteins involved in the maintenance of protein homeostasis, mitochondrial integrity and release of neurotransmitter-containing vesicles [2]. One of the major pathological hallmarks of PD is the accumulation of α-synuclein-containing aggregates (Lewy bodies) in neuronal perikarya and processes as a consequence of the proteolytic deficit, typical of the pathology.

On the clinical side, cardinal signs of PD include resting tremor, bradykinesia (slowness of movement), rigidity and postural instability (loss of upright stability). These motor dysfunctions are attributable to the progressive loss of dopaminergic cells within the substantia nigra pars compacta (SNc) and become overt when approximately 80 % of striatal dopamine (DA) and 50 % of nigral neurons are lost [3]. In fact, the SNc sends dopaminergic projections to the corpus striatum, and both the SNc and the striatum contribute to the basal ganglia circuitry, a system of nuclei involved in the modulation of voluntary movement. In addition, various non-motor symptoms may develop, such as autonomic dysfunctions, sleep disturbances, depression (see chapter "Major depressive disorder") and cognitive impairment, indicating that the neurodegenerative process is not limited to dopaminergic cells but involves other neurotransmitter systems. Non-motor symptoms often precede the onset of classical motor manifestations and contribute considerably to lower quality of life [4].

Pathophysiology of Parkinson's Disease and Metabolic Alterations

Metabolic changes associated with PD have been evaluated in the brain as well as in peripheral fluids such as blood, and may reflect alterations

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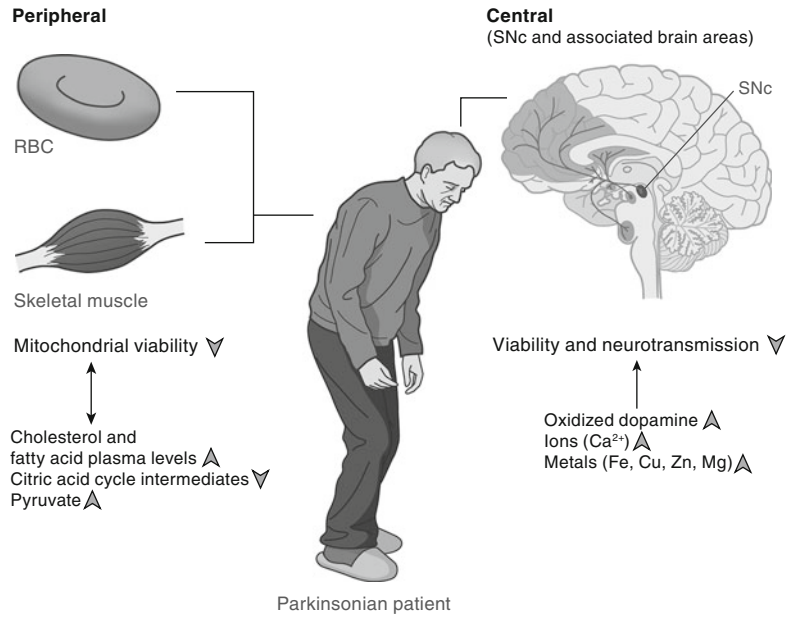

Fig. 1 Metabolic changes in Parkinson's disease. Metabolic changes in Parkinson's disease include central (*right side*) and peripheral (*left side*) alterations. Metabolic changes in the brain affect the substantia nigra pars compacta (*SNc*) and (non)-dopaminergic associated areas. Increased levels of Ca^{2+}, oxidized dopamine, and other metals ions such as iron induce neuronal death and alter neurotransmission. Mitochondrial viability and integrity are also strongly affected, both in the brain and in peripheral cells such as lymphocytes, platelets, red blood cells (*RBCs*) and skeletal muscle cells. Changes in lipid content and metabolism, together with energetic imbalances, can also be found in the blood plasma

occurring at central level and/or represent biomarkers of ongoing pathology.

Selective vulnerability of dopaminergic neurons likely involves DA oxidation and Ca^{2+} homeostasis, which are both elevated in the SNc of animal models of PD and patients [5]. In a rodent model of PD, ions such as iron, manganese, copper and zinc are increased in the brain regions associated with the dopaminergic pathway [6]. Changes in the striatal levels of excitatory (glutamate) and inhibitory (γ-aminobutyric acid or GABA) neurotransmitters were found in another rodent model of PD indicating imbalanced neurotransmission in PD basal ganglia [7].

Epidemiologic data show that low levels of circulating fatty acids and cholesterol increase the risk of developing PD, suggesting that also lipid metabolism is affected [8]. The involvement of mitochondrial dysfunctions in the etiopathogenesis of PD suggests the existence of defects in energy metabolism. Reduced complex I activity was observed in mitochondria from SNc, platelets, lymphocytes, and skeletal muscle in PD patients [9]. Concerning metabolic intermediates, increased pyruvate concentrations, as well as decreased levels of citrate, acetate, succinate, and malate – intermediates of the citric acid cycle (also called tricarboxylic acid cycle) – were detected in the plasma of naïve PD patients [10]. All these conditions ultimately favor neurodegeneration, suggesting that changes in energy metabolism contribute to PD (Fig. 1).

Treatment of Parkinson's Disease

The pharmacological treatment currently available for PD is purely symptomatic and is based on the restoration of DA levels in the brain. The typical treatment consists in the administration of L-3,4-hydroxyphenylalanine (L-dopa), which crosses the blood-brain barrier (unlike DA itself) and is directly converted into DA by the aromatic L-amino acid decarboxylase. In everyday

PD therapy, L-dopa is administered in combination with decarboxylase inhibitors (benserazide or carbidopa), which prevent its peripheral transformation into DA, thereby increasing the drug's availability in the brain. L-dopa significantly ameliorates PD motor deficits. However, chronic treatment is frequently associated with progressive reduction of drug's efficacy and the development of complications such as involuntary movements known as L-dopa-induced dyskinesia (LIDs). LIDs are the result of pre- and postsynaptic changes induced by chronic and pulsatile stimulation of striatal dopaminergic receptors [11]. Therefore, complementary drugs are given in order to counteract side effects or improve efficacy. One class of drugs is based on DA agonists, which activate DA receptors by mimicking the endogenous neurotransmitter. They can be divided into two groups: the ergot (cabergoline, bromocriptine) and the non-ergot (rotigotine, pramipexole) derivatives. The two groups are different not only in terms of structure but also for their spectrum of activity, with the non-ergot derivatives being more selective on dopaminergic D2/D3 receptors and the ergot acting also on non-dopaminergic targets, thereby inducing more side effects. They can be used as adjunctive therapy or as monotherapy, before L-dopa or after motor complications have appeared. DA agonists are less efficacious than L-dopa in treating motor symptoms of PD and are associated with the development of psychiatric side effects and impulse control disorder [12].

Monoamine oxidase-B (MAO-B) inhibitors (selegiline, rasagiline) block the oxidation of DA by MAO-B, which is part of the physiological inactivation of DA in the brain, thus increasing DA levels at the synapse. MAO-B inhibitors have a modest effect and are used as monotherapy at early stages or as adjuncts to L-dopa for reducing motor fluctuations [13]. Further interest was dedicated to MAO-B inhibitors, in particular rasagiline, because of their neuroprotective properties and therefore their ability to slow PD progression [14].

Non-dopaminergic drugs, such as anticholinergics and amantadine, may also be adopted. In early phases of PD, anticholinergic drugs (trihexyphenidyl, benzatropine) may improve tremor by antagonizing muscarinic acetylcholine receptors on striatal interneurons. Their use is restricted to short periods because of the side effects observed both at central (cognitive decline) and peripheral (tachycardia, meaning increased heart rate, and constipation) level. Amantadine, an antagonist of the N-methyl-D-aspartate (NMDA) receptor (an ionotropic glutamate receptor), has shown antidyskinetic effects in advanced PD patients under L-dopa treatment [15] acting on central glutamatergic neurons.

Over the past decades, neurosurgical interventions have also been performed in PD patients. Deep brain stimulation (DBS), based on the implant of electrodes mainly in the subthalamic nucleus of PD patients, is the most common surgical therapy. PD patients with intractable tremor and major side effects due to chronic L-dopa, but free from dementia and psychiatric comorbidities, are typical candidates for DBS [16].

Influence of Treatment on Metabolism and Consequences for Patients

Only few studies have investigated changes in metabolism due to antiparkinsonian treatment. Altered levels of methylation products, such as increased concentrations of homocysteine, were found in plasma from PD patients under L-dopa medication as a consequence of the catabolism of this molecule (to 3-O-methyldopa) [17].

Many studies have found that PD patients undergoing treatment show increased body weight. DBS is accompanied by weight gain in the first postoperation months. Reasons might include lower energy expenditure, fewer motor complications and altered eating behavior [18], and might involve DBS-induced modulation of hypothalamic areas, essential in maintaining homeostatic control of bodily functions such as feeding and sleeping [19]. Compulsive eating and weight gain are also observed after treatment with DA agonists such as pramipexole. These disturbances have been attributed to excessive

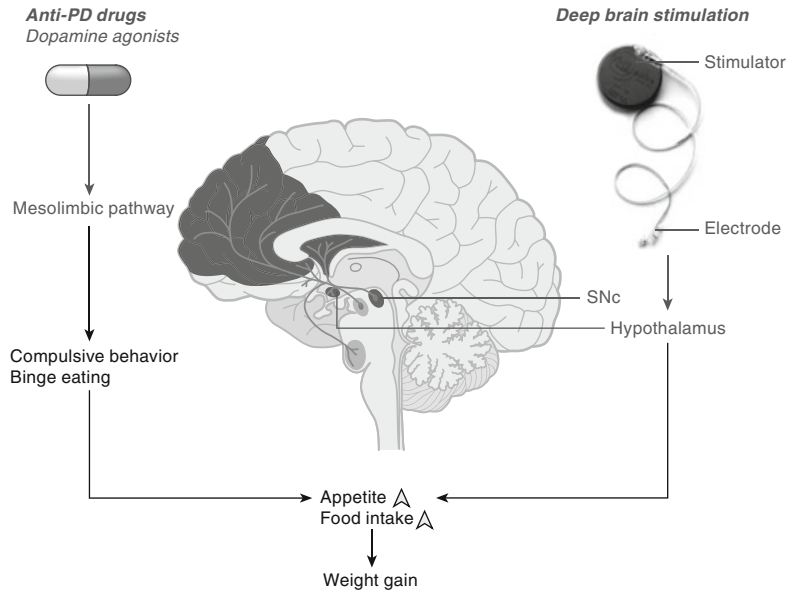

Fig. 2 Influence of Parkinson's disease treatment on metabolism. Metabolic changes after antiparkinsonian therapy and surgical interventions are due to secondary effects on the intact mesolimbic pathway parallel to the affected nigrostriatal system and on the hypothalamus. Dopamine-based medication (*left side*) hyperactivates the mesolimbic pathway, associated with the brain nuclei dedicated to the perception of reward, thereby causing compulsive behavior and binge eating. Deep brain stimulation (*right side*) affects mostly the hypothalamus, a brain nucleus dedicated to control of homeostatic behaviors such as eating and sleeping. In both cases, the effects are increased appetite and food intake leading to weight gain and therefore complications of the clinical spectrum. *SNc* substantia nigra pars compacta, *PD* Parkinson's disease

activation of the mesolimbic pathway, connecting the dopaminergic ventral tegmental area with limbic structures such as the nucleus accumbens and the amygdala. This pathway has been linked to the biological perception of reward and the activation of responses associated with it; therefore, PD therapy causes compulsive behaviors and binge eating through the hyperactivation of this system [20]. Finally, weight gain in PD patients increases the risk for other metabolic disturbances, such as diabetes (see chapter "Diabetes mellitus") and cardiovascular diseases (see chapter "Atherosclerotic heart disease"), thereby adding further levels of complexity to the clinical phenotype (Fig. 2).

Perspectives

Identification of metabolic changes in the brain or peripheral fluids is essential to develop biomarkers and to unravel the mechanisms that underlie PD pathogenesis, since metabolites act as indicators of cellular physiology and homeostasis. Indeed, the identification of biomarkers to diagnose and monitor the progression of the disease is currently one of the most intriguing and challenging areas of PD research. The evaluation of metabolomic profiles is a promising tool for supporting the diagnosis of PD, possibly in the very early phases of the disease [10], and might also be useful to identify prognostic markers, as well as to anticipate the response to pharmacological treatment. These studies will eventually lead to a better description of PD molecular and clinical phenotypes and therefore optimization of therapeutic intervention. New possible pharmacological strategies to improve both neuroprotection and motor dysfunction are in development. Thus far, encouraging results have been obtained by adopting antagonists of adenosine and glutamate receptors [11] and compounds that increase the endogenous levels of antioxidants [21].

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