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Physiopathology of Parkinson's disease

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily characterized by the selective loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). This dopaminergic depletion underlies the cardinal motor symptoms: bradykinesia, rigidity, tremor, and postural instability. While the exact physiopathology remains incompletely understood, a complex interplay of genetic and environmental factors contributes to disease onset and progression. A hallmark of PD is the presence of Lewy bodies, intracellular inclusions composed primarily of α-synuclein. The aggregation of α-synuclein is thought to be a central pathogenic event, potentially initiating a cascade of events leading to neuronal dysfunction and death. This process involves mitochondrial dysfunction, oxidative stress, impaired protein degradation (e.g., through ubiquitin-proteasome system dysfunction), and neuroinflammation. Mitochondrial impairment contributes to energy deficits and increased production of reactive oxygen species, further exacerbating neuronal damage. The compromised proteasomal system allows for the accumulation of misfolded proteins, contributing to the formation of Lewy bodies and further cellular stress. Neuroinflammation, involving both microglia and astrocytes, plays a complex role, potentially contributing to both neuroprotection and neurotoxicity depending on the inflammatory milieu. Genetic factors contribute significantly to PD risk, with mutations in genes like SNCA (encoding α-synuclein), PARKIN, PINK1, and LRRK2 identified as causative or strongly associated with increased susceptibility. These genes are involved in various cellular processes including protein degradation, mitochondrial function, and autophagy. While these genetic mutations explain a fraction of PD cases, most cases are sporadic, suggesting a significant contribution of environmental factors such as exposure to pesticides and toxins. Further research focusing on the intricate interplay between genetic predisposition, environmental triggers, and the molecular mechanisms underlying α-synuclein aggregation and subsequent neuronal damage is crucial for developing effective disease-modifying therapies. Understanding the precise sequence of events and the relative contribution of each factor to the physiopathology of PD remains a key challenge in the field.

Keywords: *Physiopathology, Parkinson's disease*

Introduction.

Parkinson's disease (PD) is a chronic disorder of the central nervous system with symptoms appearing gradually with the increase in age [1]. PD was first described by James Parkinson in 1817 in an essay titled

"shaking palsy" [1]. In the late nineteenth century, the description of the disease was further refined by Charcot based on the cardinal clinical features [1]. PD is the second most common motor disorder next to Alzheimer's disease (AD) [2].

With an aging population, both the prevalence and incidence of PD are expected to increase by more than 30% by 2030, which will result in both direct and indirect costs on both society and the economy as a whole [3].

Epidemiology

The Global Burden of Disease Study estimates that the number of PD cases will double from about 7 million in 2015 to about 13 million in 2040 [4]. Aging is an evolutionarily conserved natural process that involves dysregulation of several pathways, such as oxidative stress, mitochondrial dysfunction, autophagy, and neuroinflammation, many of which are also involved in neurodegenerative conditions [5].

In humans, brain weight is greatest in the early teens and remains relatively stable until the fifth decade [6]. From 50 to 90 years of age, the loss of brain weight is approximately 2–3% per decade. Accordingly, a reduction in SN volume with aging has also been reported in humans and monkeys [7]. It has been estimated that the number of SN neurons declines by 7 to 9.8% per decade in healthy individuals without neurological disorders [8].

Risk/protective factors

The contributions to PD pathology are multifactorial, stemming from multiple risk and protective factors and resulting from an interaction between genetic and environmental influences. A meta-analysis of 30 possible environmental risk factors identified 11 factors that either increased or decreased the risk of PD. Factors increasing PD risk included exposure to pesticides, history of head injury, living in a rural area, using beta-blockers, agricultural work, and drinking well water [9].

Age and gender

Age is the most significant risk factor for developing Parkinson's disease, and men are more susceptible than women with a prevalence ratio of approximately 3:2 [10]. The relationship between estrogen exposure and PD risk was investigated, and women with higher cumulative estrogen exposure had a significantly reduced PD risk. The epidemiological evidence of sex differences in PD suggests a possible beneficial activity of female gonadal hormones on the dopaminergic system, particularly of circulating estradiol, which may act as a neuroprotective agent [11]. Estrogens have also proved effective in improving PD symptoms and levodopa-induced dyskinesia. One study reported beneficial effects of 17β-estradiol also in a male PD patient with severe motor fluctuations and dyskinesias [12].

Cigarette smoking

Most epidemiological reports are case-control studies showing a reduced risk of developing PD, with larger cohort studies also in agreement [13]. A large meta-analysis including 44 case-control studies and 8 cohort studies from 20 countries showed an inverse correlation between smoking and PD, with a pooled relative risk of 0.39 for current smokers [14]. They also reported an inverse correlation between the number of pack years,

the number of years smoking, and the risk of PD, with the risk of developing PD being significantly reduced in heavy or long-term smokers compared with nonsmokers [15]. The reasons underlying this associated reduced risk are not fully understood. Activation of nicotinic acetylcholine receptors on dopaminergic neurons by nicotine or selective agonists has been shown to be neuroprotective in experimental models of PD. Nevertheless, nicotine can also stimulate the release of dopamine [16].

Caffeine

Several studies have investigated the effect of caffeine on the development of PD and reported a reduced risk of developing PD among coffee drinkers [17]. Caffeine is an adenosine A2A receptor antagonist, which is believed to be protective in PD and has been shown to be neuroprotective in a mouse model of PD. It has been previously reported that there is a 25% risk reduction in developing PD among coffee drinkers [18].

Physical activity

Physical activity is another important lifestyle factor that may affect PD onset, severity, and progression. High levels of exercise in midlife are associated with lower PD risk, better disease prognosis, and lower rates of serious complications [19].

Pesticides, herbicides, and heavy metals

In 1983, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was first discovered to be associated with nigrostriatal degeneration when several people developed typical PD signs after injecting themselves with a drug contaminated with MPTP. MPTP is metabolized into the neurotoxin, MPP+ (1-methyl-4-phenylpyridinium), which is a mitochondrial complex-I inhibitor that selectively damages dopaminergic cells in the substantia nigra. The identification of MPTP as a cause of nigral degeneration led to the idea that PD could be caused by an environmental toxin [20]. Paraquat (a herbicide which is structurally very similar to MPP+) and rotenone (a pesticide) are also selective complex-I inhibitors and induce dopaminergic depletion in animal models of PD. The relationship between exposure to these chemicals and the risk of developing PD has been investigated in other epidemiological studies. It has also led to the study of surrogate markers, including the association of farming, drinking well water, and living in rural areas with PD risk [21].

Genetics

Although PD is generally an idiopathic disorder, there is a minority of cases (10–15%) that report a family history, and about 5% have Mendelian inheritance [22]. Furthermore, an individual's risk of PD is partially the product of as-yet poorly defined polygenic risk factors. The genes that have been found to potentially cause PD are assigned a "PARK" name in the order they were identified. To date, 23 PARK genes have been linked to PD. Mutations in the PARK genes demonstrate either autosomal dominant (e.g., SNCA, LRRK2, and VPS35) or autosomal recessive inheritance (e.g., PRKN, PINK1, and DJ-1) [23].

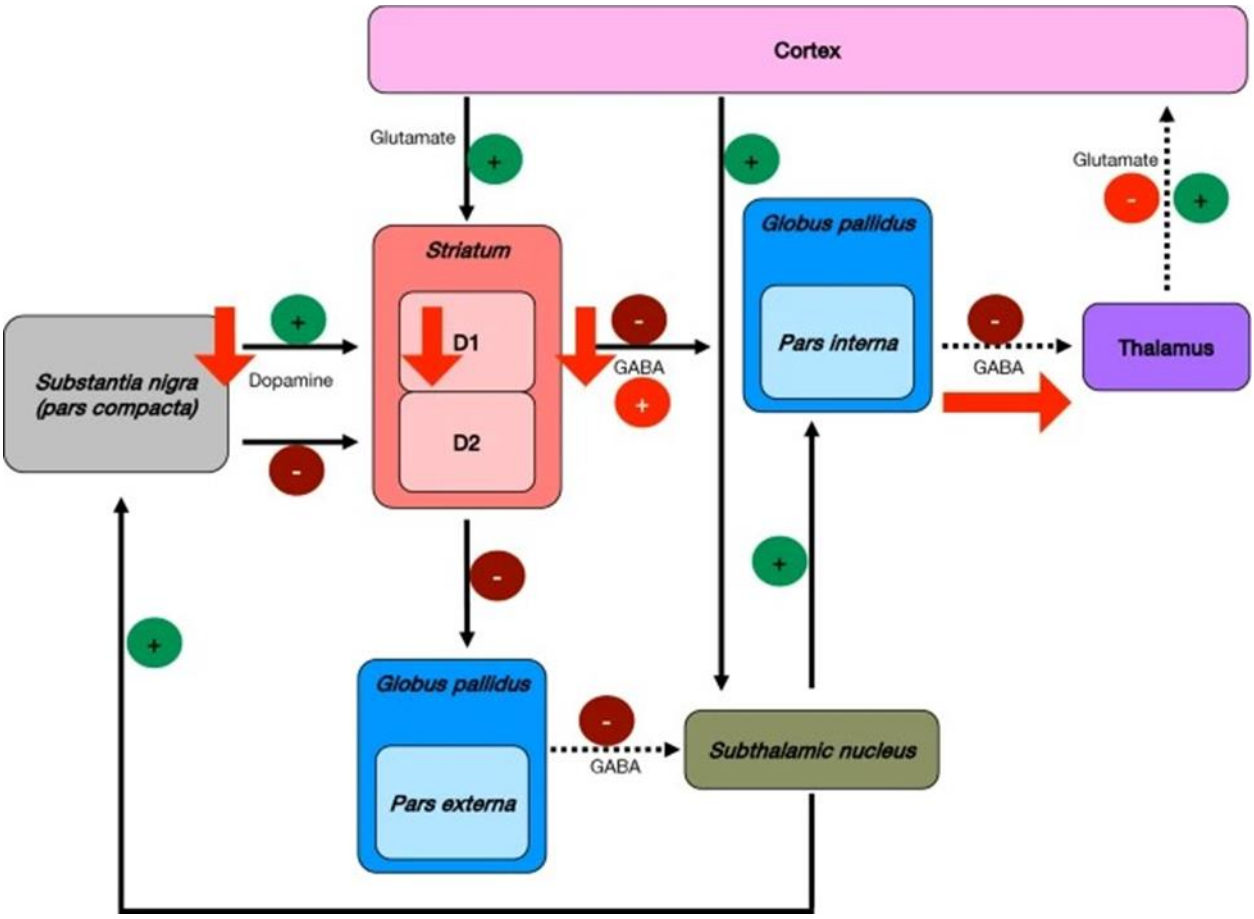
Metabolic syndrome:

Metabolic syndrome (MetS) is characterized by the presence of a minimum of three metabolic risk factors, such as central obesity, dyslipidemia, impaired glucose metabolism, elevated blood pressure, and low levels of high-density lipoprotein cholesterol [24]. The pathogenesis of MetS is triggered by some factors such as oxidative

stress, which attacks cellular macromolecules such as proteins, lipids, and nucleic acids and promotes cellular dysfunction [25]. Evidence shows that MetS is associated with a higher risk of developing Parkinson's disease (PD) because of the increase in oxidative stress as well as other factors such as neuroinflammation and mitochondrial dysfunction [26].

Physiopathology of Parkinson's disease

The function of basal ganglia is determined by the balance between direct and indirect pathways activated by gamma-aminobutyric acid (GABA) neurotransmitter. The direct pathway starts with the activation of D1 dopamine receptors by dopamine in the striatum, which inhibit (via GABA) the globus pallidus pars interna. This last brain structure, in the absence of dopamine, would inhibit the thalamus. Consequently, the direct pathway hinders the inhibition of the thalamus, thus stimulating the cortex [27]. On the other hand, the indirect pathway starts with the activation of dopamine D2 receptors in the striatum, inhibiting the globus pallidus pars externa, which in turn would inhibit (via GABA) the subthalamic nucleus. Due to the lack of inhibition by globus pallidus, the subthalamic nucleus activates the globus pallidus pars interna, which hinders (via GABA) the thalamus, hence inhibiting the cortex (Fig. 2). As follows, the direct pathway results in an excitation of the cortex, as opposed to the indirect pathway, where an inhibition of the cortex occurs [27]. The balance between these two pathways, regulated by dopaminergic afferent neurons in the substantia nigra pars compacta ascending to the basal ganglia, is progressively affected in PD. Thus, gradual loss of dopaminergic projections hinders the direct pathway, stimulating the globus pallidus pars interna that inhibits (via GABA) the thalamus leading to cortical dysfunction. Motor activation alterations in PD patients reflect basal ganglia projection dysfunctions towards motor cortex as a result of the nigrostriatal degeneration, typified by progressive cell death in the central nervous system (CNS). The abnormal neuronal activity in areas receiving excessive inhibition of thalamo-cortical projections in PD has been evident in neuroimaging studies where they are hypoactive, such as the primary motor area (M1), supplementary motor area (SMA), and the lateral prefrontal cortex (DLPFC) [27].



Pathophysiology

A number of mechanisms have been implicated in PD pathogenesis, with α-synuclein aggregation central to the development of the disease. Multiple other processes are thought to be involved, with several studies suggesting that abnormal protein clearance, mitochondrial dysfunction, and neuroinflammation play a role in the onset and progression of PD. However, the relationship between these pathways remains unclear.

α-synuclein misfolding and aggregation

Native α-synuclein in the brain is mostly unfolded without a defined tertiary structure although in aqueous solutions it can be present in stable tetramers that resist aggregation Upon interaction with negatively charged lipids, such as the phospholipids that make up cell membranes, α-synuclein folds into α-helical structures through its N-terminal In PD, α-synuclein adopts a β-sheet-rich amyloid-like structure that is prone to aggregate. Indeed, misfolded α-synuclein is found within LBs as 5–10 nm long filaments. Several mechanisms have been proposed for the conformational changes that lead to abnormal α-synuclein aggregation, including serine 129 phosphorylation, ubiquitination, and C-terminal truncation Hence, different species of α-synuclein are found in the PD brain, including unfolded monomers, soluble oligomers, protofibrils, and high molecular weight insoluble fibrils [29].

indicated that the most neurotoxic α-synuclein species is the early oligomeric form, rather than the mature insoluble fibrils The increased toxicity of these oligomers, as opposed to the fibrillary α-synuclein, was validated in cell-based assays The oligomeric species of α-synuclein are capable of “seeding” and accelerating

abnormal protein aggregation and Danzer et al. (2011) proposed that this might be the mechanism underlying the spread of α-synuclein pathology in the brain [29].

Mitochondrial dysfunction

Mitochondrial dysfunction is considered a key element in the pathogenesis of both idiopathic and familial PD Early postmortem studies in the SNpc of PD brains reported a deficiency of the mitochondrial complex-I, which is a vital component of the electron transport chain. These data provided one of the first direct links between mitochondrial dysfunction and PD Complex-I deficiency was also found in skeletal muscle and platelets of PD patients compared to healthy subjects Further evidence arose by the discovery that abuse of the substance MPTP caused permanent Parkinsonian symptoms, with postmortem examination revealing dopaminergic cell loss Follow-up studies showed that MPTP when oxidized is taken up by DA neurons and leads to complex-I inhibition Other toxins and pesticides that impair mitochondrial complex-I activity, like rotenone and paraquat, also cause a Parkinsonian phenotype and DA cell loss in animals, and potentially in humans Defects in the mitochondrial complex-I may be crucial in driving DA cell death due to energy depletion [30].

Another major clue pointing to the role of mitochondria in PD pathogenesis is that many of the known genes that cause familial PD play a role in mitochondrial homeostasis. One example is the involvement of PINK1 and parkin (PARK2 and PARK6, respectively), both of which are vital components of the pathway that regulates the removal of dysfunctional mitochondria, a process called mitophagy . Loss-of-function mutations in either gene lead to impaired mitochondrial quality control and cause autosomal recessive PD [31].

Finally, α-synuclein by itself is known to interfere with mitochondrial function. For instance, α-synuclein can interact with the mitochondrial membrane and accumulate inside the organelles. This leads to the damage of complex-I activity, ultimately resulting in mitochondrial dysfunction and increased oxidative stress A more recent study reported an interaction between oligomeric (but not monomeric or fibrillar) α-synuclein and the mitochondrial receptor TOM20This interaction resulted in impairment of the mitochondrial protein import machinery, reduced respiration, and led to excessive production of reactive oxygen species (ROS). [29].

Dysfunctional protein clearance systems

There are two central protein clearance systems within cells responsible for the removal of dysfunctional proteins: the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway. The UPS is primarily responsible for breaking down abnormal proteins, and it does so by “tagging” them with ubiquitin and transporting them to the proteasome for degradation. The autophagy-lysosome pathway is divided into three constituents: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). Briefly, in macroautophagy, intracellular components, including cytosolic proteins, are engulfed by the autophagosome, which then fuses with the lysosome, leading to the breakdown of its contents. On the other hand, in microautophagy, the lysosome alone engulfs and destroys cytoplasmic components. CMA is a more selective process, whereby molecular chaperones target specific proteins and transport them to the lysosome for degradation Monomeric α-synuclein is generally cleared by both the UPS and the autophagy-lysosome pathway, and damage in either of their machineries is implicated in the pathogenesis of PD by contributing to the accumulation of defective proteins, in particular soluble misfolded α-synuclein [32].

Ubiquitin-proteasome system

Proteasomal abnormalities are a shared feature among many proteinopathies, that is, neurodegenerative diseases characterized by abnormal protein accumulation (33). Evidence of such abnormalities in PD was first provided by postmortem studies in the SNpc, where the catalytic activity of the UPS was found substantially reduced compared to healthy brains (34). The same findings were later reported in peripheral blood mononuclear cells of PD but not in healthy individuals (35). Apart from diminished activity, a lower expression of different proteasomal components has also been identified in the SNpc of PD brains. Specifically, the 20S

proteasome α-subunit (36) and other molecules involved in the normal function of the UPS, like PA700 and PA28 (proteasome activators), are reduced (37). Additional evidence is provided from genetic studies and the discovery that two of the PARK genes linked to monogenic PD encode proteins involved in UPS function, namely, parkin (PARK2; E3 ubiquitin ligase) (38) and UCH-L1 (PARK5; Ubiquitin C-terminal hydrolase).
Following on from findings in human PD, altered proteasome activity was observed in different disease models. Marmosets injected with the toxin MPTP had diminished enzyme activity in the UPS, in addition to decreased levels of the 26*S* subunit components (39). In a second set of experiments, the same group showed that pharmacological inhibition of the proteasome in wild-type rats leads to dopaminergic cell death (40). Similarly, Bedford and colleagues using transgenic mice with proteasomal defects (knockout for 26*S* proteasome regulatory subunit 4) showed dopaminergic cell degeneration and observed LB-like inclusions in the brain, which however lacked the dense core of classical human LBs, and it is unclear whether they contained aggregated α-synuclein (41). Nevertheless, all these studies show that dysfunction of protein turnover can result in neuronal cell death, thus providing a potential pathogenic mechanism for PD.

Autophagy- lysosome system

Similar to findings in the UPS system, numerous lysosomal and autophagy-related components are malfunctioning or differentially expressed in PD. In nigral neurons of PD brains, the levels of the autophagosome marker LC3-II were increased, suggesting an accumulation of autophagic vacuoles (42, 43). In contrast, vital proteins of lysosomal membranes (LAMP1 and LAMP2A), and several molecular chaperones from the heat-shock protein family (such as hsc70 and hsp35) were found to be decreased at postmortem examination (44, 45). Furthermore, of particular note is the discovery of a point mutation in the gene of the lysosomal protein ATP13A2 (PARK9), leading to an autosomal recessive atypical Parkinsonian syndrome, referred to as Kufor–Rakeb syndrome. Point mutations in two more PARK genes impair the function of either parkin (PARK2) or PINK1 (PARK6), both of which are involved in the autophagic turnover of mitochondria. Additionally, the emergence of *GBA1* mutations, which result in dysfunction of the lysosome-autophagy system, as a strong genetic risk factor for PD adds weight to the idea that this system is important in the development of PD These studies lend support to the hypothesis that malfunction in the autophagy-lysosome pathway may be contributing to the pathogenesis of PD.

Neuroinflammation

Postmortem brain studies have described microglial and complement activation, T-lymphocyte infiltration, and increased concentration of pro-inflammatory cytokines in the SNpc and striatum of PD patients compared to healthy individuals (46–49). Furthermore, positron emission tomography (PET) neuroimaging with the [^{11}C]-PK11195 radioligand has demonstrated increased microglial activation early on in PD in the brainstem, basal ganglia, and frontotemporal cortices, with added involvement of the parietal and occipital cortices in patients with PD dementia, compared to healthy subjects (50, 51).
While initially thought to be a secondary phenomenon, there is now evidence that inflammatory responses can by themselves contribute to disease pathogenesis. It has been demonstrated in early studies with rodent models of PD (6-hydroxydopamine and MPTP) that inhibition of microglial activation with minocycline pre- and post-neurotoxic insult led to a significant attenuation of DA cell death in the SNpc, suggesting that microglia-induced inflammatory processes may be contributing to the degeneration of these cells (52, 53). There is also a plethora of evidence suggesting that α-synuclein can directly trigger microglial activation and initiate inflammatory processes. For instance, in primary cultures, α-synuclein mediates a dose-dependent activation of microglia (54).
Genetic clues suggesting that immune activation might contribute etiologically in PD come from the identification of a strong association between the human leucocyte antigen (HLA) class II region (a key

molecule of the immune system) and the risk of developing PD (55)—a finding that was later confirmed in genome-wide association studies (42). Additionally, extensive epidemiological studies suggest a decreased PD risk with regular use of the nonsteroidal anti-inflammatory drug ibuprofen (56). Finally, recent data showed that in PD patients at diagnosis a more 'pro-inflammatory' immune marker profile in the serum is associated with a faster motor symptom progression and more impaired cognitive function (57).
Regardless of whether neuroinflammatory responses are a direct trigger of neurodegeneration in PD or are activated as a response to neuronal damage, it is now becoming clear that the engagement of the immune system can initiate a vicious cycle, thereby exacerbating neuronal dysfunction. Hence, manipulation of the immune system remains a promising topic for disease-modifying therapies.

Clinical features

Parkinson's disease comprises a range of motor and non-motor features (Table 1), the expression of which may vary to some degree between patients; however, all patients must exhibit the core clinical features and respond to dopaminergic therapy to satisfy the criteria for the diagnosis of PD. The cardinal motor symptoms include tremor, bradykinesia/hypokinesia/akinesia, rigidity – which are usually asymmetric – and postural instability; other motor features are postural abnormalities (camptocormia and Pisa syndrome), gait disturbances and 'freezing', micrography, disturbances of speech, hypomimia, and alteration of blinking and eye movements, amongst others. The responsiveness of motor symptoms to levodopa administration is an important and diagnostic feature of PD [32].

Table 1. Motor and non-motor symptoms of Parkinson disease (PD)

Motor symptoms	Non-motor symptoms
Tremor	Hyposmia
Rigidity	Psychiatric symptoms: depression, anxiety, apathy hallucinations, psychosis
Bradykynesia/akinesia/hypokinesia	Dementia/cognitive impairment
Postural instability	Sensory symptoms
Postural abnormalities (camptocormia, Pisa syndrome)	Genitourinary symptoms: urinary frequency, urgency, reduced libido, sexual dysfunction
Gait disturbances (freezing of gait, festination, start/target/obstacle hesitation)	Gastrointestinal symptoms: constipation
	n, delayed/reduced stomach emptying
Alterations in blinking/eye movements	Dysphagia, sialorrhoea, dysarthria, hypophonia
Hypomimia	Disturbances of sleep and wakefulness
Micrographia	Cardiovascular symptoms: blood pression variations (postural, postprandial), dysrhythmias

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