Point of View

A global view of Parkinson's disease pathogenesis: Implications for natural history and neuroprotection

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Abstract

Neuroprotection in PD remains the most important goal of current research. Most of presently used strategies are directed at interfering with signalling pathways involved in neuronal death. However, the influence of compensatory alterations in neurotransmitter receptors and related signalling pathways, as well as the role of aging and associated lesions, are not taken into consideration. Their progressive failure might contribute to the appearance and/or progression of the disease. Thus, early restoration of basal ganglia physiology will support the compensatory events and delay the irreversible modification of circuitry that characterizes the clinical progression of PD. Enhancing neuronal plasticity and avoiding the negative effects of aging and associated lesions might help the remaining neural circuits to compensate for lost or broken circuits and improve overall network performance and neurological function. These modulating factors represent potential targets for therapeutic intervention resulting in lasting clinical benefit for the patient. The concept of neuroprotection should be modified, shifting the focus from neurons that are lost to those that survive.

1. Introduction

The natural history of PD seems to be well defined: the gradual loss of neurons results in a slow progression of symptoms and signs [1,2]. PD is a multisystemic disorder characterized by a combination of motor and non-motor symptoms and signs. This is particularly evident in late stages of the disease. The motor syndrome consists of a combination of rest tremor, rigidity, bradykinesia and postural abnormalities. It is linked to the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Non-motor symptoms and signs are related to the degeneration of other neuronal groups (i.e. serotonergic neurons of the raphe nucleus, noradrenergic neurons of the locus ceruleus or cholinergic neurons of the nucleus basalis of Meynnert). Progression of PD results from the continuous loss of neurons within a nucleus which in turn results in a worsening of already existent symptoms and from the spread of the degenerative process to new nuclei yielding to the appearance of new symptoms and signs [2].

In spite of this apparently stereotypic natural history, PD is highly heterogeneous [3]. The clinical picture, as well as the rate of progression, are extremely variable. Two clinical observations illustrate this heterogeneity: patients with tremoric forms of the disease have a more benign course than patients in whom axial symptoms predominate [4] and young onset patients do not develop extra-dopaminergic symptoms until very late [5]; in contrast, they are specially prone to suffer from dyskinesias and impulse control disorders [5]. These observations are related to the central core of this article.

The progressive loss of different types of neurons is the hallmark of PD [1,2]. It accounts for the appearance of symptoms. However, some neurological impairment may reflect dysfunction rather than loss of neurons [6]. In fact, the extent to which neurological deficits in PD relate directly to neuronal loss is controversial [7]. This is due to the capacity of the brain to adapt to damage, including even severe neuronal loss, which results in a notable, albeit variable, capacity to maintain neurological functions [3,8]. However, this adaptive, plastic or compensatory capacity is not taken into account when disease progression, clinical expression and outcome are discussed [9,10]. Similarly, current neuroprotective strategies do not envisage the possibility that modifying these mechanisms could provide effective neuroprotection or increase the potency of other interventions. In fact, main therapies are directed to interfere with the signalling pathways involved in the death of neurons [11,12]. The goal of this brief review is to discuss the role of compensatory mechanisms, as well as aging and the presence of other pathologies, in PD. These ideas could provide new insights into the physiopathology of the disease and contribute to the delineation of new therapeutic targets.
2. Modulation of pathophysiology and clinical expression of PD

Pathophysiology and clinical expression of PD can be modulated by the action of several factors, such as compensatory mechanisms, aging and the presence of associated lesions (i.e. vascular lesions and Alzheimer-like pathology).

2.1. Compensatory mechanisms

PD is a multisystem disorder though its more relevant symptoms derive from a disruption of the physiology of cortical-basal ganglia-thalamo-cortical circuits [13]. These circuits function as a highly ordered and interconnected network with multiple feedback regulatory mechanisms. There are several subcircuits with intrinsic neurophysiological properties and regulatory systems [13]. It is for this reason that compensation is so strong in basal ganglia diseases. Compensation can be illustrated by the well-known fact that the majority of acute and focal lesions of basal ganglia are unnoticed by the patient. Moreover, when they are symptomatic (i.e. hemiballismus by a subthalamic lesion), a relatively rapid recovery occurs. Thus, these structures are extremely plastic. Plasticity refers to the ability of the nervous system to adapt to new situations by changing the effectiveness of transmission in neural circuits [8,14,15]. It is almost always regarded as a useful phenomenon that is important in learning and memory and could potentially compensate for dysfunction after injury.

The molecular and physiological basis of neural plasticity can involve functional changes in membrane properties, such as a reduction in the threshold for initiation of an action potential, or changes in the effectiveness of synaptic transmission by an increase in transmitter release or receptor regulation. Anatomical modifications, which major representatives are axonal regeneration, sprouting, synaptogenesis and neurogenesis, can also take place [14,15].

Several characteristics of PD are clear expressions of compensatory mechanisms. Firstly, pathological studies have shown that a proportion as high as 30% of normal individuals have alpha-synuclein inclusions in their brains and that 15% have Lewy bodies [16]. Secondly, PD has a long presymptomatic period of at least 5–6 years [17]. This indicates that many neurons in the SNpc can die before they are missed at the clinical level. Parkinsonian signs appear when dopaminergic neuronal death exceeds a critical threshold (70–80% of striatal nerve terminals and 50–60% of SNpc cell bodies). Thirdly, its progression is slow and gradual. Finally, there is a non-linear relationship between dopamine-containing neuron loss and functional impairment [17,18]. These points result largely from adaptive neurochemical changes that occur within the striatum or in other parts of the basal ganglia circuitry [19]. Their goal is to maintain dopamine-mediated homeostasis and a correct activation of premotor cortical areas. The MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) monkey model of PD has contributed to gaining insight into compensatory mechanisms. The most relevant ones are the increase in D2-receptor binding at the striatal level, the increase in the expression and activity of encephalin, the overactivity of the subthalamic nucleus (STN) and internal globus pallidus (Gpi) and the increase in the activity of some premotor cortical regions [19].

Many factors might influence the power of compensatory mechanisms. These include genetic factors, aging and the presence of comorbidities (see below) [20–22]. Furthermore, the ongoing neurodegenerative process might affect them. For instance, in AD, synaptic loss exceeds neuronal loss, and depletion of synapses and synaptic proteins correlates better with cognitive decline than does the abundance of plaques or tangles; comparable findings have also been made in PD [23,24]. Compensation occurs since the very beginning. In this setting it would be interesting to know whether the mechanism(s) underlying the onset and the progression of PD are similar. Some data indicate that the onset of PD could be directly related to the cause of PD and is quite rapid. In contrast, the progression of PD could be more linked to the pathogenesis of the disease and is much more slower than the onset. A consistent observation is that deterioration in motor impairment is non-linear, with steeper declines occurring earlier versus later in the disease. UPDRS motor scores deteriorate more rapidly in the first versus the 10th year of disease [25] and they stabilize with disease duration of more than 9 years [26]. This was originally proposed by Fearnley and Lees, based on their finding of an exponential decline over time in dopamine neurons in the SNpc in PD brains [17]. PET studies with markers of the presynaptic slope of the nigrostriatal pathway have found a similar pattern of reduction of tracer uptake [18,27]. Studies with sophisticated imaging methods on transgenic models of AD have shown a kinetic of plaque formation remarkably different from expected: new plaques formed in only 24 h, and their size and final characteristics stabilized within a week [28]. Likely these results could be extrapolated to other neurodegenerative disorders.

One intriguing clinical observation lends support to this view of a separate pathophysiological basis of onset of disease and disease progression. Non-genetic young onset PD may be due to a particularly high vulnerability of damaged cells and/or to a contact with a specially high dose of the toxic agent. This elicits an earlier disease onset and a rapid, acute exhaustion of compensatory mechanisms. However, disease progression in younger patients is slower than the progression rate observed in older patients. If rate of progression is related to the strength of compensatory mechanisms, this finding means that the compensatory mechanisms regulating the onset of the disease are different to the ones regulating disease progression. Alternative explanations are also likely. For instance, the same compensatory mechanisms might be acting at different levels of the basal ganglia circuitry or associated lesions and aging are the crucial factors instead of compensation. It would be important to disentangle these relationships owing to the possibility of new and specific targets to modify disease onset and/or progression.

Plasticity also might be on the basis of pathological situations such as addiction, epilepsy, pain and movement disorders. Dyskinesias and impulse control disorders could be seen as its clinical expression in the case of PD [29,30]. In these cases, plasticity should be regarded as an abnormal phenomenon. The dopamine nigrostriatal system regulates plasticity at the glutamatergic cortico-striatal and cortical synapses. This fine regulation is disrupted in PD and further abnormalities are induced by the chronic administration of levodopa. Therefore, it can be proposed that the typical clinical outcome seen in patients with young onset PD is a direct reflection of compensation [3,8,29,30]. These patients have more competent compensatory mechanisms and a low risk of suffering from the effects of aging and associated pathologies. They show a slow rate of progression of the disease and less diffuse pathology. Consequently, their risk of experiencing levodopa-resistant symptoms is quite low, at least until they get older than 70. However, they are more prone to develop aberrant, pathological and longstanding forms of plasticity in striatal and motor cortical neurons which are expressed as dyskinesias and impulse control disorders (Table 1).

Tremor could be another expression of compensatory mechanisms or, alternatively, patients with tremor could display stronger mechanisms than patients without tremor. In fact, cerebral activation studies indicate that networks involving the cerebellum are overactive in PD [31,32], suggesting a possible role for the cerebello-thalamocortical network in compensatory mechanisms.
Table 1

<table>
<thead>
<tr>
<th>The brain of young onset PD patients.</th>
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<tr>
<td>1. No extra lesions (i.e., vascular, AD-like or aging-related)</td>
<td>Non-aberrant</td>
</tr>
<tr>
<td>2. Slow disease progression &amp; Strong compensatory mechanisms (NEURAL PLASTICITY)</td>
<td>No levodopa-resistant symptoms</td>
</tr>
<tr>
<td></td>
<td>Aberrant</td>
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<tr>
<td></td>
<td>No levodopa-resistant symptoms</td>
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<td>Levodopa-induced dyskinesias</td>
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<td></td>
<td>Impulse control disorder</td>
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Parkinsonian rest tremor is related to a dysfunction in cerebello-thalamic connections and tremoric forms of PD are particularly benign. Thus, the presence of tremor would reveal the activity of this network which in turn is acting as a compensatory mechanism, avoiding or delaying the appearance of bradykinesia and rigidity. This idea fits with the clinical observation showing that tremor disappears when bradykinesia and other symptoms emerge in advanced stages of PD.

2.2. Aging

The role of aging in PD pathogenesis is not well established [32–35]. While PD is an aging-related disorder, many clinical, pathological, and biochemical investigations show qualitative differences between patients and healthy elderly subjects. However, conceivably the progressive loss of neurons and synapses with age may favour the development of PD. Indeed, the possibility of presenting alpha-synuclein inclusions and Lewy bodies in the brain increases with aging [16].

Aging could act by increasing the vulnerability of cells to the action of damaging molecules, as well as by reducing the strength of compensatory mechanisms, particularly in non-dopaminergic structures. Genetic mechanisms regulating plasticity are under the control of age [20–22]. This has been shown in the human prefrontal cortex and rat hippocampus. Interestingly, the expression profile of these genes in people younger than 40 and older than 71 is quite homogeneous [20]. Aging might interact with neuronal function at the level of axonal transport (PD mainly affects neuronal groups origin of long and myelinated fibers), integrity and physiology of synapsis, total amount of trophic factors, defence mechanisms against oxidative and proteolytic stresses, neurogenic capacity, integrity of brain–blood barrier (BBB) and vascularization [33,34].

Several data support the existence of such a relationship. Firstly, recent experimental work suggests that degeneration of nigral dopaminergic neurons could be related to changes in their neuro-physiological characteristics owing to age-related modifications in the type of ionic channels present in the cell membrane [36]. Dopamine cells fire automatically (pacemaker-like activity) thanks to the existence of sodium channels. The authors showed that during the normal aging process, these channels were substituted for calcium channels yielding to an increase in firing rate which in turn increased the entry of calcium into the cytoplasm producing the death of the cell. When applied in dopamine cell cultures, isradipine, a calcium channel blocker belonging to the dihydropyridine family, prevented these changes, thereby ‘rejuvenating’ the cells and precluding their death [36]. In keeping with these experimental data, an epidemiological study showed that the intake of calcium antagonists of the same family of isradipine was associated with a reduced risk of developing PD [37].

Secondly, a pathological study in 97 patients showed that the most determinant factor for the appearance of dopamine-resistant symptoms (i.e. dementia, visual hallucinations, falls) in PD patients was aging. Furthermore, it was independent of the duration of PD, the dose of levodopa and the presence of motor complications [38].

Most of the patients developed these problems after the age of 70. More than 50% of brains showed changes typical of AD and vascular lesions were found in 20% of them. The pathological study of patients included in the Sydney cohort [39] also showed that a high proportion of older patients with dementia presented changes typical of AD [40]. Furthermore, the clinical outcome of older patients was more aggressive. Similarly, a clinical study conducted with 451 PD patients indicated that axial (gait and postural) impairment in PD could result from the combined effect of the disease and the aging process on non-dopaminergic subcortical structures [41]. Another longitudinal study found that the development of dementia was related to the age of the patients rather than to disease-related parameters [42]. Finally, further evidence comes from the critical role of age of onset of PD in the final outcome: the older the onset, the worst the prognosis [43,44]. Overall, these studies suggest that aging is determinant in PD outcome by influencing its progression rate and way [33,34].

Against these findings suggesting a pivotal role of aging in PD outcome, is the existence of a marked difference in the topography of pathological abnormalities found in aging and PD brains [17]. Whereas in PD nigral cell loss is maximal in the ventrolateral SNpc, the dorsomedial part is most affected by aging. Fibers projecting to the motor part of the striatum (putamen) arise from the former whilst the latter one sends its projections to the associative and limbic portions of the striatum (caudate and accumbens nuclei). Thus, aging may be involved in the late appearance of cognitive and emotional symptoms. Likewise, some evidence indicates that the linkage between PD and aging goes far beyond of the pure association. In fact, a biologic interaction between aging and neuronal degeneration has been suggested [33]. According to this idea, aging influences clinical progression of the disease rather than clinical onset or disease initiation, and involves an underlying mechanism acting on non-dopaminergic rather than dopaminergic structures. Indeed, the appearance of non-motor symptoms is related to aging rather than to disease duration or severity [reviewed in [33,38]]. This relationship is not found in the case of cardinal motor symptoms which are more related to the deficiency of dopamine. The mechanism(s) responsible for this biologic interaction between aging and neuronal degeneration are not totally known (see above). Their identification could lead to new drug targets.

2.3. Associated lesions

Most of the brains of PD patients included in large pathological studies, present with a mixture of changes characteristic of PD with abnormalities typical of AD [17,38,40]. Most of these patients were demented during the last years of their life. Importantly, the percentage of senile plaques and neurofibrillary tangles increased in parallel with age. Vascular lesions were present in a proportion close to 20% of cases [38,40].

The role of these pathological abnormalities in the clinical outcome of PD is not well-known. Even more, it is very difficult to infer owing to the high prevalence of these kinds of lesions in elderly people who died with any neurological dysfunction. However, the relationship between the possibility of becoming
demented and the presence of AD-like and vascular pathology is highly likely.

3. Concept of neuroprotection

Neuroprotection can be defined as the consequence of any intervention that produces enduring benefits by favourably influencing underlying etiology or pathogenesis and thereby forestalling onset of illness or clinical decline [11,12]. Neurorescue is defined as the capacity of any intervention to normalize the function of injured (but not dead) neurons [11,12]. This implies that neurons may be dysfunctional but not irreversibly damaged and therefore capable of being restored to normal functioning. Both concepts can be included under the umbrella of “disease modification” which can be seen as the clinical face of neuroprotection and/or neurorescue.

All these concepts imply that the main actors in neuroprotection are the pathogenesis of PD (particularly cell death) and the clinical evolution [11,12]. However, PD is better defined as the final consequence of a degenerative process linked to a special vulnerability of cathecholaminergic cell groups and a failure of compensatory mechanisms associated with the effects of aging and brain lesions (Table 2). In other words, it is the final result of neuronal death, neuronal damage, neuronal dysfunction and the effects of modulatory factors on them (Fig. 1). Therefore, it could be worth including their contribution in the concept of neuroprotection. Furthermore, the preservation of function of normal neurons can also lead to a better outcome and, consequently, it should be considered an important target for any neuroprotective therapy. This fits nicely with the concept of neuronal vitality or disease activity [45].

In keeping with this line of thinking, I would like to propose a new view of the concept of neuroprotection: An intervention able to slowdown PD clinical progression by directly or indirectly influencing disease pathogenesis with a resultant reduction of cell death, cell damage and cell dysfunction. This concept covers the classical ones. From a practical point of view, it implies that an improvement in general health, which can reduce the risk of vascular lesions, or in the aging process, could exert a neuroprotective effect. Finally, it emphasizes the importance of gaining insight into the interaction between these new elements, PD pathogenesis and clinical expression since this could result in new therapeutic targets.

4. Therapeutic implications of these ideas

At present, neuroprotective strategies are not aimed at treating the consequences of the disease, but rather seek to interfere with the basic pathogenic mechanism(s) of nigral cell death in PD [11,12]. Here discussed ideas could have some relevant therapeutic implications. Firstly, it is crucial to determine whether the phenomenon we are trying to interfere with is a compensatory or a pathogenic mechanism. Otherwise, interventions aimed at their reversal might worsen rather than ameliorate the disease. In this setting, it could be of great relevance to establish precisely the role of Lewy bodies and STN hyperactivity in the death of dopamine neurons. It is likely that the observable aggregates may be relatively innocuous and that the soluble precursors to the filamentous lesions, the so-called protofibrils, may be more important toxic intermediates [46]. Thus, preventing aggregation may have untoward adverse effects if the inclusion is actually an adaptive or protective cellular response to abnormal proteins. The case of STN hyperactivity is quite similar. STN neurons release glutamic acid on the SNpc. While their hyperactivity is an early compensatory mechanism [47], it would also lead to a profound excitotoxic stress on already damaged dopamine neurons. Animal data suggest that STN inhibition could protect dopaminergic neurons against the toxic effects of 6-hydroxydopamine or MPTP. However, this has not been proven in patients in whom the STN has been inhibited by the application of deep brain stimulation electrodes [48].

Finally, some life style recommendations, such as the intake of hypocaloric diets with a high antioxidant content and salt free and the performance of regular physical and intellectual activities, might positively influence the final outcome by strengthening the compensatory mechanisms. All of these interventions have been shown to exert neuroprotective effects in experimental models by increasing the levels of trophic factors [49], by reducing the likelihood of suffering from stroke and by contributing to the correct functioning of the regenerative neural stem cells system.

5. Conclusion

PD is a multisystemic, progressive neurodegenerative disorder in which symptoms appear when neuronal death exceeds a critical threshold. The final development of symptoms with increasing neuronal loss and neurotransmitter(s) depletion might result from the failure of, as yet, not totally identified compensatory mechanism(s) that counter the abnormal activity arising from the basal ganglia. PD is the final result of neuronal death, neuronal damage and the effects of modulatory factors on them. Compensatory mechanisms, aging and associated lesions are the most important modulatory elements. Current descriptions of the pathogenic cascade(s) involved in PD should further

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**Table 2**

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<th>Key elements in PD pathogenesis.</th>
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<td>Cell death</td>
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<td>Cell damage</td>
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<td>Cell dysfunction</td>
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<tr>
<td>Compensatory mechanisms</td>
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<tr>
<td>Aging</td>
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<td>Associated lesions</td>
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**Fig. 1.** PD process begins at the molecular level and eventually affects the whole organization of neural networks (passing through neurons, synapses and circuits). The neurodegenerative process underlying PD has two well differentiated phases: a more or less acute onset is followed by a slow progression. Clinical manifestations appear after considerable loss of neurons have occurred and are quite heterogeneous. PD degenerative process and clinical symptoms are related to cell death, cell damage and cell dysfunction along to modulatory factors which can influence onset and/or progression of the disease. Cell vulnerability and compensatory mechanisms are crucial. The role of aging, plasticity and associated lesions seems to be particularly important. Thus, PD is the final consequence of a degenerative process linked to a special vulnerability of cathecholaminergic cell groups and a failure of compensatory mechanisms associated with aging and brain lesions.
account not only for the involvement of cell death mechanisms but also for the role of these factors. Gaining insight into their interactions with onset and progression of PD might eventually offer opportunities to modify the clinical course of the disease. Indeed, tremendous benefits might be reaped from therapeutic interventions that maximize a patient’s opportunity for optimal performance, shifting the focus from neurons that are lost to those that survive.

References