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Pathophysiology of Parkinson's disease behavior – a view from the network

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SUMMARY

Advancements in neuroscience have uncovered an amazing complexity of connectivity between nuclei sites and circuits within the brain. Moreover, clinical and neuropathological study has revealed diffuse involvement of the nervous system in Parkinson's disease associated with early and/or significant clinical symptoms. Behavior manifestations in Parkinson's disease include cognitive decline and unwanted positive behaviors such as hallucinations and impulse-control disorders. The pathophysiology of Parkinson's disease can be conceptualized at multiple levels that include: (1) Molecular pathogenesis, (2) Cellular/Tissue abnormalities, (3) Neurochemical changes, (4) Site and circuit dysfunction, and (5) Network dysfunction. Currently, there is only a vague correlation with genetic abnormalities that manifest worse Parkinson's disease behavior problems, but abnormalities in misfolded proteins such as α-synuclein and Aβ peptide that are increased in cortical and subcortical areas do correlate with worse behavior signs and symptoms. Both Lewy-type synucleinopathy and Alzheimer's disease pathologies, along with loss of synaptic integrity, seem to correlate with Parkinson's disease cognitive decline. Neurochemical changes of dopamine, acetylcholine, and other monoamines are associated. The frontostriate circuit is most commonly implicated in Parkinson's disease behavior. However, there is now beginning to be evidence that diffuse global network dysfunction is possibly the unifying pathophysiology from all of these level abnormalities.

1. Introduction

For most of neurology's history, we have been concerned with correlating clinical signs and symptoms with relatively circumscribed sites and/or circuits of nervous system dysfunction. Initially, even in the case of neurodegenerative illness, the hallmark of each disorder was thought to be relatively isolated. With better tools and more study, multiple sites of involvement were realized. This has given rise to a more complex picture when trying to explain the clinical syndrome pathophysiology in neurodegenerative diseases. For Parkinson's disease (PD), the substantia nigra (SN) was the focus of attention for decades. With greater understanding of basal ganglia physiology, the concept of "circuit abnormalities" caused by the SN lesion provided a simplistic but workable model for the negative motor symptoms of PD. However, greater attention to behavioral symptoms in PD has given rise to a variety of discovered correlates that include behavioral basal ganglia circuit dysfunction, diffuse projection abnormalities of acetylcholine and monoamines, and intrinsic cortical dysfunction [1]. Accordingly, this has produced different possible explanations for PD behavior pathophysiology. However, these different correlates have also given an opportunity to consider ways in which anatomically distinct pathological correlates can produce a combined pathophysiology via a global network dysfunction. Thus, the search is on for how these correlates contribute to a network dysfunction that can be directly related to the behavioral problems of PD.

Manifestations of abnormal behavior in PD most notably include cognitive decline and unwanted positive behaviors such as hallucinations and impulse-control disorders. When compared to Alzheimer's disease (AD), frontal/executive cognitive problems are more prominent. Nevertheless, memory problems are very significiant. Over time, multi-domain cognitive dysfunction fulfilling the criteria for dementia includes problems with frontal/executive dysfunction, memory, and visuospatial functions. In addition, hallucinations, impulsive behavior problems, and psychotic tendencies are common. Such problems cause enormous disability and are additive to the motor disability [1]. Treatment of such symptoms is modest and often temporary. Acetylcholinesterase inhibitors may offer mild relief in memory problems, and certain psychotropic medications can partially treat unwanted behaviors. However, better treatments are clearly needed. In order to improve treatment, a better understanding of PD behavior pathophysiology is needed.

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Multiple levels of abnormalities for the pathophysiology of PD behavior have been studied. These may be depicted as follows:

Abnormal Behavior
⇑
Global Network Activity Dysfunction
⇑
Site and Circuit Dysfunction
⇑
Neurochemical Changes
⇑
Cellular/Tissue Abnormalities
Molecular Pathology

In this article, we will discuss these levels of dysfunction, but special emphasis will be placed on global network dysfunction and its correlation with abnormal behavior in PD.

2. Molecular pathogenesis

The molecular changes in PD must be ultimately responsible for producing the behavioral changes in PD, but currently, the specific connection is not clear. Behavior problems are common in all types of PD, so it remains to be clarified whether molecular differences between parkinsonism disorders can even account for the presence or absence of behavior changes seen in these parkinsonian syndromes. Genetic mutations that are associated with PD and which commonly have dementia include PARK1, PARK4, and PARK8 [2]. It is difficult to know how much PD behavior pathophysiology to attribute to the presence of a mutation per se, since sporadic PD also commonly demonstrates cognitive decline and other behavior abnormalities. The presence of ApoE4 was initially reported to be associated with PD dementia. More recent studies have suggested a lack of association [3]. The possibility remains that ApoE4 produces increased risk of dementia in PD, but this possibility needs more study. Differences in gene expression levels have been found in PD with dementia in the cingulate cortex, many of which are down-regulated [4]. The significance of these changes is not clear, but such expression changes may begin to provide insight as to how molecular changes in PD can give rise to behavioral changes.

The presence of the abnormal misfolded proteins α-synuclein, amyloid beta (Aβ) peptide, and tau in limbic and cortical structures represent logical possibilities for producing behavioral problems in PD. It has been established that the increases in the concentrations of α-synuclein and amyloid peptide precede the formation of plaques and Lewy-type synucleinopathy (LTS) pathologies [5–7]. Their altered forms and modifications, such as phosphorylated α-synuclein, have been found to precede microscopically visible cellular changes such as the Lewy body in limbic and cortical areas [8]. The mechanism by which higher α-synuclein levels could directly cause or be associated with cerebral neuron toxicity is currently unknown. Several mechanisms have been proposed for α-synuclein neuronal toxicity, including membrane disruption; interference with signaling pathways; altering vesicle trafficking; post-translational modification; and others [1]. α-synuclein oligomers have been suggested to cause neurotoxicity through calcium influx and seeding [9]. Evidence of oxidative stress is also apparent in these areas early. Membrane disruption of α-synuclein can alter the electrical properties of neurons, causing abnormal neuron firing [10]. Such membrane changes may cause the electrophysiology correlates of cognitive decline, such as slower electroencephalography frequencies, and small amplitude cortical myoclonus [10]. More research is needed to determine how abnormal α-synuclein may be toxic to cortical neuron function.

3. Cellular/tissue abnormalities

PD dementia is associated with the later Braak stages that coincide with LTS in cortical regions, and multiple studies show correlation with worse cognitive status and more advanced LTS. There is also literature that supports cortical AD pathology to be a contributing factor to PD dementia [1]. There are different views about which of the two pathology types plays the dominant role, and both factors continue to be investigated [11].

Neocortical synaptic density demonstrates correlation with cognitive impairment in AD [12]. Synaptophysin is a 38 kilodalton Ca^{2+} binding integral protein of vesicle membranes, and thus detecting its presence provides a presynaptic marker. Synaptic density has been rarely studied in Lewy body disorders (PD, PD dementia, dementia with Lewy bodies [DLB]). Decreases in synaptophysin have been found in the frontal and temporal lobes and hippocampus in Lewy body disorders [13]. In comparative studies, the synaptophysin loss is AD > DLB > PD dementia > PD [14]. While the pattern of synaptophysin loss was diffusely distributed across the cortical layers in AD, the loss in PD and PD dementia was greatest around layer V. Thus, there are both qualitative and quantitative differences in synaptic density loss between AD and Lewy body disorders. Elucidating the significance of these differences may provide insight for the pathophysiology of PD behavior.

4. Neurochemical changes

In PD, the neurons of diffusely projecting acetylcholine, dopamine, and serotonin systems that project to cortical areas which are important for behavior do undergo neurodegeneration. We also know that in the later Braak PD stages, the subcortical LTS pathology is more severe. All these changes seem to correlate with cognitive deterioration and behavioral abnormalities [15]. The acetylcholine and monoamine neurotransmitter systems arising from basal forebrain and brainstem project onto all cortical layers but there is a preference to layers I–III [16]. There is evidence that these systems perform a "modulation influence" by their use of presynaptic and extrasynaptic transmission [16]. Acetylcholinesterase inhibitors are a popular treatment for memory decline in PD, although the effects are modest. It may be that such treatment partially normalizes the "modulation influence" of cholinergic activity.

5. Site and circuit dysfunction

The most famous site of dysfunction in PD is the substantia nigra, and the most famous circuit is the frontostriate circuit. This comes from the converging evidence that striatal dopamine depletion alters the basal ganglia output to the frontal cortex through the thalamus, frontal cortical areas are commonly affected by Lewy pathology, and frontal/executive cognitive deficits are common in PD [17]. The frontal/executive deficits do not respond well to dopamine replacement therapy, and this may be related to frontal lobe intrinsic pathology or other non-dopamine influences on the circuit. Since there is some segregation of frontostriate circuitry anatomically as well as with regard to different aspects of behavior, non-dopamine influences may differentially affect this circuit segregation [18]. Executive dysfunction, mood alteration, apathy, and poor motivation are all behavioral manifestations related to frontal lobe dysfunction in PD. There are anterior cingulate, dorsolateral prefrontal, and orbitofrontal cortical areas that represent three separate frontostriate circuits. Each of these "subcircuits" may have quite different connections with other subcortical projections from acetylcholine and monoamine