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Hyper-serotonergic state determines onset and progression of idiopathic Parkinson's disease

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ABSTRACT

Despite decades of research on Parkinson's disease (PD), the etiology of this disease remains unclear. The present manuscript introduces a new hypothesis proposing a hyper-serotonergic state as the main mechanism leading to axonal impairment both in dopaminergic and serotonergic neurons in PD. The strong serotonergic connection between the raphe nuclei and the dorsal raphe nuclei with the basal ganglia, all important brain structures associated with the pathophysiology of PD, emphasize a potential role for this neurotransmitter in PD. Importantly, a hyper-serotonergic state can lead to axonal growth impairment, an effect that seems to be selective to axons that can respond to this neurotransmitter. Serotonin seems to be a promising candidate to explain several of the poorly understood early symptoms of PD, including sleep impairment, anxiety, altered gastrointestinal motility and hallucinations. The hypothesis proposed here emphasizes that a hyper-serotonergic state would initially cause disruption of axonal transportation, an acute state in which axonal changes are reversible and the neurodegenerative process can be halted. As the hyper-serotonergic state persists, the accumulation of neurotoxic products and a sustained impairment in axonal transportation would lead to axonal death and culminate in an irreversible neurodegenerative process. The potential implications of this hypothesis are discussed, as well as how future research can be employed to further elucidate the role of serotonin on PD progression.

Introduction

Since its first description by James Parkinson in the early 19th century, the field of Parkinson's disease (PD) research has changed in terms of what scientists and physicians understand of its pathology and onset. While several insights and new perspectives have been proposed on the risk factors and processes involved in PD [1–6], the specific events that trigger the neurodegenerative process and lead to these disruptions remain unknown. Therefore, two hundred years after its discovery, there is still no major advance in PD therapy.

When it comes to explaining the natural course of the disease, there is no consensus regarding the ongoing process that leads to neuronal death. However, several studies have proposed PD to be an axonopathy [7–8]. Theories, such as the one linking an axonal "dying back" mechanism as a main neurodegenerative process in PD progression [9,2], point out to factors that are a consequence of underlying processes, but not the main mechanism involved in axon degeneration. Others, such as the oxidative stress theory, have important roles in partially explaining the progression of PD [10–11].

According to these theories, impairment in axon function and consequent axonal transport, leading to synaptic disturbances, soma alteration and neuronal death, appear to be strongly correlated with the course of the disease and a determinant of its onset [12]. For instance, while an increase in α-synuclein levels has been considered one of the most important factors of neurodegeneration in PD [13–15], a recent study has shown that an alteration in proteins related to axonal transport was more markedly associated with non-motor symptom progression than α-synuclein levels [16].

However, the mechanisms underlying axonal disruption in PD remain poorly understood. It remains unknown whether altered axonal function in PD is related to a dying back mechanism and, consequently, neurodegenerative processes, or if genetic factors play a major role in axonal impairment, as seen in Perry's syndrome [17]. The present hypothesis proposes a role for the neurotransmitter serotonin in modulating axonal impairment in PD, leading both to axonal death and to the activation of cascades responsible for widely spread neuronal death.

The strong serotonergic connection between the raphe nuclei and the dorsal raphe nuclei with the basal ganglia, all important brain structures associated with the pathophysiology of PD, emphasize a potential role for this neurotransmitter in PD [18–22]. However, the

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actual role of serotonin in axon degeneration and how this neurotransmitter affects axonal function, whether directly or indirectly, has not yet been fully elucidated. Therefore, the objective of this manuscript is to introduce a new theoretical approach proposing a hyper-serotonergic state as the main mechanism leading to axonal impairment both in dopaminergic and serotonergic neurons in PD.

Role of axon impairment in symptoms and neuronal death associated with PD

PD is an extremely peculiar condition. Despite the loss of dopaminergic neurons and impaired axonal connection associated with this disease, most of its clinically recognized symptoms do not reflect the extent of the alleged amount of neuronal loss in the substantia nigra (SN) [23]. Such a major neuronal loss would be expected to impair nearly all SN functions, from behavior to brain functions associated with the basal ganglia and dopaminergic systems. Notwithstanding, according to the current classification of PD, its predominant symptoms are primarily motor, and include tremor, bradykinesia, rigidity and/or postural instability. In fact, motor symptoms seem preponderant, at least clinically, in PD onset, and are the only symptoms considered in PD diagnosis. However, several non-motor symptoms have been attributed to early PD, and their importance and/or influence on PD development are still a matter of debate.

Nevertheless, the pattern of the neurological and motor symptoms in PD suggests a close relationship with the extension of the dopaminergic system. Three major categories have been proposed regarding the length of efferent dopamine axons: ultrashort systems, intermediate-length systems and long-length systems [24]. Early symptoms of PD, such as olfactory impairment and blinking rate, seem to be associated with the ultrashort system [25–26]. Therefore, short axons seem to degenerate more rapidly than longer axons, which further suggests that axon degeneration is a key factor in the onset of PD. It is important to note, however, that the vagus nerve, which is a long axonal system, is among the first to degenerate in PD, with autonomic dysfunctions being present in early PD. As explained below, serotonin seems to play a role in modulating vagal impulses and may be responsible for autonomic symptoms in early PD, which would explain this discrepancy [27]. Among others, these features further implicate the role of axons in the onset of PD, and emphasize that the idea of axon impairment as a key factor in modulating the onset of PD appears to be anatomically grounded. Finally, strong evidence suggests that microtubule dynamics are altered in PD [28], with an impairment in the function of these cytoskeletal structures further implicating axonopathy as the leading neurodegenerative process in PD. Because anterograde and retrograde axonal transport can affect synaptic and soma function, impairment in axonal function would then lead to decreased neurotransmitter release and cell death. Among the neurotransmitter systems involved in this process, serotonin dysfunction seems to be an important contributor to the progression of PD [19,29].

Altered serotonergic neurotransmission as a leading process in PD axon degeneration

Serotonin seems to be a promising candidate to explain several of the poorly understood early symptoms of PD. Most of the early non-motor symptoms of the disease appear to be, to some degree, related to a hyper-serotonergic state. For instance, PD symptoms such as sleep impairment, anxiety, altered gastrointestinal motility and hallucinations can be linked to an altered serotonergic activity [29].

Sleep problems are reported by nearly 70% of patients with PD [30–31]. Sleep complaints can begin as early as 5–10 years before the appearance of motor symptoms, and are one of the earliest symptoms in PD, suggesting an early disturbance in sleep-related pathways. The most prominent of these symptoms are increased micro arousals, insomnia and Rapid eye movement (REM) sleep disruption [30]. Serotonergic neurons in the dorsal raphe nuclei have been proposed to be involved in sleep-wake cycle disturbances observed in PD, with increased serotonin neuron firing rates being associated with arousal, and decreased firing rates being associated with sleep [32–33]. The fact that PD patients frequently present REM sleep disturbance also points to a role of serotonin in this disease. Increased serotonergic dorsal raphe nuclei activity has been shown in cats with REM sleep disruption produced by bilateral lesions of the pontine tegmentum, which resulted in the expression of REM sleep without muscle atonia and increased motor activity [34]. PD patients also present lack of muscle atonia during REM sleep and increased motor activity, suggesting an important role of serotonin in these phenomena [35].

Anxiety is another early non-motor symptom of PD [36] that seems to have a serotonergic component. Although some theories proposed low serotonergic input in the amygdala as one of the mechanisms for anxiety disorders [37], increased serotonin release both in the raphe nuclei and amygdala, contributing to a hyper-serotonergic state, have also been proposed [38]. Regardless of the specific mechanisms, an altered serotonergic state seems to be one of the underlying factors of anxiety disorder [37,39]. Therefore, the fact that anxiety appears in the early stages of PD suggests that brain structures involved in serotonin production might be affected early on in the progression of this disease.

The gut-brain axis has been increasingly implicated in neurodegenerative processes associated with several diseases, including PD [40]. The influence of the gut-brain axis in PD further emphasizes a potential role for serotonin in this disease. Recent studies have reported a strong correlation between inflammatory states occurring in the gut, the increase in intestinal permeability, changes in the microbiome and PD onset [41–42]. Because enterochromaffin cells in the gastrointestinal epithelium account for almost 90% of the body synthesis of serotonin [43], systemic levels of serotonin are easily changed depending on diet and ongoing processes in the gastrointestinal tract. In fact, gut inflammatory processes, which are thought to deleteriously impact the progression and increase the likelihood of PD development, contribute to an increase in blood levels and production of serotonin [44]. Furthermore, the vagus nerve is one of the anatomical structures responsible for the connection between the brain and the gut serotonergic system [43], and a relationship between the vagus nerve and PD has also been reported [45,46]. Finally, another important symptom involving the gastrointestinal tract is the lack of motility reported by patients with PD. This non-motor symptom is, among others, one of the earliest symptoms in PD [47]. Although most of the available literature has proposed this phenomenon as an autonomic dysfunction [48], serotonin plays an important role in intestinal motility and can modulate sympathetic activity [49], and might play a role in the underlying process of gastrointestinal PD symptoms.

Hypothesis

Based on the assumptions described above and the anatomical correlation between the brainstem and its serotonergic connection with the basal ganglia, a hyper-serotonergic state seems to be present in PD and be involved even in the earliest non-motor symptoms of the disease. Importantly, a hyper-serotonergic state can lead to axonal growth impairment, an effect that seems to be selective to axons that can respond to this neurotransmitter [50], which would explain why the neurodegenerative process in PD is slow and selective. Therefore, selective serotonin-induced regulation of axonal growth and maintenance could explain most of the symptoms of PD.

Serotonin has been shown to play an inhibitory role in axon growth or regeneration of mature neurons, from invertebrates to mammals [51]. For instance, fluoxetine, a selective serotonin reuptake inhibitor, suppressed axonal growth *in vitro* [52]. However, the specific mechanisms underlying the interaction between serotonin and the axon remain poorly understood. Here I propose that a direct serotonin receptor-mediated modulation of axonal growth could play a prominent

role in this phenomenon. Although the role of serotonin receptors in serotonin-mediated suppression of axonal growth has been investigated [51], contradictory findings have been obtained because of the complexity of receptor subtype-specific signaling and the large number of receptors through which serotonin can exert its effects. Therefore, further research is needed in order to identify specific receptors mediating this effect.

Regardless of the specific receptor subtype, I hereby propose that a hyper-serotonergic state would initially cause disruption of axonal transportation, an acute state in which axonal changes are reversible and the neurodegenerative process can be halted. As the hyper-serotonergic state persists, the accumulation of neurotoxic products and a sustained impairment in axonal transportation would lead to axonal death in both serotonergic and dopaminergic neurons. In fact, a recent study proposes a potential role for serotonin in the clearance of misfolded protein [19], which highlights its function in regulating axonal transportation by modulating protein trafficking in this cellular structure. Moreover studies have shown an increase in striatal serotonin innervation in PD patients [53]. Further corroborating this hypothesis, recent studies have shown a correlation between a hyper-serotonergic state and autism [54], a disease associated with altered axonal function, among other neuropathological findings [55].

Therefore, I hypothesize that a hyper-serotonergic state leads to a selective axonal impairment, defining the pattern of axonal degeneration. A limitation of the current hypothesis, however, is that it does not elucidate the mechanisms by which the firing pattern of neurons in the raphe nuclei is disrupted. This effect would create a cascade of axonal and cellular changes, inflammatory responses, and an increase in the amount of reactive oxygen species due to the exacerbated activation of neurotransmitter enzymes responsible for degrading it, ultimately leading to broad neuronal death. A hyper-serotonergic state would alter axonal function, and this effect would be selective to axons that are sensitive to serotonin, which would define the pattern of axonal injury. The accumulation of axonally-transported proteins (e.g., α-synuclein) in PD emphasizes axonal disruption as an important process in this disease. This cycle would continue until a major neuronal loss is observed, when the neurodegenerative process becomes unstoppable. Pathological findings such as Lewy bodies and α-synuclein changes could be caused by compensatory cellular mechanisms of adaptation or changes in the expression of genetic material in response to axonal injury. These would be secondary deleterious factors that could contribute to PD progression, but that have no role in the onset of the disease.

Consequences of the hypothesis

Our understanding of the mechanisms underlying PD onset is still a matter of discussion, and most of the current therapeutic approaches for PD do not change the course of the disease. However, important medical implications can arise from the present hypothesis. If, as proposed in the present hypothesis, a hyper-serotonergic state contributes to axon impairment and PD progression, an early therapeutic intervention could be proposed using serotonergic antagonists in order to prevent further development of PD upon presentation of early symptoms. Treatment with the serotonin 5-HT_{2A} receptor antagonists has been shown to improve motor symptoms in animal models of PD [56]. In addition, the antagonist/inverse agonist at serotonin 5-HT_{2A} and 5-HT_{2C} receptors pimavanserin has been recently proposed as a novel antipsychotic for PD psychosis [57–59], further emphasizing a potential therapeutic approach for PD by using serotonergic compounds. However, these studies were conducted once the disease had already been established and on its later stages. The use of serotonergic antagonists in early PD targeting non-motor symptoms would be challenging as the clinical diagnosis relies on motor symptoms, when the pathological process is already widespread in the brain. Although non-motor symptoms are present in almost every patient with idiopathic PD [60–61], linking non-motor symptoms to a neurodegenerative process before the motor symptoms are clinically observed can be difficult.

Therefore, although promising, an interventional approach with serotonergic drugs could prove unsuccessful. As proposed here, the hyper-serotonergic state would cause a neurodegenerative process, which can be irreversible when the disease becomes clinically evident. In order for a serotonergic interventional therapy to work, it would have to be administered in the very early stages of PD. Future studies in animal models of PD could further elucidate whether the current hypothesis is correct by administering serotonin receptor antagonists at the beginning of PD induction. Because of the large number of excellent selective serotonin agonists, antagonists, and inverse agonists available, such studies could also further elucidate the role of specific receptor subtypes on serotonin-induced axonal death and neurodegeneration in PD.

Conclusion

Understanding processes underlying neurodegenerative diseases has been a challenge throughout the years. The hypothesis proposed in this manuscript brings together most of the pathological, anatomical and physiological findings of PD, proposing that a hyper-serotonergic state could lead to selective axonal impairment and axonal dysfunction as the main process leading to a neurodegenerative process. This process seems to explain most of the unveiled mechanisms of neurodegeneration in PD and might help guide future studies towards identifying a treatment and cure for this debilitating disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Appendix A. Supplementary data

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