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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.