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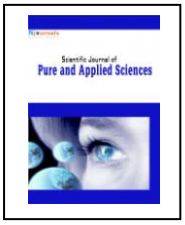

Perspective article

Proteasome Activity in Parkinsonism through D1 Dopamine Receptor

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ABSTRACT

As of today, L-DOPA is recognized as the most efficacious drug to alleviate the typical signs and symptoms of Parkinson disease (PD). It is most effective for the akinetic symtoms, and its use is indicated when the disease becomes disabling or it cannot be controlled by other antiparkinsonian drugs. Unfortunately, response to medication changes during the progression of the disease, with the patients developing tolerance to treatment and the need for higher doses that lead to the development of side effects. The Ubiquitine-proteosome system (UPS) is key in regulating the degradation of normal and abnormal intracellular proteins linked to signal transduction, cell cycle progression, apoptosis and differenciation; therefore it dysregulation would be expected to impact several systems. UPS dysregulation has been implicated in cancer, neurodegenerative and autoimmune diseases.

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A considerable amount of patients end up developing L-DOPA induced complications within several years of starting treatment; these may include motor fluctuations, dystonia, and most importantly dyskinesia. It is estimated that about 40% of patients develop dyskinesia after 5 years of therapy, with the figure surpasing the 60% by 10 years (Ahlskog and Muenter, 2001).

Pathophysiology of L-DOPA-induced dyskinesia (LID) remains unclear. Most knowledge corncerns alterations in the basal ganglia circuitry signaling, with maladaptive neuroplasticity postsynaptic dopamine receptors and transporters, most likely due to secondary to the nonphysiologic fluctuations in plasmatic dopamine levels in patients treated with L-DOPA (Troiano et al., 2009).

Prevention and treatment of LID has become a central focus for basic and clinical PD researchers. Studies on animal models, especially rodents and nonhuman primates, reveal interesting aspects of this complex entity, and have allowed researchers to ellucidate some of the main mechanisms involved. A recent article by Bethet et al. published in the Journal of Neuroscience proposed that disregulation in D1 dopamine receptor (D1R) in PD patients treated chronically with L-DOPA is associated with impaired proteosome activity. In order to prove it, rodent and primate sporadic PD models were used, comparing protoeosome activity between subjects receiving L-DOPA treatment, placebo or left untreated. The research team was able to identify prove that parkinsonian animals with chronic L-DOPA treatment developed striatum-specific decrease in proteasome chymotripsin-like cathalytic activity dependent on D1R activation. Therefore, D1R can be identified as the first step leading to inhibited cathalytic activity and intraneural accumulation of proteins (Berthet et al., 2012).

The Ubiquitine-proteosome system (UPS) is key in regulating the degradation of normal and abnormal intracellular proteins linked to signal transduction, cell cycle progression, apoptosis and differenciation; therefore it dysregulation would be expected to impact several systems. UPS dysregulation has been implicated in cancer, neurodegenerative and autoimmune diseases.

The role of UPS dysregulation in PD pathogenesis has been evidenced by multiple authors, with the detection of decreased proteosome activity and accumulation of ubiquinated proteins in the substancia nigra of PD patients, and the observation that subjects receiving proteosome inhibitors may replicate parkisonian symptoms (Cook et al., 2009). However the originality of Bethet's research lies in the fact that it proves UPS dysregulation is directly linked to L-DOPA, rather than it just being inheren to PD.

We must take into account that although these new findings are encouraging, they are only but one part of the whole spectrum of dysregulations in the synapse that must take place for the development of LID. For example, Troiano et al. have found that the onset of dyskinesias coincides with a downregulation in presinaptic dopamine transporters, leading to oscilating levels of DA at the synaptic cleft (Troiano et al., 2009), and probably contributing to alterations in postsynaptic regulation. L-dopa treatment also induces sprouting of serotonin axon terminals in the dopamine-denervated striatum. Remarkable postsynaptic changes after chronic L-DOPA intake include dysfunctions in NMDA receptors and maladaptative plasticity of serotonin axon terminals (Bagetta et al., 2010; Rylander et al., 2010).

As our knowledge of the mechanisms ivolved in the development of LID increases, new therapeutic approaches may be attempted. Bethel et al. have an interesting proposal: if proteasome inhibition leads to the development of parkinsonian symptoms, would the increase in proteasome activity decrease them? So far no medication is known to have this effect, but it would undoubtly be an interesting and novel approach to PD therapeutics. Opening a new array of possible therapeutical targets for LID focused on improving preteasome function.

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