**INTRODUCTION**

Parkinson disease (PD) is the most common movement disorder affecting over 6 million people worldwide. PD can present with a juvenile or early onset, but it predominantly affects individuals over the age of 55 and the incidence of disease rises after the age of 65. It is characterized by bradykinesia, postural instability, resting tremor, and rigidity associated with the progressive loss of dopaminergic neurons in the substantia nigra pars compacta. During normal aging approximately 0.1–0.2% of the dopaminergic neurons in this area are lost per year, but this rate is accelerated in patients with PD and symptoms manifests when 70–80% of these neurons have been lost. Another pathological marker of PD is the presence of α-synuclein proteinaceous inclusions, known as Lewy bodies. Both genetics factors (such as duplications, triplications or missense mutations in the gene for leucine-rich repeat kinase 2 LRRK2/PARK8) and environmental factors (such as excessive exposure to manganese) may contribute to the etiology of PD.

**RESULTS**

The role of α-synuclein in PD: mutations in the gene for α-synuclein (SNCA) are associated with the phosphorylation of ser 129 of the protein that cause proteinaceous inclusions which can be observed in a spectrum of neurodegenerative diseases termed “synucleinopathies.” α-Synuclein is a highly charged 140-aminoacid heat stable protein that is soluble and natively “unfolded.” It is predominantly expressed in neurons of the central nervous system (CNS), where it localizes to presynaptic terminals in close proximity to synaptic vesicles. Several studies suggest that it is involved in modulating synaptic transmission and neuronal plasticity as well as providing support in the assembly and folding/refolding of SNARE proteins critical for neurotransmitter release, vesicle recycling, and synaptic integrity. In vitro the A53T and the E46K mutations can both increase the rate of fibril formation suggesting a link between α-synuclein aggregation and disease.

The role of LRRK2: recently, LRRK2 has generated most attention in PD research due to the identification of numerous mutations that are associated with disease. LRRK2 is a 2527 aminoacid kinase protein with multiple complex domains associated with various organelles such as the Golgi, mitochondria, and ER. In human LRRK2 is expressed and localized to a variety of neuronal populations, but it is highly expressed in the dopaminceptive regions, such as the caudate-putamen, and frontal cerebral cortex. LRRK2 requires the formation of an ATP-divalent metal cation (Mg2+) complex for the phosphoryl transfer of the γ-phosphate of ATP to a protein substrate. The motif is located at the N-terminal hinge region of the activation loop that switches from an open and extended conformation in the active state to a more closed conformation in the inactive state. The G2019S mutation may disrupt the ability of this movement so that Mg2+ can’t recognize the site of the kinase determining protein aggregation, oxidative stress, and disruption of neurotransmitter synthesis.

**DISCUSSION**

Although direct evidence linking manganese and the demise of neurons in PD is still limited, some of the studies in vitro seem to build circumstantial evidence that dysregulation of manganese homeostasis at the cellular level may play an important role in the etiology of PD. These hypothesis will have to be validated in vivo: “in vivo veritas”.

**REFERENCES**

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α-Synuclein,leucine-rich repeat kinase-2, and manganese in the pathogenesis of Parkinson disease-Neurotoxicology. In press (2011)