

Potential Role of Alpha-Synuclein in the Pathogenesis of Neurodegeneration in a Rat Animal Model

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Editorial

Parkinson's disease (PD) is the most common movement disorder and second most common, after Alzheimer's disease, neurodegenerative disorder in humans. It affects over one million people in North America and over four millions people worldwide and influences all races and both sexes. PD is defined clinically by four characteristic motor symptoms: uncontrollable resting tremor, slowness in movement (bradykinesia) and postural instability. Neuronal accumulation of a protein called alpha synuclein (α -syn) appears to be a critical step in the development of PD and other neurodegenerative diseases, collectively referred to as synucleinopathies. Genetic and biological studies support a role for α -syn in the pathophysiology of these diseases. Therefore, research must be continued in order to better understand the functions of the synuclein proteins under normal physiological conditions as well as their role in disease.

The main goal of our laboratory is to validate a novel and unique rat model for neurodegenerative disorder that mimics some pathological aspects of Parkinson's disease (PD), which is spontaneous, inherited autosomal recessive. The PD-like is affecting a colony of Berlin-Druckrey (BD IV) rats, which is maintained at Texas A&M University, Lab Animal Facility, USA. The affected rats clinically show tremor, rigidity, spasticity and incoordination. They also demonstrated decrease dopamine level and loss of dopaminergic neurons in specific areas of the brain. A protein, α -syn also, a common finding in human PD, was highly elevated in the brain of neurologically affected rats. The genetic alteration responsible for this neurological disorder is not determined, yet.

The spontaneous mutant model was developed by the PI, Dr. George Stoica, in a colony of Sprague Dawley (SD) rats maintained at the Texas A&M University. This phenotype has been maintained in a line of rats through sib-mating, and pedigree information demonstrates clear autosomal-recessive transmission of this trait. Due to the fact that SD rats are an outbreed strain of rats we transferred the phenotype into a syngeneic black hooded rat, Berlin-Druckrey (BD-IV) by inbreeding. The affected BD-IV offspring can be identified during the first few days post natal by the gray color of their coat.

The clinical phenotype is characterized by progressive development of tremor, spasticity and rigidity, bradykinesia, and postural instability and first appears at 15-20 days postnatal, resembling juvenile onset PD in humans. Pathological characterization at 30 days postnatal shows no weight or gross difference between brains of affected versus nonaffected littermates; however, close histological examination reveals a loss of neurons in the mesencephalon, motor cortex and brain stem with associated gliosis (microglia and astrocytes). H&E staining reveals perikaryal Lewy bodies in the striatum and intense axonal eosinophilia in the substantia nigra indicative of dying back neuronal degeneration. Immunohistochemistry with antibodies specific for α -syn intensely labels these key pathological features of PD-like in affected rats. Preliminary data from our laboratory have demonstrated that the expression of α -syn mRNA is increased 3.5-fold and 11-fold in the mesencephalic brain region of affected rats at 20 and 27 days postnatal, respectively, compared to unaffected littermates. No increase in α -syn mRNA was observed at 7 days or 10 days postnatal. By western analysis, we found that levels of total α -syn and serine 129 phosphorylated α -syn were significantly increased in the brains of affected rats compared to unaffected littermates at 25 days postnatal. Western analysis showed a significant decrease in tyrosine hydroxylase protein levels in the striatum of affected rats, indicating nigrostriatal pathway neurodegeneration.

Overexpression of α -syn protein in the brain of affected rats may provide a naturally occurring animal model that reproduces significant pathological, neurochemical, and behavioral features of human Parkinson's disease and has a great potential not only for studying the mechanism of PD but also for prevention and therapy which can lead to translational studies. [1,2].

References

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