Sjournals
Scientific Journals
Scientific Journal of Medical Science (2013) 2(3) 45-47

Contents lists available at Sjournals
Scientific Journal of Medical Science
Journal homepage: www.Sjournals.com

Perspective article

Genetic mice models of Parkinson's disease

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ARTICLE INFO

Article history:
Received 24 Jul 2012
Accepted 15 Aug 2012
Available online 27 March 2013

Keywords:
Parkinson's disease
Dopaminergic neurons
Neurodegeneration
Substantia nigra pars compacta
Gene
Mutation

ABSTRACT

The loss of dopaminergic neurons in the substancia nigra pars compacta leads to the characteristic symptoms of Parkinson's disease (PD), whose Lewy bodies is a pathologic sign almost always found. Various monogenic forms account for a minority of cases of PD, but have provided crucial insight into disease mechanism. However, genetically faithful models have not been exposed to putative toxicants in a manner that is clearly relevant to human exposures, and most of studies have used conventional genetically modified animals and convenient dosing paradigms. Better translation between preclinical, neuropathologic animal model and, clinical research would be important for future clinical trials.

Parkinson's disease (PD) is due to the loss of dopaminergic input to the striatum as a consequence of neuronal degeneration of the *substantia nigra pars compacta* (SNpc) (Hirsh et al., 1988), which causes a severe dopamine deficit and results in the basal ganglia circuits dysfunction (Lewis and Barker, 2009). Consequently, disabling motor symptoms appear and are the most distinctive and debilitating manifestations of the malady.

Parkinson's disease is the second most prevalent neurodegenerative disorder after Alzheimer's disease and worldwide it afflicts up to 0.3% of people and 1-2% of adults over 60 years old (De Lau and Breteler, 2006). Nowadays we count with several therapeutic options only to palliate symptoms. Presently no progression-stopping treatment is available.

The aim of most researches focused on understanding PD is to determinate the causes and mechanisms implicate in the progressive neurodegeneration, to develop approaches in the hope of developing a significant neuroprotective or curative therapy. An ideal mouse model of PD would be progressive in nature permitting the characterization of degenerative changes and the onset of early symptoms with time. However, toxin-based mice model decrease in this respect since their acute nature, a single or several injections administrated over a short period of time followed by prompt or abrupt onset of symptoms, restricts their helpfulness.

Recently, Chesselet and Richter (2011) conducted a review of models utilizing hereditary mutated familial genes aimed to generate null mutations of recessive genes or to express additional copies of dominant genes in mice. One of the mouse models expresses the human α-synuclein gene with two mutations (A30P/A53T) that generate an age-dependent loss of TH-positive neurons in the SNpc is perceived with deterioration in motor activity. In an additional approach for overexpressing α-synuclein, a stereotactic injection of the gene transmitted on viral vectors into the SNpc is applied, which created rodents with dopaminergic neuron degeneration. Nevertheless, only the mouse prion promoter A53T α-synuclein transgenic mouse expresses the similar α-synuclein and age-dependent neurodegenerative changes identified in persons. A recent α-synuclein model of PD that expresses the wild type gene with the regulated tetracycline system; loss of neurons in the SNpc, gradual motor deterioration and cognitive deficiency were observed. There has been so much limited success in creating a genetic model of PD applying several autosomal recessive genes involving DJ-1, PINK1 and Parkin (Dawson et al., 2010). *LRRK2* is a novelty identified causative gene for PARK8 type of PD with autosomal dominant inheritance, is a fact that dopamine transmission is defective in LRRK2 mutant mice. Oddly, overexpressing either wild type mouse LRRK2 produces no phenotypes that are relevant to PD, nevertheless these data demonstrate that the mutated LRRK2 protein are necessary to further pathogenic toxicity (Qing, 2012). LRRK2 mutations cause improved kinase activity to different degrees: G2019S being the strongest, and R1441G being moderate (West et al., 2005). Also has been shown that the LRRK2 molecule can dimerize and that the GTPase domain in LRRK2 can regulate its kinase activity (Greggio et al., 2008). While the data of several environmental factors in LRRK2 transgenic mice are obtained, result from LRRK2 knockout mice was no enhancement or suppression of sensitivity to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) (Andres-Mateos et al., 2009). It will be interesting to see whether LRRK2 transgenic mice behave differently. In the other hand has been shown that L-DOPA-induced dyskinesia associated with chronic L-DOPA treatment in rodent and monkey experimental parkinsonism is associated with a striatum-specific decrease in proteasome chymotrypsin-like catalytic activity that such decreased proteasome catalytic activity results from D1R activation and feeds back the D1R abnormal trafficking (Berthet et al., 2012). Finally, no mouse model is known to develop Lewy bodies and other important aspect is the nonexistence of neuromelanin, which might be implicated in PD pathophysiology.

Mice are extensively used for modeling PD, but no genetic or toxic model completely replicates the pathophysiology noticed in humans. Because it is currently thought that environmental influences and genetic susceptibility play a role in the pathogenesis of PD, possibly the most encouraging models are those that associate genetic models with exposure to toxins such as MPTP.

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