Experimental Neurology 256 (2014) 117–125

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Review

Using viral-mediated gene delivery to model Parkinson's disease: Do nonhuman primate investigations expand our understanding?

Massimo S. Fiandaca, Howard J. Federoff *

Department of Neurology, Georgetown University, Washington, D.C. 20007, USA
Department of Neuroscience, Georgetown University, Washington, D.C. 20007, USA

ARTICLE INFO

Article history:
Received 29 October 2012
Revised 8 February 2013
Accepted 14 March 2013
Available online 22 March 2013

Keywords:
Parkinson's disease
Gene transfer
Animal models

ABSTRACT

In this review, we consider the use of nonhuman primate (NHP) models of Parkinson's disease (PD) produced using viral-mediated gene delivery and information they provide in comparison to other model systems in rodents and NHPs. To date, rodent and NHP PD models have found it difficult to fully recapitulate the human disorder and, therefore, provide little actual insight into disease progression. The viral-mediated gene delivery method for α-synuclein has been shown to produce a parkinsonian rodent and NHP. This novel viral-mediated gene transfer model in the NHP appears to provide a significant advance beyond neurotoxicant models, by more closely mimicking the more chronic time course of developed behavioral deterioration and neuropathology. Although we agree that the use of these novel methods inducing parkinsonian NHPs may provide relevant treatment insights, beyond those of more standard PD models, we remain cautious as to the preclinical models' ability to predict outcomes in human trials. In specific cases of certain novel medical therapeutics, therefore, we also consider the phase 0 clinical trial as offering an alternative to the currently non-predictive preclinical models, including those in the NHP.

Contents

Introduction

Until the last 30 years, the majority of preclinical Parkinson's disease (PD) research was performed in rodents. With the advent of nonhuman primate (NHP) toxicant models, however, additional preclinical information for various medical and surgical therapeutic strategies has been developed and translated into human trials. The most common path for clinical therapeutic development, therefore, typically features *in vitro* studies, followed in turn by *in vivo* experiments in rodents and finally, non-rodent species, including NHPs. The recent development of a parkinsonian NHP using viral-mediated gene transfer allows an additional preclinical investigative option for researchers to consider. Unfortunately, the record of preclinical NHP PD modeling being able to accurately predict subsequent clinical success (as opposed to failure) has been less than impressive. This discordance between preclinical NHP results (Herzog et al., 2007) and clinical trial results has been

* Corresponding author at: Department of Neurology, Georgetown University, Washington, D.C. 20007, USA. Fax: +1 202 687 1110.
E-mail address: hjf8@georgetown.edu (H.J. Federoff).

0014-4886/$ – see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.expneurol.2013.03.014

observed most recently with a gene therapy trial for PD (Marks et al., 2010). It remains unknown, however, whether the NHP viral-mediated gene transfer paradigm provides any significant insights above and beyond those of the more classic NHP models, and under what circumstance the use of the new model system fulfills an unmet need.

In an effort to understand where the new NHP model system fits into the investigative armamentarium, our discussion begins with a brief overview of PD and PD models. We then compare the two most common types of PD NHP models, toxicant and genetic, paying particular attention to the prototypical one, central to this review, which is produced *via* viral-mediated gene delivery. Specifically, we discuss how the novel gene transfer model of familial PD compares to the most common NHP toxicant model in use, and contrast insights from the NHP models with information obtained using similar models in rodents. We conclude the discussion with a summary of insights obtained to date, using the novel viral-mediated gene delivery NHP model, and offer our opinions regarding the role and limitations it may have in developing future therapeutic options for PD.

PD and nigrostriatal neuronal pathology

Sporadic/idiopathic PD cases account for approximately 90% of afflicted individuals, and have been postulated to develop as a result of the combined effects of inherited vulnerability and environmental exposure (Maguire-Zeiss and Federoff, 2003; Tsuboi, 2012). The remaining 10% of PD patients fall into a hereditary/familial/genetic category (Lesage and Brice, 2009; Tan and Skipper, 2007). Both forms of PD share responsiveness to dopamine (DA) therapy (Marsden and Parkes, 1977), without sequelae in early stages of the illness, and with associated dyskinesia in later stages of the disease. The sporadic form of the disease differs from some familial forms in age of onset and disease progression (Dauer and Przedborski, 2003; Tsuboi, 2012), with the latter occurring in a younger age group and having a more rapid and relentless course. The classic neurodegeneration associated with PD features loss of pigmented dopaminergic (DA-ergic) neurons (DANs) within the substantia nigra pars compacta (SNpc) (Forno, 1996), and has been reported to differ (Fearnley and Lees, 1991) or been similar to (Collier et al., 2011) nigrostriatal reductions associated with normal aging, in both severity and topology. Similarly, tyrosine hydroxylase immunoreactive (TH-IR) fiber loss within the striatum (Hornykiewicz, 1975), occurs preferentially in the putamen, as opposed to the caudate. Within the putamen, TH-IR fiber losses develop in a gradient; with more severe deficits noted caudally and medially, than rostrally and laterally (Brooks et al., 1990; Hornykiewics and Kish, 1987; Kaufman and Madras, 1991). A pathologic hallmark of PD is the α-synuclein (SYN) intracellular inclusions, Lewy bodies, within various neurons, but especially within the pigmented neurons of the SNpc (Dickson, 2012), as well as in some astrocytes and oligodendrocytes (Arai et al., 1999; Hishikawa et al., 2001).

The neuropathology associated with both sporadic/idiopathic and genetic/familial PD includes discriminate nigrostriatal DAN damage with accumulation of SYN aggregates within neuronal cell perikarya (Lewy bodies) and neuronal processes (Lewy neurites) (Dickson, 2012), as well as within glia (Takahashi and Wakabayashi, 2001; Wakabayashi et al., 1998). SYN is a protein without a clearly determined cellular function, but with suggested roles in both synaptic function and synaptic vesicle maintenance and cycling (Clayton and George, 1999; Fortin et al., 2010). Commonly localized in presynaptic cytoplasm of synaptic terminals of DANs (George, 2002), native SYN protein is unfolded (Weinreb et al., 1996), but features helical regions that may promote aggregation into fibrils and association with membranes (Eliezer et al., 2001). Pathologic findings in early PD (and Lewy body diseases) feature the primary loss of DA-ergic fibers within the striatum, coupled with the accumulation of SYN (Duda et al., 2002; Lotharius and Brundin, 2002). In pathologic states, such as PD, SYN monomers aggregate into prefibrillar intermediates, before forming SYN fibrils, eventually forming mature amyloid fibers (Horvath et al., 2012). Prefibrillar SYN has been shown to be toxic *in vivo* (Winner et al., 2011), and promote dopamine vesicle instability and breakdown (Volles et al., 2001). It is postulated that pathologic accumulation of SYN (and especially the prefibrillar forms) in the presynaptic terminals leads to dysfunctional DA vesicles, vesicle membrane pore formation (Tosatto et al., 2012), increased cytoplasmic DA levels, increased cellular stress with resultant cytotoxicity due to mitochondrial failure, retrograde degeneration of SNpc DANs, and surrounding reactive gliosis (Lotharius and Brundin, 2002).

The aging central nervous system (CNS) features a reduction in the ability to handle oxidative stress (Smith et al., 1991). DANs have a high potential for oxidative stress due to the tendency of cytoplasmic DA to auto-oxidize and form reactive species (Graham, 1978). These reactive entities are further catalyzed to cytotoxic hydroxyl radicals in the presence of iron, which is highest in the SNpc than any other brain region (Kienzl et al., 1999; Lotharius and Brundin, 2002). Under normal circumstances, containment of DA within synaptic vesicles is effective in reducing DA-related neurotoxicity, but as described above, less so in PD. Both genetic and environmental factors have been implicated through this mechanism to progress to selective cell death of DANs seen in PD.

Human consequences of direct environmental and genetic/familial factors

Environmental factors, either alone or in combination with genetic predisposition, probably account for the majority of the idiopathic cases of human PD. The discovery of a selective nigrostriatal DA-ergic neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), as a byproduct of illicit opiate synthesis and human use (Burns et al., 1985; Langston et al., 1983), has provided significant insights to possible environmental connections to sporadic PD. Similarly, the DA-ergic alterations in humans noted with the pesticides paraquat (PQ) and rotenone, strengthen the environmental link to the human PD (Brooks et al., 1999; Jones and Miller, 2008). The toxicity is linked to MPTP's conversion to the 1-methyl-4-phenylpyridinium derivative, MPP+, by monoamine oxidase B (MAO-B) (Yang et al., 1988), with concentration of this toxic byproduct within nigrostriatal DANs. PQ, is an herbicide analog of MPP+ (Cicchetti et al., 2009), and shares a final common pathway with MPTP within the CNS, leading to mitochondrial failure (specifically mitochondrial complex I) within DANs (Langston et al., 1999; Przedborski and Vila, 2001). Rotenone, a known mitochondrial complex I inhibitor, is associated with similar neurotoxicity, and cytoplasmic SYN accumulations within SNpc DAN (Betarbet et al., 2000; Sherer et al., 2003). Neurotoxic parkinsonism features hypokinesia, tremor, and rigidity of relatively sudden onset, with a pertinent clinical history of drug abuse or environmental exposure (Burns et al., 1985; Langston et al., 1983). Pathologically, the typical degeneration of striatal fibers and perikarya of SNpc DANs is prominently seen (Burns et al., 1985; Langston et al., 1983), and typically occurs in a much younger individual than would be expected in idiopathic PD, and even most genetic/familial cases.

The direct link between a genetic abnormality and clinical PD was previously associated with hereditary familial studies until the advent of genome sequencing, which now allows the direct investigation of sporadic gene mutations within the population. Both dominant and recessive monogenic defects have been examined in familial PD (designated PARK1–PARK18) (Kumar et al., 2011). Although clinically rare, an autosomal dominant, familial form of PD occurs with three point mutations (A30P, E46K, and A53T) in the gene encoding SYN (Kruger et al., 1998; Polymeropoulos et al., 1997; Zarranz et al., 2004), *SNCA* (*PARK1* locus), with almost complete penetrance (Berg et al., 2005a, 2005b), suggesting altered function or processing of the gene (or gene product) may participate in a neurodegenerative cascade. *SNCA* is located on human chromosome 4, and is composed