European Journal of Pharmacology 759 (2015) 118–126

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Translational research for Parkinson's disease: The value of pre-clinical primate models

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ARTICLE INFO

Article history:
Received 16 January 2015
Received in revised form
10 March 2015
Accepted 12 March 2015
Available online 2 April 2015

Keywords:
NHP
Viral vectors
Cell transplantation
Functional assessment
Translational neuroscience

ABSTRACT

Animal models have been highly questioned for their ability to predict the efficacy of different therapeutic strategies for neurodegenerative diseases. The increasing number of phase I/II clinical trials that fail to proceed to further stages of drug development has discredited the pertinence of such investigations. However, critical analysis of the data has often revealed errors and partially explained the lack of efficacy, opening the way to a refinement in designing pre-clinical studies.

In parallel, many promising methods of drug delivery to the brain such as gene therapy or cell therapy have considerably advanced thanks to the clinical failures in the past 10 years. As methodological advances appear and knowledge becomes available, scientists will be faced with the choice of how to test new strategies or re-test old ones. With the hardening of social views and legislation regarding animal experimentation, there is increasing pressure to find alternative methods of assessment that predict efficacy (such as computational based models), or to perform efficacy trials directly in patients and only safety assays in animals.

In this review we will focus on Parkinson's disease and on the impact of a body of data issued from NHP studies. We will attempt to critically examine the advantages and limitations of various approaches from the perspective of the animal model used to address specific questions.

1. Introduction

Translational research in neurodegenerative diseases is still struggling to make significant advances in prevention, diagnosis and treatments despite the wealth of information provided by preclinical research. Although many experimental models have given invaluable insight on the pathological processes underpinning neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (PD), our understanding of the triggering events, and the biological correlates of the rates of progression and severity of a given disease still remain unclear. However, many advances have been made and have helped to develop new therapeutic strategies against protein unfolding for example or to characterize the contribution of specific genes to the neuropathological process. These strategies have been mainly tested in rodent models of disease, some have been tested in NHP models and a small percentage is currently being tested in the clinic. The key to their success will be to have enough insight into the mechanisms leading to the disease, in order to identify the molecular/cellular dysfunctions driving the pathological cascade and target them with either neuroprotection or disease modification strategies. This remains one of the main reasons for developing animal models of diseases (Fig. 1).

The clinical description of a constellation of symptoms triggers a working hypothesis of a particular molecular/cellular aspect of the human disease of interest. NHPs can be used to mimic the phenotypic, genetic, histopathological aspects of the disorder (bed-to-bench approach). As fundamental knowledge of the disease arises from observations made in the models, these can be confronted to novel clinical findings. Such progressive iterative loops allow both the refinement of the models and a better understanding of the

Abbreviations: PD, Parkinson's disease; SNpc, substantia nigra pars compacta; L-DOPA, Levodopa, 3,4-dihydroxyphenylalanine; 6OHDA, 6-hydroxydopamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; AADC, L-aromatic amino acid decarboxylase; TH, tyrosine hydroxylase; GCH1, GTP cyclohydrolase 1; BH4, 5,6,7,8-tetrahydro-L-biopterin; AAV, adeno-associated viruses; EIAV, equine infectious anemia virus; UPDRS, unified Parkinson's disease rating scale; PET, positon emission tomography; [^{18}F]-FMT, fluoro-meta-tyrosine; GABA, gamma-amino butyric acid; GAD, glutamic acid decarboxylase; GDNF, glial-cell-derived neurotrophic factor; NRTN, neurturin; MRI, magnetic resonance imaging; GP, Globus pallidum (i, internal, e, external); GI, gastro-intestinal; VMAT2, vescicular monoamine transporter 2; NA, noradrenaline; 5HT, Serotonin; AchE, acetylcholine; HLA-DR, human leukocyte antigen complex; Iba1, Ionized calcium-binding adapter molecule 1

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http://dx.doi.org/10.1016/j.ejphar.2015.03.038
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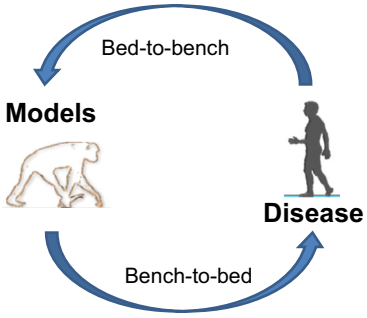

Fig. 1. General principles in translational research: step 1.

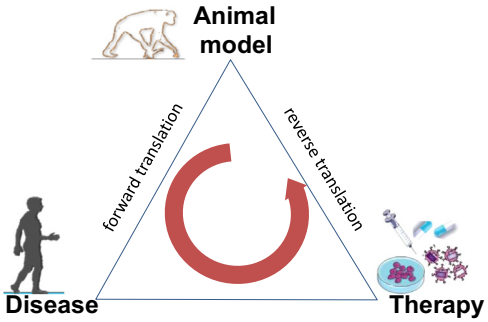

Fig. 2. General principles in translational research: step 2.

human disorder. In this process, multiple models can therefore be generated at any given time to describe different aspects of the disease thus enriching their face and construct validity.

Ideally, a model of neurodegenerative disease should be triggered by the same (or at least similar) molecular/cellular alterations as the human disease itself. It should also replicate at best the diversity of cell loss that has been identified in patients as well as their known rate of progression. Finally, the model should also mimic the diversity of symptoms, which will depend heavily on the behavioral repertoire of the animal species selected to develop the model.

In the case of PD, the rationale adopted by the community to develop a model was first to postulate that a dopamine deficiency was the primary consequence of this human pathology. Then, the next step relied on the elaboration of an experimental paradigm capable of mimicking/testing this hypothesis in an animal species. To this purpose, well-controlled methods capable of reproducing this primary event leading to PD had to be developed and validated. Finally, it remained to expect that in the animal species selected for this purpose, a progressive dopaminergic dysfunction would trigger the symptoms, disease evolution and cell degeneration similar to those observed in the human condition.

2. Parkinson's disease

Parkinson's disease is a progressive neurodegenerative disorder clinically characterized by motor symptoms like tremor, rigidity, akinesia and postural imbalance. Although it is well established that it is the decrease in dopamine availability in the striatum that gives rise to these symptoms, the causes are still unknown. Dopaminergic deafferentation of the caudate and putamen in particular results from the loss of axonal projections coming from dopaminergic neurons located in the substantia nigra pars compacta (SNpc) and 50–70% of these neurons are lost before the appearance of clinical symptoms (Lee et al., 1994; Bonnet et al., 2012).

The focus over the last decades has been to palliate the motor component of the disease but PD is a multisymptomatic neurological disease that includes cognitive and psychiatric non-motor symptoms. In fact, manifestations such as depression, hypomania and visual hallucinations are not uncommon, alongside with executive symptoms and dementia. Depression, often associated with anxiety, classically precedes the first motor symptoms in 50% of cases. Other common symptoms are reduced appetite, sleep disturbances, loss of libido, fatigue, and inability to work (Wirdefeldt et al., 2011; Bonnet et al., 2012).

Currently, there is not curative treatment to prevent or slow the progression of disease in PD patients. Therapies available aim at controlling symptoms and include both pharmacological replacement and surgical approaches but display severe adverse events. Among these, the most effective and the most commonly prescribed symptomatic pharmacotherapy remains the precursor of dopamine, L-3,4-dihydroxyphenylalanine (L-DOPA). However, chronic administration leads to an increase in motor fluctuations and abnormal movements termed dyskinesias in 80% of patients between 5 and 8 years of use, that are thought to arise with the increasing loss of dopaminergic neurons over time and the intermittent availability of L-DOPA (Lee et al., 1994; Wirdefeldt et al., 2011; Bonnet et al., 2012).

The pathological hallmark of the disease are Lewy bodies, inclusions present in the brain that result from the accumulation of α-synuclein and other proteins that are thought to begin years before the appearance of motor symptoms. Only a minority of PD patients carries genetic mutations and over 90% are sporadic cases where other genetic predispositions, age and environmental factors such as toxin exposure are thought to be determinant risk factors (Wirdefeldt et al., 2011).

3. Modeling Parkinson's disease in animals: a translational bed-to-bench approach

After the initial description of the disease by James Parkinson which was essentially describing a syndrome with no indication of any mechanism of cell death or even a description of a particular cell degeneration associated with this condition, the development of a pertinent animal model of PD remained difficult (Parkinson, 1817). It is only after a specific method was developed to identify the dopamine-producing cells in the brain (Fuxe et al., 1970) that the severe degeneration of the nigrostriatal dopamine pathway was identified in Parkinson's disease. Moreover, it was only after Hornykiewicz et al. discovered that striatal tissue levels of dopamine and its metabolites were profoundly depleted in parkinsonian patients that some experimental models could be proposed and evaluated and even an effective palliative treatment (L-DOPA therapy) tested (Ehringer and Hornykiewicz, 1960).

Although PD is now recognized as a more complex disorder, in those early days, the pathology was principally recognized as a 'pure' dopaminergic deficiency. It is therefore understandable that the first attempts made to develop an animal model were initially targeting the nucleus at the origin of the dopaminergic nigrostriatal path i.e. the ventral mesencephalon. At that stage, the only experimental method available to induce a lesion of a given brain nucleus was the in situ delivery of an electric current delivered through stereotactic placement of an electrode (Agid et al., 1974), so-called electrolytic lesion. Despite the fact that lesioned animals presented some symptoms reminiscent of akinesia, one of the cardinal features of PD, it appeared subsequently that this type of model was suboptimal – as it severed passing fibers in addition to the cell bodies of the 'treated' region.

Again, it was only after the discovery of 6-hydroxydopamine, a neurotoxic analog of dopamine, that an almost pure severing of the nigral dopaminergic neurons could be achieved in experimental animals, giving raise to the well-known 6-OHDA lesion models,