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Are Animal Models of Parkinson's Disease as Bad as they Seem to Be?

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"The patient, a forty-two-year-old drug addict, sat frozen and mute, looking more like a mannequin than a man…" So begins Dr. J. William Langston his wonderful story called 'The Case of the Tainted Heroin' [1]. Dr. Langston also added an illustrative subtitle: '*a Trail of Tragedies Leads to a New Theory of Parkinson's Disease*'. What the author recounts in this scientific article (and posteriorly in a book called 'The Case of the Frozen Addicts' [2]) is the story of a number of heroin abusers who presented at different emergency rooms with indistinguishable symptoms from those of Parkinson's disease (PD) and the common thread that all of them self-administered 'synthetic' heroin contaminated with a meperidine analogue: MPTP .

Although 6-OHDA was firstly used to lesion the nigrostriatal dopaminergic system in the rat [3] and to model parkinsonism, the discovery of MPTP as a dopaminergic neurotoxin in the brain (first in humans; then in non-human primates and several rodent species) opened a new era in the use of animals to study PD.

There are some 'desirable' characteristics in an 'ideal' animal model of PD that can be listed as follows: i) animals should have a progressive loss of dopamine neurons, if possible, starting in their adulthood; ii) this loss should be easily detectable with conventional histopathological techniques; iii) animals should present some (if not all) of the clinical symptoms of PD (bradykinesia, rigidity and resting tremor); and iv) dopaminergic cells should exhibit the characteristics intracytoplasmic inclusions called Lewy bodies [4]. Unfortunately, to this end, none of the known animal models (neither MPTP nor 6-OHDA nor the more recent genetic models) meet all these features together, and this fact looks to be the Achilles heel to arguing against them.

However, animal models have offered, in the last decades, important insights into the understanding of the etiopathology/ies and molecular mechanisms of PD, not to mention that, thanks to them, researchers have been able to recreate specific pathogenic events and behavioral outcomes that have helped to find missing pieces in this complex puzzle.

Another salutary lesson that comes from *in vivo* models is the study of Levodopa (L-DOPA)-induced dyskinesias (LID). L-DOPA is a precursor of dopamine capable of crossing the blood brain barrier and be converted into dopamine in the brain. It is (so far) the most effective symptomatic treatment to replace dopamine deficits in patients with PD. However, although effective in the 'acute phase', L-DOPA induces abnormal involuntary movements (dyskinesias) and psychiatric complications that, overall, represent the real disability in PD. Monkeys injected with MPTP and treated with L-DOPA develop LID and respond to dopamine treatments in a similar way as PD patients [5], which make this model attractive for studying molecular pathways and potential therapeutics to prevent this phenomenon.

Finally, and perhaps most importantly, *in vivo* models show how cells behave in an interactive environment, in the context of functional circuits with very complex and intricate patterns of communication. For example, it is widely recognized that inflammation plays a prominent role in PD. Assessing whether this role is beneficial or detrimental, and the relative contribution that each of the cells make to the neurodegenerative process can only be achieved by carefully studying all these components in their natural environment.

Therefore the question arises: are animal models of PD as bad as they seem to be? By seeing how they have helped us to improve our understanding of PD, it looks clear that the problem of the animal models is not their lack of predictive validity. Our current understanding of PD is the result of an integrated approach of *in vitro* and *in vivo* studies, in close association with clinical findings obtained from studies in PD patients [6]. Believing that animal models of PD are a dismal failure is to be prone to mislead. And mislead, in a scientific context, means being just a stone's throw of mistake.

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