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Parkinson's disease: Exit toxins, enter genetics

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ABSTRACT

Parkinson's disease was long considered a non-hereditary disorder. Despite extensive research trying to find environmental risk factors for the disease, genetic variants now stand out as the major causative factor. Since a number of genes have been implicated in the pathogenesis it seems likely that several molecular pathways and downstream effectors can affect the trophic support and/or the survival of dopamine neurons, subsequently leading to Parkinson's disease. The present review describes how toxin-based animal models have been valuable tools in trying to find the underlying mechanisms of disease, and how identification of disease-linked genes in humans has led to the development of new transgenic rodent models. The review also describes the current status of the most common genetic susceptibility factors for Parkinson's disease identified up to today.

Contents

1. Introduction

Paralysis agitans or Parkinson's disease is well described in the ancient Indian medical treatise *Ayurveda* (Sanskrit: *ayur*, life; *veda*, science) with the oldest material dating from 2000–4000 B.C. and a complete treatise completed around 1000 B.C. According to

Abbreviations: *ATP13A2*, ATPase type 13A2; *LRRK2*, leucine-rich repeat kinase 2; *PINK1*, PTEN induced putative kinase 1; *SNCA*, synuclein alpha; *TFAM*, mitochondrial transcription factor A; *UCH-L1*, ubiquitin C-terminal esterase L1.

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Ayurveda, the disorder was referred to as *Kampavata* (*Kampa*, tremor; *vata*, lack of movements) and manifested symptoms such as rigidity, akinesia, tremors, depression, somnolence, "loss of mind" and mental confusion. It was treated with seeds from *Mucuna pruriens*, a plant in the *Leguminosae* family. At that time the active substance in the plants was unknown, and it was not until the 1930s that the active component L-3,4-dihydroxyphenylalanine (L-dopa) was isolated (Damodaran and Ramaswamy, 1937). However, this finding had limited impact at that time, since the involvement of dopamine in the disease had not yet been discovered.

For long, Parkinson's disease, as we know it today (Parkinson, 1817), was considered a typical non-genetic disorder. However, the fact that Parkinson's disease has been present since ancient times, presumably without major changes of prevalence caused by the industrial revolution and the increasing use of man-made chemicals as well as the findings of similar prevalences in different populations across the world, suggest that environmental factors play a less important role in Parkinson's disease than previously thought.

Even though the underlying mechanisms of Parkinson's disease remain partly unknown, several hypotheses have been put forward for its causes. Implicated mechanisms involve protein misfolding, mitochondrial and ubiquitin-proteasome dysfunction, oxidative stress, inflammation, apoptosis, exposure to and/or increased vulnerability to environmental toxins and infectious agents. It is unclear, however, how these different pathogenic events, and others yet to be discovered, cause Parkinson's disease. The variable phenotypes observed among Parkinson patients suggest involvement of several different molecular pathways. Moreover, it remains to be resolved if the underlying causes act separately or if they converge into one or only a few final common pathways. All pathogenic events however will affect the survival and/or death of neurons in vulnerable brain areas including the substantia nigra, locus coeruleus and the dorsal motor nucleus of the vagus nerve (Braak et al., 2004).

2. Dopamine neurotoxins

The use of toxin-based animal models has given useful insights into the pathology of Parkinson's disease. Ideally, a valuable and reliable animal model of disease should mimic one or preferably several of the specific features of the human disease. The Parkinson's disease-like rodent models used today can mimic motor dysfunctions, dopamine neuron degeneration, olfactory loss and, albeit to a lesser degree, formation of intracellular inclusion bodies in affected neurons.

2.1. Toxin-based animal models

Two commonly used rodent models of Parkinson's disease are based on administration of 6-hydroxy-dopamine (6-OHDA) (into the brain) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (systemically) in order to rapidly and selectively destroy catecholaminergic neurons. 6-OHDA is a hydroxylated analogue of dopamine (Blum et al., 2001) which was first shown to cause noradrenergic depletion of sympathetic nerves to the heart (Porter et al., 1963, 1965) and destruction of noradrenergic nerves (Tranzer and Thoenen, 1973). In the CNS, 6-OHDA causes destruction of dopaminergic and noradrenergic neurons (Ungerstedt, 1968). The toxin is taken up by dopamine and noradrenaline membrane transporters and accumulates in the cell cytosol. Cell death is caused by formation of reactive oxygen species and mitochondrial respiratory chain deficiency (Blum et al., 2001). The drug does not cross the blood-brain barrier and hence, has to be stereotaxically injected to striatum, substantia nigra, the medial forebrain bundle, or administered directly into the ventricular system. Intrastriatal injection of 6-OHDA can result in a progressive, retrograde partial lesioning, whereas injection into the substantia nigra or medial forebrain bundle results in complete lesioning of the nigrostriatal pathway (Ungerstedt and Arbuthnott, 1970; Ungerstedt, 1971a,b; Sachs and Jonsson, 1975). The strength of the lesioning is dependent on the site of injection, the amount of 6-OHDA administered and on the species used (Betarbet et al., 2002). Both unilateral (hemiparkinsonian model, where the unlesioned hemisphere serves as an internal control) and bilateral lesioning models are used. Unilateral lesioning causes asymmetrical and quantifiable motor behaviors induced by systemic administration of dopamine receptor agonists, levodopa or dopamine-releasing drugs (Ungerstedt and Arbuthnott, 1970; Hefti et al., 1980). The bilateral model on the other hand, results in parkinsonian motor complications, but due to the need for intensive nursing care of the animals, the use of the model is less common (Cenci et al., 2002). While the 6-OHDA model is widely used in Parkinson's disease research, the model does not recapitulate all pathological features of the disease. For instance, the animals do not develop cytoplasmic Lewy bodies. Moreover, intracerebral injection of 6-OHDA does not affect other brain areas involved in Parkinson's disease such as locus coeruleus, the brain stem or olfactory areas (Betarbet et al., 2002) or cortex cerebri.

A link between parkinsonism and mitochondrial dysfunction, a suggested causative event for the disease, was established when the neurotoxic substance MPTP was found to cause severe and irreversible parkinsonism in a small group of drug addicts in California (Langston et al., 1983). The affected individuals displayed several clinical and neuropathological characteristics of Parkinson's disease. MPTP is a lipophilic molecule which readily crosses the blood–brain barrier. In non-dopaminergic neurons (mostly astrocytes) MPTP is converted by monoamine oxidase B (MAO-B) to 1-methyl-4-phenyl-2,3-dihydropyridinium (MPDP) which is oxidized to 1-methyl-4-phenylpyridinium (MPP^+) (Nicklas et al., 1985, 1987; Przedborski and Vila, 2003). The active metabolite MPP^+ is taken up by dopamine neurons through the dopamine transporter (DAT), and acts as an inhibitor of mitochondrial complex I of the respiratory chain (Nicklas et al., 1987; Mizuno et al., 1987). MPTP functions as a potent neurotoxin in both mice and primates, although mice are less sensitive than monkeys (Nicklas et al., 1985; Blum et al., 2001).

It is well known that agricultural chemicals such as the pesticide rotenone can induce specific parkinsonian symptoms (Betarbet et al., 2000, 2002). Structurally and functionally rotenone is related to MPTP and also acts as an inhibitor of mitochondrial complex I (Perier et al., 2003). Studies of rotenone thus add to the evidence that dopamine neurons may be particularly vulnerable to mitochondrial dysfunction. However, while there are some epidemiological studies to indicate that pesticide exposure may increase the risk to develop Parkinson's disease, the relative importance of such exposure for the prevalence of Parkinson's disease worldwide is not clear.

Most toxin-based animal models used today are focused on the nigrostriatal system and the loss of dopamine neurons, which is a prerequisite for understanding the underlying mechanisms of the disease, and for developing symptomatic treatments. However, the animal models are limited in that they do not recapitulate the complete spectrum of symptoms seen in humans, and in particular not the slow and progressive loss of dopamine neurons, which is characteristic of Parkinson's disease.

3. Genetics

Today, the underlying pathology of Parkinson's disease is well explored, but we have limited understanding of the etiology. Long