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Movement Disorders Induced by Neurotoxins

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ABSTRACT

Parkinson's disease (PD), first described by James Parkinson, remains the most prevalent neurological movement disorder in aging populations. This debilitating condition is characterized by the progressive degeneration of dopaminergic neurons within the substantia nigra (SN) pars compacta. Despite its discovery over two centuries ago, the etiology of PD remains elusive. To gain deeper insights into the underlying pathology, disease progression mechanisms, and potential therapeutic targets for symptom amelioration, animal models have emerged as invaluable tools. Among these, neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) are extensively utilized to induce acute PD models in mice and rats, respectively. This review comprehensively explores the contributions of these neurotoxin-induced models toward enhancing our understanding of PD pathogenesis and advancing therapeutic interventions. Additionally, it highlights key findings and promising avenues for future research in this critical area of movement disorders.

KEYWORDS

movement disorder, disability, Parkinson's disease

HISTORY

Two centuries ago, James Parkinson, a British physician, wrote a seminal essay reporting his clinical observations of six individuals with "paralysis agitans" or "the shaking palsy." James Parkinson described the clinical picture of the disease as "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured" (Parkinson, 2002). Sixty years later, Jean-Martin Charcot made the next important contribution by differentiating the disease from other disorders associated with tremors such as multiple sclerosis. Also, he explained in detail some of the changes that occur with the disease, e.g. arthritic changes, dysautonomia, and pain. In order to honor James Parkinson, his name became a term that describes the disease "Parkinson's disease" (PD) by Charcot, who found that PD patients do not necessarily have tremors (Charcot, 1872). In 1880, William Gowers, who worked in London with 80 patients with PD, was the first to correctly identify the slight predominance of the male gender in his study "Manual of Disease of the Nervous System." Clinical and morphological details of the progressive stages of disabilities associated with PD were reported by French neurologists (Richer and Meige, 1895). Motor fluctuations were noted by Babinski et al. (1921).

The pathology of the disease was first proposed by Brissaud (1925), who proposed damage to the SN, followed by further studies demonstrating the involvement of the SN in the disease (Foix and Nicolesco, 1925). Biochemical changes in the brain were identified in the 1950s after a large amount of work by Arvid Carlsson, Oleh Hornykiewicz, and Isamu Sano. The most comprehensive analysis of PD pathology was performed by Greenfield and Bosanquet (1953). Since the pathology of the disease is associated with dopamine (DA), extended and short-term benefits of oral levodopa were confirmed, which made levodopa the primary medication for those with PD, by Yahr et al. (1969) (Fig. 1).

ETIOLOGY AND RISK FACTORS OF PD

Degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) is a major hallmark of PD.

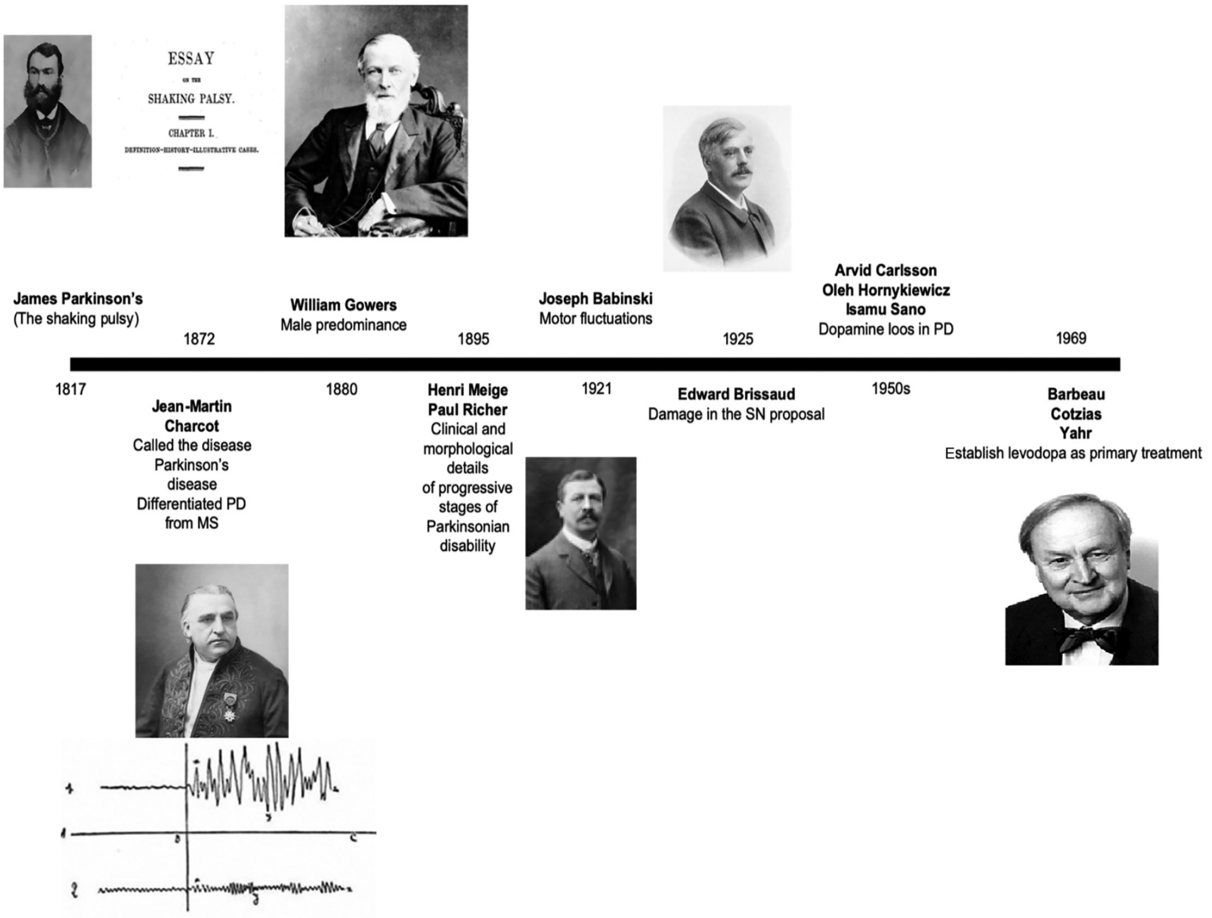

Figure 1: Breakthroughs in PD history. This diagram illustrates the timeline of the discovery of PD and the development of our understanding of the disease. Abbreviation: PD, Parkinson's disease.

This loss of dopaminergic neurons is believed to be caused by intraneural inclusions known as Lewy Bodies, which are composed of proteinaceous deposits of α-synuclein aggregates and ubiquitin. Also, dopaminergic neurons in the SNpc are characterized by the presence of a brown pigment content that is known as neuromelanin and in patients with PD the depigmentation of neurons (Choong and Mochizuki, 2022). Once degeneration starts to take place, [^{11}C]FeCIT positron emission tomography scan revealed 25 and 41% reduction in dopamine transporter (DAT) in the SNpc and striatum, respectively (Caminiti et al., 2017). Once PD patients lose ~80% of striatal dopamine and ~60% of dopaminergic neurons in the SNpc, PD symptoms start to appear (Uhl et al., 1985).

PD etiology is not completely understood. There are multiple epidemiological risk factors that contribute to the disease. (1) Age: the risk of developing PD increases with aging. Approximately 1% of individuals over the age of 65 have PD and the risk increases proportionally with age (Miller and O'Callaghan, 2015). (2) Gender: the incidence rate of PD is higher in males than in females with a ratio of 2 to 1 (Miller and Cronin-Golomb, 2010). In males, the incidence rate increases from 3.6 per 100,000 between the ages of 40 and 49 to around 258 per 1,000,000 for those over 80. At the same time, the incidence rate in females over the age of 80 is approximately 66 per 100,000 (Hirsch et al., 2016). (3) Race/ethnicity: epidemiological studies that were carried out in the US concluded that Hispanics have the highest risk of developing PD, followed by nonHispanic White, Asian, finally African American persons, the latter having been found to be at low risk to develop PD (Pringsheim et al., 2014). (4) Environmental factors: investigation of environmental toxins linked insecticides, pesticides, and herbicides to PD causes. In 1996 a study in Germany involving 380 PD patients and 379 healthy subjects concluded that exposure to preservatives of wood and to heavy metals had a significant correlation with the development of the disease (Seidler et al., 1996). Additionally, drinking rural well water for more than 5 years showed an increase in the risk of developing PD by around 90% in rural California. The reason is believed to be due to contamination of the well water by pesticides, which explains the increase in the incidence rate in rural and agricultural states (Gatto et al., 2009). (5) Genetic factors: large number of genetic studies on families with a high prevalence of PD revealed several genes linked to PD, which include α-synuclein, leucine-rich repeat kinase 2 (LRRK2), parkin, PTEN-induced putative kinase 1 (PINK1), and DJ-1.

NEUROTOXINS THAT CAUSE MOVEMENT DISORDERS

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

In the late 1970s and early 1980s, self-administration of contaminated synthetic heroin led to severe and permanent movement disorders resembling PD (Langston et al., 1984). Samples of synthetic heroin revealed that they were composed of almost pure 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which was identified as the likely reason for developing permanent PD (Langston et al., 1983). MPTP is highly lipophilic, which allows it to pass the blood–brain barrier. Once MPTP is in the brain, it is rapidly metabolized into 1-methyl-4-phenylpyridine (MPP+) by monoamine oxidase B (MAO B) (Langston et al., 1984). MPP+ is then taken up by dopaminergic neurons, since MPP+ is a substrate for DAT that leads to the accumulation of MPP+ (Choi et al., 2015). The neurotoxic effect of MPP+ primarily occurs by inhibiting complex I of the mitochondrial respiratory chain leading to impaired production of ATP, elevated intracellular calcium concentration, and free radical generation that causes oxidative stress and thus cell death (Chiueh and Rauhala, 1998).

Given how MPTP can induce similar effects to typical PD in humans, it was used to generate animal models to study the pathophysiological changes, behavioral abnormalities, and the effect of drugs on the symptoms. Various mammalian species were treated with MPTP to model PD, including sheep, dogs, guinea pigs, cats, mice, and monkeys (Bezard et al., 1998). The first attempts to generate PD using MPTP in monkeys in 1984 showed all motor symptoms typically seen in PD patients, and these were responsive to levodopa treatment. Also, MPTP was able to induce a loss in the dopaminergic neurons in the SNpc, which terminates in the putamen (Burns et al., 1984). MPTP treatment was also able to induce similar effects in mice, but not in rats. The reason why rats are resistant to MPTP toxicity was found to be the very high level of MAO in their blood–brain barrier that converts MPTP to MPP+, which is not lipophilic, and thus MPP+ cannot permeate into the rat brain (Riachi et al., 1989).

6-Hydroxydopamine

In 1968, 6-hydroxydopamine (6-OHDA) was introduced as the first neurotoxin to induce dopaminergic neuronal death in SNpc (Ungerstedt, 1968). To date, 6-OHDA has been widely used to lesion the nigrostriatal pathway to produce a PD animal model. However, it is not specific for DA neurons only, but can induce degeneration of noradrenergic neurons as well (Ungerstedt, 1968). It exerts its toxic effect when accumulated in the cytosol by generating reactive oxygen species and, as a result, oxidative stress-related toxicity (Blum et al., 2001). To bypass the blood–brain barrier, 6-OHDA is usually injected stereotaxically into a specific region of the brain to induce the desired effect. In addition, 6-OHDA was found to successfully induce PD in rats, cats, guinea pigs, dogs, and monkeys (Bezard et al, 1998). 6-OHDA is most commonly injected unilaterally to different areas of the brain, e.g. SN, medial forebrain bundle, or striatum (Malmfors and Sachs, 1968). Generally, 6-OHDA is more toxic to nerve terminals than the axon and cell body. However, when injected into the SN, it produces a complete and rapid degeneration of the nigrostriatal pathway in ~2-3 days (Jeon et al., 1995).

Rotenone

Rotenone is a widely used pesticide to kill insects. It is naturally found in the Leguminosa family of plants such as *Derris elliptica*, *Lonchocarpus nicou*, and *Tephrosia vogelii* (Angioni et al., 2011). Rotenone can cross the blood–brain barrier rapidly due to its high lipophilicity and does not require a specific transporter to cross into the cell. Rotenone is a selective inhibitor of complex I that can reduce its activity by 75% without affecting the enzymatic activity of succinate dehydrogenase (complex II) or cytochrome oxidase (complex IV) (Betarbet et al., 2000).

Rotenone was first used to generate a PD model in 1985 when Hiekkila injected a 5 mM solution directly into a rat brain, which is approximately 500,000-fold higher than the IC_{50} of 10 nM (Heikkila et al., 1985). However, at that high concentration, any toxin might induce similar results. Besides, it was reported that it also produces nonspecific peripheral toxicity in addition to nonspecific brain lesions (Ferrante et al., 1997). Greenmyre and colleagues later developed a low-dose chronic regimen (Betarbet et al., 2000). Jugular vein infusion of rotenone produced selective nigrostriatal neurodegeneration in addition to α-synuclein inclusions. Despite the advantages of rotenone over other neurotoxins, it has not been widely used. The main reason is related to its high variability that depends on animal sensitivity (Zhu et al., 2004).

Paraquat

Paraquat (1,1′-dimethyl-4,4′-bipyridine) is a bipyridylium compound that is commonly used as a herbicide in several corps, such as soybeans, sugar cane, cotton, corn, apple, and others. The use of paraquat has already been banned in many countries due to its pulmonary-induced lesions, which are often fatal (Vaccari et al., 2017). It is still unclear how paraquat affects dopaminergic neurons, but it is believed that paraquat toxic effects are primarily through oxidative stress by depleting glutathione and increasing the level of oxidized glutathione (Kang et al., 2009). Paraquat accumulation in the brain is age-dependent, which was confirmed when 2-week and 3-, 12- and 24-month-old rats received subcutaneous injection of paraquat and were euthanized after 1 hour. Results demonstrated higher concentrations in the 2-week-old animals, suggesting a role of the blood–brain barrier (Corasaniti et al., 1991). Motor deficits and dopaminergic neuron degeneration in mice were found to be induced in a dose- and age- (McCormack et al., 2002) dependent manner.

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