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Disturbance of sensorimotor filtering in the 6-OHDA rodent model of Parkinson's disease

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ABSTRACT

Aims: Parkinson's disease (PD) is a movement disorder that involves non-motor symptoms including cognitive dysfunction. L-DOPA (L-3,4-dihydroxyphenylalanine), the most effective treatment for PD, might cause the development of abnormal involuntary movements and psychotic symptoms. It has been argued that a complex interaction between drug- and intrinsic disease-related components is enrolled in PD psychotic symptoms. Prepulse inhibition (PPI) is a cross-species measure of sensorimotor gating often disrupted in disorders either with basal ganglia dysfunction or with psychotomimetic drugs. There are controversial results concerning PPI in PD patients. Nevertheless, clinical studies are difficult to interpret because of differences in disease severity, concomitant medications, and comorbidities. Our aim was to investigate the functioning of sensorimotor gating in the 6-OHDA-inducing partial or complete dopaminergic degeneration of the nigrostriatal pathway.
Main methods: Since several studies suggested that PD-associated psychosis results from interaction between disease-related factors and dopamine replacement, we also analyzed in rats with complete unilateral lesion of the nigrostriatal pathway the effect of L-DOPA treatment (30 mg/kg, daily) for 1, 7 or 14 days.
Key findings: Complete and unilateral dopaminergic striatal depletion disrupted PPI response in rats. In mice, partial dopaminergic loss in the dorsal striatum, unilateral or bilateral, did not determine PPI changes. L-DOPA treatment determined either no PPI alteration or PPI increase in the 6-OHDA-lesioned rats.
Significance: Complete striatal degeneration induced by 6-OHDA discreetly reproduced the impairment of PPI found in PD patients. Additionally, L-DOPA at a therapeutical dose, despite adverse motor effects, should not induce an impairment of sensorimotor response.

Introduction

Parkinson's disease (PD) is a progressive movement disorder characterized by resting tremor, bradykinesia and rigidity, resulting mainly from progressive loss of dopaminergic neurons in the substantia nigra compacta [24] and reduction of dopamine levels in the striatum [44].

Despite the well-known movement disorder, PD is also characterized by cognitive and emotional alterations ([33,58]). Several psychiatric non-motor symptoms might accompany the motor-stages of PD and comprise depression, psychosis, anxiety and dementia [13,14,19]. Psychosis in PD patients is represented mainly by visual hallucinations and could appear with the use of dopaminergic medication [16]. The origin of these symptoms could be related to a complex interaction between the disease-related components and non-physiological dopamine replacement to reverse motor symptoms [20,23]. The metabolic precursor of dopamine L-DOPA (L-3,4-dihydroxyphenylalanine) is the most widely used pharmacological agent to enhance the dopaminergic signaling in PD [25]. Despite its significant improvement of PD motor symptoms, L-DOPA treatment induces dyskinesia, the most important side effect usually associated with L-DOPA long-term use [26].

The malfunctioning of cortico-striato-pallido-thalamic neuronal networks determines deficits in the general gating process mechanisms [7]. Several psychopathological patients that exhibit alteration in this brain circuitry exhibit poor gating of motor, sensory or cognitive information and corresponding prepulse inhibition (PPI) deficits [7,46]. PPI is a measure of sensorimotor gating and PPI deficits are not unique to a single pathology [52]. For example, PPI may be altered in basal ganglia disorders including schizophrenia, Tourette's syndrome, and post-traumatic stress disorder [7,8]. Animal models of PPI deficits have been considered ideal candidates for cross-species translational research [6]. Pharmacological manipulations in healthy human subjects and rodents produced similar effects on PPI [52,53]. Precisely, dopamine agonists disrupt PPI in rodents, and in at least some human studies [7,47,49].

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Regarding PD patients, there are controversial results concerning PPI [59,60]. Animal models may represent an interesting pre-clinical tool since factors such as disease severity, drug treatment and comorbidities are easily controlled. Animal models of PD are usually based on the cellular dysfunction and death of dopaminergic neurons of the substantia nigra induced by toxins, such as 6-hydroxydopamine (6-OHDA), 1-methyl- 4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone and paraquat [3,5]. In general, these models reflect cardinal symptoms of PD that include both behavioral and biochemical features [3]. Some animal models of PD have shown also non-motor features and abnormalities outside of the substantia nigra such as abnormal olfactory function, gastrointestinal problems and sleep disorders ([11] and references therein).

Based on the hypothesis that abnormalities in cortico-striato-pallido-thalamic loop may induce sensorimotor deficits, we first aimed to determine how 6-OHDA-inducing partial or complete dopaminergic degeneration of the nigrostriatal pathway would influence sensorimotor gating using the PPI test to detect such changes. Because it is likely that PD-associated psychosis may rise from an interaction between disease-related factors and non-physiological dopamine replacement, our second aim was to analyze the effects of early (acute) and long-term L-DOPA treatment in the PPI test in 6-OHDA-lesioned rats with severe unilateral lesion of the nigrostriatal pathway.

Material and methods

Animals

Adult male *Wistar* rats (n = 14; 200–250 g; housed in groups of 2-3 per cage) and *Swiss* albino mice (n = 32; 25–30 g; housed in groups of 5-6 per cage) were used. Animals were maintained in separate rooms, temperature-controlled (23 ± 1 °C) with a 12/12 h light/dark cycle with free access to food and water. All experiments were conducted according to the principles and procedures described by the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (ILAR, USA). The local Animal Ethics Committee had previously approved the institution's housing conditions and experimental procedures.

Drugs

Apomorphine hydrochloride (Sigma-Aldrich, St. Louis, MO, USA) was administered subcutaneously (s.c.; 0.5 mg/kg; 1 ml/kg). In rats, L-DOPA/benserazide-HCl (Prolopa dispersive, Hoffman-LaRoche, Brazil) was given orally (gavage, 2 ml/kg), once a day, at the dose of 30/7.5 mg/kg.

6-OHDA lesion in the nigrostriatal pathway

The stereotaxic surgery was conducted as previously described [21]. Briefly, rats or mice were anesthetized with a mixture of ketamine (100 mg/kg) and xylazine (14 mg/kg, both i.p.). In rats, to avoid the damage of noradrenergic neurons, desipramine hydrochloride (25 mg/kg i.p., Sigma-Aldrich, St. Louis, MO, USA) was administered 30 min before 6-OHDA injection.

Rats received a single injection of 6-OHDA (Sigma-Aldrich, St. Louis, MO, USA, 16 μg in 3 μl 0.9% saline solution containing 0.05% ascorbic acid) into the right medial forebrain bundle at the following coordinates relative to the bregma [41]: anteroposterior: 4.4 mm; lateral: 1.2 mm; and dorsoventral: 8.2 mm. In rats, the 6-OHDA-induced injury to the dopaminergic neurons was tested with three different behavioral tests: open field test, apomorphine-induced rotational behavior and the stepping test.

Mice received two injections (2 μl each) of 6-OHDA into the striatum unilaterally (right) or bilaterally (first site: 1.0 mm anteroposterior, 2.1 mm lateral and 2.9 mm dorsoventral; second site: 0.3 mm anteroposterior, 2.3 mm lateral and 2.9 mm dorsoventral). In mice with unilateral injection of 6-OHDA the apomorphine-induced rotational behavior was used to estimate the dopaminergic neurons' injury.

The neurotoxin was infused at 1 μl/min in rats, and at a rate of 0.5 μl/min in mice. In both rats and mice, the cannula was left in place for 3 min before withdrawal. The efficacy of 6-OHDA-induced dopaminergic depletion was confirmed with immunohistochemistry for tyrosine hydroxylase (TH) in both rats and mice. The same experimental procedure was performed for the Sham-operated animals and the same volume of 0.9% saline solution containing 0.05% ascorbic acid was injected in the coordinates described above.

Behavioral analysis

Apomorphine-induced rotational behavior in rats and mice

Unilaterally 6-OHDA-lesioned rats and mice were challenged with an acute dose of apomorphine to estimate the extent of 6-OHDA-induced dopaminergic neuron injury 21 days post-surgery. For rats, the rotational behavior was measured for 45 min [39] and only animals presenting more than 90 contralateral turns were included on the study (Fig. 2A). For mice, rotational behavior was recorded for 10 min, and only mice that presented at least 65 contralateral rotations were analyzed in this study (data not shown). The PPI test was evaluated 7 days after the rotational test to allow apomorphine washout (Fig. 1).

Open field test, stepping test and L-DOPA-induced AIMs in rats

Locomotor activity was measured during 5 min in a circular arena (open field) specific for rat (75 cm diameter) surrounded by 49-cm-high walls made of transparent plastic. Each animal was individually

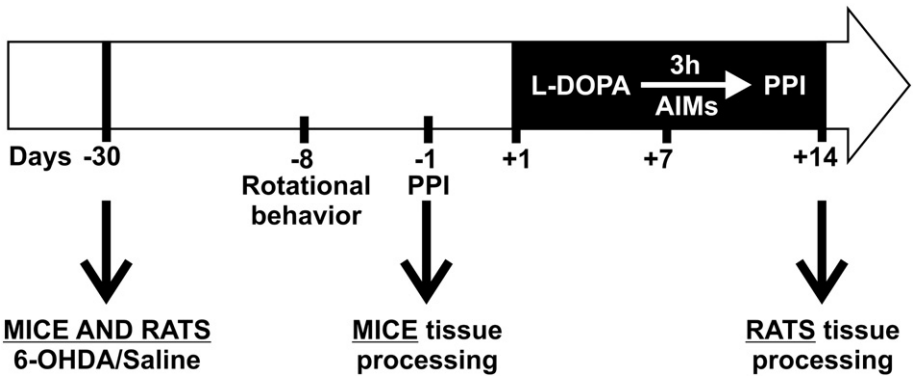

Fig. 1. Time line of treatments and analyses. The 6-OHDA-induced lesion was confirmed three weeks after surgery by the apomorphine-induced rotational test. The first PPI analysis (basal) was evaluated four weeks after the 6-OHDA-induced lesion. Rats were resubmitted to the PPI test after 1, 7 and 14 days of L-DOPA treatment.