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Research article

Early life exposure to permethrin: a progressive animal model of Parkinson's disease

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ABSTRACT

Introduction: Oxidative stress, alpha-synuclein changes, mitochondrial complex I defects and dopamine loss, observed in the striatum of rats exposed to the pesticide permethrin in early life, could represent neuropathological hallmarks of Parkinson's disease (PD). Nevertheless, an animal model of PD should also fulfill criteria of face and predictive validities.

This study was designed to: 1) verify dopaminergic status in the striatum and substantia nigra pars compacta; 2) recognize non-motor symptoms; 3) investigate the time-course development of motor disabilities; 4) assess L-Dopa effectiveness on motor symptoms in rats previously exposed to permethrin in early life.

Methods: The permethrin-treated group received 34 mg/kg daily of permethrin from postnatal day 6 to 21, whereas the age-matched control group was administered with the vehicle only.

Results: At adolescent age, the permethrin-treated group showed decreased levels of dopamine in the striatum, loss of dopaminergic neurons in the substantia nigra pars compacta and cognitive impairments. Motor coordination defects appeared at adult age (150 days old) in permethrin-treated rats on rotarod and beam walking tasks, whereas no differences between the treated and control groups were detected on the foot print task.

Predictive validity was evaluated by testing the ability of L-Dopa (5, 10 or 15 mg/kg, os) to restore the postural instability in permethrin-treated rats (150 days old) tested in a beam walking task. The results revealed full reversal of motor deficits starting from 10 mg/kg of L-Dopa.

Discussion: The overall results indicate that this animal model replicates the progressive, time-dependent nature of the neurodegenerative process in Parkinson's disease.

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1. Introduction

Progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) and the resultant depletion of dopamine (DA) from the striatum (Str) underlie the motor behavior deficits observed in patients and animals with Parkinson's disease (PD). The classical motor symptoms of PD are akinesia, bradykinesia, rigidity, tremor and postural abnormalities. There is also a collection of non-motor symptoms, such as poor sense of smell, constipation, depression, cognitive impairment, fatigue, and other impairments that also accompany PD. Some of these symptoms may develop years before the onset of motor problems.

PD is caused by both genetic and environmental factors, and by interactions among these factors. However, heritable forms of the disease account for only 5–10% of cases. Environmental factors, for example pesticides seem to be implicated in the etiology (Betarbet et al., 2000; McCormack et al., 2002).

Due to increasing concerns on adverse health consequences, organophosphates, carbamates and organochlorines, are being phased out leading to the escalating use of an alternative class of pesticides, the pyrethroids. Pyrethroids are now the most commonly used pesticides for residential pest control and public health purposes (including control of vector-borne diseases) and they are also increasingly being used in agriculture with biomonitoring studies confirming widespread exposure to one or more pyrethroids (Morgan, 2012; Barr et al., 2010; Roberts & Karr, 2012). Although pyrethroid pesticides are often considered a "safer" choice because they are generally not as acutely toxic as organophosphates (Casida & Durkin, 2013), our previous studies indicate that exposure to pyrethroid compounds such as permethrin (PERM), in neonatal age, may not be innocuous. For instance, we found that rats exposed to PERM during a critical period of brain development, have a significant increase in lipid peroxidation and NO levels (Carloni et al., 2012), and depletion of reduced glutathione (Nasuti et al., 2007) in the Str suggesting the involvement of oxidative stress. We

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also observed a selective inhibitory effect of permethrin on mitochondrial complex I of the electron transport chain (Falcioni et al., 2010). Furthermore, additional data from our laboratory indicates that PERM exposure negatively impacts the immune system such as the systemic inflammatory response (e.g. higher plasma levels of IL-1β, IL-2, IFN-γ) in animals previously exposed to this pesticide (Vadhana, Carloni, Nasuti, Fedeli, & Gabbianelli, 2011). In PERM exposed newborn rats, we also observed increased α-synuclein in the free form and increased levels of the aggregated form, in adolescent age and adult age, respectively (Fedeli, Montani, Nasuti, & Gabbianelli, 2014). Most importantly, in previous studies we detected a significant decrease in striatal DA levels in adolescent rats exposed to PERM earlier in life (Nasuti et al., 2007). Given that, oxidative stress, α-synuclein changes and DA loss in the Str have been demonstrated to be hallmarks of PD (Lee Mosley et al., 2006; Nagatsu & Sawada, 2007), it is plausible to hypothesize that early life exposure to PERM may represent a causal factor in disease expression.

In the present study, we intended to explore whether PERM exposure, in neonatal age from postnatal day (PND) 6 to PND 21, could reliably reproduce progressive PD symptomatology in the rat. By extension, our study would generate information on whether early life PERM exposure represents a suitable animal model of PD.

Animal models should fulfill a multidimensional set of criteria of validity in order to be considered relevant for human pathology such as face, predictive and construct validity. A criterion of face validity includes phenomenological similarities with the human disease (e.g. motor and non-motor symptoms of PD); a criterion of predictive validity is to assess in the animal model the efficacy of drugs (e.g. L-Dopa) clinically effective to relieve the motor symptoms in patients; a criterion of construct validity is satisfied when the animal model shares the same underlying mechanism as the disease does (Duty & Jenner, 2011). Unfortunately, to date there are no animal models of PD that faithfully mimic the human disease. The standard toxin-based models of PD reproduce the canonical loss of midbrain DA neurons but fail to replicate the progressive, time-dependent nature of the degenerative process (Duty & Jenner, 2011).

The present study was designed to provide support for the face and predictive validity of our model by evaluating in early life PERM exposed rats: 1) their dopaminergic status in Str and SNc; 2) cognitive impairments, non-motor symptoms preceding motor impairments; 3) time-course development of motor disabilities; 4) L-Dopa effectiveness on motor symptoms.

2. Materials and methods

All experiments were conducted in accordance with the European Guidelines (Directive 2010/63/EU) for the Care and Use of Laboratory Animals and approved by the local ethic Committee.

2.1. Materials

Technical grade (75:25, trans:cis; 94% purity) 3-phenoxybenzyl-(1*R*,*S*)-*cis*,*trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate, PERM (PubChem CID: 40326) was generously donated by Dr. A. Stefanini of ACTIVA (Milan, Italy). Corn oil, L-Dopa and benserazide hydrochloride were obtained from Sigma (Milan, Italy).

2.2. Animals

Male and female Wistar rats aged about 90 days weighing 250–270 g were obtained from Charles River (Calco, LC, Italy). Animals were housed in pairs in a room with artificial 12:12 h light/dark cycle (lights off at 8:00 a.m.), at constant temperature (21 ± 5 °C) and humidity (45–55%). All training and experimental sessions were conducted once a day during the nocturnal phase of the light/dark cycle. Food and water were always available in the home cages. Male rat pups born in our laboratory from primiparous dams were assigned to two treatment groups ($n = 28$ PERM-treated rats and $n = 26$ controls) so that each group contained no >3 pups from any litter. The first group was treated daily by gavage with PERM (34 mg/4 mL/kg body weight) from PND 6 to PND 21, whereas the second group (control) was treated with the vehicle (corn oil 4 mL/kg body weight) on a similar schedule as previously described (Nasuti et al., 2007). PERM was prepared by dissolving the substance in the corn oil.

2.3. Experimental procedures

Animals were brought to the testing room in their home cages and allowed to acclimate for approximately 15 min before initiating the experiments. Behavioral assessments were performed by two observers blind to treatment conditions. Outlines of experimental procedures are schematically depicted on Fig. 1.

2.3.1. T-maze test followed by chemical and immunohistochemical analysis

A first batch of animals (control group, $n = 10$; PERM-treated group, $n = 12$) at PND 50 was evaluated in a T-maze apparatus commonly used for assessing spatial working memory; ten days later the rats were sacrificed for chemical (control group, $n = 7$; PERM-treated group, $n = 7$) or immunohistochemical analysis (control group, $n = 3$; PERM-treated group, $n = 3$).

2.3.2. Motor coordination tests

A second batch of rats was monitored for motor performances (control group, $n = 8$; PERM-treated group, $n = 8$) over a 150-day follow-up period. A battery of behavioral tests sensitive to nigrostriatal impairment, including rotarod, footprint and beam walking was adopted.

2.3.3. L-Dopa challenge test

A third batch of animals (control group, $n = 8$; PERM-treated group, $n = 8$) was subjected to L-Dopa challenge in order to assess the efficacy of L-Dopa on motor deficits in a beam walking test at PND 150.

2.4. T-maze test

The T-maze test is widely used to assess spatial working memory. The apparatus and procedures have been reported in a previous study (Nasuti et al., 2013). Briefly, rats were subjected to the T-maze training for 10 daily consecutive choice trials for 7 consecutive days for a total of 70 trials. Animal behavior is scored for accuracy (% correct response), choice reaction time (CRT) and perseveration (number of consecutive incorrect choices) for each trial.

2.5. Chemical analysis

On PND 60, animals were sacrificed by CO_2 inhalation, the brains were rapidly removed and the two halves of Str were hand-dissected out as previously described (Nasuti et al., 2013). Striatal tissue was stored at −70 °C until use for DA analysis.

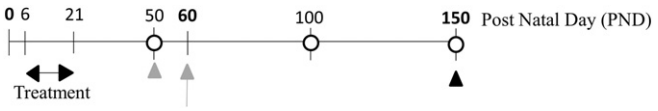

Fig. 1. Schematic outlines of experimental procedures. A) First experiment: two experimental groups of animals were treated with PERM or vehicle from PND 6 to PND 21. At PND 50, cognitive assessment was conducted (grey arrowhead). At PND 60, rats were sacrificed and brain tissue was collected for chemical or immunohistochemical analysis in Str and SNc, respectively (grey arrow). B) Second experiment: two experimental groups of animals were treated with PERM or vehicle from PND 6 to PND 21. At PND 50, 100 and 150, assessment of motor abilities was conducted (open circles). C) Third experiment: two experimental groups of animals were treated with PERM or vehicle from PND 6 to PND 21. At PND 150, rats were subjected to a L-Dopa challenge to assess the drug efficacy on motor deficits in a beam walking test (dark arrowhead).

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