Pharmacological Reports 69 (2017) 985–994

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Depressive-like neurochemical and behavioral markers of Parkinson's disease after 6-OHDA administered unilaterally to the rat medial forebrain bundle

Kinga Kamińska, Tomasz Lenda, Jolanta Konieczny, Anna Czarnecka, Elżbieta Lorenc-Koci*

Institute of Pharmacology, Polish Academy of Sciences, Department of Neuro-Psychopharmacology, Kraków, Poland

ARTICLE INFO

Article history:
Received 27 March 2017
Received in revised form 26 May 2017
Accepted 26 May 2017
Available online 3 June 2017

Keywords:
Asymmetric behavior
Depressive-like behavior
Monoamine levels
Sucrose solution intake
Unilateral 6-OHDA lesion

ABSTRACT

Background: Although Parkinson's disease (PD) is characterized by progressive neurodegeneration of multiple neurotransmitter systems, 6-hydroxydopamine (6-OHDA) as a model substance is mainly used to selectively damage the nigrostriatal dopaminergic neurons and induce parkinsonian-like motor disturbances in rats. We hypothesized that high doses of this neurotoxin affecting other monoaminergic systems may also evoke the depressive-like behavior.
Methods: The impact of 6-OHDA (8, 12, 16 μg/4 μl) administered unilaterally into the medial forebrain bundle on the sucrose solution intake (a measure of anhedonia) and on the tissue levels of noradrenaline (NA), dopamine (DA) and serotonin (5-HT) in the striatum (STR), substantia nigra (SN), prefrontal cortex (PFC) and hippocampus (HIP) was examined in rats pretreated or non-pretreated with desipramine.
Results: The highest dose of 6-OHDA reduced the preference for 3% sucrose solution both in rats without and with desipramine pretreatment. All used doses of 6-OHDA dramatically decreased DA content in the studied brain structures on the ipsilateral side. NA levels were severely decreased in the ipsilateral STR, HIP and PFC of rats non-pretreated with desipramine and to a much lesser extent in those pretreated with desipramine. In the SN, moderate decreases in NA level were found both in rats pretreated and non-pretreated with desipramine. Higher doses of 6-OHDA reduced 5-HT content in the ipsilateral STR, HIP and PFC, but not in the SN, only in rats non-pretreated with desipramine.
Conclusions: Administration of the highest dose of 6-OHDA without desipramine pretreatment evoked neurochemical and behavioral changes resembling the advanced PD with coexisting depression.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by a clinical picture dominated by major motor symptoms that include bradykinesia, rigidity, tremor and postural instability [1]. However, besides motor impairment, PD patients suffer from a multitude of non-motor symptoms, such as neuropsychiatric symptoms (e.g. depression, anxiety, apathy, psychosis), autonomic dysfunction and sleep problems [1,2] which are often even more debilitating than the movement disorders. PD was initially recognized as a purely motor disorder, but a high prevalence of non-motor symptoms has led to its current conceptualization as a neuropsychiatric disorder [3].

PD-associated depression is an important neuropsychiatric symptom that contributes to significant impairments in cognitive, motor, and social performance. A growing body of evidence suggests that depression in PD is secondary to neuroanatomical changes caused by a progressive neurodegenerative process rather than being a reaction to psychosocial stress and disability [4]. Hence, the pathophysiology of depressive symptoms in this disease is complex and probably includes dopaminergic, serotonergic and noradrenergic mechanisms. Also the diagnosis of PD-related depression is complicated because its symptoms, such as psychomotor slowing, retardation and the reduced facial expression may result from motor deficits.

The proposed neurobiological background of the pathological state includes a progressing impairment of mesocortico-limbic

Abbreviations: APO, apomorphine; DA, dopamine; HIP, hippocampus; 5-HT, serotonin; LC, locus coeruleus; MFB, medial forebrain bundle; NA, noradrenaline; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; PFC, prefrontal cortex; SN, substantia nigra; STR, striatum.

* Corresponding author.
E-mail address: lorenc@if-pan.krakow.pl (E. Lorenc-Koci).

http://dx.doi.org/10.1016/j.pharep.2017.05.016
1734-1140/

dopaminergic denervation accompanied by dysfunction of noradrenergic and serotonergic routes caused by neurodegenerative changes in the locus coeruleus (LC) and the brainstem raphe nuclei [5–8]. As demonstrated earlier, anhedonia, a prominent sign of depression in PD, is believed to be caused by the impairment of dopaminergic reward mechanisms which are closely linked to the degeneration of the ventral tegmental area and limbic projections [9]. Consistently with this, there is evidence from imaging studies confirming that limbic noradrenergic/dopaminergic pathways are more severely dysfunctional in PD patients with depression compared to those without depression [10]. Regarding serotonergic neurons, a greater neuronal loss in the dorsal raphe nuclei was observed in depressed than in non-depressed PD patients [7]. Furthermore, in PD a significant reduction of serotonin (5-HT) concentrations was found not only in the basal ganglia including the caudate nucleus, putamen, globus pallidus, substantia nigra (SN) and thalamus [11,12] but also in the frontal, cingulate and enthorinal cortices (by 40–60%) as well as in the hippocampus (HIP) [13,14]. Comprehension of alterations in the above-described neuronal networks, involved in the mood regulation is fundamental for understanding of PD-associated depression.

Recently, a lot of studies have focused on the examination of emotional and cognitive alterations in animal models of PD that correspond to the premotor stage of this illness [15–19]. On the other hand, the use of antidepressant drugs is often necessary in the symptomatic phase of the disease when patients are given anti-parkinsonian drugs. However, in the literature there is no such animal model that could adequately reflect the above-mentioned characteristic neurochemical changes of the disease both in the motor and limbic brain structures. Therefore, in order to establish a rat model of PD corresponding to the advanced-stage of the disease with coexisting depressive-like symptoms, we applied the classic neurotoxin, 6-hydroxydopamine (6-OHDA). In general, the 6-OHDA lesion model is reliable, leads to robust motor deficits, and is most commonly used to study pathomechanisms and potential therapeutic strategies in PD [20]. In our study, we checked the efficacy of 3 different doses of 6-OHDA administered unilaterally into the medial forebrain bundle (MFB), with or without desipramine (DES) pretreatment, on the degenerative process which takes place in the ipsilateral motor (striatum, STR; SN) and limbic (prefrontal cortex, PFC; HIP) brain structures. Pretreatment with desipramine (DES) at a dose of 25 mg/kg before surgery is usually applied in order to inhibit 6-OHDA-induced degeneration of the forebrain noradrenergic pathways [21]. In our study, we used DES to examine to what extent it protects noradrenergic fibers in the MFB projecting to the motor and limbic structures of the rat brain. The degree of dysfunction of noradrenergic, dopaminergic and serotonergic systems was assessed based on the tissue concentrations of NA, DA, 5-HT and their metabolites in the studied brain structures. In all groups of rats, anhedonia as a core symptom of depression was evaluated by means of the sucrose preference test while damage of the nigrostriatal system was estimated based on the level of contralateral rotations measured in the apomorphine (APO) test two weeks after lesion. We intend to use the established neurochemical model of the advanced PD with coexisting depressive-like symptoms and motor impairment in the future to study the effect of interaction between the selected antidepressant drugs and L-DOPA on behavioral and biochemical parameters. We hope that these experiments bring a new quality to research on the broad concept of the pathomechanism of PD.

Materials and methods

The experiments were carried out in compliance with the Act on Experiments on Animals of January 21, 2005 reapproved on January 15, 2015 (published in Journal of Laws no 33/2005 item 289 and no 23/2015 item 266, Poland), and according to the Directive of the European Parliament and of the Council of Europe 2010/63/EU of 22 September 2010 on the protection of animals used for scientific purposes. They received also an approval of the Local Ethics Committee at the Institute of Pharmacology, Polish Academy of Sciences. All efforts were made to minimize the number and suffering of animals used.

Animals

The studies were conducted on male Wistar Han rats (Charles River, Sulzfeld, Germany) of an initial body weight between 290 and 320 g kept under standard laboratory conditions; 5 animals per a large cage, at room temperature (22 °C) under an artificial light/dark cycle (12/12 h), with free access to standard laboratory food and tap water.

6-OHDA rat model of PD

In order to develop the symptomatic rat model of PD reflecting the neurochemical changes in the limbic and motor brain structures observed in this disease, the classic neurotoxin 6-OHDA was administered at three doses of 8, 12, 16 μg/4 μl unilaterally into the MFB. Rats were allocated randomly to 8 groups, six of them were injected unilaterally with 6-OHDA while two others with vehicle. Three of 6 groups receiving 6-OHDA were pretreated *ip* with a single injection of desipramine hydrochloride (DES; 25 mg/kg) 30 min before surgery. The sucrose preference test was performed in all groups of rats 1 week before as well as 1 and 3 weeks after stereotaxic surgery. The APO-induced (0.25 mg/kg *sc*) rotations were recorded 2 and 4 weeks after surgery (14th and 27th day, respectively). Only rats exhibiting more than 100 contralateral turns/1 h two weeks after surgery, occurrence of which corresponds to the extensive unilateral lesion of the nigrostriatal dopaminergic system, as previously described [22,23], were analyzed in behavioral and biochemical tests. Four weeks (28th day) after injection of the studied doses of 6-OHDA rats were sacrificed by decapitation and their left and right STR, SN, PFC and HIP were dissected on an ice-chilled plate. Then the tissues were stored at −80 °C until the neurochemical quantification.

Sucrose preference test

The sucrose preference test is commonly used as a measure of anhedonia in rodents [24,25]. Rats were transferred individually to single housing cages with free access to food. During a 24-h training phase, each rat was provided with two pre-weighted bottles of water. After the training day, one of the bottles was switched to that containing 3% sucrose solution and 24 h later the bottles were reversed to avoid development of a position-specific bias. The bottles were weighed and filled with fresh liquids daily. The percentage sucrose consumption was calculated according to the formula (% sucrose preference = sucrose intake × 100/total intake). The sum of water and sucrose consumption was defined as total liquid intake. During a 3-day sucrose preference test, a water or sucrose solution intake was recorded every day between 9:00 and 11:00 am After termination of the sucrose preference test, each rat was transferred from a single housing cage to a common home cage with free access to drinking water and standard laboratory chow.

Stereotaxic surgery

Each rat was anesthetized with a mixture (1:1 v/v) of ketamine (50 mg/kg *ip*, Biowet, Poland) and diazepam (2.5 mg/kg *ip*, Polfa Warszawa, Poland) administered in a volume of 1 ml/kg of body