Brain Research Bulletin 132 (2017) 75–81

Contents lists available at ScienceDirect

Brain Research Bulletin

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

Research report

Fluvoxamine maleate effects on dopamine signaling in the prefrontal cortex of stressed Parkinsonian rats: Implications for learning and memory

Ernest Dallé[a], Willie M.U. Daniels[b], Musa V. Mabandla[a,*]

[a] School of Laboratory Medicine and Medical Sciences, College of Health Sciences, University of KwaZulu-Natal, Durban 4000, South Africa
[b] School of Physiology, University of the Witwatersrand, Johannesburg, South Africa

ARTICLE INFO

Keywords:
Prefrontal cortex
Cognitive impairment
Dopamine
Serotonin
Parkinson's disease

ABSTRACT

Parkinson's disease (PD) is also associated with cognitive impairment and reduced extrinsic supply of dopamine (DA) to the prefrontal cortex (PFC). In the present study, we looked at whether exposure to early life stress reduces DA and serotonin (5-HT) concentration in the PFC thus leading to enhanced cognitive impairment in a Parkinsonian rat model. Maternal separation was the stressor used to develop an animal model for early life stress that has chronic effects on brain and behavior. Sprague-Dawley rats were treated with the antidepressant Fluvoxamine maleate (FM) prior to a unilateral 6-hydroxydopamine (6-OHDA) lesion to model motor deficits in rats. The Morris water maze (MWM) and the forelimb use asymmetry (cylinder) tests were used to assess learning and memory impairment and motor deficits respectively. Blood plasma was used to measure corticosterone concentration and prefrontal tissue was collected for lipid peroxidation, DA, and 5-HT analysis. Our results show that animals exposed to early life stress displayed learning and memory impairment as well as elevated basal plasma corticosterone concentration which were attenuated by treatment with FM. A 6-OHDA lesion effect was evidenced by impairment in the cylinder test as well as decreased DA and 5-HT concentration in the PFC. These effects were attenuated by FM treatment resulting in higher DA concentration in the PFC of treated animals than in non-treated animals. This study suggests that DA and 5-HT signaling in the PFC are responsive to FM and may reduce stress-induced cognitive impairment in PD.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative condition in which dementia or cognitive dysfunction may precede the motor dysfunction that follows midbrain dopaminergic neuron loss (Narayanan et al., 2013). The prevalence of cognitive dysfunction is high with reports indicating this non-motor symptom to negatively affect the quality of life of about 60% of patients with PD and to cause morbidity and mortality in 36% of patients at the early onset of the disease (Cools et al., 2002; Foltynie et al., 2004; Forsaa et al., 2010; Solari et al., 2013). Patients suffering from PD, therefore, appear to be particularly susceptible to develop cognitive impairments with rates of 4–6 times that of normal aging being recorded (Aarsland et al., 2005; Narayanan et al., 2013). More importantly, studies have shown that cognitive impairment may occur at an early stage of PD and this seems to correlate well with dopaminergic dysfunction in the prefrontal cortex (PFC) (Brück et al., 2005; Chudasama and Robbins, 2006). However, to date, the cellular mechanism underlying the development of cognitive impairment in PD remains largely unknown.

The PFC is known to play a key role in short and long-term learning and memory processes (Takashima et al., 2006; Corcoran and Quirk, 2007). Deficits in cognitive planning and spatial working memory that occur in PD and progressively increase in intensity with time, have been associated with damage of the PFC (Cools et al., 2002; Solari et al., 2013). During the early stages (non-motor symptoms) of PD, cognitive impairment may correlate with dopaminergic dysfunction in the PFC, while during advanced stages (motor symptoms) of PD, the direct dopaminergic projection from the ventral tegmental area to the frontal cortex is affected resulting in cortical dopamine (DA) depletion (Javoy-Agid and Agid, 1980; Scatton et al., 1983; Lupien et al., 2009; De la Fuente-Fernandez, 2012; Yuen et al., 2012; Solari et al., 2013). The PFC area of the brain receives a broad range of sensory and limbic inputs critical for appropriate behavioral task execution. However, altered DA transmission within the PFC results in abnormal information processing, leading to learning and memory deficits (Solari et al., 2013). In this regard, it has been suggested that learning and memory impairment may predict the development of dementia in PD that is so highly prevalent across the entire course of the disease (Aarsland et al., 2005;

* Corresponding author.
E-mail address: mabandlam@ukzn.ac.za (M.V. Mabandla).

http://dx.doi.org/10.1016/j.brainresbull.2017.05.014
Received 21 February 2017; Received in revised form 9 May 2017; Accepted 22 May 2017
Available online 24 May 2017

Aarsland and Kurz, 2010).

We have recently shown that the antidepressant Fluvoxamine maleate (FM) is not only useful in treating major anxiety/depressive-like symptoms but also attenuates neurotoxin induced-DA degeneration in an animal model for PD (Dallé et al., 2017). The effects of antidepressants on serotonergic and dopaminergic transmission are well established (Tao et al., 2016). These effects include increasing serotonin (5-HT) and DA levels in the striatum and the PFC (Lupien et al., 2009; Hemmerle et al., 2012). More importantly, the effects of antidepressants on cognition are widely known since long-lasting cognitive deficits induced by stress can be attenuated by some antidepressant (Nikiforuk and Popik, 2011). However, finding the mechanism of cognitive dysfunction in PD is critical for treating cognitive symptoms of PD, since to date, only few effective treatments are available. Moreover, to the best of our knowledge, apart from Levodopa that has been shown to improve cognitive symptoms of PD depending on the stage of the disease and the integrity of striatal DA signaling, no studies have looked at the effects of an antidepressant to treat PD-induced DA depletion in the PFC (Kulisevsky et al., 2000; Cools et al., 2002; Muller et al., 2001; Cools, 2006; Pascual-Sedano et al., 2008). We hypothesized that chronic treatment with FM will reduce learning and memory deficits and counteracts 6-OHDA-induced Parkinsonian symptoms in stressed rats. The present study consequently aimed to investigate the effects of FM treatment on cognitive deficits in a Parkinsonian rat model and whether serotonergic and/or dopaminergic mechanisms of FM in the PFC could contribute to an anti-parkinsonian effect in stressed rats.

2. Materials and methods

2.1. Animals

The experimental protocol used in this study was reviewed and approved by the Animal Research Ethics Committee of the University of KwaZulu-Natal (018/15/Animal) in accordance with the guidelines of the National Institutes of Health, USA. The sample size was set according to previous studies where the statistical power was shown (Eng, 2003; Dalle et al., 2016). A total of 60 male Sprague-Dawley rats obtained from the Biomedical Resource Unit of the University of KwaZulu-Natal were used in this study. They were housed in polypropylene cages (38 × 32 × 16 cm) under controlled temperature (21 ± 2 °C) and humidity (55–60%). Food and water were freely available. The daily light/dark cycle was 07:00–19:00 (Mabandla and Russell, 2010). On post-natal day (PND) 1, the rats were sexed and culled to 6 male pups per litter and randomly divided into 6 equal groups as follows: non-stressed (NS), non-stressed treated with saline (NSS), non-stressed treated with FM (NSF), maternally separated (MS), maternally separated treated with saline (MSS) and maternally separated treated with FM (MSF). The rats were weaned on PND 21 after which they were kept 6 per cage (Dalle et al., 2016). On PND 29, all treated groups received saline or FM intraperitoneally from PND 29–59 once daily. NSS and MSS rats received vehicle injections (saline 1 ml/250 g of body weight) and were lesioned with saline to control for the effects of handling, stress, lesion and the injection itself. NSS and MSS data were not included since no significant effect was found between saline treated rats and non-treated rats. Lesion refers to the intracerebral injection of the neurotoxin 6-OHDA on PND 60 in all groups. The animals were weighed prior to all experimental procedures and were brought to the experimental room at least 1 h before experimentation. The learning and memory ability test was assessed on PND 28, 58 and 74 using the Morris water maze (MWM) apparatus (Vorhees and Williams, 2006; Beraki et al., 2009). Limb-use asymmetry was assessed on PND 59 and 75 using the cylinder test (Mabandla and Russell, 2010). The rats were sacrificed on PND 76. All experimental procedures were conducted between 09:00 and 16:00.

2.2. Drugs and reagents

The drug Fluvoxamine maleate, Temgesic and Biotane were obtained from Pharmed Pharmaceuticals LTD (Rochdale Park, Durban, South Africa). Desipramine (D3900), atropine, pentobarbital and 6-OHDA were purchased from Sigma (St. Louis MO, USA). The Corticosterone (RE52211), Dopamine (RE59161) and Serotonin (RE59121) ELISA kits were purchased from IBL International GmbH (Hamburg, Germany). The lipid peroxidation (MDA) assay kit (K739-100) was obtained from BioVision (Mountain view, CA, USA).

2.3. Maternal separation

Maternal separation was the stressor used to enhance learning and memory deficits (non-motor symptoms of PD) as per study by Lupien et al. (2009) and Hermmerle et al. (2012). This protocol was also used so as to investigate whether addressing these symptoms at their early stage with FM could delay the motor symptoms in a model of PD. The maternal separation stress protocol was carried out once a day from PND 2 to PND 14. We used a stress protocol previously described in Mabandla and Russell (2010) and Dalle et al. (2016). Briefly, the pups were taken away from their dams and kept in a separate room for 3 h (09:00–12:00). All normally reared pups were left undisturbed with their dams.

2.4. Behavioral tests

Behavioral tests were used to assess the effects of FM on learning and memory in a maternally separated rat as well as to assess the effects of the drug on motor dysfunction in a Parkinsonian rat model. The behavioral tests used included the MWM test and the limb-use asymmetry test (cylinder test). The tests were performed pre- as well as post-lesion with 6-OHDA. All behavioral tests were video-recorded for subsequent scoring and manually analyzed by an evaluator blind to the study.

2.4.1. Morris water maze (MWM) test

The MWM test was used to assess spatial learning and memory (D'hooge and De Deyn, 2001). The MWM apparatus used was a circular tank (1 m in diameter) that is divided into 4 quadrants filled with water (22–23° C) in where a hidden square plexiglass platform (10 × 10 cm wide and 20 cm high) is submerged (1 mm) bellow the water surface. The hidden platform was placed in one of the quadrants and each quadrant had a visual cue to help the rat in its navigation. All animals were exposed to training sessions (4 trials per day) over consecutive days (PND 25–27) (Vorhees and Williams, 2006). The latency time (time taken to reach the hidden platform) was recorded and was taken as the learning process (Morris, 1984). A probe test was conducted (without the platform) to assess the ability of the rats to remember the quadrant in which the platform was located (Garthe and Kempermann, 2013).

2.4.2. The limb-use asymmetry test (Cylinder test)

The cylinder test was used to assess the forelimb used during exploratory activity in the plexiglass cylinder and for landing over a period of 5 min. As the neurotoxin 6-OHDA was injected into the left hemisphere, a successful model of Parkinsonism would result in a bias towards left forelimb use after lesion (Tillerson et al., 2001; Mabandla and Russell, 2010). The cylinder was made of transparent plexiglass (20 cm in diameter and 30 cm in height). The rats were assessed for percentage limb-use of the impaired (right) limb by using the following equation: % limb use of impaired = [(impaired + ½ both)/(impaired + unimpaired + both)] × 100. Both, refers to the use of both the impaired and unimpaired limbs during exploratory activity (Tillerson et al., 2001).