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Research report

Fluvoxamine maleate normalizes striatal neuronal inflammatory cytokine activity in a Parkinsonian rat model associated with depression

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HIGHLIGHTS

- Early maternal separation caused anhedonia and exacerbated the effects of 6-OHDA in lesioned rats.
- Fluvoxamine reversed the effects of 6-OHDA lesion by modulating cytokine gene expression in the striatum of treated rats.
- Fluvoxamine normalized pro- and anti-inflammatory cytokine expression in the striatum of treated rat.

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ABSTRACT

Cytokine dysfunction is associated with both depression and Parkinson's disease (PD) pathophysiology. Inflammatory cytokines in neural and behavioral processes are involved in the production and/or maintenance of depression in PD. In this study we looked at how Fluvoxamine treatment regulates depressive-like signs, motor impairments and the expression of IL-1β, IL-6, TNF-α, TGF-β and IL-10 cytokines in the striatum of a stressed Parkinsonian rat model. Early maternal separation was used to model stress and depressive-like signs in rats. Maternally separated adult rats were treated with Fluvoxamine for 30 days prior to 6-hydroxydopamine (6-OHDA) lesion. The sucrose preference test (SPT) and the limb-use asymmetry test (cylinder test) were used to evaluate anhedonia and motor impairments respectively. Lipid peroxidation and cytokine expression were measured in striatal tissue using ELISA and real-time PCR techniques respectively. Our results show that maternal separation resulted in anhedonia and exacerbated 6-OHDA lesion but Fluvoxamine treatment attenuated these effects. Lipid peroxidation, mRNA levels of IL-1β, IL-6 and TNF-α were down-regulated while IL-10 and TGF-β levels were up-regulated in the lesioned striatum of Fluvoxamine treated rats. This study shows that early treatment with Fluvoxamine may attenuate inflammation on injured striatal neurons by favoring anti-inflammatory cytokine expression while decreasing pro-inflammatory cytokine release in the brain. This suggests a role of Fluvoxamine as a potential therapeutic intervention targeting neuronal inflammation associated with PD.

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1. Introduction

Early exposure to emotional stress such as maternal separation has been shown to cause long-term neurochemical and behavioral changes later in life [1]. These changes include depression, a psychiatric disorder commonly encountered non-motor features of Parkinson's disease (PD) [2]. The estimated prevalence of depression in PD is between 40–50% in all PD cases [3]. This high prevalence of depression in PD has prompted the idea that degenerated nigrostriatal system may play a key role in depression [4].

The pathophysiology of PD also includes the presence of α-synuclein-containing aggregates in the substantia nigra pars compacta (SNpc) which may suggest the activation of glial cells and dysfunction in pro and/or anti-inflammatory factor levels common in PD associated with depression [5,6]. For instance, the chronic release of pro-inflammatory cytokines by activated astrocytes and microglia (the resident innate immune cells) leads to the exacerbation of DA neuron degeneration in the SNpc [6,7]. Anti-inflammatory cytokines may also inhibit microglial activation by reducing reactive oxygen species which can be evaluated via lipid

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peroxidation levels [8]. Moreover, at a cellular level, cytokines are expressed in microglia and play a critical role on neuron-microglia interactions in the regulation of neuroinflammation in both depression and PD [6,9]. Studies have shown that there are high levels of pro-inflammatory cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6) and lower levels of anti-inflammatory cytokines (transforming growth factor (TGF)-β, IL-10) in the midbrain of patients with depression and PD [3,6,10]. This strongly suggests the involvement of these immune components in PD pathogenesis associated with depression.

Studies have shown that in a 6-OHDA lesioned animal model of PD, cytokine dysfunction may result in increased DA cell death rate in the striatum [6,9,11]. However, a better understanding of the role of inflammation caused by any stressor and treated with an antidepressant is still lacking. An animal model that mimic depressive-like signs and motor deficits of PD may be useful in establishing effective therapeutic strategies on the pathological processes of the depression in PD.

Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI) is one of the antidepressants commonly used as first line treatment for major depressive disorders [12,13]. Studies have shown that antidepressants may possess potent anti-inflammatory effects which attenuate cytokine expression by inhibiting infiltration of peripheral immune cells, blocking glial activation to reduce oxidative stress [14,15]. However, little is known about the effects of Fluvoxamine in the central nervous system, especially in the nigrostriatal DA system in the context of PD associated with depression. In an animal model of PD, the generation of free radicals can suggest an increase in pro-inflammatory cytokines along with decreased anti-inflammatory molecules in the striatum [8,16,17]. These observations may suggest that depression in PD is similar to a psychoneuroimmunological disorder where the increase in neuronal pro-inflammatory cytokines is likely to result in adverse consequences on functional activity of the neurochemical system implicated in the symptoms of the disorder. Therefore, in this study, we aimed to investigate whether early exposure to maternal separation may exacerbate neuronal inflammation. We further looked at the effects of Fluvoxamine exerted in the expression of pro-inflammatory cytokines (neurotoxic factors) and anti-inflammatory cytokines (neuroprotective molecules) in a PD rat model.

2. Materials and methods

The experimental protocol (Fig. A) used in this study was reviewed and approved by the Animal Research Ethics Committee of the University of KwaZulu-Natal (018/15/Animal). The sample size was set according to previous studies where the statistical power was shown [18–20]. A total of 40 male Sprague-Dawley (SD) 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 to 19:00 [21]. On post-natal day (PND) 1, the rats were sexed and culled to 6 male pups per litter. The rats were randomly divided into two equal groups as follows: normally reared (NS) and maternally separated (MS). The rats were weaned on PND 21 after which they were kept 6 per cage [21]. On PND 29, the groups were subdivided into 2 groups as follows: (1) normally reared pre-lesion treated (NSF: treated with Fluvoxamine from PND 29 – 59) and (2) maternally separated pre-lesion treated (MSF: treated with Fluvoxamine from PND 29 – 59). Lesion refers to the intracerebral injection of the neurotoxin 6-hydroxydopamine (6-OHDA) on PND 60 in all groups. Anhedonia was assessed on PND 28, 58 and 74 using the sucrose preference test (SPT) [22]. Limb-use asymmetry was assessed on PND 58 and 75 using the cylinder test [21]. All rats were sacrificed on PND 76. All experimental procedures were conducted between 09:00 to 16:00. The animals were weighed prior to all experiments and were brought to the experimental room 1 h before experimentation [1,21].

2.1. Drugs and reagents

The drug Fluvoxamine is manufactured by Pharmed Pharmaceuticals LTD (Rochdale Park, Durban, South Africa). Desipramine (D3900), atropine, pentobarbital and 6-OHDA-HCL were purchased from Sigma (St. Louis MO, USA). Temgesic and Biotane were obtained from Pharmed Pharmaceuticals LTD (Rochdale Park, Durban, South Africa). The lipid peroxidation (MDA) assay kit (K739-100) was obtained from BioVision (Mountain view, CA, USA). Real-time PCR kits were purchased from BioRad Laboratories (CA, USA).

2.2. Maternal separation

Maternal separation took place from PND 2 – 14. The maternal separation stress protocol was based on previous studies [20,21,23]. Briefly, the pups were taken away from their dams and kept in a separate room for 3 h (09:00–12:00) once a day. All normally reared pups were left undisturbed with their dams.

2.3. Behavioral tests

Behavioral tests were set to assess the effect of Fluvoxamine in attenuating depressive-like signs in a rat model of depression as well as to assess the effects of the drug on motor dysfunction in a Parkinsonian rat model. The behavioral tests included the sucrose preference test (SPT) and the limb-use asymmetry test (cylinder test). The tests were performed pre- as well as post-lesion with 6-OHDA.

2.4. The sucrose preference test (SPT)

The SPT was conducted over a 24 h period (9:00 a.m. to 9:00 a.m.) on PND 28, 58 and 74. A day prior to the test, the rats were weighed and placed in separate cages for a 24 h training period. The training phase consisted of placing two bottles of water preweighed, on opposite sides of the cage [24,25]. After the 24 h had elapsed, one bottle was replaced with one containing 2.5% sucrose solution. For the test phase, the two bottles (one containing tap water and the other containing 2.5% sucrose solution) were placed such that the bottle containing tap water was on the left side and the sucrose containing on the right. After 24 h, the bottles were weighed to determine consumption in grams (converted to ml). The sucrose preference ratio was calculated as a volume of sucrose drunk over the total fluid consumed (sucrose + water). A decreased amount of sucrose solution drunk is suggestive of anhedonia thus of depressive-like behavior [22,24].

2.5. The limb-use asymmetry test (cylinder test)

The cylinder test device was similar to the one described by [21] that consists of a transparent plexiglass cylinder of 20 cm in diameter and 30 cm in height. The test was conducted on PND 59 and 75. For Limb-use during exploratory activity (touching the wall of the cylinder and landing), each animal was scored over a 5 min period. The test was video-recorded using a camera and manually analyzed by an evaluator blind to the study. The animals were assessed for percentage limb-use of the impaired (contralateral) limb by using the following equation: % limb use of impaired = [(impaired + ½

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