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Depression-related behavior and mechanical allodynia are blocked by 3-(4-fluorophenylselenyl)-2,5-diphenylselenophene in a mouse model of neuropathic pain induced by partial sciatic nerve ligation

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ABSTRACT

Clinically, it is suggested that chronic pain might induce mood disorders like depression and anxiety. Based on this antidepressant drugs have emerged as a new therapy for pain. In this study, the effect of acute and subchronic treatments with 3-(4-fluorophenylselenyl)-2,5-diphenylselenophene (F-DPS) on behavioral changes induced by partial sciatic nerve ligation (PSNL) was evaluated. At the 4th week after surgery, PSNL caused a significant depression-like behavior in mice evaluated in the forced swimming test (FST) and the tail suspension test (TST), which was accompanied by increased pain sensitivity. The anxiety-like behavior assessed in the light–dark test (LDT) was not modified by PSNL. Acute treatment with F-DPS, at a dose of 1 mg/kg, intragastrically (i.g.) administered 30 min before the FST, produced a significant anti-immobility effect in PSNL mice. The antidepressant drug paroxetine showed acute antidepressant-like action at a dose 10 times higher than F-DPS. Subchronic treatment with F-DPS (0.1 mg/kg, i.g.) reversed depression-like behavior of sciatic nerve-ligated mice in the TST and FST and produced a significant anxiolytic-like action in both sham-operated and PSNL animals. Although the acute F-DPS treatment did not produce anti-allodynic effect, F-DPS subchronic treatment significantly reduced pain sensitivity in PSNL mice. These findings demonstrated that F-DPS blocked behavioral changes induced by neuropathic pain, suggesting that it might be attractive in the pharmacological approach of pain-emotion diseases.

1. Introduction

Mood disorders such as depression and anxiety are frequently observed in patients suffering from chronic pain (Goldberg and McGee, 2011). This comorbidity leads to serious clinical problems and has a larger negative impact on the quality of life (Arnow et al., 2006; Goldberg and McGee, 2011). Although the mechanisms concerning pain-emotion diseases have not been defined, preclinical studies have demonstrated a relationship between neuropathic pain and mood disorders in animal models (Arnow et al., 2006; Matsuzawa-Yanagida et al., 2008; Yalcin et al., 2011). In fact, previous studies have shown depression-related behavior in rodents subjected to sciatic nerve injury, a well-recognized model for neuropathic pain (Fukuhara et al., 2012; Jesse et al., 2010). The partial sciatic nerve ligation (PSNL), model of Narita et al. (2005), incorporates a less peripheral inflammatory component compared with other peripheral nerve injury models and has a robust mechanical hypersensitivity and high responsiveness to analgesic drugs and novel therapies for chronic pain (Crisp et al., 2003; Dowdall et al., 2005; Narita et al., 2005; Roeska et al., 2008; Seltzer et al., 1990).

In the last decade, antidepressant drugs have emerged as first-line drugs for neuropathic pain, a chronic condition, severe, and resistant to most analgesics (Attal et al., 2006; Mico et al., 2006). It has been clinically and pre clinically demonstrated that treatment with drugs that increase extracellular concentrations of serotonin (5-HT), dopamine (DA), and noradrenaline (NA) seems to be effective in improving both pain and depression symptoms (Attal et al., 2006; Blier and Abbott, 2001; Hauser et al., 2013; Thaler

Abbreviations: F-DPS, 3-(4-fluorophenylselenyl)-2,5-diphenylselenophene; PSNL, partial sciatic nerve ligation; FST, forced swimming test; LAM, locomotor activity monitor; LDT, light–dark test; SRI, serotonin reuptake inhibitor; TST, tail suspension test; VFH, Von-Frey hair.

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et al., 2012). These actions are mainly related to changes on cellular signaling pathways by inhibiting reuptake transporters and interacting with monoaminergic membrane receptors (Blier and Abbott, 2001). However, exact mechanisms underlying their effectiveness in anti-nociception/pain are unknown.

Over the past decade, it has been shown the efficacy of organoselenium compounds in many experimental models of chronic pain and depression-like behavior (Gai et al., 2012; Gay et al., 2010; Jesse et al., 2010; Nogueira and Rocha, 2011). 3-(4-fluorophenylselenyl)-2,5-diphenylselenophene (F-DPS) is an organoselenium drug belonging to the selenophene class which has shown antidepressant-like action (Gai et al., 2012; Gay et al., 2010). Its mechanism of action still remains unclear; however, a previous study showed that 5-HT receptor antagonists block its acute antidepressant-like effect on the mouse forced swimming test (FST). Further, F-DPS seems to increase serotonergic neurotransmission by inhibiting presynaptic 5-HT transport (Gay et al., 2010).

Taking into account the abovementioned points, the main objective of this study was to investigate whether acute and subchronic F-DPS treatments could be effective in reducing depression-related behavior and pain sensitivity in sciatic nerve-ligated mice.

2. Materials and methods

2.1. Animals

The experiments were conducted using male Swiss mice (25–30 g) maintained at 22–25 °C with free access to water and food, under a 12:12 h light/dark cycle with lights on at 7:00 a.m. All manipulations were carried out between 08:00 a.m. and 04:00 p.m. and mice were acclimated to the behavioral room at least 2 h before the test. The experiments were performed according to a randomized schedule and each animal was used only once in each test. The animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources of the Federal University of Santa Maria, Brazil (# 124/2010). The procedures in this study were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals. All efforts were made to minimize animal suffering and to reduce the number of animals used in the experiments.

2.2. Drugs

3-(4-fluorophenylselenyl)-2,5-diphenylselenophene (F-DPS, Fig. 1) was prepared and characterized in our laboratory based on a previous study (Stein et al., 2008). Analysis of the ^{1}HNMR and ^{13}CNMR spectra showed analytical and spectroscopic data in full agreement with its assigned structure. The chemical purity of studied compound (99.9%) was determined by GC/MS.

Paroxetine was purchased from Sigma–Aldrich (St. Louis, MO, USA). All other chemicals were of analytical grade and obtained from standard commercial suppliers.

F-DPS was dissolved in canola oil and administered by intragastric (i.g.) route. I.g. procedure is commonly used by our research group for administration of organoselenium compounds and oil-soluble drugs (Gai et al., 2012; Gay et al., 2010), compounds are administered by using a gastroesophageal probe that releases them directly into the stomach. Paroxetine was dissolved in saline with dimethyl sulfoxide (DMSO) 1% and administered intraperitoneally (i.p.) (Gay et al., 2010).

2.3. Surgical procedure

PSNL has been shown to produce neuropathic pain and increased depressive-like behavior in rodents (Jesse et al., 2010; Yalcin et al., 2011). PSNL was performed based on the original description (Narita et al., 2005) under intraperitoneal ketamine/xylazine (150 and 10 mg/kg, respectively) anesthesia. Briefly, the right sciatic nerve was exposed after the incision of skin and blunt separation of the muscle. The sciatic nerve was freed of the adhering tissue gently for about 7 mm, and one ligature (8/0 Ethicon GmbH, Norderstedt, Germany) was made around approximately 1/3–1/2 the diameter of the sciatic nerve. Great care was taken to tie the ligatures so that the diameter of the nerve was just barely constricted. Sham operation was performed by exposing sciatic nerve except for nerve ligation.

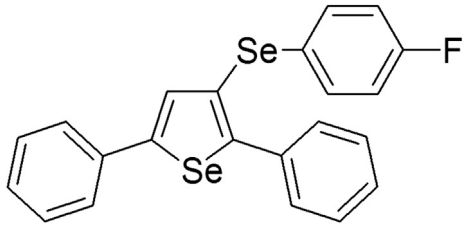

Fig. 1. Chemical structure of 3-(4-fluorophenylselenyl)-2,5-diphenylselenophene (F-DPS).

2.4. Experimental design

This study was divided into 2 experimental protocols (Fig. 2). The first protocol aimed to investigate the acute effect of F-DPS on the depression-like behavior and mechanical allodynia induced by PSNL in mice. In this experiment, we used the classical antidepressant drug, paroxetine, as a positive control. In the Experiment 2, we investigated whether an acute subeffective dose of F-DPS would be effective if subchronically administered to mice. Thus, we treated sham and PSNL-subjected animals with F-DPS at a dose of 0.1 mg/kg, during 1 or 2 weeks.

2.4.1. Experiment 1

At the end of the 4th week after surgery, PSNL mice were treated with vehicle (10 ml/kg) or F-DPS (dose range: 0.1–10 mg/kg) by the intragastric (i.g.) route ($n = 9$ animals/group). Thirty minutes after treatment, mice were then tested in the forced swimming test (FST). In order to investigate changes on the mouse locomotion, before the FST mice were observed in the locomotor activity monitor (LAM). The F-DPS pretreatment time was based on a previous study from our research group, which established 30 min as the maximum acute F-DPS antidepressant-like effect (Gay et al., 2010).

In order to compare the antidepressant-like effect of F-DPS with a classical antidepressant drug, PSNL mice received vehicle (10 ml/kg) or paroxetine at doses of 1 and 10 mg/kg ($n = 7$ animals/group), intraperitoneally (i.p.), forty five minutes before the FST. Spontaneous locomotor activity of mice was also observed into LAM.

For the purpose of investigating the effect of F-DPS on the neuropathic pain induced by PSNL, a separate group of animals received vehicle (10 ml/kg) or F-DPS at a dose of 10 mg/kg, i.g., and was evaluated in the mechanical allodynia test 30 min after treatment ($n = 7$ animals/group). The anti-allodynic effect of paroxetine at doses of 1 and 10 mg/kg ($n = 7$ animals/group), intraperitoneally (i.p.), forty five minutes before VFH, was also investigated.

2.4.2. Experiment 2

The second part of this study investigated the antidepressant-like effect of F-DPS after subchronic treatment. For this purpose, animals were divided into six groups ($n = 10$ animals/group) and a subeffective dose of F-DPS, selected in the Experiment 1 (0.1 mg/kg), or vehicle (10 ml/kg), was administered daily to sham and sciatic nerve-ligated mice during the 3rd and/or 4th weeks after surgery. At the end of the 4th week, twenty-four hours after the last dose of F-DPS, mice were evaluated in the LAM, tail suspension test (TST) and FST. Pain sensitivity of mice was accompanied by using Von-Frey Hair (VFH) paradigm. Further, the possible anxiolytic-like action of F-DPS was performed in the light–dark test (LDT).

2.5. Behavioral testing

2.5.1. Spontaneous locomotor activity

To discard non-specific effects of treatments, spontaneous locomotor activity of mice was performed in the locomotor activity monitor (LMA). LMA is a Plexiglas cage (45 × 45 × 45 cm) surrounded by a frame consisting of 32 photocells mounted on opposite walls (16 L × 16 W, spaced 2 cm apart) that continuously tracks the animal's movement. Animals were placed in the center of the apparatus and allowed to freely explore the arena during 4 min. Motor activity was monitored with the Insight® Monitor Activity System. Data were collected in the form of photobeam breaks as an indication of activity within different predetermined "zones" in the open field using Monitor Activity® software (Insight). Number of crossings and rearings, average velocity (mm/s) and total distance traveled (dm) were recorded.

2.5.2. Tail suspension test (TST)

The TST was performed in a quiet experimental room according to the method reported by Steru and collaborators (Steru et al., 1985). Each mouse was suspended by its tail to a horizontal wooden bar located inside a yellow plastic box (40 cm × 46 cm × 40 cm) approximately 30 cm above the floor. The mouse was secured to the bar by adhesive tape placed 1 cm from the tip of the tail, such that the mouse's head was about 20 cm above the floor. The trial was conducted for 6 min during which a blinded observer scored the latency for the first immobility episode and total duration of immobility by using a stopwatch. The mouse was considered immobile only when it hung passively and completely motionless. Mice that climbed their tails were eliminated from further analyses.

2.5.3. Forced swimming test (FST)

The FST is one of the most widely used tools for evaluation of antidepressant drugs, antidepressant efficacy of new compounds, and experimental manipulations that are aimed at rendering or preventing depressive-like states. The procedure used in this study was based on that previously described (Porsolt et al., 1979). Mice were