Name: Fernanda Sousa

Position: Post doctor

Department: Postgraduate Program in Biotechnology (PPGB), Research Group on Oncology (GPO), Department of Biotechnology

Institution: Federal University of Pelotas, Pelotas, RS, Brazil.

Complete Adress: Av. Eliseu Maciel, s/n, CEP 96010-900, Universitary Campus of Capão do Leão, Pelotas, RS, Brazil

Phone: + 55 53 999634983

e-mail: nandinha_sousa4@hotmail.com

Project Title: Evaluation of chronic administration of α- (phenylselenyl) acetophenone in dyad pain and stress-induced depression in mice

Key words: Stress, Selenium, Pain, Antidepressants.

Introduction

On average 65% of people with pain have comorbidity with depression worldwide. Individuals suffering from both conditions are less likely to adhere to treatments and are more likely to relapse after the same. In addition, they show prolonged disability and a lower quality of life compared to those who only have pain or depression. Thus, several research groups have promoted their studies in the search for new therapies for the treatment of dyad pain and depression, which can improve patients' quality of life. In particular, organic selenium compounds demonstrate antidepressant and antinoceptive activity in different animal models. In view of this, the α- (phenylselenyl) acetophenone (PSAP) molecule has been the subject of several studies, since it has been described in the literature that the acute administration of this molecule presents antidepressive-type activity with involvement of the serotoninergic system and interaction with the enzyme monoamine oxidase A. In addition, PSAP also showed antioxidant, antinociceptive and toxicity. In this way, the development and validation of a study to verify its effect through the chronic administration in pain model and stress-induced stress of restriction in mice proves to be of extreme importance. For the accomplishment of this study, the effect of the chronic administration of the PSAP in front of the restraint stress will be evaluated. In addition, a new model of pain and depression comorbidity that may be useful in investigating mechanisms of action of new compounds with action in both pain and depression will be validated. In addition, the implementation of this proposal will contribute significantly to the enrichment of the research group through the implementation of a new experimental model and new methodologies.

General objective

Considering the aspects, the objective of this work is to evaluate the effect of chronic administration of α- (phenylselenyl) acetophenone on dyad pain and depression induced by restriction stress in mice.

Specific objectives

The specific objectives of this project include evaluating:

- The possible activity of chronic administration of PSAP in the reduction of hyperalgesia induced by acute stress of restriction;
- Improvement of type-depressive symptoms through chronic administration of PSAP in mice submitted to acute restraint stress;
- Possible mechanisms involved in the effects of chronic PSAP administration through quantitative real-time polymerase chain reaction (qRT-PCR) and Western Blotting analysis in total cortex and mouse hippocampus.
- The possible involvement of reactive species levels of thiobarbituric acid, reactive oxygen species and nitric oxide, catalase activity, superoxide dismutase and monoamine oxidase A and B, in the antidepressive and antihyperalgesic action of the chronic administration of PSAP in mice submitted to acute stress restriction.

METHODOLOGY

The methodologies to be used in this project are routine in the laboratory. We will also use a new animal model, which will be implemented by the scholarship holder. A summary of the methods to be used are described below.

Animals

Experiments will be conducted using male Swiss adult mice (25-35g). The animals will be kept 5 animals in each box in a light / dark cycle of 12 h with lights on at 7:00 am at room temperature (22 ± 1 ° C) with free access to water and food. All experimental procedures will be performed according to the guidelines of the Committee for Care and Use of Experimental Animal Resources of the Federal University of Pelotas, Brazil.

Compounds

The PSAP (Fig. 1) will be prepared and characterized in the Laboratory of Clean Organic Synthesis (LASOL) according to the method described previously (VICTORIA et al., 2009). The PSAP will be diluted in canola oil and administered intragastric (i.g.) in the mice at a dose rate of 1-10 mg / kg in a volume of 10 ml / kg. The standard drug used will be imipramine (IMI) at the dose of 10 mg / kg (i.g.) in a volume of 10 mL/kg, and will be purchased at a commercial pharmacy. All other chemical reagents will be purchased from Sigma-Aldrish.

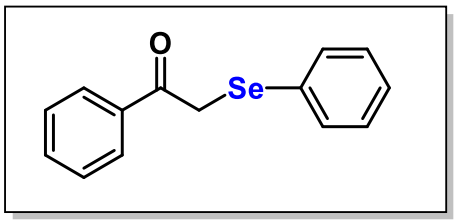


Figure 1. Representation of the chemical structure of α- (phenylselenyl) acetophenone (PSAP).

The acute stress restriction procedure will be performed by a previously described method (CHU et al., 2016; FREITAS et al., 2014; KUMAR; GOYAL, 2008). The immobilization will be applied for a period of 7 hours using an individual rodent containment device made of fenestrated acrylic. This process restricts all physical movements without causing pain. The animals will be deprived of food and water throughout the period of exposure to stress. Non-stressed groups will be treated with vehicle or PSAP or IMI and will have free access to water and food.

Experimental Protocol

The animals will be randomly divided into six experimental groups to evaluate the chronic effect of PSAP administration (i.g.) on mice with hyperalgesia and depression induced by acute restriction stress. In this study two experiments will be carried out:

Experiment 1: The mice will be subjected to restriction stress for 7h. After 30 min of stress, the mice will receive PSAP (1-10 mg / kg, i.e.) or IMI (10 mg / K, i.e.) and after 30 min the behavioral tests will be performed.

Experiment 2: The mice will be subjected to restriction stress for 7h. After this time the mice will receive PSAP (1-10 mg / kg) or IMI (10 mg / kg) for 20 days. On the 21 st day, the animals will be submitted to behavioral tests such as forced swimming test (TNF), open field test (TCA), tail suspension test (TSC), sucrose preference test, splash test, test of the hot plate and Von Frey filaments test.

All observations will be made by a blind observer to the study plan. The biochemical parameters will be evaluated with the same group of animals (following the same experimental model). Animals used for neurochemical determinations will be euthanized by cervical dislocation, followed by removal of the brain and isolation of the total cortex and hippocampal structures for analysis.

Perspectives

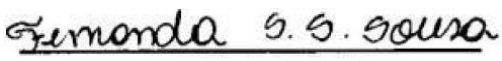
Since depression is the leading cause of disability among people worldwide, increasing attention is focused on studying the mechanisms of action involved in the pharmacology of new molecules with therapeutic potential. In addition to this, studies have pointed out that the development of the pain-depression dyad may be closely related to inflammatory events, and neuroinflammation would be the common mechanism of this comorbidity (WALKER et al., 2013). It is noteworthy that there is a communication between the immune system, central nervous system (CNS) and inflammatory conditions

can affect the neuronal environment and induce depressive symptoms (DANTZER et al., 2008), but at the same time can also lead to development and maintenance of chronic pain (VALLEJO et al., 2010).

Thus, in this project we intend to develop and validate a model of depression induced by restriction stress and seek a new alternative for the treatment of depressive patients who are more effective, with less adverse effects and with a faster onset of action. Thus, this study will allow a better understanding of both the mechanisms by which stress induces depression and the mechanisms by which the chronic administration of PSAP acts on the antidepressant and antihyperalgesic effect, increasing confidence in the potential of this molecule. This protocol was elaborated considering that this research group has already published articles in periodicals reporting on the acute effect of PSAP administration in the type-depressive state, nociception, oxidative stress and dyad pain and depression in mice. Considering the experience of our research group in evaluating the pharmacological and toxicological activity of bioactive molecules, especially organic compounds of selenium, it is expected that at the end of the present project a new promising molecule will be identified to aid in the treatment of dyad pain and depression. The use of different behavioral models seeks to validate broadly and precisely the activity of the molecule.

In view of the above, it is expected that the knowledge generated can contribute to the development of scientific articles and patentable and marketable products, contributing to the advancement of technology and science in the country. Therefore, it is hoped to contribute to the scientific dissemination (national and international congresses) and to the training of human resources (undergraduate and graduate students) that will focus on strengthening the innovative capacity of national companies

From the point of view of the training of human resources, it is hoped to contribute to their qualification and to increase the capacity of generation, diffusion and use of scientific knowledge in the Institution and in the region. The publication of the results obtained in international journals, with Qualis classification in the area, is an expected contribution to this proposal.



Fernanda Severo Sabedra Sousa