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Depressive-like symptoms in a reserpine-induced model of fibromyalgia in rats

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HIGHLIGHTS

- Repeated administration of reserpine produced depressive-like symptoms in rats.
- NSFT successfully detects the presence of depressive behavior in reserpinized rats.
- Effect of reserpine on motor and eating functions had no influence on the results.
- Results support the validity of reserpine-induced animal model of fibromyalgia.
- Central depletion of monoamines may be implicated in pathogenesis of fibromyalgia.

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ABSTRACT

Since the pathogenesis of fibromyalgia is unknown, treatment options are limited, ineffective and in fact based on symptom relief. A recently proposed rat model of fibromyalgia is based on central depletion of monamines caused by reserpine administration. This model showed widespread musculoskeletal pain and depressive-like symptoms, but the methodology used to measure such symptoms has been criticized. Evidence relates the high prevalence of pain and depression in fibromyalgia to common pathogenic pathways, most probably focused on the monoaminergic system. The present study aims at a validation of the reserpine model of fibromyalgia. For this purpose, rats undergoing this model have been tested for depressive-like symptoms with a Novelty-Suppressed Feeding Test adaptation. Animals administered with reserpine and subjected to forced food deprivation performed a smaller number of incursions to the center of the open field, evidenced by a decrease in the per-minute rate of the rats' approaching, smelling or touching the food. They also took more time to eat from the central food than control rats. These NSFT findings suggest the presence of depressive-like disorders in this animal model of fibromyalgia.

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1. Introduction

Fibromyalgia is characterized by the presence of widespread musculoskeletal pain, usually associated with other symptoms such as intense fatigue, non-restorative sleep, cognitive impairment and mood disorders [1].

Recent studies indicate that fibromyalgia affects a range of between 2 and 4% of the general population, with a slight predominance in women [2]. Despite its epidemiological relevance, its etiopathogenesis still remains unknown, which has resulted in a lack of fully satisfactory treatments. It is therefore essential to improve our knowledge concerning the origin of fibromyalgia in order to develop new therapeutic strategies that are more specific as well as more effective [3].

Animal models reproducing the symptoms of fibromyalgia as accurately as possible are crucial in this field of study. The majority of the proposed models are limited in reproducing the painful symptomatology of fibromyalgia [4]. Widespread pain is induced by means of intramuscular injection of various irritants such as carrageenan [5], acidic saline [6], tumor necrosis factor [7], hydrochloric acid [8], or even by inducing stress through the exposure to forced swimming test on rats [9] or stressful sounds [10].

Although pain is certainly the main symptom of fibromyalgia, the comorbid symptoms are becoming even more important due to the impact that they have on the patients' quality of life, as well as the socio-economic repercussions that come with treatment [11]. Among these

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associated symptoms, mood and sleep disorders stand out the most as major concerns [2]. The involvement of monoamine systems in both pain processing and sleep and mood regulation has long been acknowledged [12–15]. More recently, in preclinical and clinical studies, central amplification among patients suffering from fibromyalgia has been identified alongside a suppression of descending inhibitory monoamine pathways, as well as an increase in facilitators of pain [16]. Furthermore, studies on genetic polymorphisms in serotonin, dopamine, and norepinephrine highlight the importance of the monoamine systems in the etiopathogenesis of fibromyalgia [17].

Based on this knowledge, Nagakura et al. described in 2009 a model of fibromyalgia in rats based on central monoamine depletion through the administration of reserpine. These authors claimed that their model not only caused a decrease of pain thresholds, but also reproduced depressive-like symptoms.

However, the model proposed by Nagakura et al. [22] was criticized and its validity was questioned [18], due to the methodology used to measure depressive symptoms. Munro suggested that immobility found could be caused by the effect of reserpine on motor activity, and not by the depressive condition.

The present study aims at a vindication of the reserpine-model of fibromyalgia proposed by Nagakura et al. [22] as a valid animal model of this pathology. For this purpose we checked whether reserpine-treated rats following this procedure show depressive symptoms by using a different test from the one employed by Nagakura et al.: an adaptation of the Novelty-Suppressed Feeding Test (NSFT). This test has been successfully used in the evaluation of different antidepressant treatments (for review see Samuels and Hen [19]). In contrast to other tests, motor exertion is not required of the animal. Subsequently, data interpretation is not limited by a possible motor affliction.

2. Material and methods

2.1. Animals

Male Sprague–Dawley rats (Janvier Labs, Saint Berthevin, France) weighing 350 ± 50 g were used. Animals were housed in the Central Unit of Investigation of University of Valencia, with a controlled cycle of 12 h light–12 h darkness, and constant temperature (22 ± 2 °C) and humidity (55 ± 10%). Rats acclimated to their cages during at least one week after their transfer, prior to the start of the experiments. Water and food were provided ad libitum.

All experiments were carried out in accordance with the Ethics Committee of the University of Valencia (Procedure number: A1385127985666) and the ethical guidelines of the IASP [20].

2.2. Experimental procedure

2.2.1. Habituation

During the first five days of procedures animals were habituated to the researcher handling, as well as to the different maneuvers, in order to reduce the rat's discomfort caused by the experiments. The purpose of the habituation process was to minimize the bias that stress response could introduce in our results [21].

2.2.2. Reserpinization

Reserpine administration was performed after the habituation process, by a single daily subcutaneous injection of 1 mg/kg during three consecutive days [22]. Reserpine (Sigma-Aldrich, crystallized, ≥99.0% (HPLC)) was diluted in glacial acetic acid to a final concentration of 0.5% acetic acid in distillated water (vehicle). Animals from the control group received the same volume of vehicle, but they were administered no reserpine. Reserpine dilution was prepared every day before the experiments.

2.2.3. Motor activity control

The scoring of hypokinesia symptoms was performed by the evaluation scale reported by Colpaert [23,24]. Score 0: rats normally walk some distance when placed on the table; Score 1: rats move head and limbs without walking; and Score 2: rats fail to move head or limbs. Motor tests were performed daily since the first reserpine administration.

2.3. Pain thresholds

2.3.1. Electrovonfrey test (EVF)

Animals were placed on an elevated grid floor, inside a 20 cm diameter, 30 cm high, clear methacrylate cylinder. An electronic Von Frey Tester (Electrovonfrey, model no: 2290, IITC Inc., Woodland Hills, CA), with a 0.8 mm diameter rigid tip was used. In order to acquire pain thresholds, a growing pressure was exerted on the right hind paw sole, until the withdrawal phenomenon occurred; this was done making sure that the animal had its four paws on the grid floor at the same time while the test was being performed. Three measurements with an inter-stimulus range of 30 s were taken.

2.3.2. Randall and Selitto Test (R&S)

An elevated fabric support was used in this test. The center section of the animal's body was held as the hindpaws were introduced through holes in the fabric in order to keep the animal as comfortable, still and relaxed as possible. Once placed, a growing pressure was exerted on the right hind paw, specifically on the midsection of the gastrocnemius muscle, using an adapted Randall and Selitto Tester (IITC Inc., Woodland Hills, CA). Three measurements with an interstimulus range of 30 s were taken.

2.4. Both tests were performed in each animal

At the end of the habituation and two days before the first administration of reserpine, a baseline was established. It came from the mean of two measures of both R&S and EVF. Each pain measure was compared to its baseline.

2.4.1. Novelty-Suppressed Feeding Test [25]

A Novelty-Suppressed Feeding Test adaptation was used in order to measure depressive symptoms. Standard food pellets were enriched from the first habituation day. They were enriched by dipping them into a solution of water and 50% sucrose for some seconds for increased palatability and desirability. The amount of food ingested by each rat was registered daily throughout the procedure from the beginning of the habituation. The food was weighed every morning before starting the habituation or treatment procedure.

Prior to the test performance, rats underwent a food restriction period divided in two stages. In the first stage food was reduced to 80% of each rat's normal consumption, which was calculated with the mean consumption during the 5 habituation days. This restriction happened on days 4 and 5 after the last reserpine dose. The second restriction stage consisted of complete food deprivation during the 24 h previous to the test. Rats had free access to water during the whole procedure.

To perform the test an open field was used, which consisted of a black 100 × 100 × 40 cm methacrylate box. The ground was covered with sawdust, which was changed after each single animal experiment. In the center a Petri dish was placed with a small amount of 50% sucrose-enriched food on a white platform. The center of the field was lighted with an intensity of 1000 lm, while in the periphery the intensity was 800 lm. The surrounding environment remained lightless. The whole procedure was video recorded.

To begin with the test the animal was introduced in a corner of the open field and the time it took the rat to approach the center and eat from the highly-illuminated food was recorded. The following parameters were registered: (1) times per minute the animal approached the food, i.e., touching the white platform where the Petri dish with the

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