European Journal of Pharmacology 699 (2013) 207–212

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmacology

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

Neuropharmacology and analgesia

The effect of progesterone on expression and development of neuropathic pain in a rat model of peripheral neuropathy

Javad Verdi [c], Majid Jafari-Sabet [d], Rasool Mokhtari [a], Azam Mesdaghinia [a,b], Hamid Reza Banafshe [a,b,*]

[a] Physiology Research Center, Kashan University of Medical Sciences, Kashan, Iran
[b] Department of Pharmacology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran
[c] Department of Applied Cell Sciences, School of advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
[d] Department of Pharmacology, School of Medicine, AJA University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Received 21 July 2012
Received in revised form
27 November 2012
Accepted 28 November 2012
Available online 5 December 2012

Keywords:
Progesterone
Allodynia
Hyperalgesia
chronic constriction injury
Rat

ABSTRACT

Neuropathic pain results from lesions or diseases affecting the somatosensory system. The management of patients with chronic neuropathic pain remains a challenge. Several studies support the crucial role of neuroactive steroids in the modulation of pain. The present study was designed to investigate the effect of systemic administration of progesterone on expression and development of hyperalgesia and allodynia scores in chronic constriction injury model of neuropathic pain in rat. Progesterone at doses of 5, 10 and 15 mg/kg and its vehicle were injected intraperitoneally on days 1–13 after the surgery to study the effect of progesterone on development of neuropathic pain and only on 14th day post-surgery in order to assess its effect on expression of neuropathic pain.The chronic administration of progesterone significantly reduced the behavioral scores of cold- and mechano-allodynia and heat hyperalgesia but single dose of progesterone did not have any effect on behavioral scores of neuropathic pain. Our data indicate that the early chronic administration of progesterone prevents the development of neuropathic pain but its acute injection does not change the expression of neuropathic pain. These results suggest that progesterone could be considered as a new approach for management of neuropathic pain.

© 2012 Elsevier B.V. All rights reserved.

1. Introduction

Neuropathic pain results from lesions or diseases affecting the somatosensory system and is characterized by the presence of exaggerated response to painful stimuli (hyperalgesia), pain response to normally innocuous stimuli (allodynia) and spontaneous pain (Treede et al., 2008). The management of patients with chronic neuropathic pain is challenging. Despite several attempts to develop more rational therapeutic approaches that may improve the therapeutic response, the response to most treatments of neuropathic pain is generally modest (Finnerup et al., 2010). Several studies support the crucial role of neuroactive steroids in the modulation of pain (Mensah-Nyagan et al., 2009; Meyer et al., 2011). Progesterone and its derivatives as neurosteroid also produce antinociception and contribute to sex-based differences in pain sensation (Frye and Duncan, 1994; Liu and Gintzler, 2000). In addition, progesterone reduces neuronal damage and improves functional outcome in animal models of several types of neurological disorders (Schumacher et al., 2007). Neuroprotective effects of progesterone were also reported in model of spinal cord injury and diabetic neuropathy (Labombarda et al., 2002; Leonelli et al., 2007). Recently, a few studies have shown that progesterone attenuates neuropathic pain-related behavior in animal model of neuropathic pain (Roglio et al., 2008; Coronel et al., 2011). Therefore, the present study was designed to study the effect of systemic administration of progesterone on expression and development of hyperalgesia and allodynia scores in chronic constriction injury (CCI) model of neuropathic pain.

2. Materials and methods

2.1. Animals and surgery

Experiments were carried out on male Sprague-Dawley rats (230–280 g). Three to four rats were housed in a cage under a 12 h light/dark cycle with food and water available ad libitum. The chronic constriction injury (CCI) model of neuropathic pain was performed on the common sciatic nerve as described in detail

* Corresponding author at: Kashan University of Medical Sciences, Department of Pharmacology, Physiology Research Center, Amir Kabir Street, Kashan 971871243, Iran. Tel.: +98 361 5550021; fax: +98 361 5551112.
E-mail address: banafshe57@hotmail.com (H.R. Banafshe).

0014-2999/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejphar.2012.11.052

previously (Bennett and Xie, 1988). Briefly, the rats were anaesthetized with sodium pentobarbital (50 mg/kg) injected intraperitoneally. The common sciatic nerve was exposed and dissected from surrounding connective tissue near the trocanter, just distal to the branching point of the posterior biceps semitendinosus nerve. Four ligatures (4.0 chromic gut) were tied loosely around the nerve with a 1–1.5 mm interval between ligatures so that the circulation through the superficial epineuria vasculature was not totally interrupted. Sham-operated rats had the same surgery, the left sciatic nerve was exposed but no ligation was made. The rats were housed individually in cages after the surgery. All experiments followed the guide lines on ethical standard for investigation of experimental pain in animals (Zimmermann, 1983) and were also approved by the Research and Ethics Committee of Kashan University of Medical Sciences, Kashan, Iran.

2.2. Behavioral studies

The behavioral experiments included allodynia and hyperalgesia phenomena. The animals in the allodynia experiments were subdivided into cold- and mechano-allodynia groups. Radiant heat was applied as thermal stimulation for heat hyperalgesia. The cold and mechanical stimulations were applied through acetone and von Frey filament, respectively. The stimuli were applied to the soft tissue of the plantar surface of the hind paw. Behavioral tests were performed on the animals prior to surgery (the day 0) and 7, 14 and 21 days post-surgery. The rats were adapted to the testing situation for at least 30 min before the stimulations were initiated (Banafshe et al., 2012). The Hargreaves' method was employed to assess thermal hyperalgesia (Hargreaves et al., 1988). In this method the rats stood upon an elevated plexiglass cages on elevated glass platform and were allowed to acclimate to their environment for an addition al 15–25 min prior to testing. A radiant heat source (i.e. high intensity projector lamp) was activated along with a timer and focused onto the plantar surface of the affected paw of nerve injury or sham operated rats. A motion sensor activated by paw withdrawal halted both lamp and timer. The heat stimulation was repeated three times in 10 min interval for the injured (the left) and intact (the right) paws. A maximal cut-off of 22 S was used to prevent tissue damage. The mean latency of the withdrawal responses for each foot was calculated.

Cold allodynia was assessed using the acetone spray test modified from Choi et al. (1994). Rats standing upon the perforated floor, 250 μl of acetone were squirted onto the plantar skin using a blunt needle connected to a syringe without the touching of skin. The stimulation was applied five times (once every 3 min) to each paw. The frequency of the withdrawal reflex was expressed as the following formula: (Number of trials accompanied by brisk foot withdrawal/ total number of trials) × 100.

The assessment of tactile hypersensitivity was determined based on the method described in detail by Kingery et al. (2000). Rats were placed on a mesh (0.8 × 0.8 cm cell) floor, covered by an inverted transparent plastic box (18 × 18 × 25 cm) and allowed to adapt approximately for 15 min, or until the cessation of exploratory behavior. A series of von Frey filament stimuli (with bending forces ranging from <2 to 60 g, Stolting Inc., Wood Dale, IL) were delivered in an incremental order of forces to the central region of the plantar surface of the hind paw. The stimulation was applied three times consecutively, pushing up on the plantar surface of the hind paw until the rat withdrew its paw or the fiber bowed. Lifting of the paw due to normal locomotors behavior was ignored. The withdrawal threshold was for the smallest filament size which evoked at least two withdrawal responses during three consecutive applications with the same filament. Each filament was applied for approximately 1 S with an inter-stimulus interval of about 5 S.

2.3. Drug treatment

Progesterone powder (Sigma-Aldrich, P0130) dissolved in peanut oil and injected at doses of 5, 10 and 15 mg/kg. Animals in vehicle group received peanut oil (0.1 ml/100 g). Progesterone and its vehicle were administered intraperitoneally in two types of treatment; in chronic treatment, they were administered daily on days 1–13 after the surgery to study the effect of progesterone on development of neuropathic pain and in acute treatment they were injected only on 14th day post-surgery, 30 min before the behavioral tests in order to assess its effect on expression of neuropathic pain.

2.4. Statistical analysis

For chronic progesterone administration, data were analyzed using analysis of variance (repeated measures ANOVA), followed by Tukey HSD post hoc analysis with the least significance difference for multiple comparisons. Drug treatment was considered as the between-subjects and day as within-subject. A one-way ANOVA was used for acute progesterone treatment. All values were presented as mean ± S.E.M. and differences were considered significant if the P value was less than 0.05.

3. Results

3.1. Behavioral responses of chronic constriction injury (CCI) model of neuropathic pain

The majority of the nerve-ligated rats appeared healthy and well-groomed. None of them showed signs of autotomy after loose ligation of sciatic nerve. Paw gesture of the ipsilateral paw was slightly altered; but this did not interfere with the normal activity of the rats. The loose ligation of sciatic nerve decreased paw withdrawal latency to the thermal stimulus in ipsilateral paw significantly ($P<0.001$), but sham operation did not produce any significant change in withdrawal latency of control group in radiant heat plantar test (Fig. 1A). Application of acetone to the medial surface of the left hind paw led to a substantial augmentation in the withdrawal frequency of the CCI compared to the control group. Fig. 1B indicates that the difference between behavioral scores of two groups is significant in all testing days ($P<0.001$). The results of the behavioral tests for mechanical allodynia are shown in Fig. 1C. After ligation of the sciatic nerve, the ipsilateral hind paw became sensitive to mechanical stimuli, even with the weaker von Frey filament testing. Fig. 1C shows that there is a significant enhanced response to the stimulus in the CCI rats compared to the control animals ($P<0.001$). There was no evidence for the occurrence of contralateral hyperalgesia and allodynia throughout the experiment in all groups.

3.2. The effects of progesterone on the development of neuropathic pain

To study the effect of progesterone on the development of neuropathic pain, it was injected chronically on days 1–13 after the surgery. The effects of progesterone on the development of thermal hyperalgesia have been shown in Fig. 2A. Repeated administration of progesterone (5, 10 and15 mg/kg, i.p.) increased the withdrawal latency of hind paw in radiant heat plantar test in 14 ($F(3,28)=17.254$, $P<0.001$) and 21, days post-surgery ($F(3,28)=5.712$, $P<0.01$). Fig. 2B indicates that progesterone with

Download English Version:

https://daneshyari.com/en/article/5829076

Download Persian Version:

https://daneshyari.com/article/5829076

Daneshyari.com