Biomedicine & Pharmacotherapy 94 (2017) 557–563

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Research article

Neuropathic pain attenuating effects of perampanel in an experimental model of chronic constriction injury in rats

Ravneet Kaur Khangura[a], Anjana Bali[b], Gunjanpreet Kaur[a], Nirmal Singh[a], Amteshwar Singh Jaggi[a,*]

[a] Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, 147002 India
[b] Akal College of Pharmacy and Technical Education, Mastuana Sahib, Sangrur, India

ARTICLE INFO

Article history:
Received 23 December 2016
Received in revised form 20 July 2017
Accepted 26 July 2017

Keywords:
Chronic constriction injury
Perampanel
Neuropathic pain
Naloxone

ABSTRACT

The present study explores the pain attenuating effect of perampanel, AMPA receptor antagonist, in chronic constriction injury-induced neuropathic pain. Chronic Constriction Injury was performed by putting four loose ligatures around the sciatic nerve. Pain was assessed by determining mechanical hyperalgesia, cold allodynia and heat hyperalgesia on 7th and 14th day post surgery. Perampanel (3 mg and 6 mg/kg, *p.o.*) was administered 30 min before pain assessment test on 14th day post-surgery. CCI led to significant development of pain and peak symptoms were observed on 14th day. Perampanel significantly attenuated CCI-induced mechanical hyperalgesia, cold allodynia and heat hyperalgesia, at different time intervals 30, 60, 90, 120 min, with more substantial effect observed at dose of 6 mg/kgNaloxone was administered in CCI subjected rats before perampanel treatment to explore the potential role of opioids in anti-nociceptive effects of perampanel. Naloxone decreased the pain attenuating effects of perampanel significantly, indicating a critical role of opioid system in anti-nociceptive potential of perampanel. Perampanel has pain attenuating potential in CCI-induced neuropathic pain, which may be due to partly mediated through the opioid system.

© 2017 Elsevier Masson SAS. All rights reserved.

1. Introduction

Neuropathic pain is one of the most persistent types of chronic pain conditions that results from the damage or dysfunction in the somatosensory nervous system [1]. Neuropathic pain can be peripheral or central pertaining to the localization and level of injury. It is associated with the exaggerated pain perception which may be in the form of increased sensitivity to normal stimulation (hyperalgesia) or pain from stimuli which normally do not provoke pain (allodynia) [2]. Other pain sensations may include dysesthesia a burning pain sensation (dysesthesia) and unpleasant heightened pain, which may last for a persistent time even after resolution of primary cause of injury. Till date the effective management of neuropathic pain is difficult and involves the use of very few potent therapies that mostly comprises anti-epileptic agents and anti-depressants in combination with opioid analgesics [3]. These agents provide a limited relief from pain symptoms and are associated with various risks and adverse effects. While most of the conventional anti-epileptic drugs act as blockers of sodium channels, the novel anti-epileptics however, provide additional mechanisms like potentiation of GABAergic inhibition [4], binding on specific sub-type of calcium channels [5], a decrease in glutamate release and blockade of a-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) or kainate receptors [6].

The AMPA receptors are present on both pre and post-synaptic membranes [7] of neurons and glial cells, with glutamate as its primary agonist [8]. It comprises a hetero tetrameric complex, with Glu1 to Glu4 subunits [9], where Glu2 subunit offers cation permeability [10]. Activation of AMPA receptor triggers intracellular cation influx resulting in membrane depolarization, which in turn leads to N-methyl-D-aspartate (NMDA) activation, resulting in massive influx of Ca^{2+} in intracellular space [11]. The increased concentration of intracellular Ca^{2+} activates signal transduction pathway which is responsible for the hyper-excitability of post-synaptic neurons [12]. Therefore, activation of AMPA receptors may be regarded as a critical factor in initiation of patho-physiological changes after nerve injury. The newer pharmacological agents targeting specific AMPA receptor subunits can be

* Corresponding author.
E-mail address: amteshwarjaggi@yahoo.co.in (A.S. Jaggi).

http://dx.doi.org/10.1016/j.biopha.2017.07.137
0753-3322/© 2017 Elsevier Masson SAS. All rights reserved.

explored for their antiallodynic and anti-hyperalgesic effects in animal models of neuropathic pain.

Perampanel[2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydro-pyridin-3-yl)benzonitrile hydrate 4:3] is the first selective non-competitive AMPA receptor antagonist to be successfully developed for treatment of epilepsy [13]. Perampanel is presumed to inhibit the AMPA-induced increase in intracellular Ca^{2+} and hence, selectively blocks AMPA receptor-mediated synaptic transmission involved in neuronal excitation [14]. In context to its effect on NMDA receptors, perampanel had negligible direct effect on inhibition of NMDA-induced Ca^{2+} responses [13], suggesting its high selectivity for AMPA receptors. Since, many studies imply a prominent role of AMPA receptors in induction of neuropathic pain [15,16,17], it accounts for additional studies using a potent antagonist of AMPA receptor like perampanel to better define its place in the treatment of neuropathic pain. Therefore, the present study was designed to explore: (a) the neuropathic pain resolving potential of perampanel in chronic constriction injury-induced neuropathic pain in rats, and (b) the possible mechanism in perampanel-mediated modulation of neuropathic pain.

2. Material and methods

2.1. Experimental animals

Wistar albino rats (procured from Lala Lajpat Rai University of Veterinary and Animal Sciences Hisar, Haryana, India) of either sex, weighing 150–200 g were employed for the present study. Animals were housed in cages in a controlled environment (constant temperature 24 ± 1 °C: humidity 50–60%; 12-h dark/light cycle) in the departmental animal house with free access to food (Aashirward Industries, Kharar, Mohali, India) and water. The experimental protocol was duly approved by Institutional Animal Ethics Committee (Reg. No: 107/99/CPCSEA/2016-03) and care of the animals was carried out as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forest, Government of India (Reg. No: 107/99/CPCSEA).

2.2. Drugs and chemicals

Perampanel (Fycompa, Eisai Co. Ltd, Kawashima, Japan) was suspended in 0.5% carboxy methyl cellulose to form a suspension. Drug was administered through an oral route (3 mg/kg and 6 mg/kg) after 14 days of Chronic Constriction Injury. The injection of naloxone hydrochloride (Samarth Life Sciences Pvt. Ltd, India), a competitive non-selective antagonist of μ-opioid receptors, was administered after 14 days of nerve injury and 30 min before perampanel treatment. Naloxone hydrochloride was administered intraperitoneally (1 mg/kg).

2.3. Induction of neuropathic pain by chronic constriction injury

Peripheral neuropathic pain was induced in rats by Chronic Constriction Injury (CCI) [18,19]. In brief, CCI was performed under sodium thiopental anaesthesia (40 mg/kg *i.p.*). The hair from the left hind limb of rat were shaved and the skin was sterilized with the application of 70% isopropyl alcohol and iodine solution. An incision was made in the skin of the lateral surface of the left thigh, and a deep cut was made 3–4 mm below the femoris muscle to expose the sciatic nerve. Using a curved blunt-tipped forceps and micro-scissors, approximately 10 mm of the sciatic nerve (proximal to the sciatic trifurcation) was freed from the surrounding connective tissue and four chromic gut ligatures were placed around the sciatic nerve with a double knot at 1 mm intervals, to just occlude, but not arrest epineural blood flow. After performing the nerve ligation, muscular and skin layer was immediately sutured with silk thread, and topical antibiotic was applied. All surgical procedures were carried out under normal sterile conditions. The animal was then allowed to recover from surgery and pain hypersensitivity tests were performed on different days i.e. 7th and 14th day after CCI.

2.4. Behavioral examination

2.4.1. Mechanical hyperalgesia (Pin prick test)

A Pinprick test was used to assess the degree of mechanical hyperalgesia in which a bent gauge needle was slightly pricked on the planter surface of hind paw to induce a reflex withdrawal action. The time taken to return back the hind paw on the mesh wire was recorded in terms of paw withdrawal duration. A normal quick hind paw withdrawal followed by quickly placing the paw on mesh wire was assigned a value of 0.5 s [20].

2.4.2. Paw cold-allodynia (acetone drop test)

The extent of neuropathic pain development was also assessed by measuring the development of cold allodynia. It was measured using acetone drop test, in which 100 μl of acetone was sprayed on the plantar surface of hind paw of rat. The normal reaction of rat is quick withdrawal of paw in response to acetone application followed by quickly placing the paw on mesh wire. The quick recovery of paw was assigned a value of 0.5 s. However, in neuropathic pain, rat keeps its hind paw in air for a sufficient period of time and time taken to place its hind paw back to mesh wire is termed as paw withdrawal duration. In this study also, paw cold allodynia was assessed by measuring paw withdrawal duration in seconds in response to acetone application [21,20].

2.4.3. Paw heat-hyperalgesia (hot plate test)

Heat hyperalgesia was assessed using Eddy's hot plate. In this method, the temperature was maintained at 52.5 ± 1.0 °C and time taken to withdraw the hind paw or lick the paw was noted in as withdrawal latency. The cut-off time of 15 s was set to avoid the injury to hind paw [22,20].

2.4.4. Open field test

This test was performed on 14th day after CCI injury to assess the influence of nerve injury and pharmacological agents on the motor activity. After performing pain assessment tests, the animals were placed in open field for 10 min to note the number of line crossings.

2.5. Experimental protocol

Eight groups, each group comprising six Wistar albino rats, were employed in the present study.

2.5.1. Group I: normal control

Rats were not subjected to any treatment and were kept for 14 days. The behavioral tests were employed on day 7th and day 14th.

2.5.2. Group II: sham control

Rats were subjected to surgical procedure to expose the left sciatic nerve on day 1 without any nerve ligation. The behavioral tests were performed on day 7th and day 14th.

2.5.3. Group III: chronic constriction injury control in male rats

Rats were subjected to surgical procedure to expose and ligate the left sciatic nerve on day 1 as described earlier. The behavioral tests were performed on day 7th and day 14th as described in group II.

2.5.4. Group IV: chronic constriction injury control in female rats

Rats were subjected to surgical procedure to expose and ligate the left sciatic nerve on day 1 as described earlier. The behavioral

Download English Version:

https://daneshyari.com/en/article/5552862

Download Persian Version:

https://daneshyari.com/article/5552862

Daneshyari.com