Available online at www.sciencedirect.com

SCIENCE DIRECT®

Brain Research 1045 (2005) 124 – 133

BRAIN RESEARCH

www.elsevier.com/locate/brainres

Research report

Oxytocin actions on afferent evoked spinal cord neuronal activities in neuropathic but not in normal rats

Miguel Condés-Lara[a,b,*], Idil Ahmed Sh. Maie[c], Anthony H. Dickenson[c]

[a]*Departamento de Neurofisiología, Instituto de Neurobiología, Universidad Nacional Autónoma de México, Campus UNAM-Juriquilla, México*
[b]*Instituto Nacional de Psiquiatría "Ramón de la Fuente", México D. F., México*
[c]*Department of Pharmacology, University College London, Gower Street, London WC1E 6BT, UK*

Accepted 15 March 2005
Available online 21 April 2005

Abstract

A hypothalamic oxytocinergic-descending pathway that reaches the dorsal horn of the spinal cord has been well documented and recently related to states of pain and analgesia. In order to study the action of the neuropeptide oxytocin (OT) on pain-related responses, we compared dorsal horn neuronal responses to electrical and mechanical stimulation of receptive fields in normal and neuropathic rats. Spinal nerve (L5 and L6) ligation (Chung rats) was used to produce experimental neuropathy. Single unit activity was recorded at the L4–L5 level from neurons identified as wide dynamic range presenting latency responses corresponding to A-beta, A-delta, C fibers and also exhibiting post-discharge, and wind-up. We tested intrathecally applied doses of 0.05, 0.1, 1, 2, 5, 10 I.U. of OT. Minor effects on responses to electrical stimulation were present in normal rats. Mechanical responses evoked by von Frey filaments were slightly reduced in normal animals. In neuropathic rats a dose of 1 I.U. produced a significant reduction in C-fibers and post-discharge activities, and doses of 2 I.U. caused a further, pronounced reduction in post-discharge, wind-up, and input values. However, the most marked change was the post-discharge reduction at 10 and 20 min after OT administration. Mechanical responses were significantly reduced in terms of their discharge rate response in neuropathic rats. The contrasting results obtained in normal and neuropathic rats revealed an important distinction between these animals and indicate that plastic changes occur as a consequence of nerve damage. In neuropathic rats, mechanisms involving ascending noxious information to the paraventricular nuclei and descending OT activities could be altered so sensitizing the OT receptors of the spinal dorsal horn cells and could explain our observations. Our results point out an anti-algesic OT effect in neuropathic rats.
© 2005 Elsevier B.V. All rights reserved.

Theme: Sensory systems
Topic: Pain modulation: pharmacology

Keywords: Spinal cord cells; Post-discharge; Wind-up; Receptive field stimulation; Pain states

1. Introduction

Chronic pain after nerve or tissue injury includes a variety of symptoms and clinical characteristics; spontaneous and repetitive pain episodes, allodynia, hyperalgesia, and abnormal temporal summation of pain being the most frequent and representative symptoms. Increased knowledge about the pathophysiological mechanisms related to pain and analgesia may aid us to develop more effective therapies. One important area is endogenous systems that may control pain.

Kabat et al. [15] and Magoum [23] described a descending hypothalamic pathway to the spinal cord that may be involved in autonomic function. In fact, the hypothalamic paraventricular nucleus (NPV) reaches the spinal cord by a direct pathway [18,29]. Using immunohistochemical procedures it was been demonstrated that this descending pathway involves oxytocin (OT), vasopressin (VP), neurophysin, and orexin [3,27,31–33]. Moreover,

* Corresponding author. Departamento de Neurofisiología, Instituto de Neurobiología, Universidad Nacional Autónoma de México, Campus UNAM-Juriquilla, México.
E-mail address: condes@servidor.unam.mx (M. Condés-Lara).

0006-8993/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2005.03.020

using in situ hybridization, dynorphin and oxytocin mRNAs are expressed in the 40% of the PV neurones projecting to the spinal cord, and enkephalin mRNA is present in 20% of these neurons [13]. It is interesting to note that OT has been studied in different experimental pain models in order to obtain evidence for its analgesic effect [2,4,10,21,28,37]. Also, in humans lower OT concentrations in spinal fluid and plasma were associated with pain states [1,36], and OT administration relieved the pain sensation [22,36]. On the other hand, several studies reported that systemic OT did not produce any analgesic effect [26,35]. In an attempt to clarify the role of OT in pain, we performed the present study to document the effect of different OT doses on the neuronal responses of the dorsal horn to electrical and mechanical stimulation in normal and neuropathic rats. The lack of effect of the peptide in some studies (see above) could relate to the experimental model and stimuli tested; therefore, we have used a wide variety of peripheral stimuli in both normal and neuropathic rats.

2. Methods

Experiments were carried out on 48 male Sprague–Dawley rats from the University College of London animal house. Animals were housed five per cage with a 12:12-h light–dark cycle, water and food ad libitum. Experimental procedures for the electrophysiological studies have been previously described [6]. Animals were anaesthetized with 3.5% halothane in a gaseous mixture of 66% N_2O and 33% O_2, which was maintained throughout the experiment via a cannula inserted into the trachea. All experimental procedures were done in accordance with the U.K. Home Office legislation for animal experimentation and the IASP [38]. Rats were divided into two groups, normal rats (n = 36) weighing 220–250 g and spinal nerve L5 and L6 rats (n = 12) weighing 120–150 g at the beginning of the study [16]. Rats with nerve ligation will be referred as “Chung rats”. All animals weighed 220–250 g at the time of the electrophysiology studies.

3. Normal rats

The animals were placed in a spinal cord unit frame, and the vertebrae rostral and caudal to L1–L3 were clamped to improve stability at the recording site. A laminectomy was performed at the L1–L3 vertebrae, the segments L4–L5 of the spinal cord were exposed, and the level of halothane was reduced to 1.0–1.5%. Body temperature was maintained at 37°C with a heating blanket connected to a rectal thermal probe. A parylene-coated tungsten electrode was then inserted into the spinal cord and recordings were made from neurones of the exposed segments, which receive afferent input from the toe region. The depth of the recording was assessed from the microdrive readings.

For electrical stimulation, two fine needles attached to a stimulus isolator unit were inserted into the somatic receptive field of the recorded neurons. The electrical test stimulations consisted of a train of 16 stimuli at 0.5 Hz, with 2 ms pulse duration at 3 times the threshold intensity required to evoke a C-fiber response. This threshold was determined by giving single electrical pulses with progressive intensity increases (0.1–3.3 mA) until a C-fiber response was evoked. Peri-stimulus time histograms were constructed using the Spike2 software (Fig. 1). The histograms allowed us to specify the amount of Aβ-fiber (0–20 ms), Aδ-fiber (20–90 ms), and C-fiber (90–300 ms) action potentials produced by each train of stimuli. Action potentials arriving 300–800 ms after simulation were classed as post-discharge (P-d). Wind-up (W-up) was calculated as the difference between the total number of action potentials (90–800 ms) produced by the 16 stimuli and the input ×16 [30]. Also, we considered the P-d during the 2-s interval (300–1900 ms) between the stimulations. The electrical test was repeated each 10 min.

3–4 min after each train of electrical stimulation, we tested the cell responses to mechanical stimulation using 2, 5, 9, 15, 30, and 75 g von Frey filaments. Each von Frey was applied during 10 s on the receptive field, and we measured the frequency of cell responses. The interval for each different von Frey test was 20 s.

Rats were divided into groups of 6, and each group was used to test the following oxytocin (alpha-hypophamine from Sigma) concentrations: 0.05, 0.1, 1, 2, 5, and 10 international units (I.U.). OT was dissolved in 50 μl of saline solution and administered intrathecally. First, we recorded the electrophysiological responses in a control situation consisting of three consecutive, stable electrical and mechanical responses with variation less than 10%. After this control period we continued testing the electrical and mechanical stimulations during 1 h of intrathecal OT application. After washing (0.9% NaCl) the recorded cells were again tested with electrical and mechanical stimulations during 30 min, then a second OT application was made, and the tests were repeated for 1 h.

4. Chung rats

The Chung rat model [16] was used to study neuropathic pain. Briefly, the rat was first anaesthetized with a mixture of halothane (3.5% for induction, 1.5% for maintenance) and a 1:1 flow ratio of N_2O/O_2. The rat was placed in a prone position, a midline incision was made from L4 to S2, and the left side of the spinal nerves L5 and L6 was exposed and tightly ligated using 6-0 silk thread. The L4 sciatic nerve was left intact. Hemostasis was confirmed, the wound sutured, and the animal was withdrawn from anesthesia. For details, see [30].

The electrophysiological study of Chung rats was started 15–17 days after the surgery. In the Chung rats,

Download English Version:

https://daneshyari.com/en/article/9416291

Download Persian Version:

https://daneshyari.com/article/9416291

Daneshyari.com