Neuroscience 286 (2015) 37–44

EFFECT OF PAIN CHRONIFICATION AND CHRONIC PAIN ON AN ENDOGENOUS PAIN MODULATION CIRCUIT IN RATS

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Abstract—We tested the hypothesis that chronic pain development (pain chronification) and ongoing chronic pain (chronic pain) reduce the activity and induce plastic changes in an endogenous analgesia circuit, the ascending nociceptive control. An important mechanism mediating this form of endogenous analgesia, referred to as capsaicin-induced analgesia, is its dependence on nucleus accumbens μ-opioid receptor mechanisms. Therefore, we also investigated whether pain chronification and chronic pain alter the requirement for nucleus accumbens μ-opioid receptor mechanisms in capsaicin-induced analgesia. We used an animal model of pain chronification in which daily subcutaneous prostaglandin E_2 (PGE_2) injections into the rat's hind paw for 14 days, referred to as the induction period of persistent hyperalgesia, induce a long-lasting state of nociceptor sensitization referred to as the maintenance period of persistent hyperalgesia, that lasts for at least 30 days following the cessation of the PGE_2 treatment. The nociceptor hypersensitivity was measured by the shortening of the time interval for the animal to respond to a mechanical stimulation of the hind paw. We found a significant reduction in the duration of capsaicin-induced analgesia during the induction and maintenance period of persistent mechanical hyperalgesia. Intra-accumbens injection of the μ-opioid receptor selective antagonist Cys^2,Tyr^3,Orn^5,Pen^7amide (CTOP) 10 min before the subcutaneous injection of capsaicin into the rat's fore paw blocked capsaicin-induced analgesia. Taken together, these findings indicate that pain chronification and chronic pain reduce the duration of capsaicin-induced analgesia, without affecting its dependence on nucleus accumbens μ-opioid receptor mechanisms. The attenuation of endogenous analgesia during pain chronification and chronic pain suggests that endogenous pain circuits play an important role in the development and maintenance of chronic pain. **© 2014 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: pain chronification, chronic pain, endogenous analgesia, nucleus accumbens, μ-opioid receptors.

INTRODUCTION

Chronic pain syndromes cause enormous morbidity, social cost and damaging effect on quality of life (Porreca et al., 2002; Curkovic, 2007; Bushnell et al., 2013). They result from the transition from acute to chronic pain, but the mechanisms involved in this process are not very well understood. This may be due, at least in part, to the lack of experimental models to study chronic pain development and ongoing chronic pain with a good degree of human therapeutic predictability. In this study, we refer to chronic pain development as pain chronification, and ongoing chronic pain as chronic pain.

There are several causes of chronic pain but certainly many of them result from a previous inflammatory episode and are accompanied by hyperalgesia. Persistent hyperalgesia is generated by frequent periods of sensitization of the nociceptor and lasts several weeks (Woolf, 1983, 2011).

The animal model of pain chronification developed by Ferreira et al. (1990) induces a state of sensitization of the nociceptors that lasts for at least 30 days following the cessation of 14 successive daily intraplantar injections of prostaglandin E_2 (PGE_2). In this model, the 14-day period of successive daily intraplantar injections of PGE_2 correspond to the induction period of persistent mechanical hyperalgesia and allows to study the mechanisms involved in pain chronification, while the 30-day period following the cessation of the PGE_2 injections corresponds to the maintenance period of persistent mechanical hyperalgesia and allows to study the mechanisms involved in chronic pain.

The persistence of nociceptor sensitization in the absence of any peripheral stimulus suggests that plastic changes in the nervous system lead to pain chronification. However, whether plastic and functional changes occur in endogenous control circuits during pain chronification is not known.

In this study, we used the pain chronification model developed by Ferreira et al. (1990) to test the hypothesis that pain chronification and chronic pain reduce the activity and induce plastic changes in an endogenous analgesia circuit, the ascending nociceptive control.

This endogenous analgesia circuit is physiologically activated by a peripheral noxious stimulus such as a subcutaneous capsaicin injection at a site remote from

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Abbreviations: ANOVA, analysis of variance; CTOP, Cys^2,Tyr^3,Orn^5,Pen^7amide; E-capsaicin, capsaicin; PBS, phosphate-buffered 0.9% NaCl; PGE_2, prostaglandin E_2; SEM, standard error of mean.

http://dx.doi.org/10.1016/j.neuroscience.2014.10.049
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the nociceptive testing and induces heterosegmental analgesia equivalent in magnitude to a high dose of morphine for more than an hour (Gear et al., 1999). This form of endogenous analgesia, referred to as capsaicin-induced analgesia, is mediated by multiple mechanisms in nucleus accumbens (Schmidt et al., 2001, 2002a,b, 2003), but its dependence on nucleus accumbens μ-opioid receptor mechanisms is one of the most studied (Gear et al., 1999; Schmidt et al., 2002a, 2003). Therefore, we also investigated whether pain chronification and chronic pain alter the requirement for nucleus accumbens μ-opioid receptor mechanisms in capsaicin-induced analgesia.

EXPERIMENTAL PROCEDURES

Animals

Male albino Wistar rats (200–300 g) were obtained from the Multidisciplinary Center for Biological Research – University of Campinas. The animals were housed in plastic cages with soft bedding (five rats/cage) on a 12:12-h light cycle (lights on at 6:00 A.M.) with food and water available *ad libitum*. The animals were maintained in a temperature-controlled room (±23 °C) and handled for at least 1 week prior to the experiments (Rosland, 1991). The Committee on Animal Research of the University of Campinas approved the experimental protocols (protocol number 1952-1), which conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996. All effort was made to limit the number of animals used (168) and their discomfort.

Experimental design

A guide-cannula was bilaterally stereotaxically implanted in the nucleus accumbens 1 week before the initiation of the PGE_2 injection into the rat's hind paw used to induce the persistent hyperalgesia. The μ-opioid receptor antagonist Cys^2,Tyr^3,Orn^5,Pen^7amide (CTOP) (1.0 ng/0.25 μl) or its vehicle was injected bilaterally into nucleus accumbens 10 min before the induction of acute peripheral noxious stimulation by capsaicin injection or before its vehicle injection into the left fore paw on day 1, 7 or 14 after initiating the PGE_2 injection into the rat's left hind paw (induction period) or on day 1, 7, 14, or 21 after discontinuing the PGE_2 injection (maintenance period of the persistent hyperalgesia model). Each rat received only one bilateral injection of CTOP or its vehicle into nucleus accumbens and only one capsaicin injection into the left fore paw. Therefore, there were three groups of rats during the induction period and four groups of rats during the maintenance period of the persistent hyperalgesia model. The nociceptive threshold of the left hind paw was recorded immediately (0), 15, 30, 45 and 60 min after the subcutaneous injection of capsaicin or its vehicle into the ipsilateral fore paw. The locomotor activity was evaluated in the "rota-rod" equipment immediately after the nociceptive test to exclude the possibility that the effect of intra-accumbal treatments on the intensity of the nociceptive response was due to altered motor activity (Fig. 1).

Persistent mechanical hyperalgesia model

The persistent mechanical hyperalgesia was induced as previously described (Ferreira et al., 1990) by daily subcutaneous injection of PGE_2 (100 ng/50 μl/paw) into the dorsal surface of the rat's left hind paw over 14 days. In order to avoid a local release of PGE_2 as a result of successive injections, all animals were treated with indomethacin (2 mg/kg) by intraperitoneal route 30 min before the PGE_2 injection. After the discontinuation of the 14 successive daily injections of PGE_2, the hyperalgesia persists for approximately 30 days. Therefore, there are two well-defined periods in this persistent hyperalgesia model, the induction and the maintenance period. The induction period was defined as the 14-day period of daily subcutaneous injections of PGE_2 into the rat's hind paw, and the maintenance period the 21-day period after discontinuing the daily PGE_2 injections. The intensity of hyperalgesia was evaluated by the mechanical nociceptive threshold

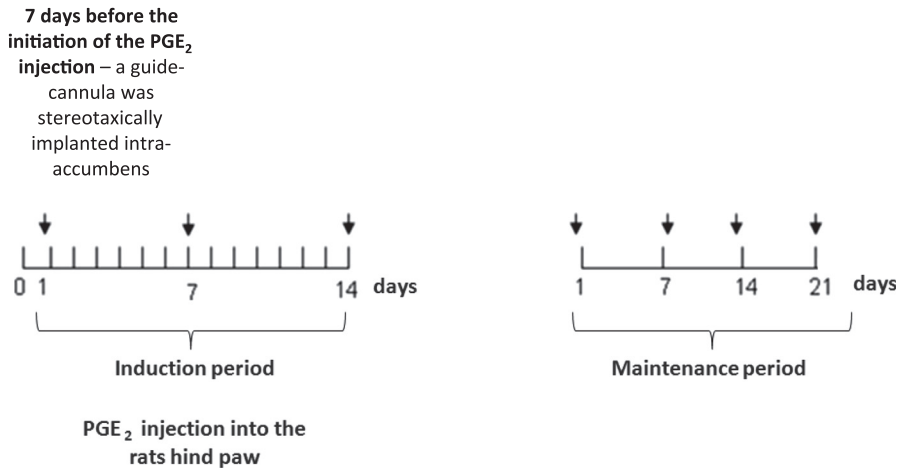

Fig. 1. Experimental design. On the days indicated by the arrows, CTOP or its vehicle was injected into nucleus accumbens 10 min before the injection of capsaicin or its vehicle into the fore paw. The nociceptive threshold was recorded in the hind paw immediately, 15, 30, 45 and 60 min after the capsaicin injection.

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