The Journal of Pain, Vol 9, No 6 (June), 2008: pp 497-505
Available online at www.sciencedirect.com

ELSEVIER

Original Reports

The Analgesic Effect of Paeoniflorin on Neonatal Maternal Separation–Induced Visceral Hyperalgesia in Rats

Xiao-jun Zhang,* Zhi Li,* Wai-mui Leung,* Liang Liu,* Hong-xi Xu,† and Zhao-xiang Bian*

**School of Chinese Medicine, Hong Kong Baptist University, Kowloon Tong, Hong Kong, China.*
†Hong Kong Jockey Club Institute of Chinese Medicine Limited, Kowloon, Hong Kong, China.

Abstract: **Paeoniflorin (PF) is one of the principle active ingredients of the root of *Paeonia lactiflora* Pall (family Ranunculaceae), a Chinese herb traditionally used to relieve pain, especially visceral pain. The present study aimed to investigate both the effect of PF on neonatal maternal separation–induced visceral hyperalgesia in rats and the mechanism by which such effect is exerted. A dose-dependent analgesic effect was produced by PF (45, 90, 180, and 360 mg/kg i.p.). Centrally administered PF (4.5 mg/kg i.c.v) also produced a significant analgesic effect. The analgesic effect of PF (45 mg/kg i.p.) was maximal at 30 minutes after administration. Furthermore, it was found that nor-binaltorphimine (nor-BNI, 3 mg/kg i.p.), DL-α-methyltyrosine (α-AMPT, 250 mg/kg i.p.), and yohimbine (3 mg/kg i.p.) could block the analgesic effect of PF (45 mg/kg i.p.). Time course determination of PF in brain nuclei showed that the maximal concentration of PF was 30 minutes after intraperitoneal administration of PF (180 mg/kg) in cerebral nuclei, involving the amygdala, hypothalamus, thalamus, and cortex. These data indicate that PF has an analgesic effect on visceral pain in rats with neonatal maternal separation and that this effect may be mediated by κ-opioid receptors and α_2-adrenoceptors in the central nervous system.**

***Perspective:** This study demonstrates that PF has an analgesic effect on pain in visceral hyperalgesic rats. These results suggest that PF might be potentially useful in clinical therapy for irritable bowel syndrome as a pharmacological agent in alleviating visceral pain.*

© 2008 by the American Pain Society

Key words: *Paeoniflorin, neonatal maternal separation, visceral hyperalgesia, analgesic effect.*

Visceral pain is one of the cardinal features of irritable bowel syndrome (IBS), a highly prevalent functional gastrointestinal disorder affecting up to 15%, statistically, of the adult population in Western countries.[2,33] Drugs in development for visceral pain of IBS mainly target the serotonergic, α-adrenergic, and opioid systems, as well as neurokinin receptors.[2] Despite considerable pharmacological studies, there are still few agents that can relieve visceral pain associated with IBS with satisfactory effects in humans, and further research is warranted.[2]

Paeoniflorin (PF), a monoterpene glucoside, is one of the principal active ingredients of Paeonia Radix, a traditional Chinese herbal medicine derived from the root of *Paeonia lactiflora* Pall (family Ranunculaceae), which is traditionally used to alleviate pain, especially visceral pain.[26] One study has shown that Tong-xie-yao-fang, a classical Chinese herbal formula, in which the root of *P lactiflora* is a main component, can attenuate visceral pain of IBS.[5] Previous studies have showed that PF has an analgesic effect on the somatic pain in rodents.[15,32] Although these data suggest that PF may be effective to alleviate visceral pain of patients with IBS, to the best of our knowledge, no study has been published to determine whether PF, specifically, has an analgesic effect on visceral pain.

Received August 28, 2007; Revised December 6, 2007; Accepted December 6, 2007.

Supported by the Hong Kong Jockey Club Institute of Chinese Medicine (JCICM-16-02) and a Faculty Research Grant, Hong Kong Baptist University (FRG /04-05/II-54).

Address reprint requests to Dr. Zhao-xiang Bian, School of Chinese Medicine, Hong Kong Baptist University, Kowloon Tong, Hong Kong, China. E-mail: bzxiang@hkbu.edu.hk

1526-5900/$34.00

© 2008 by the American Pain Society

doi:10.1016/j.jpain.2007.12.009

Visceral pain differs from somatic pain not only in the nociceptive sense but also in the signal transduction pathways in the central nervous system (CNS).[8] Recently, more and more clinical studies are showing that stress is an important physiological factor that can induce and/or exacerbate functional visceral pain and hyperalgesia in patients with IBS.[23] In addition, rats that have experienced neonatal maternal separation (NMS) in early life can develop chronic visceral hypersensitivity and can exhibit enhanced stress-induced colonic motility and increased anxiety-like behavior when exposed to acute psychological stressors in adulthood, mimicking the cardinal features of patients with IBS.[7,27] Therefore, in this study, we investigated the analgesic effect of PF on colorectal distention (CRD)-induced visceral pain in NMS-induced visceral hyperalgesic rats to test the hypothesis that PF can have an analgesic effect on visceral pain and to determine, at least initially, the underlying mechanism. The results were presented in the 26th Annual Scientific Meeting of the American Pain Society in May 2007, in Washington, D.C.[36]

Materials and Methods

Animals

Primiparous timed-pregnant Sprague-Dawley female rats were obtained from the Laboratory Animal Services Centre, the Chinese University of Hong Kong, on gestational day 13 to 14. Rats were kept in rooms with temperature kept at 23° ± 2°C, with an alternating 12-hour light-dark cycle. Food and water were provided ad libitum. Adult NMS and normal handling (NH) rats were fasted overnight before experiments. All of the experimental protocols were approved by the Committee on Use of Human and Animal Subjects in Teaching and Research of the Hong Kong Baptist University and were carried out according to the Regulations of the Department of Health of Hong Kong Special Administration Region. In addition, the ethical guidelines for investigating experimental pain in conscious animals recommended by the International Association for the Study of Pain were followed.[37]

Study Design

Maternal separation started from postnatal day 2 to 14. All male pups were randomly separated into 2 groups in which 1 was assigned to the NMS group and the other to the NH control group. On postnatal day 22, rats were weaned and group-housed until they reached the appropriate weight (250–300 g) for the designated experiment. Adult NMS and NH rats were assigned to 5 experiments. The first experiment was to evaluate whether PF (22.5, 45, 90, 180, and 360 mg/kg i.p.) has dose-dependent analgesic effects on NMS rats by evaluating electromyographic (EMG) response to gradient CRD, with morphine (5 mg/kg i.p.) and saline as positive and negative controls, respectively (n = 6 ~ 10 in each group). PF (intraperitoneal) or morphine (intraperitoneal) dissolved in saline was given 30 minutes before EMG recording. The second set of experiments was to study the time course of PF's analgesic effect by detecting pain threshold pressure by a blinded observer in abdominal withdrawal reflex (AWR) test at 15, 30, 45, 60, 90, and 120 minutes after PF given by intraperitoneal administration (n = 6 in each group). The third set of experiments was to evaluate the possible involvement of κ-opioid receptors and α_2-adrenoceptors in PF's analgesic effect. The influences of norbinaltorphimine (nor-BNI, κ-opioid receptor antagonist), DL-α-methyltyrosine (α-AMPT, catecholamine synthesis inhibitor), and yohimbine (α_2-adrenoceptor antagonist) on PF's analgesic effect were examined by AWR test 30 minutes after intraperitoneal administration of PF (n = 5 ~ 6 in each group). Yohimbine (2 mg/kg i.p.)/saline was given immediately after baseline pain threshold measurement,[3] and PF/saline treatments were given 20 minutes afterward. Nor-BNI (3 mg/kg i.p.) and α-AMPT (250 mg/kg i.p.) were given 4 and 6 hours before PF/saline administrations, respectively.[18,20] Because previous studies showed that PF could produce analgesic effects to somatic pain through central administration,[32] the fourth set of experiments was designed to investigate the central analgesic effect of PF (4.5 mg/kg) by intracerebroventricular (i.c.v.) injection through detecting the pain threshold pressure at 30 minutes after administration and comparison with the control group. PF was dissolved in artificial cerebrospinal fluid (aCSF) in a concentration of 4 μL/100g body wt for intracerebroventricular injection and was given 30 minutes before pain threshold pressure measurement in the treatment group; aCSF was given to the control group (n = 6 in each group). In the fifth set of experiments, the kinetic distribution of PF in NMS rats' cerebral nuclei was determined with HPLC to investigate whether there is correlation between pharmacokinetic character and pharmacological effect (n = 3 ~ 6 in each group).

Neonatal Maternal Separation

The NMS was performed as described previously.[4,6] Briefly, pups were separated from their mothers and placed into individual cages 180 minutes daily from postnatal days 2 to 14. On postnatal day 22, pups were weaned, and female pups were excluded for further procedures. To avoid additional stress, 6 pups were then raised in a standard macrolin cage until each weighed 250 to 300 g. The pups of the NH group were normally nursed.

Electromyographic Recording

Surgical procedures and EMG recording were performed as previously described.[6] Briefly, rats were deeply anesthetized with midazolam hydrochloride (3.5 mg/kg i.p.). A pair of Teflon-coated stainless wires (Cooner Wire, Chatsworth, CA) was sutured in parallel into the external abdominal oblique muscle and tunneled subcutaneously, with the recording ends of the electrodes exposed. Rats were allowed to recuperate for 5 days to ensure complete recovery from surgery before testing. Before testing, rats were given brief ether anesthesia; then, a 4-cm-long flexible latex balloon was inserted

Download English Version:

https://daneshyari.com/en/article/2723655

Download Persian Version:

https://daneshyari.com/article/2723655

Daneshyari.com