Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

Intra-periaqueductal gray infusion of zeta inhibitory peptide attenuates pain-conditioned place avoidance in rats

Jianliang Sun[a], Bo Lu[b], Juan Yao[c], Weiping Lei[c], Yaqin Huang[c], Honghai Zhang[a], Chun Xiao[a,d,*]

[a]Department of Anesthesia, Hangzhou Hospital Affiliated to Nanjing Medical University, Hangzhou First People's Hospital, Hangzhou 310006, PR China
[b]Department of Anesthesia, Ningbo Second Hospital, Ningbo 315000, PR China
[c]Department of Anesthesia, Second Affiliated Hospital and Yuying Children Hospital of Wenzhou Medical University, Wenzhou 325000, PR China
[d]Department of Anesthesia, Jiaxing First Hospital, Jiaxing 314000, PR China

ARTICLE INFO

Article history:
Accepted 17 July 2014
Available online 24 July 2014

Keywords:
Periaqueductal gray
Conditioned place avoidance
Pain
Nociceptive behavior

ABSTRACT

Pain is a complex experience that made up of sensory, emotional and cognitive dimensions, and the emotional factors have an important influence on intensity of pain perception. The role of periaqueductal gray (PAG) in sensory component of pain has been extensively studied, while data about pain affect are quite limited. Using formalin-induced conditioned place avoidance (F-CPA) test and inflammatory pain model, present study investigated the effect of intra-PAG infusion of zeta inhibitory peptide (ZIP) on noxious stimulation induced aversion, and the sensory component of pain. Intra-PAG injection of ZIP is sufficient to disrupt pain-induced aversion, but the ZIP infusion did not change inflammation induced pain hypersensitivity in rats. These findings suggest that PAG contributes to pain-related aversion in rats, and the mechanism of pain emotion encoding in PAG may attribute to the activation of targets of ZIP.

1. Introduction

Pain is a complex experience that is made up of sensory, emotional, and cognitive dimensions. Brain imaging and lesion studies indicate that brain regions play different roles in these aspects of the pain experience. The somatosensory cortices (S1 and S2) encode information of sensory features (Kenshalo et al., 1988; Chudler et al., 1990; Ploner et al., 1999;

Abbreviations: ZIP, zeta pseudosubstrate inhibitory peptide; PKMζ, protein kinase m zeta; S-ZIP, scrambled-zeta pseudosubstrate inhibitory peptide; LTP, long-term potentiation; PAG, midbrain periaqueductal gray; ACC, anterior cingulate cortex; RVM, rostral ventromedial medulla; mPFC, medial prefrontal cortex; F-CPA, formalin-induced conditioned place avoidance; CPP, conditioned place preference; PWT, mechanical paw withdrawal thresholds; PWL, paw withdrawal latency; CFA, complete Freund's adjuvant

*Corresponding author. Fax: +86 573 82082937.
E-mail address: xiaochunmz@gmail.com (C. Xiao).

http://dx.doi.org/10.1016/j.brainres.2014.07.027
0006-8993/

Greenspan et al., 1999). In contrast, the anterior cingulate cortex (ACC), amygdala, medial prefrontal cortex (mPFC), and insula mainly contribute to the motivational–affective component of pain (Rainville et al., 1997; Tolle et al., 1999; Craig, 2011). Clinical and animal studies have shown that emotional factors had an important influence on intensity of pain perception (Benedetti et al., 2005; Villemure and Bushnell, 2002).

The role of periaqueductal gray (PAG) in sensory component of pain has been extensively studied, while the data about the pain affect are quite limited. PAG receives projections from ACC, amygdala, and mPFC, and sends afferents to rostroventral medulla (RVM) and locus coeruleus to regulate the activity of spinal cord projection neurons (Ossipov et al., 2010). This suggests that the descending systems could be modulated by psychological factors. Several functional magnetic resonance imaging studies showed that painful stimulations increased the activity in PAG region (Petrovic et al., 2000; Frankenstein et al., 2001; Tracey et al., 2002), and that distraction from pain decreased pain intensity with combination of a significantly activation in the PAG (Tracey et al., 2002). Brain imaging studies also demonstrated that an expectation of pain relief activated ACC-fronto-PAG pathway and significantly increased the "analgesic" effect of placebo treatment in volunteers (Wager et al., 2007). Moreover, the expectation of placebo analgesia altered endogenous opioid activity in parts of this pathway, including the PAG and ACC (Wager et al., 2004). Using formalin-induced conditioned place avoidance (F-CPA) test, which could distinguish pain emotion from pain sensation, Lei et al. (2004) demonstrated that the pain aversive rats without pain sensation exhibited the elevation of *Fos* expression in various aversion-related brain areas including the PAG. Thus, above-mentioned evidences support the view that the PAG is an important brain area for modulation of pain sensation and expression of pain affect. However, the molecular mechanisms underlying pain affect in PAG circuitry are poorly understood.

Zeta pseudosubstrate inhibitory peptide (ZIP) is an inhibitor of atypical protein kinase C (aPKC). There are several isoforms of aPKC: PKMζ, PKCζ, and PKCλ. Recently, PKM ζ was found to be both necessary and sufficient for maintaining the late-long-term potentiation (LTP) and long-term memory, and ZIP was widly used in the studies as a reagent to inhibit the function of PKMζ. Although recent studies have called the role of PKMζinto question (Lee et al., 2013; Volk et al., 2013), several studies showed that ZIP is able to reverse the established LTP and to erase long-term memory (He et al., 2011; Migues et al., 2010). Due to parallels between molecular mechanisms of long-term memory and pain plasticity, ZIP has been elucidated as a potential painkiller. Recent work has demonstrated that the inhibition of PKMζ in the rACC with ZIP relieved pain sensation and tonic pain-related aversion induced by peripheral nerve injury (Li et al., 2010; King et al., 2012). Subsequent studies demonstrated that spinal injection of ZIP led to the suppression of pain sensation induced by inflammation and nerve injury (Asiedu et al., 2011; Marchand et al., 2011; Laferrière et al., 2011). In this study, we investigated the effects of intra-PAG injection of ZIP on inflammatory pain sensory component and pain-related aversion.

2. Results

2.1. *Effect of intra-PAG injection of ZIP on F-CPA*

When formalin-induced nociceptive stimulus was paired with a particular compartment in the place-conditioning apparatus, rats spent less time in this compartment on the post-conditioning day compared with the pre-conditioning

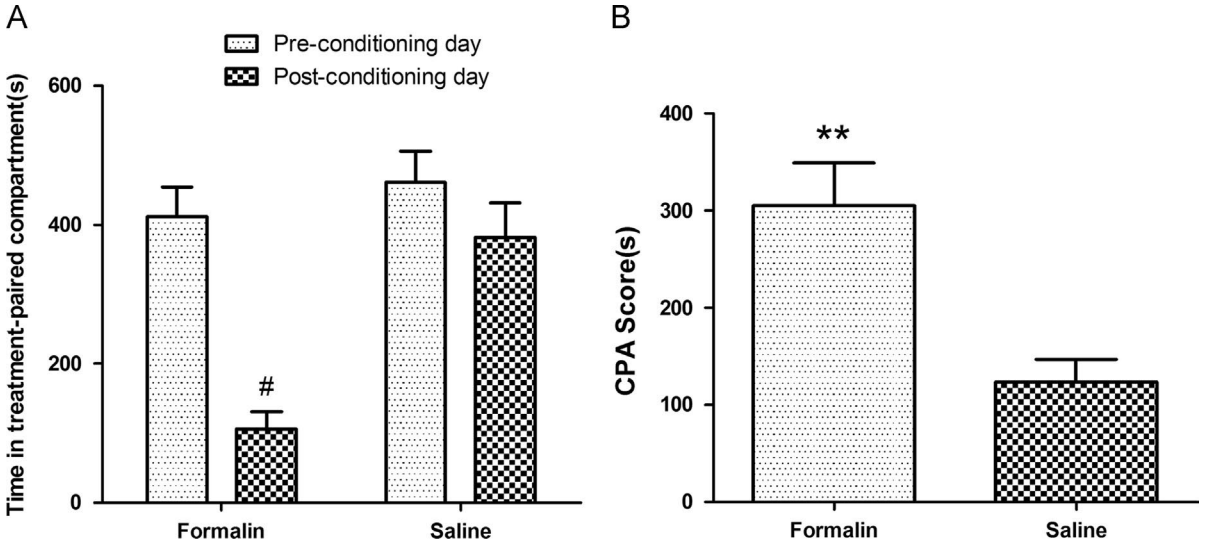

Fig. 1 – Hindpaw intraplantar (i.pl.) injection of formalin, but not saline, induced conditioned place avoidance in rats. (A) The time of rats spent in the treatment (intraplantar saline or formalin)-paired compartment on pre-conditioning and post-conditioning days. (B) The CPA score of formalin group ($n=8$) and saline group ($n=8$). The magnitude of CPA in formalin group is higher than that in saline group. Data are presented as mean ± SEM. $^{\#}P<0.001$, compared with the pre-conditioning day (Paired *t*-test); $^{**}P<0.01$, compared with the saline-injected rats (Student's *t* test).