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Chronic activation of sigma-1 receptor evokes nociceptive activation of trigeminal nucleus caudalis in rats

Ki Hyun Pyun [a,1], Ji Seon Son [b,1], Young Bae Kwon [c,*]

[a] Department of Computer Science and Engineering, Chonbuk National University, Jeonju 561-180, Republic of Korea
[b] Department of Anesthesiology and Pain Medicine, Chonbuk National University Medical School, Jeonju 561-180, Republic of Korea
[c] Department of Pharmacology, Institute for Medical Science, Chonbuk National University Medical School, Jeonju, Republic of Korea

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ABSTRACT

Primary headache disorders, including migraine, are thought to be mediated by prolonged nociceptive activation of the trigeminal nucleus caudalis (TNC), but the precise mechanisms are poorly understood. Our past studies demonstrated that sigma-1 receptors (Sig-1R) facilitate spinal nociceptive transmission in several pain models. Based on these findings, this study asked if chronic activation of Sig-1R by intracisternal administration of the selective Sig-1R agonist, PRE084, produced TNC neuronal activation as a migraine trigger in rats. A single infusion of PRE084 (10, 50, 100, 500 nmol) significantly increased the number of Fos immunoreactive neurons (Fos-IR) in TNC, which BD1047 (a Sig-1R antagonist) reversed. Chronic infusion of PRE084 (100 nmol for 1, 3, 7 and 14 days) time-dependently elevated Fos-IR in TNC. The number of Fos-IR elevation from day 7 of infusion was comparable with a single capsaicin infusion as a headache model. Increase in face grooming/scratching behavior was evident from day 7, and peaked at day 14 of chronic PRE084 infusion, which was correlated with ΔFosB elevation and phosphorylation of extracellular signal-regulated kinase, and the NMDA receptor NR1 subunit in TNC. Following 14 days of PRE084 infusion, the number of Fos-IR increased until day 7 after final infusion. Moreover, by day 14, Fos-IR associated with PRE084 infusion was significantly reversed by NMDA receptor antagonist MK801, rather than BD1047. These findings indicated that chronic activation of Sig-1R could evoke prolonged neuronal activation in the trigeminovascular system.

1. Introduction

Migraine is a primary headache disorder characterized by episodic or chronic attacks of disabling head pain, resulting from activation of the trigeminovascular system (Colombo et al., 2008). It is has been assumed that brains of susceptible subjects have a low 'migraine threshold', and recurrent attacks are initiated by a variety of trigger factors (Lambert and Zagami, 2009). Human genetic analysis reveals that progesterone and other hormone dysfunctions may impact 'migraine susceptibility'. Neurotransmitter pathway genetic alterations are also involved (Colson et al., 2006). Consistent with this, progesterone's prophylactic effect on migraine is demonstrated in a clinical trial (Lundberg, 1969). An animal study also demonstrates that progesterone blocks substance P-induced plasma extravasation through endogenous neurosteroidal action within the dura mater (Limmroth et al., 1996). Therefore, we hypothesize that neural mechanisms underlying neurosteroid-induced triggering pathways might be responsible for migraine development.

Progesterone, like pregnenolone and dehydroepiandrosterone (DHEA), is a neurosteroid synthesized in the central nervous system (CNS), which plays a role in CNS excitatory and inhibitory balance. For example, progesterone negatively modulates NMDA-receptor-mediated responses, and thus appears to be an inhibitory neurosteroid. Excitatory responses are mediated by pregnenolone or DHEA (Monnet and Maurice, 2006). Some neurosteroids share the same binding sites as the atypical protein, sigma-1 receptor (Sig-1R), which acts as an intracellular amplifier of signal transduction, including elevation of intracellular calcium, or glutamate release (Monnet and Maurice, 2006). DHEA is an excitatory neurosteroid that produces pain sensations reversed by Sig-1R antagonist, BD1047 (Yoon et al., 2009). Our previous study revealed that intrathecal injection of PRE084 (a selective Sig-1R agonist) significantly increased pain behavior and spinal Fos expression, which is mediated by NMDA receptor phosphorylation and protein kinase A activation (Kim et al., 2008, Roh et al., 2008). Consistent with this evidence, activation of Sig-1R elicits nociceptive responses, which are reversed by progesterone (Ueda et al., 2001). Therefore, it is reasonable to assume that chronic activation of Sig-1R originating from CNS neurosteroid dysfunction may be a triggering mechanism reducing migraine threshold.

Abbreviations: Sig-1R, sigma-1 receptor; TNC, trigeminal nucleus caudalis; Fos-IR, Fos immunoreactive neurons; CNS, central nervous system.

* Corresponding author at: Department of Pharmacology, Institute for Medical Science, Chonbuk National University Medical School, Jeonju 561-180, Republic of Korea. Tel.: +82 63 270 3088; fax: +82 63 275 2855.
E-mail address: 1972y@jbnu.ac.kr (Y.B. Kwon).

[1] Ki Hyun Pyun and Ji Seon Son contributed equally to this study.

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The trigeminovascular system is generally activated in experimental animals by either electrical or chemical (i.e. capsaicin) stimulation of meninges, which evokes Fos expression as a marker of functional activity in neurons within the trigeminal nucleus caudalis (TNC) (Mitsikostas and Sanchez del Rio, 2001). This study evaluated Sig-1R-induced nociceptive activation in TNC using Fos expression as a biomarker after acute or chronic intracisternal administration of Sig-1R agonist PRE084 compared to an intracisternal capsaicin-induced model. Moreover, we asked if PRE084 could initiate migraine-like pain symptoms using face grooming/scratching as a behavioral marker (Kemper et al., 1998), and expression of ΔFosB as a molecular marker of sustained pain (Luis-Delgado et al., 2006). Finally, we evaluated the precise mechanism underlying Sig-1R-induced trigeminal sensitization through NMDA receptor activation and its related mitogen-activated protein kinase.

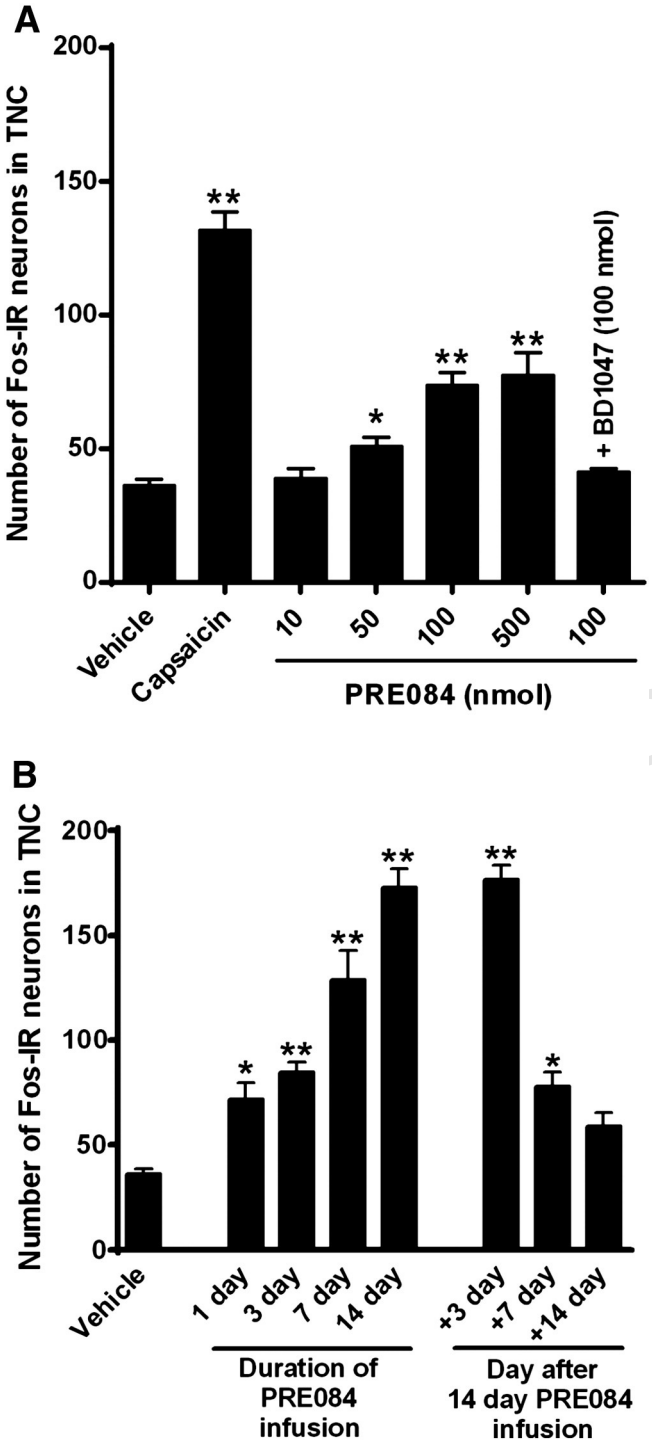

Fig. 1. The number of Fos-immunoreactive (Fos-IR) neurons in the trigeminal nucleus caudalis (TNC) after intracisternal single infusion of capsaicin (2.5 nmol/rat) or PRE084 (A) and repeated PRE084 (100 nmol/rat) for 1, 3, 7 and 14 days in rats (B). Fos immunohistochemistry was performed 2 h after final infusion. BD1047 was delivered 10 min prior to PRE084 infusion. Each group contained 6 animals. *$p < 0.05$ and **$p < 0.01$: compared with the vehicle control group. Error bars represent standard error of the mean.

2. Methods

2.1. Animals

Male Sprague-Dawley rats (Dae Han Biolink Co., Eumsung, South Korea) were housed in colony cages with free access to food and water, and maintained in temperature and light controlled rooms (23 ± 2 °C, 12/12 h light/dark cycle with lights on at 08:00). Methods were approved by the Institute of Animal Care and Use Committee at Chonbuk National University, and conformed to NIH guidelines (NIH publication No. 86-23, revised 1985).

2.2. Cisterna magna cannula implantation and drug infusion

Rats (200–220 g) were anesthetized with intraperitoneal injection of a mixture of ketamine (90 mg/kg) and xylazine (9 mg/kg). Craniotomy was performed above the junction of the superior sagittal and transverse sinuses, and an intracisternal cannula (7-cm length PE-10 tube connected with 6.5-mm length 30 gage stainless steel needle) was affixed to the bone around the opening in the skull with small screws and dental cement. The cannula's needle end opened into the dura over the transverse sinus along the midline. PE-10 tube end was led to the back and closed. Correct placement of the cannula was confirmed by withdrawal of artificial cerebrospinal fluid (aCSF). After surgery, rats were allowed to recover for 3 days, then used for the experiment.

PRE084 and BD1047 purchased from Tocris (Bristol, UK) were dissolved in distilled water, then diluted with aCSF. Capsaicin (Sigma, MO, USA) stock solution [3.05 mg capsaicin per 1 ml of vehicle buffer (saline–ethanol–Tween 80; 8:1:1; v/v)] was further diluted with aCSF. To determine the optimal dose of PRE084, rats were injected with a single intracisternal infusion of PRE084 (10 nmol, 50 nmol, 100 nmol and 500 nmol) or capsaicin (2.5 nmol/rat) as previously described (Ter Horst et al., 2001). To test this effect, the specific Sig-1R antagonist, BD1047 (100 nmol/rat), was injected 10 min before PRE084 infusion as previously described (Kwon et al., 2009). Following PRE084 single infusion, the optimal dose of PRE084 (100 nmol/rat) was selected and repeatedly infused on days 1, 3, 7, and 14. After 14 days of PRE084 infusion, either MK801 (7 nmol/rat, NMDA receptor antagonist) or BD1047 (100 nmol/rat) was infused intracisternally 2 h before cardiac perfusion for immunohistochemistry. Fifty μl of all drugs or vehicle (aCSF) was infused into the dura via intracisternal cannula with a micro-infusion pump (model 310 Plus, KD Scientific Inc., MA, USA) at a rate of 50 μl per min. Overall experiment groups contain six animals.

2.3. Behavioral assay

Rats were placed in transparent individual home cages immediately after each drug infusion, and behavior was recorded with a video camera. Face grooming has been shown to be a nocifensive response to noxious chemical stimuli in several facial nociceptive experiments (Kemper et al., 1998, Yao and Sessle, 2008). Preliminary observation showed that capsaicin-induced (2.5 nmol/rat) grooming/scratching behavior was evident for 10 min after infusion. Behavior exhibited during the 2 min directly after infusion was not analyzed to allow time for drugs to take effect. The remaining 8 min were analyzed by two experienced investigators who were blinded to the experimental conditions.