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Research Report

Effects of prostaglandin E_2 on synaptic transmission in the rat spinal trigeminal subnucleus caudalis

Yuka Mizutani[a,b], Yoshiaki Ohi[a], Satoko Kimura[a], Ken Miyazawa[b], Shigemi Goto[b], Akira Haji[a,*]

[a]Laboratory of Neuropharmacology, School of Pharmacy, Aichi Gakuin University, Nagoya 464-8650, Japan
[b]Department of Orthodontics, School of Dentistry, Aichi Gakuin University, Nagoya 464-8650, Japan

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ABSTRACT

The spinal trigeminal subnucleus caudalis (Vc) receives preferentially nociceptive afferent signals from the orofacial area. Nociceptive stimuli to the orofacial area induce cyclooxygenase both peripherally and centrally, which can synthesize a major prostanoid prostaglandin E_2 (PGE_2) that implicates in diverse physiological functions. To clarify the roles of centrally-synthesized PGE_2 in nociception, effects of exogenous PGE_2 on synaptic transmission in the Vc neurons were investigated in the rat brainstem slice. Spontaneously occurring excitatory and inhibitory postsynaptic currents (sEPSCs and sIPSCs) were recorded, respectively, under pharmacological blockade of inhibitory and excitatory transmission by whole-cell patch-clamp mode. Perfusion of PGE_2 (1–5 μM) increased the frequency of sIPSCs in a concentration-dependent manner but had no significant effect on the amplitude. Similarly to the effects on sIPSCs, PGE_2 increased the sEPSC frequency without any effect on the amplitude. These facilitatory effects of PGE_2 on spontaneous synaptic transmissions were blocked by an EP1 antagonist SC19220 but not by an EP4 antagonist AH23848. Electrical stimulation of the trigeminal tract evoked short latency EPSCs (eEPSCs) in the Vc neurons. PGE_2 (5 μM) was ineffective on the eEPSCs. The present study demonstrated that PGE_2 facilitated spontaneous synaptic transmissions in the Vc neurons through activating the presynaptic EP1 receptors but had no effect on the trigeminal tract-mediated excitatory transmission. These results suggest that centrally-synthesized PGE_2 modifies the synaptic transmission in the Vc region, thereby contributing to the processing of nociceptive signals originated from the orofacial area.

Abbreviations: COX2, cyclooxygenase 2; EPSC, excitatory postsynaptic current; IPSC, inhibitory postsynaptic current; PGE_2, prostaglandin E_2; Vc, spinal trigeminal subnucleus caudalis; Vsp, spinal trigeminal nucleus

*Correspondence to: Laboratory of Neuropharmacology, School of Pharmacy, Aichi Gakuin University, 1-100 Kusumoto-cho, Chikusa-ku, Nagoya 464-8650, Japan. Fax: +81 52 757 6799.
E-mail addresses: ag123d26@dpc.agu.ac.jp (Y. Mizutani), yohi@dpc.agu.ac.jp (Y. Ohi), s-kimura@dpc.agu.ac.jp (S. Kimura), miyaken@dpc.agu.ac.jp (K. Miyazawa), shig@dpc.agu.ac.jp (S. Goto), haji@dpc.agu.ac.jp (A. Haji).

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1. Introduction

Tooth movement is widely used in orthodontics, aiming to give firm, correct bite and/or good alignment of teeth. However, it may cause discomfort, unpleasant or painful sensations. Immediate and delayed painful responses after application of orthodontic force are reported in clinical studies (Krishnan, 2007; Sessle, 2000). The pain sensation after tooth movement is derived from a process of pressure, local ischemia and tissue inflammation (Furstman and Bernick, 1972; Giannopoulou et al., 2006). It has been reported that a marked expression of cyclooxygenase 2 (COX2) is found not only locally at the site of damaged tissue but also centrally at the site related to nociceptive transmission (Samad et al., 2001; Vardeh et al., 2009). Consequently, prostaglandin E_2 (PGE_2) can be synthesized by COX2 in the central neurons and glia (Bishai and Coceani, 1992) and influences various physiological functions (Liu et al., 2005; McCullough et al., 2004; Wolfe and Coceani, 1979).

The spinal trigeminal nucleus (Vsp) located within trigeminal sensory nuclei is the relay site of somatosensory information, mostly coming from orofacial areas, to be transferred to higher central regions (Olszewski, 1950). The Vsp consists of three subnuclei, oralis (Vo), interpolaris (Vi) and caudalis (Vc) that are interconnected each other by excitatory and inhibitory synaptic transmissions (Han et al., 2008). Previous studies demonstrated that experimental tooth movement induced an intense Fos response predominantly in the Vc region (Aihara et al., 1999; Magdalena et al., 2004; Badral et al., 2013), suggestive of a potential correlation between the activation of Vc neurons and painful sensations induced by tooth movement. Therefore, it is thought that the Vc neurons receive preferentially the orofacial nociceptive signals and play important roles in the regulation and transmission processes of such information (Balam et al., 2005; Krishnan, 2007). Furthermore, there are some interesting results that the tooth movement-induced c-Fos expression in the Vc region was inhibited by morphine (Aihara et al., 1999) and by acetaminophen or cerecoxib (Stabile et al., 2009). Selective anesthesia on pain fibers reduced the brainstem c-Fos response after tooth extraction (Badral et al., 2013). Together with the histological evidence that co-localization of COX2-like immunoreactivity with Fos-like immunoreactivity was found in the Vc region after orofacial nociceptive stimuli (Gao and Duan, 2010), it seems likely that central control of COX2 induction is one of key factors for managing the painful sensation after orthodontic treatment. Among the metabolites from arachidonic acid, PGE_2 has the greatest impact on processing of pain signals (Kawabata, 2011; Omote et al., 2002). Additionally, PGE_2 has been reported to exert the most potent action on glutamate release than PGD_2 and $PGF_{2\alpha}$ in cultured astrocytes (Bezzi et al., 1988). Until now, however, the physiological roles of PGE_2 synthesized by COX2 in the Vc region have not been clarified yet.

To solve this issue, the present study was undertaken to investigate the effects of exogenously applied PGE_2 on synaptic transmission in the Vc neurons. We recorded spontaneously occurring excitatory and inhibitory postsynaptic currents (sEPSCs and sIPSCs) and the trigeminal tract-evoked EPSCs (eEPSCs) from the Vc neurons in the rat brainstem slice by using a whole-cell patch-clamp technique.

2. Results

At the end of each experiment, the location of the recorded neuron was identified under microscope using infrared-differential interference contrast (IR-DIC). Fig. 1 displays a microscopic image of a horizontal brainstem slice including the Vc region (A) and representative recording sites ($n=17$) in a schematic drawing (B). We confirmed that the neurons recorded in the present study were largely distributed in or around the substantia gelatinosa (SG) region of Vc.

2.1. *Effects of PGE_2 on sIPSCs*

Modulation of spontaneous inhibitory transmission by PGE_2 (1–5 μM) was investigated in 36 Vc neurons under perfusion of DNQX (10 μM) which blocked excitatory synaptic transmission. In control condition with a holding potential at –60 mV, sIPSCs were detected as inward currents (Fig. 2A). The mean amplitude and frequency of sIPSCs were 36.1 ± 4.2 pA and 1.8 ± 0.2 Hz ($n=36$), respectively. The sIPSC amplitude was increased when the holding potential was set at a more negative level, while it decreased when set at more positive levels. At a holding potential of 0 mV, sIPSCs were not detected. The sIPSCs were abolished by co-application of picrotoxin (100 μM) and strychnine (1 μM) in 5 neurons tested (Fig. 2B).

A typical example of effects of PGE_2 on sIPSCs is shown in Fig. 3A. Exogenous application of PGE_2 (5 μM) increased the frequency of sIPSCs but had a negligible effect on the amplitude. Merged traces showed no change in the time course of sIPSCs during PGE_2. The baseline current was not changed. The PGE_2's action waned gradually during washout and the sIPSC frequency recovered to the control level until 10 min after washout. Fig. 3B shows the cumulative probabilities of inter-event interval (IEI) and amplitude of sIPSCs in the same cell represented in Fig. 3A.

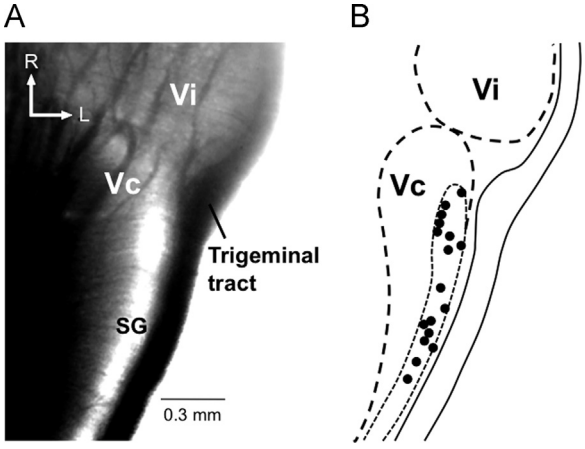

Fig. 1 – (A) An infrared microscopic image of a horizontal brainstem slice including the Vc area. (B) Distribution of recording sites (indicated by dots, $n=17$) in a schematic drawing. Abbreviations: Vc; spinal trigeminal subnucleus caudalis, Vi; spinal trigeminal subnucleus interpolaris, SG; substantia gelatinosa, L; lateral, R; rostral.