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BRAIN RESEARCH

Research Report

The Fos expression in rat brain following electrical stimulation of dura mater surrounding the superior sagittal sinus changed with the pre-treatment of rizatriptan benzoate

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ABSTRACT

Fos expression in the brain was systematically investigated by means of immunohistochemical staining after electrical stimulation of the dura mater surrounding the superior sagittal sinus in conscious rats. Fos-like immunoreactive neurons are distributed mainly in the upper cervical spinal cord, spinal trigeminal nucleus caudal part, raphe magnus nucleus, periaqueductal gray, ventromedial hypothalamic nucleus, and mediodorsal thalamus nucleus. With the pre-treatment of intraperitoneal injection of rizatriptan benzoate, the number of Fos-like immunoreactive neurons decreased in the spinal trigeminal nucleus caudal part and raphe magnus nucleus, increased in the periaqueductal gray, and remained unchanged in the ventromedial hypothalamic nucleus and mediodorsal thalamus nucleus. These results provide morphological evidence that the nuclei described above are involved in the development and maintenance of the trigeminovascular headache.

1. Introduction

Over the past decades, much work has been done to help us understand the migraine mechanism. Although it is still unclear, the activation of the trigeminovascular nociceptive pathway is considered to be essential for the development and maintenance of a migraine headache (Tepper et al., 2001). Many migraine animal models were constructed using electrical stimulation of trigeminal nerve-innervating tissues, such as trigeminal ganglion models (Clayton et al., 1997; Goadsby and Knight, 1997), dural arteries models (De Vries et al., 1999), and dura mater and superior sagittal sinus models (Benjamin et al., 2004). These models have helped to greatly expand our knowledge of the mechanisms underlying the trigeminovascular system in migraines. However, they were all performed in anesthetized animals. As an important therapeutic method for unbearable pain, anesthesia has a great deal of influence on the nociceptive information transmission and analysis during the central pain process. This would unquestionably change the property or intensity of the pain perceived, disregarding the automatic nervous system and the emotional responses complicated with pain. In order to better mimic the physical state of a migraine patient, the electrical stimulation of dura mater surrounding the superior sagittal sinus (SSS) was conducted in conscious rats in this study.

Fos is the protein product of activated c-fos proto-oncogene. It has been reported to be a third-messenger molecule that connects extracellular signals to genetic events that result in changes in cellular phenotypic expression (Dragunow and Faull, 1989; Rodella et al., 1998). Various types of peripheral stimuli,

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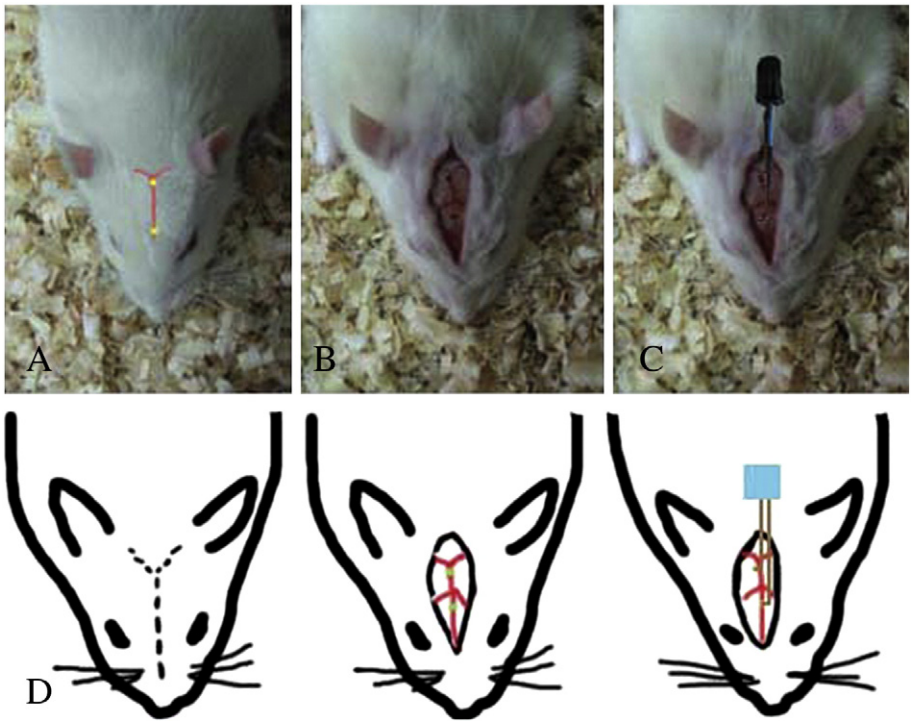

Fig. 1 – The photomicrographs (A, B, and C) and drawn picture (D) showing the procedures of establishing the model in rat. The incision on top of the head (A), the exposed parietal bone (B), and the electrode installed (C). In picture D, the dotted line indicating the incision, red lines symbolizing skull sutures, and blue square with two brown lines showing the position of the electrode installed.

especially noxious stimulation, can induce the expression of Fos in the brain. Therefore, Fos is often used as a marker of neuronal activity (Harris, 1998; Han et al., 2003).

Eletriptan is a selective 5-HT1 receptor agonist. The treatment with eletriptan is believed to reduce the swelling of the blood vessels surrounding the brain and inhibit the release of substances from nerve endings that cause neurogenic inflammation (Goadsby and Hoskin, 1997). Due to the high efficacy in relieving pain and accompanying symptoms, it is the first choice for the treatment of migraine during an acute attack. Rizatriptan benzoate is a recently developed second generation of eletriptan with rapid onset, high safety, and lipophilicity that passes through the blood–brain barrier more easily (Lines et al., 2001). Therefore, rizatriptan benzoate was employed in the study to interfere with the neurovascular inflammation induced by electrical stimulation of dura mater surrounding the SSS.

In the present study, the Fos-like immunoreactive (-LI) neurons in the brain following electrical stimulation of dura mater surrounding the SSS in conscious rats were observed by means of immunohistochemistry, and the effect of rizatriptan benzoate on the Fos expression was investigated.

2. Results

After immunohistochemical staining, the Fos-LI neurons were observed based on the results of group A. The nuclei of Fos-LI neurons were dark-brown with a brown background and were oval or round in shape and 5–8 μm in diameter, which was the same as the previous report (Chocyk et al., 2008) (shown in Fig. 1).

Fos-LI neurons are distributed widely in the brain, located mainly in the dorsal horn of the upper cervical spinal cord (UCSC), the spinal trigeminal nucleus, the caudal part (Sp5C), the raphe nuclei (especially the raphe magnus nucleus, RMg), the periaqueductal gray (PAG), the interpeduncular nucleus (IP), the ventromedial hypothalamic nucleus (VMH), the mediodorsal thalamus nucleus (MD), and so on (Fig. 2). Comparatively, Fos-LI neurons had a denser distribution in the UCSC, Sp5C, and PAG than in any other regions.

For the rats of group B, the distribution pattern and numbers of Fos-LI neurons were quite similar to those of group A, concentrating mainly in the UCSC, Sp5C, raphe nuclei, PAG, IP, VMH, and MD. For the rats of group C, the Fos-LI neuron distribution pattern in the brain was similar to that of group B but with different cell intensity in some regions. In VMH and MD, the distribution pattern and numbers of Fos-LI neurons in the two groups were similar ($P>0.05$), but there were fewer Fos-LI neurons in Sp5C and RMg ($P<0.01$) and more Fos-LI neurons in PAG ($P<0.001$) in rats of group C than in those of group B (shown in Table 1 and Fig. 3).

For the rats of group D, the distribution of Fos-LI neurons was sparse and highly variable. Only a few Fos-LI neurons were found in the Sp5C, pontine reticular nucleus, median raphe nucleus, and PAG.