

Electroacupuncture alleviates inflammatory pain via the activation of GABAergic inhibitory interneurons in mice spinal dorsal horn

Yang Bao^{#1,2}, Mengye Zhu^{#1,2}, Jinjin Zhang^{1,2}, Xuezhong Cao^{1,2}, Xuexue Zhang^{1,2}, Yong Zhang^{1,2}, Daying Zhang^{*1,2}, Tao Liu^{*3}

1. Department of Pain Medicine, The First Affiliated Hospital of Nanchang University, Nanchang 330006, China 2. Institute of Pain Medicine, Jiangxi Academy of Clinical and Medical Sciences, Nanchang 330006, China 3. Center for Experimental Medicine, the First Affiliated Hospital of Nanchang University, Nanchang 330006, China

BACKGROUND

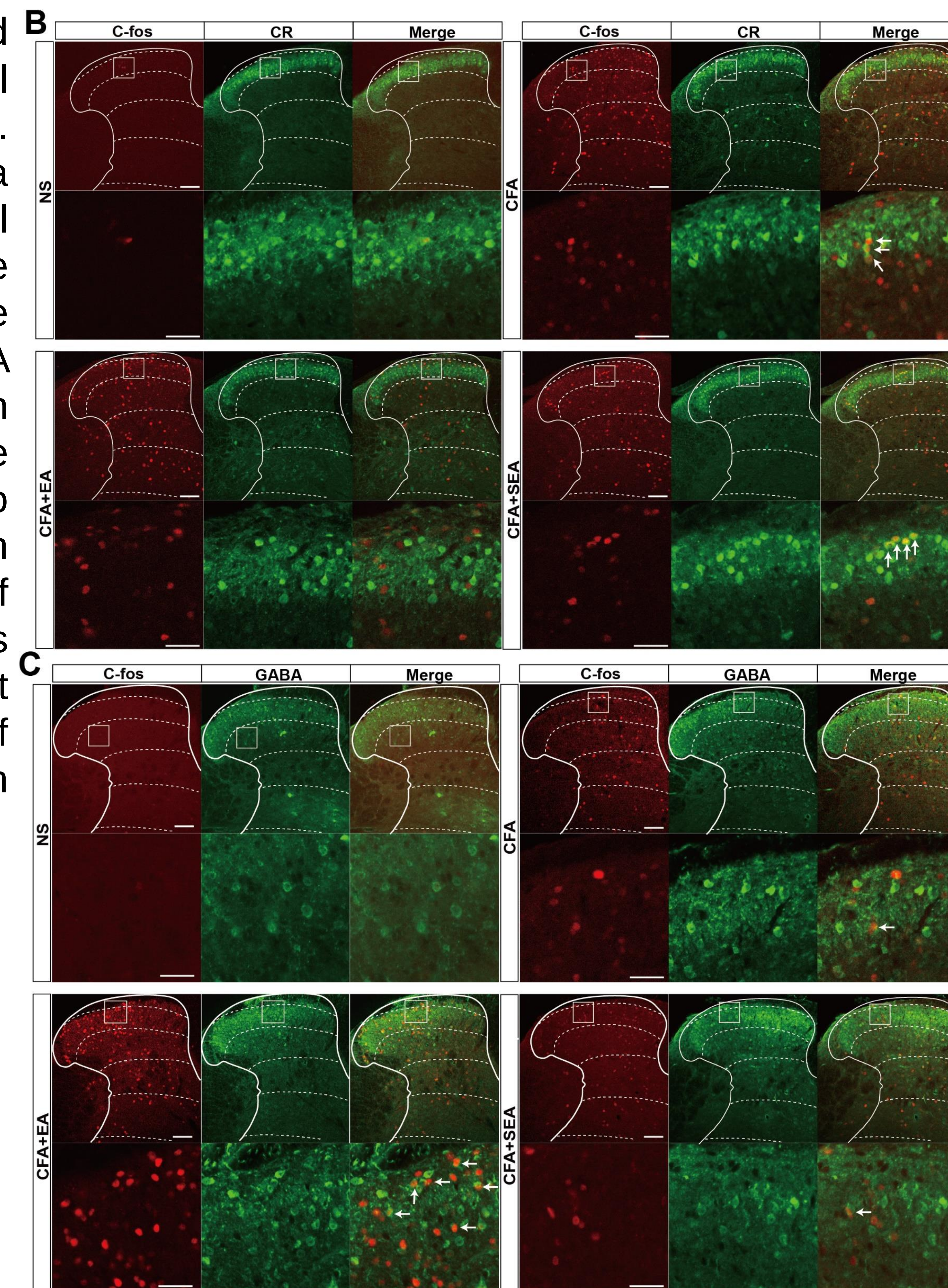
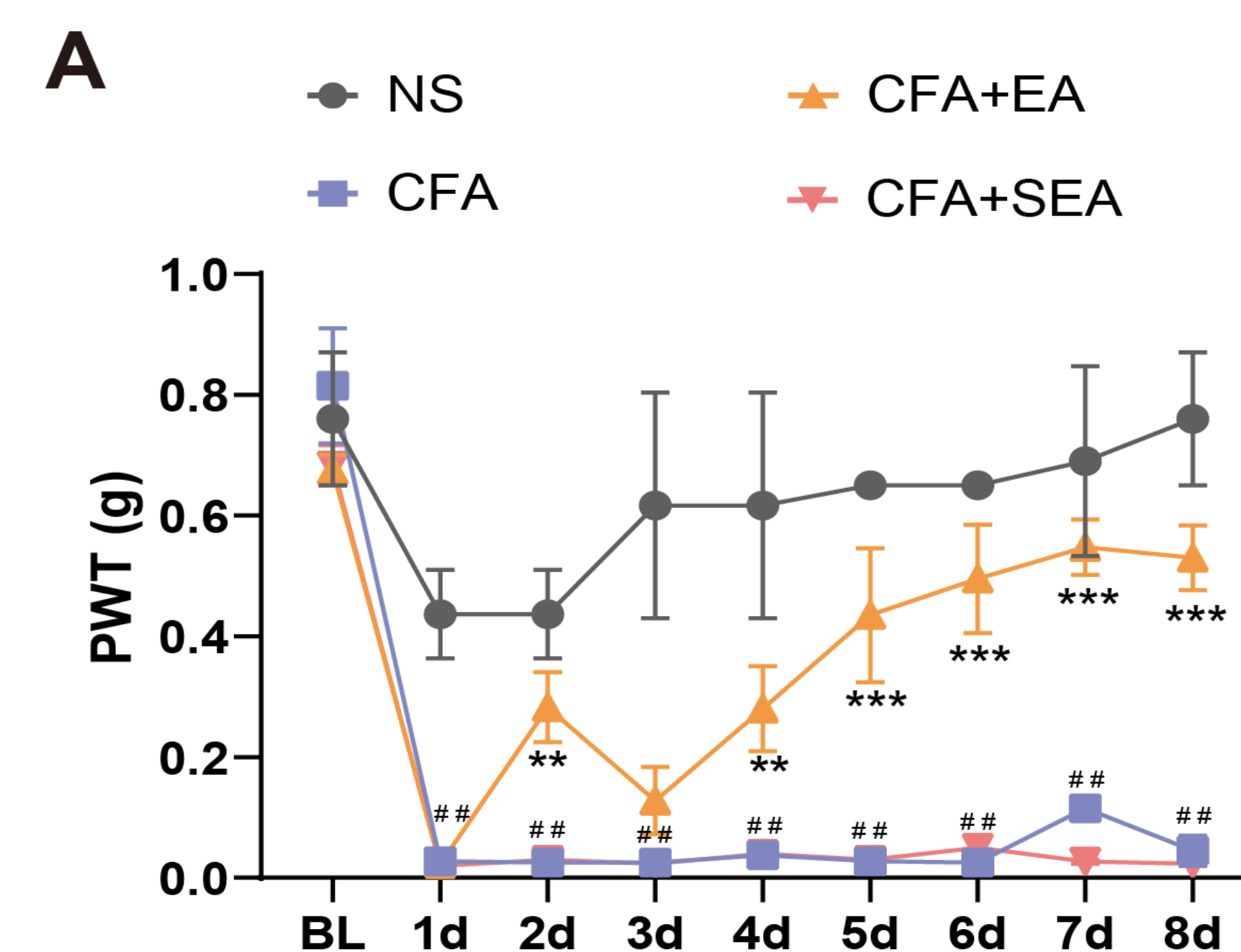
Although the analgesic effect of electroacupuncture (EA) has been suggested by large amounts of clinical and pre-clinical evidence, the fundamental neural mechanisms underlying EA-mediated alleviation of pain hypersensitivity remain poorly understood. The spinal dorsal horn (SDH) serves as the primary center for the integration of nociceptive inputs, and SDH neuronal dysfunction contributes to the development and maintenance of pathological pain. In the present study, we aimed to investigate the role of superficial SDH neurons recruited in EA's analgesic effect.

MATERIALS AND METHODS

C57BL/6 mice (20 - 30 g) were randomly divided into control (vehicle of the complete Freund's adjuvant (CFA)), CFA, CFA+EA, and CFA+sham EA groups. CFA was injected into the dorsal surface of the left hindpaw (20 μ l) for CFA-induced inflammatory pain. Mice of the CFA+EA group received EA administration on the left Huantiao (GB30) and Yanglingquan (GB34) once every other day, starting from day 1 to day 8 after CFA injection. EA (1 mA and 0.3 ms) was administered at the frequency of 2 Hz for 30 min. The tactile withdrawal threshold of mice was measured by using the “up-down” method. Immunohistochemistry was performed to observe the expression of C-fos, GABA, and Calretinin (CR) in superficial SDH.

RESULTS

CFA-injected mice rapidly and persistently presented mechanical hypersensitivity under the von Frey test. Mice in the CFA+EA group displayed a significantly raised mechanical withdrawal threshold compared to mice in the CFA group (Fig. A). Double immunostaining showed that CFA treatment induced C-fos protein expression in CR+ neurons in the ipsilateral superficial SDH compared to control mice, while EA intervention markedly decreased the percentage of C-fos/CR double-labeled SDH neurons (Fig. B). In contrast, EA treatment resulted in increased colocalization of GABAergic inhibitory interneurons with C-fos in SDH (Fig. C).



DISCUSSION

Here, we demonstrate that different neuronal populations in superficial SDH showed distinct activity changes under inflammatory pain conditions, and such aberrant alterations could be reversed by EA treatment. Specifically, the activity of CR+ neurons has been reported closely correlated with the development of inflammatory pain^[1]. Our results supported this point by showing hyperactivity of CR+ neurons after inflammatory injury and inhibition of this population by EA treatment. In addition, we examined the activity of inhibitory interneurons in superficial SDH because recent studies have indicated the essential role of GABAergic neurons in modulating sensory sensitivity^[2]. We identified the potentiation of GABAergic neurons after EA treatment, which might result in enhanced presynaptic inhibitory transmission for lowering CR+ neuronal activities. In sum, these data collectively suggest that EA intervention may restore excitatory/inhibitory balance within SDH microcircuits, and hence help to explain the effect of EA in relieving pain behavior of inflammatory pain.

References

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