Electroacupuncture regulates IL-17A pathway for the comorbidities of chronic pain and depression in mice brain

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Background&Aims

The disease of chronic pain and major depressive disorder (MDD) comorbidity is a serious health issue in the world. Patients suffered chronic pain had a higher tendency to develop depression[1]. It was estimated that around 80% of the general population presents with the comorbidity of chronic pain and depression[2]. Previous study showed that chronic pain and MDD share the neuroinflammation as the common mechanism[3]. The neuroinflammation leads to increase proinflammatory cytokines such as interleukin 17 (IL-17) in both serum and cerebrospinal fluid[4, 5]. Interleukin-17A (IL-17A), often referred to as IL-17, was known to be associated with chronic inflammatory conditions. It has a critical role in modulating the immune response involved in neuropathic pain[6] and inflammatory pain[7], and is associated with depression[8, 9] in the central nerve system (CNS). Transient receptor potential V1 (TRPV1), a Ca2+ permeable ion channel, is activated by inflammation and involved in chronic pain and depression. Previous results indicated that electroacupuncture (EA) alleviated comorbidity of depression and chronic pain through downregulated TRPV1-related PI3K–Akt–mTOR axis in mice brain and reversed the increased plasma concentration of inflammatory mediators including IL17A in the intermittent cold stress (ICS) mice model[10, 11]. Recent study indicated that cutaneous TRPV1+ neuron activation is sufficient to initiate type 17 inflammation[12]. We hypothesized that the cold stress stimulated the cutaneous TRPV1+ neuron and then activated the generalized neuroinflammation in mice brain. We also want to determine the effects of EA at ST36 acupoint on the expression of IL17A receptor (IL17AR) and TRPV1 related proteins in somatosensory cortex (SSC) in mice brain.

Materials & Methods

40 female C57BL/6 mice were subdivided into five groups: Normal mice (Control, Con), normal mice with Cold stress pain (CSP); CSP plus Electroacupuncture; CSP plus acupuncture (Sham) and TRPV1 gene knockout mice (KO) with CSP. All mice received von Frey and Hargreavers' behavior tests (PRE test) at room temperature at day 0. Then, CSP, EA, Sham and KO group had the cold stress stimulation followed our protocol[11]. After that, EA and Sham mice received 2Hz electroacupuncture and acupuncture respectively at ST36 acupoint for five days. Finally, all mice received POST behavior tests at day 8 and sacrificed for brain tissue collection for Western blot analysis.

Results

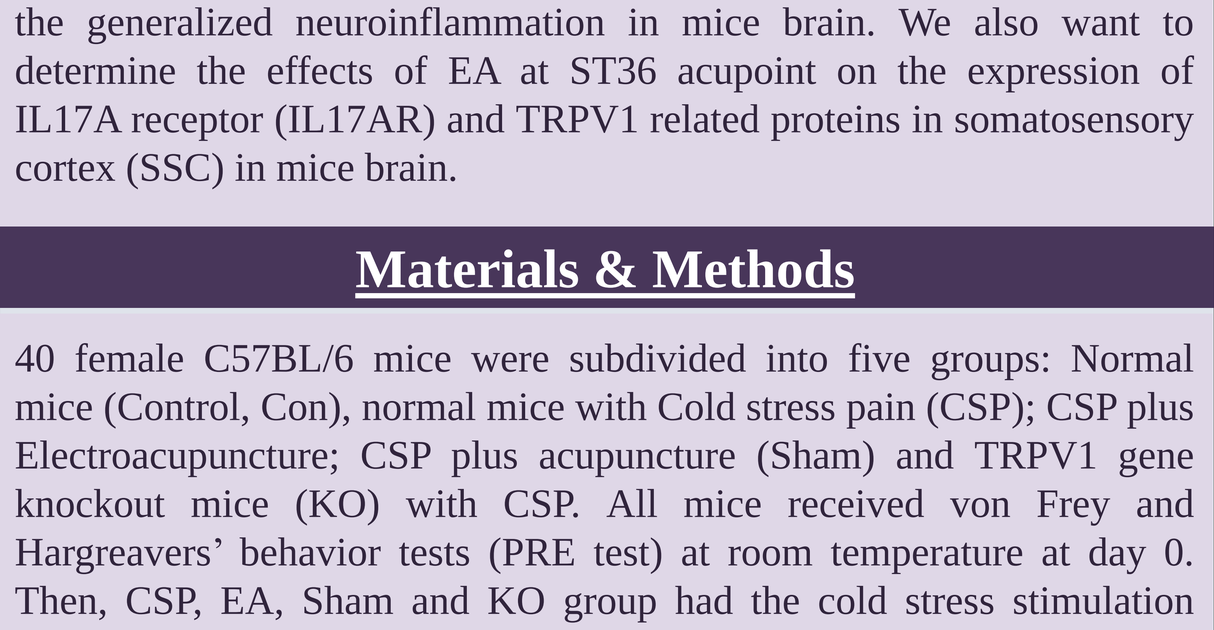

Figure 1 Cold stress caused the abnormal pain including mechanical allodynia and thermal hyperalgesia. EA and TRPV1 deletion counter these effects. (*p<0.05 when compared to the PRE test; #p<0.05 when compared to the CSP group) (n=8)

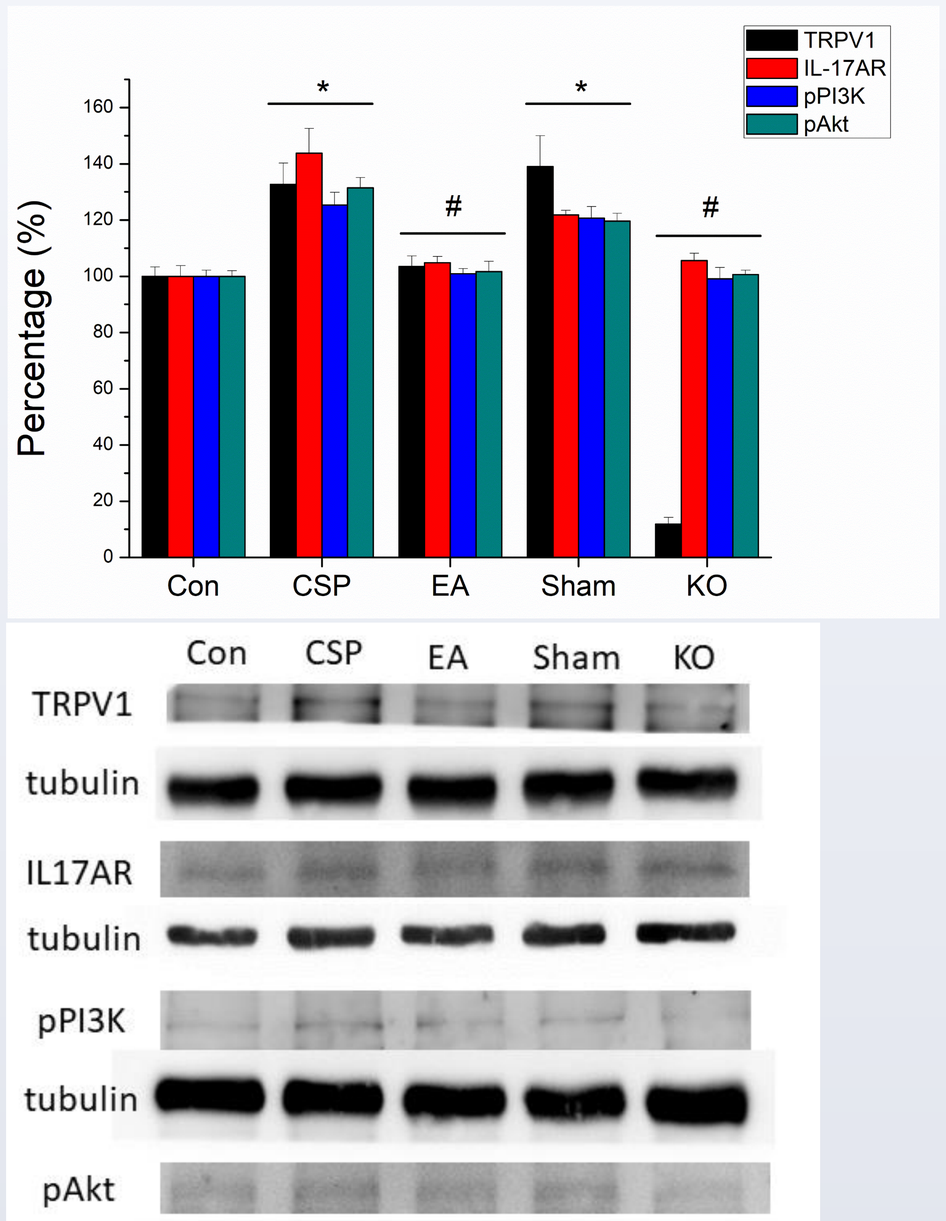

Figure 2. The expression of proteins in the mice somatosensory cortex (SSC) of brain. Compared with the controlled group, the level of TRPV1, IL17AR, pPI3K and pAkt were significantly increased after cold stress in CSP and Sham groups, and were reversed in EA and TRPV1 deletion group. (n=6)

Conclusion

We showed that EA at ST36 and TRPV1 deletion counter the mechanical allodynia and thermal hyperalgesia induced by cold stress. Moreover, the upregulated expression of TRPV1, IL17AR, pPI3K and pAkt after cold stress in the SSC of mice brain were also reversed in EA and TRPV1 deletion group.

Discussion

Our results suggest that EA at ST36 and TRPV1 deletion may alleviated comorbidity of depression and chronic pain through the reversed the upregulation of TRPV1, IL17AR, pPI3K and pAkt related pathway that may involve neuroinflammation in the brain in cold stress mice model.

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