

Electroacupuncture Alleviates Migraine Through CXCL13/CXCR5-mediated Communication

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Abstract

Rationale: Chronic migraine is characterized by persistent trigeminal sensitization and neuroinflammation. however, the molecular mechanisms underlying its maintenance and mediate the therapeutic effects of acupuncture remain incompletely understood. **Method:** A chronic migraine-like state was induced in mice by repeated dural inflammatory soup (IS), followed by electroacupuncture (EA). Behavioral hypersensitivity was assessed, and molecular changes in the spinal trigeminal nucleus caudalis (Sp5C) were analyzed using transcriptomic, biochemical, and functional approaches. **Result:** Repeated inflammatory stimulation markedly increased CXCL13 and CXCR5 expression and ERK phosphorylation in the Sp5C, accompanied by mechanical allodynia, thermal hyperalgesia, glial activation, and elevated IL-6 and CCL2 levels. EA significantly attenuated pain hypersensitivity and reduced CXCL13/CXCR5 expression, ERK activation, glial reactivity, and inflammatory mediator release. EA also decreased migraine-related neuropeptides and synaptic plasticity markers, including substance P, PACAP, and NR2B. Functional manipulation experiments demonstrated bidirectional regulation of pain behaviors by CXCR5, establishing its causal role in chronic migraine-like sensitization. MicroRNA profiling identified a dysregulated miRNA signature converging on the transcription factor FOXO3, which indirectly regulated CXCR5 transcription, defining a miRNA-FOXO3-CXCR5 regulatory pathway. **Conclusion:** Our study reveals the CXCL13/CXCR5/ERK axis as a previously unrecognized pathway in migraine neuroinflammation and demonstrates electroacupuncture's multimodal therapeutic mechanisms. These findings provide: (1) novel mechanistic insights into migraine pathophysiology through CXCR5-mediated signaling, and (2) translational implications for chronic migraine treatment by targeting the CXCL13/CXCR5/ERK axis. This work establishes a foundation for future development of targeted therapies and validates electroacupuncture as a viable intervention for migraine management.

Keywords

Migraine, Neuroinflammation, CXCR5, Neuron, Cross-talk, FOXO3