Electroacupuncture Inhibits Excessive Interferon-γ Evoked Upregulation of P2X4 Receptor in Spinal Microglia in a CCI Rat Model for Neuropathic Pain

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Abstract: Although electroacupuncture (EA) is an effective therapy for the relief of neuropathic pain, the underlying mechanisms remain unclear. Previous studies have found that EA produced an immunomodulatory effect in rats with endoxemia. Since excessive release of interferon-γ (IFN-γ) after nerve injury transforms quiescent spinal microglia into an activated state with more neuropathic pain associated purinergic receptor P2X4 expression, it is possible EA treatment may mediate its analgesic effect by attenuating IFN-γ release and subsequent generation of $P2X4R^+$ microglia. Here, chronic constriction injury (CCI) or IFN-γ intrathecal injection was conducted on male Sprague-Dawley (SD) rats, and von Frey tests were performed to evaluate the pain threshold. Spinal IFN-γ and P2X4R expression levels were measured by immunohistochemistry, real-time PCR, Elisa, and/or Western blots. In vitro primary culture of microglia was used to examine IFN-γ activation of $P2X4R^+$ cells. Results show that in CCI rats, EA treatments significantly increased paw withdrawal threshold (PWT) relative to control. IFN-γ facilitated $P2X4R^+$ microglia activation both in vitro and in vivo. EA treatments on CCI rats suppressed $P2X4R^+$ microglia activation and down-regulated both P2X4R and IFN-γexpression in the spinal cord. However, EA did not exert the same analgesic effect on tactile hypersensitivity induced by intrathecal IFN-γ injection. Thus we conclude that EA relieves tactile allodynia following peripheral nerve injury by down-regulating excessive expression of IFN-γ in the spinal cord and subsequently reducing expression of $P2X4R^+$ microglia activation.

Keywords: acupuncture, P2X4 receptor, interferon-γ, neuropathic pain, spinal cord