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Descending Noradrenergic Inhibition: An Important Mechanism of Gabapentin Analgesia in Neuropathic Pain

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Abstract

Gabapentinoids are effective in a wide range of animal pain models and in patients with neuropathic pain and has become one of first-line treatments for neuropathic pain. Because spinal plasticity and sensitization have been intensely studied in neuropathic pain, most laboratory studies have focused on actions of gabapentinoids in the spinal cord, where they reduce primary afferent traffic and excitation of spinal nociceptive neurons, via interaction with α2δ subunits of voltage-gated Ca^{2+} channels. However, a recent clinical study questioned the relevance of this in vitro and in vivo rodent studies by demonstrating a complete lack of clinical efficacy of intrathecal gabapentin in patients with chronic pain. Curiously, preclinical studies continue to focus on spinal cord actions of gabapentinoids despite this lack of translation to humans.We and others demonstrated that gabapentin inhibits presynaptic GABA release and induces glutamate release from astrocytes in the locus coeruleus (LC), thereby increasing LC neuron activity and spinal noradrenaline release, and that gabapentin relies on this action in the LC for its analgesia. We also recently discovered that, with prolonged time after neuropathic injury, noradrenergic neurons in the LC become less responsive to gabapentin, leading to impaired gabapentin analgesia, and that astroglial glutamate dysregulation is critical to this impaired LC response. The clinically available drug valproate increases glutamate transporter-1 (GLT-1) expression in the LC to restore this impaired gabapentin analgesia.

Keywords: Astrocyte; Gabapentin; Glutamate transporter; Locus coeruleus; Neuropathic pain.

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