

Pain relief by gabapentin and pregabalin via supraspinal mechanisms after peripheral nerve injury.

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Author information

Abstract

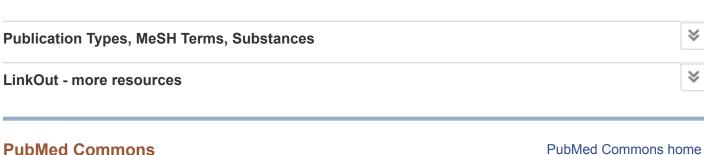
The antihypersensitivity actions of gabapentin and pregabalin have been well characterized in a large number of studies, although the underlying mechanisms have yet to be defined. We have been focusing on the supraspinal structure as a possible site for their action and have demonstrated that intracerebroventricular (i.c.v.) administration of gabapentin and pregabalin indeed decreases thermal and mechanical hypersensitivity in a murine chronic pain model involving partial ligation of the sciatic nerve. This novel supraspinally mediated analgesic effect was markedly suppressed by either depletion of central noradrenaline (NA) or blockade of spinal alpha(2)-adrenergic receptors. Moreover, i.c.v. injection of gabapentin and pregabalin increased spinal NA turnover in mice only after peripheral nerve injury. In locus coeruleus (LC) neurons in brainstem slices prepared from mice after peripheral nerve injury, gabapentin reduced the gamma-aminobutyric acid (GABA) type A receptor-mediated inhibitory postsynaptic currents (IPSCs). Glutamate-mediated excitatory synaptic transmission was hardly affected. Moreover, gabapentin did not reduce IPSCs in slices taken from mice given a sham operation. Although gabapentin altered neither the amplitude nor the frequency of miniature IPSCs, it reduced IPSCs together with an increase in the paired-pulse ratio, suggesting that gabapentin acts on the presynaptic GABAergic nerve terminals in the LC. Together, the data suggest that gabapentin presynaptically reduces GABAergic synaptic transmission, thereby removing the inhibitory influence on LC neurons only in neuropathic pain states, leading to activation of the descending noradrenergic system.

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