Mirogabalin ameliorates neuropathic pain by activating the descending noradrenergic system involving its binding to the $\alpha_2\delta$-1 subunit of voltage-gated Ca^{2+} channels

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Gabapentinoids such as gabapentin and pregabalin, which act on the $\alpha_2\delta$ subunit of voltage-gated Ca^{2+} channels, are widely used to treat neuropathic pain. They are known to activate the descending noradrenergic pain inhibitory system. Here, we investigated the analgesic effect of mirogabalin, a novel gabapentinoid recently launched for treatment of peripheral neuropathic pain including diabetic peripheral neuropathy and postherpetic neuralgia. Mirogabalin besilate produced analgesic effects on mechanical and thermal hypersensitivity developing after partial sciatic nerve ligation in mice, when it was administered systemically (10 and 30 mg/kg, i.p.) and locally (10 and 30 μg, i.c.v or i.t.). In particular, its analgesic effects (30 mg/kg, i.p. and 30 μg, i.c.v.) were largely reduced by pretreatment with yohimbine HCl (3 μg, i.t.). Moreover, in mutant mice with the substitution of arginine at position 217 with alanine (R217A) on the $\alpha_2\delta$-1 subunit, the analgesic effects of pregabalin and mirogabalin besilate (30 μg, i.c.v., respectively) on mechanical hypersensitivity were almost completely suppressed. These results demonstrate clearly that mirogabalin also employs the descending noradrenergic system, and the binding to the $\alpha_2\delta$-1 subunit is crucially important in the supraspinally mediated analgesic effects of gabapentinoids.