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Ultra-Low Doses of Naltrexone Enhance the Antiallodynic Effect of Pregabalin or Gabapentin in Neuropathic Rats.

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Abstract

Preclinical Research Treatment of neuropathic pain is an area of largely unmet medical need. Pregabalin and gabapentin are anticonvulsants widely used for the treatment of neuropathic pain. Unfortunately, these drugs are only effective in 50-60% of the treated patients. In addition, both drugs have substantial side effects. Several studies have reported that ultralow doses of opioid receptor antagonists can induce analgesia and enhance the analgesic effect of opioids in rodents and humans. The objective of the present study was to assess the antiallodynic synergistic interaction between gabapentinoids and naltrexone in rats. Oral administration of pregabalin ($ED_{50} = 2.79 \pm 0.16$ mg/kg) or gabapentin ($ED_{50} = 21.04 \pm 2.87$ mg/kg) as well as intrathecal naltrexone ($ED_{50} = 0.11 \pm 0.02$ ng) reduced in a dose-dependent manner tactile allodynia in rats. Maximal antiallodynic effects (~100%) were reached with 30 mg/kg of pregabalin, 300 mg/kg of gabapentin or 0.5 ng of naltrexone. Co-administration of pregabalin or gabapentin and naltrexone in a fixed-dose ratio (1:1) remarkably reduced spinal nerve ligation-induced tactile allodynia showing a synergistic interaction. The data indicate that combinations of pregabalin or gabapentin and ultra-low doses of naltrexone are able to reduce tactile allodynia in neuropathic rats with lower doses than those used when drugs are given individually and with an improved side effects profile. *Drug Dev Res* 78 : 371-380, 2017.

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