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Antinociceptive interaction of a GLT1 activator and a microglia inhibitor alone and in combination in chronic constriction injury model of neuropathic pain

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Background and Aims: Glutamate homeostasis plays an important role in the development and maintenance of neuropathic pain. Moreover, microglia activation has been received much interest in the pathogenesis of many CNS disorders recently. Up to now there is insufficient data on the interaction between glutamate transporters and cytokines in neuropathic pain. This investigation was designed to evaluate interaction between co-administration of a specific GLT1 activator, ceftriaxone, with a specific inhibitor of microglia, minocycline, on the characteristic signs of chronic constriction injury model (CCI) in rats and alteration of the spinal concentration of proinflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β).
Methods: Male Wistar rats were used in this study. Von Frey filaments and acetone drop were used to assess mechanical and thermal allodynia respectively. Cytokine contents were measured by means of ELISA kits. Ceftriaxone (100, 150 and 200 mg/kg/i.p.) and minocycline (25, 50 and 100 mg/kg/i.p.) were administered either alone or in combination.
Results: Each of drugs produced a dose-dependent reversal of the neuropathic pain behavior. Area under the curve (AUC) of thermal and mechanical antiallodynic effects of combination therapy revealed a potent synergistic activity. TNF-α and IL-1β were increased in the spinal cord of CCI animals. Production of these cytokines was significantly attenuated compared to control group after treatment with ceftriaxone and minocycline at the doses with an antinociceptive effect and also by combining the drugs but not significant from individual administration of drugs. The results showed that activation of GLT1 transporters and increase in uptake of glutamate could cause a significant decrease in pro-inflammatory cytokines in spinal cord.
Conclusions: it is concluded that combination of these classes of drugs would be logical and promising approach to treatment of this chronic state.

Keywords: Neuropathic pain; Microglia inhibitor; Glutamate transporter activator; Thermal allodynia; Mechanical allodynia