
ABSTRACT

BACKGROUND: Neuropathic pain is a severe painful pathology that is difficult to treat. One option for its management is the continuous intrathecal (i.t.) infusion of ziconotide (the Conus magnus peptide ω-conotoxin MVIIA), which, in addition to being effective, produces serious adverse effects at analgesic doses. Single i.t. administration of Phα1β, a peptide purified from the venom of the spider Phoneutria nigriventer, has antinociceptive effects with a greater therapeutic window than ziconotide in rodents. To further evaluate its analgesic potential, we investigated the antinociceptive and toxic effects of Phα1β after single or continuous i.t. infusion in a rat model of neuropathic pain.

METHODS: Adult male Wistar rats (200-300 g) bred in-house were used. Chronic constriction injury (CCI) of the sciatic nerve was used as the neuropathic pain model. Nociception was assessed by detecting mechanical hyperalgesia, considering a significant reduction in 50% paw withdrawal threshold values after CCI compared with baseline values. First, we assessed the antinociceptive effect of a single i.t. injection of Phα1β (10, 30, or 100 pmol/site) in a model of neuropathic pain 8 days after nerve injury. In a different experiment, we delivered Phα1β (60 pmol/μL/h) or vehicle (phosphate-buffered saline, 1.0 μL/h) through continuous infusion using an osmotic pump by spinal catheterization for 7 days in rats submitted to nerve injury. Behavioral adverse effects were evaluated after single or continuous Phα1β i.t. administration, and histopathological analysis of spinal cord, brainstem, and encephalon was performed after continuous Phα1β i.t. injection.

RESULTS: We observed that CCI of the sciatic nerve but not sham surgery caused intense (reduction of approximately 2.5 times in mechanical withdrawal threshold) and persistent (up to 14 days) nociception in rats. The single i.t. injection of Phα1β (30 or 100 pmol/site) reduced neuropathic nociception from 1 to 6 hours after administration, without showing detectable side effects. Similarly, the continuous infusion of Phα1β (60 pmol/μL/h for 7 days) was able to reverse nerve injury-induced nociception from 1 to 7 days, but did not cause either behavioral side effects or histopathological changes in the central nervous system.

CONCLUSIONS: Thus, we have shown for the first time that the
continuous i.t. delivery of Phκ1β produces analgesia disconnected from toxicity in a relevant model of neuropathic pain, indicating that it is an effective and safe drug with a great potential to treat pain.