IMIDAZOLINE RECEPTOR 2 IS AN EFFECTIVE TARGET FOR NEUROPATHIC PAIN IN A MURINE MODEL OF BORTEZOMIB-INDUCED PERIPHERAL NEUROPATHY

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Bortezomib (BTZ) is a proteasome inhibitor used as first-line therapy for multiple myeloma. However, its administration induces the development of severe painful peripheral neuropathy (PPN). This painful condition is an important medical need since the available treatments are actually ineffective. We recently described a mice model of PPN that shares most of the conditions found in patients treated chronically with BTZ (Carozzi et al., 2013). In fact, BTZ determines dysfunction of all fiber types in sensory nerves and, at least in mice, alters the electrical activity of the spinal dorsal horn neurons. This alteration of the basal electrophysiological activity induces also relevant changes in the central nociceptive transmission. In this work we characterize the neuroprotective effects of an imidazoline receptor 2 ligand (CR4056) able to allosterically inhibit the activity of monoamine oxidase-A, a key enzyme in the regulation of neuropathic pain.
Wistar rats were treated with BTZ 0.20 mg/kg, 3 times a week for 8 weeks (i.v). Then CR4056 was orally administered in a curative schedule at 6 mg/kg, once a day, for 2 weeks. Gabapentin (100 mg/kg, daily, p.o.) and buprenorphine (28,8µg/kg, daily, s.c.) were used as internal analgesic standards. At the end of both BTZ and analgesic treatments, we measured the caudal and sciatic nerve conduction velocity (NCV), the morphological/morphometrical alterations in the caudal nerve and the neuropathic pain development.
BTZ treatment induced a significant impairment of sensory, but not motor NCV, slight hyperalgesia, significant mechanical allodynia and clearing of myelinated fibers in the caudal nerves. After two weeks of follow up animals did not spontaneously recover functional, morphological and behavioral abnormalities while the 2 weeks-treatment with CR4056 (but not with gabapentine and buprenorphine) significantly resolved BTZ-induced mechanical allodynia.
Results obtained show that CR4056 produces a marked analgesic effects against BTZ-induced neuropathic pain without signs of tolerance.

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