Relief of craniofacial and hind paw mechanical hyperalgesia by endothelin receptor antagonists during the development of cisplatin-induced neuropathic pain in mice

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Cisplatin, an antineoplasic drug widely used to treat solid tumors, especially those affecting ovaries, bladder, testes and lungs, causes neuropathic pain in about 50% of the patients that receive continued treatment. Like other forms of neuropathic pain, that induced by cisplatin is frequently refractory or poorly responsive to currently available therapies. The mechanisms underlying neuropathic pain are still poorly understood, but can vary considerably depending on its etiology. Endothelins have been shown to reverse sensory alterations induced by constriction-induced nerve injury and diabetes. This study assesses if treatment with endothelin receptor antagonists affects established mechanical hyperalgesia of the forehead and hind paw throughout the progression of cisplatin-induced neuropathy in mice.

Male Swiss mice received weekly injections of cisplatin (3 mg/kg, i.p.) for 4 weeks. Responsiveness to mechanical stimulation of the forehead (% frequency of withdrawal responses to 0.04 g von Frey filament) and hind paw (50% withdrawal threshold force – Dixon's up and down method) was assessed before cisplatin treatment (basal) and then again at Weeks 1, 2 and 4 thereafter. The influence of treatments with indomethacin (non-selective COX inhibitor, 1 mg/kg, i.p.) and gabapentin (antiepileptic drug, 10 mg/kg, s.c.) were evaluated to determine the inflammatory or neuropathic nature of the sensory changes induced by cisplatin. Other mice were treated with BQ-123 or BQ-788 (endothelin ET_A and ET_B receptor antagonists, respectively; 10 and 30 nmol, s.c. in neck scruff or i.pl. in hind paw). Another group of animals received Atrasentan (non-peptidic ET_A antagonist, i.p., 3 and 10 mg/kg). Control mice were similarly treated with the corresponding vehicle. All protocols were approved by UFSC's ethics committee.

Cisplatin induced sustained mechanical hyperalgesia of both forehead and hind paw, from week 1 onwards. Indomethacin was more effective in reducing mechanical hyperalgesia at Week 1 than at Week 2, but was ineffective at Week 4 in both regions, whereas gabapentin attenuated mechanical hyperalgesia at all time points examined. Mechanical hyperalgesia of the forehead was reduced by BQ-123 or BQ-788 at Weeks 1, 2 or 4, for up to 2-3 h each time. In contrast, both antagonists were only effective in reducing hind paw mechanical hyperalgesia at Week 1. Atrasentan treatment relieved forehead mechanical hyperalgesia at Weeks 1 and 2, but not 4, whereas was effective only at Week 1 against hind paw mechanical hyperalgesia.

Thus, mechanisms operated by endothelin ET_A and ET_B receptors are implicated to varying extents in maintenance of cisplatin-induced mechanical hyperalgesia of craniofacial and hind paw regions. Both receptors contribute to the inflammatory and neuropathic stages of sensory change in the forehead, whereas in the hind paw their contribution seems limited to the inflammatory phase only.

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