Oxaliplatin elicits mechanical and cold allodynia in rodents via TRPA1 receptor stimulation

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Platinum-based anticancer drugs cause neurotoxicity. In particular, oxaliplatin produces early-developing, painful, and cold-exacerbated paresthesias. However, the mechanism underlying these bothersome and dose-limiting adverse effects is unknown.

We hypothesized that the transient receptor potential ankyrin 1 (TRPA1), a cation channel activated by oxidative stress and cold temperature, contributes to mechanical and cold hypersensitivity caused by oxaliplatin and cisplatin. Oxaliplatin induces mechanical hyperalgesia via TRPA1 activation in Sprague–Dawley rats (male, 250 g). A single dose of oxaliplatin (OXA; 2 mg/kg, i.v.) produces a time-dependent reduction in the mechanical paw-withdrawal threshold. The compound labelled as HC-030031 (2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro -purin-7-yl)-N-(4-isopropyl-phenyl)-acetamide), is the most cited TRPA1 antagonist so far reported. At days 2 and 15, the treatment with HC-030031 (HC; 100 mg/kg, p.o.) completely reverses the mechanical hyperalgesia 60 minutes after dosing. Treatment with capsazepine (CPZ; 4 mg/kg, i.p.), which completely reverses mechanical hyperalgesia induced by capsaicin (CPS; 20 µg/50 µL/paw), does not affect mechanical hyperalgesia induced by OXA either at day 2 or day 15 after treatment. The same oxaliplatin administration caused mechanical and cold allodynia in C57BL/6 wild-type mice (Trpa1+/+)(male, 25 g). Both responses were absent in TRPA1-deficient mice (Trpa1−/−). Administration of cisplatin evoked mechanical allodynia, an effect that was reduced in TRPA1-deficient mice. TRPA1 is therefore required for oxaliplatin-evoked mechanical and cold hypersensitivity, and contributes to cisplatin-evoked mechanical allodynia. One single administration of oxaliplatin produced mechanical and cold hyperalgesia in rats, an effect selectively abated by the TRPA1 antagonist HC-030031. TRPA1 is therefore required for oxaliplatin-evoked mechanical allodynia, and cold hypersensitivity. These data provide novel insights for the study and development of new classes of molecules able to gate the TRPA1 channel for the treatment of neuropathic pain induced by platinum-based anticancer drugs.