

Research on the Roles of TRPA1 in the Cancer Chemotherapy-Induced Peripheral Neuropathy

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Summary

Oxaliplatin, a platinum-based chemotherapeutic agent, causes an unusual acute peripheral neuropathy triggered by cold in almost all patients during or within hours after its infusion, while its mechanisms are poorly understood. In this study, we examined the involvement of TRPA1, which is expressed mainly in primary sensory neurons and works as a chemical nociceptive sensor. A single i.p. administration of oxaliplatin (5 mg/kg) or its metabolite, oxalate (1.7 mg/kg), into mice induced cold hypersensitivity within 2 h, while other chemotherapeutic agents, cisplatin and paclitaxel, had no effect. The time course and drug sensitivity to analgesics support the possibility that oxaliplatin-induced cold hypersensitivity observed in mice may represent cold-triggered dysesthesia as clinical symptoms of oxaliplatin-induced acute peripheral neuropathy, rather than pain. The oxaliplatin-induced acute cold hypersensitivity was abolished by TRPA1 antagonist or deficiency. In addition, oxaliplatin enhanced the TRPA1-, but not TRPV1- and TRPM8-, mediated nociceptive behaviors, suggesting the involvement of the increased sensitivity of TRPA1. In hTRPA1-expressing cells, oxaliplatin evoked TRPA1 activation through reactive oxygen species (ROS) production and oxidative modification of N-terminal cysteine residues of TRPA1. However, it required a high concentration of oxaliplatin (1 mM) and cisplatin, another platinum-based agent, also evoked TRPA1 activation, suggesting other mechanisms should underlie acute peripheral neuropathy peculiar to oxaliplatin. To further explore the mechanism of oxaliplatin-induced TRPA1 sensitization, we found pretreatment with relatively-low concentration of oxaliplatin (100 μ M) or a membrane-permeable oxalate analog, dimethyl oxalate (30 μ M) increased the H₂O₂-evoked TRPA1-activation in cultured dorsal root ganglion (DRG) neurons and hTRPA1-expressing HEK293 cells, while a platinum-metabolite, Pt(DACH)Cl₂ (30 μ M) and cisplatin (100 μ M) had no effect. Furthermore, we found that oxaliplatin or oxalate induced TRPA1 sensitization by inhibition of prolyl hydroxylase (PHD)-mediated hydroxylation of a N-terminal proline residue (Pro³⁹⁴) in TRPA1, which is the same mechanism to hypoxia-induced TRPA1 activation. These results suggest that TRPA1 is a chemical sensor to oxaliplatin, which certainly produces dysesthesia as an acute peripheral neuropathy.