TRPV4 channel, in addition to TRPA1 mediates the oxidative stress-dependent peripheral painful neuropathy induced by vincristine

I.M. Marone[1], G. Trevisan[2], F. De Logu[1], C. Fusi[1], S. Materazzi[1], S. Benemei[1], R. Nassini[1], P. Geppetti[1]

[1]Dept. of Health Sciences, Clinical Pharmacology and Oncology Unit, University of Florence
[2]Laboratory of Cellular and Molecular Biology, Graduate Program in Health Sciences, University of the Extreme South of Santa Catarina (UNESC), Criciúma 88806-000, SC, Brazil

Several anticancer medicines, including vincristine, evoke sensory adverse events, collectively referred to as chemotherapy-induced peripheral neuropathies (CIPN), which are represented by sensory symptoms (from paresthesias, allodynia and hyperalgesia to severe pain). In addition to impairing patient quality of life, CIPN may lead to dose-limitation or even discontinuation of anticancer treatment. Transient receptor potential (TRP) channels expressed by sensory neurons, including the A1 (TRPA1), V1 (TRPV1) and V4 (TRPV4) appear to contribute to CIPN (Nassini et al. 2014). Recently, vincristine has been found to produce CIPN-like symptoms via TRPA1 (Old et al. 2014),TRPV4 has been reported to contribute to mechanical hypersensitivity evoked by paclitaxel, and here we we explored, the role of TRPV4 in a mouse model of vincristine-induced CIPN.

Behavioral test (Von frey hair and acetone test) were used to study the mechanical and cold hypersensitivity, respectively. In vitro, calcium responses evoked in cultured primary sensory neurons from rat/mouse dorsal root ganglia were investigated.

Vincristine-evoked (one single i.p. administration 0.2 mg/kg) CIPN-like behaviors were reduced but not abolished in TRPA1-deleted mice. Complete attenuation was obtained by treatment with the TRPV4 antagonist, HC-067047. Vice versa, CIPN-like behaviors evoked by vincristine were partially reduced in TRPV4-deleted mice and complete abolition was produced by the addition of the TRPA1 antagonist, HC-030031. The anti-oxidant alpha-lipoic acid or a combination of the two TRPA1 and TRPV4 antagonists also abated vincristine-evoked CIPN-like behaviors. In vitro, low concentrations of H_2O_2 evoked a selective TRPA1 calcium response. However, higher concentrations were able to engage the TRPV4 channel.

While we confirmed that TRPA1 contributes to the oxidative stress-dependent mechanical and cold hypersensitivity evoked by vincristine in mice, we discovered that TRPV4 also play a major role. The contribution of TRPV4 is supported by the ability of reactive oxygen species to target this channel in primary sensory neurons.

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