

4-ONE, a product of lipid peroxidation, has both TRPA1 receptor dependent and independent effects

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We investigated the role of TRPA1 receptors as an emerging sensory nerve activating system in mediating peripheral pain and inflammatory oedema. Excess reactive oxygen species (ROS) production at inflammatory sites leads to the production of reactive chemicals such as 4-oxo-2-nonenal (4-ONE), a product of lipid peroxidation. 4-ONE was shown to be a potent TRPA1 receptor agonist *in vitro*⁽¹⁾ and we have demonstrated that it induces dose-dependent unilateral mechanical hyperalgesia and oedema formation *in vivo*. It was our aim to learn more about the *in vivo* effects of TRPA1 receptor activation by 4-ONE. To that end we utilised wildtype (WT) and TRPA1 knockout (KO) mice.

Mechanical hyperalgesic thresholds in the hindpaws of wild-type (WT) and TRPA1 KO mice were determined using a dynamic plantar aesthesiometer. Paw withdrawal thresholds (g) were measured in either hindpaw at baseline and up to 24 h post-injection of 4-ONE (10nmol/paw) or vehicle (1% ethanol, contralateral paw). Oedema formation was assessed by comparing the mean paw mass (mg) of 4-ONE treated with that of vehicle treated hindpaws. 4-ONE (10nmol/paw) induces mechanical hyperalgesia in WT mice from 0.5 h to 6 h postinjection, whereas TRPA1 KO mice only develop mechanical hyperalgesia from 1 h to 4 h postinjection. Paw mass (mg) of 4-ONE treated hindpaws was significantly increased compared to that of vehicle treated hindpaws at 24 h postinjection in both WT and TRPA1 KO mice (WT: 138.7±3.6, vehicle vs. 161.6±7.0, 4-ONE, n = 8, p<0.05 paired t-test; KO: 143.3±4.9, vehicle vs. 168.2±7.1, 4-ONE, n = 8, p<0.05 paired t-test).

This data indicates that activation of TRPA1 receptors triggers the development of mechanical hyperalgesia *in vivo*. It also highlights that whilst 4-ONE was shown to be a selective and potent TRPA1 receptor agonist *in vitro* it has both TRPA1 receptor dependent and independent effects *in vivo*.

(1) Andersson *et al.*, *J Neurosci.* 2008 , **28**, 2485-94.

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