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Coexpression of Vanilloid Receptor Subtype-1 and Acid-sensing Ion Channel Genes in the Human Trigeminal Ganglion Neurons

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Previous psychophysical experiments have shown that repeated applications of high concentrations of acids on one side of the dorsal surface of the human tongue evoke irritation or pain (Dessirier *et al.*, 2000). Under acidification, protons dissociated from the acids probably activate excitatory cation channels expressed in local nociceptors that originate from trigeminal ganglia, leading to the generation of such sensations. Recent molecular investigations into sensory neurons have revealed that a transient receptor potential/vanilloid receptor subtype-1 (TRPV1) and an acid-sensing ion channel (ASIC) mediate the greater part of proton-induced irritation or nociception in mammals (Julius and Basbaum, 2001; Ugawa *et al.*, 2003). Here we provide evidence for involvement of both channels in acid-evoked pain in humans and show their relative contributions to acid-evoked nociception. In our human pain model (approved by the Ethics Committee of Nagoya City University and conducted in accordance with the Declaration of Helsinki), direct infusion of acidic solutions ($pH \geq 6.0$) into human skin caused localized pain, which was blocked by amiloride, an inhibitor of ASICs, but not by capsazepine, an inhibitor of TRPV1. Although the efficacy of amiloride was only partially attenuated under more severe acidification (pH 5.0), capsazepine produced some blocking effect on pH 5-evoked pain. Amiloride itself neither blocked capsaicin-evoked localized pain in human skin nor inhibited proton-induced currents in TRPV1-expressing *Xenopus* oocytes (Ugawa *et al.*, 2003). *In situ* hybridization histochemistry demonstrated that more than half of TRPV1-expressing dorsal root ganglion neurons were ASIC1a- or ASIC3-positive in the rat, and that approximately half of TRPV1-expressing human trigeminal neurons were ASIC-positive (S. Ugawa, T. Ueda and S. Shimada, submitted for publication). These results suggest that ASICs are the leading acid sensors in human nociceptors and that both TRPV1 and ASIC channels are involved in acid-evoked oral irritation or pain.

References

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