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The role of TRPA1 and TRPM8 channels in vascular responses to cold

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KEY WORDS: TRPA1, cold, TRPM8, vascular response

It is well-known that cold induces vasoconstriction in skin blood vessels as a protective response against heat loss. This phenomenon is thought to be mediated by an efferent reflex to the activation of cold-sensitive afferent nerves in the skin. In contrast to this view, we found in *ex vivo* myography experiments that cooling to 10 ºC induced a 28 ± 3,01% contraction in endothelium-denuded plantar arteries dissected from wild type (WT) mice. Cold produced a significantly smaller vasoconstriction in the presence of the TRPA1 inhibitor HC030031 (9 ± 2,23%), and in arteries dissected from *Trpa1* (11,04 ± 2,78%) or *Trpm8* (10 ± 1,54%) knockout (KO) animals. Application of HC030031 virtually abolished the responses to cold in arteries from *Trpm8* KO (2 ± 1,13%). Neither TRPA1 nor TRPM8 channels could be detected in vascular smooth muscle cells, suggesting that the effects of cold are mediated by activation of these channels in perivascular sensory and/or sympathetic nerves. Cold-induced vasoconstriction was potentiated in the presence of the CGRP receptor inhibitor BIBN 4096 (40 ± 4,26%) and reduced after depletion of catecholamines from the sympathetic nerve terminals with guanethidine (9 ± 2,6%). Cold had no effect in arteries were incubated with both BIBN 4096 and guanethidine. We detected mRNA of both TRPA1 and TRPM8 channels in sympathetic ganglia isolated from WT mice and we could confirm the presence of perivascular sympathetic nerves in confocal images of plantar arteries labelled with an anti-TH antibody. Taken together, our data demonstrates that cold has a dual action, mediated by both vasodilatory and a vasoconstrictor responses via the activation of TRPA1 and TRPM8 channels. To our knowledge, our results represent the first evidence for an intrinsic response to cold in cutaneous arteries and for the presence and the functional role of sensory TRP channels in efferent nerve fibers.

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