Multiple evidence shows that nicotinic acid can prevent myocardial infarction.\(^1\) The mechanisms underlying the antiatherogenic effects of nicotinic acid have been disputed during the past decades, and there is evidence for beneficial effects on plasma lipid levels, as well as for anti-inflammatory effects.\(^1\)–\(^4\) Nicotinic acid has been suggested as an add-on therapy to the well-established statins for prevention of cardiovascular disease. However, recent clinical data indicate no additional benefit of nicotinic acid treatment in high-risk patients under optimal statin therapy,\(^5\)\(^,\)\(^6\) and it is currently only recommended in patients in whom statins cannot be given or do not lead to sufficient changes in plasma lipid levels. The most important unwanted effect of nicotinic acid is a transient skin irritation called flushing.\(^7\)\(^,\)\(^8\) Although harmless, it causes many patients to discontinue nicotinic acid therapy. Flushing has a vascular component consisting of a cutaneous vasodilation resulting in a reddening and warming of the skin. This is accompanied by a sensory component that includes tingling and burning sensations in the skin. Past research has shown that, in particular, the vascular component of flushing is mediated by the hydroxyccarboxylic acid receptor 2 (HCA2), also known as G-protein–coupled receptor 109A (GPR109A), expressed in epidermal Langerhans cells and in keratinocytes known as the capsaicin receptor 1, is a cation channel activated by nicotinic acid, mediating nicotinic acid–induced flushing. TRPV1, also (TRP) channel TRPV1 as a new direct target of nicotinic acid, shows that TRPV1 respond to nicotinic acid given orally or intraperitoneally. Also, it would be important to test whether flushing in response to other HCA2 agonists, including fumaric acid esters, is also affected in TRPV1-deficient mice. An inconsistency of the study arises from the observation that nicotinic acid showed rather low potency with regard to its TRPV1-activating activity in in vitro experiments. The intracellular nicotinic acid concentration required to activate mouse TRPV1 (EC\(_{50}=62\) mmol/L) is \(\approx 3\) orders of magnitude higher than the reported plasma concentrations in mice and men. One would have to postulate an active uptake mechanism to achieve high (millimolar) concentrations in cells. Given this low potency, it cannot be excluded that the regulation of TRPV1 in in vitro experiments is rather because of the physicochemical properties of nicotinic acid, and the authors report about a strong drop in the intracellular pH after addition of high doses of nicotinic acid, which by itself may alter TRPV1 activity. When studying the human TRPV1 channel in vitro, Ma et al\(^15\) however found that nicotinic acid has a higher potency toward the human TRPV1 and that intracellular application of nicotinic acid at concentrations that can be reached in the plasma of treated patients increases the temperature sensitivity of human TRPV1 in vitro. Although the mouse experiments in vivo and the extremely low potency of nicotinic acid toward the murine TRPV1 in vitro are difficult to reconcile, the higher sensitivity of the human TRPV1 makes it a potential target for nicotinic acid in treated patients. Given the central role of TRPV1 in sensing noxious stimuli, nicotinic acid–induced TRPV1 activation may, in particular, contribute to the sensory aspect of flushing induced by nicotinic acid and other agents, including fumaric acid esters. Given the evidence that nicotinic acid and similar flush-inducing drugs require activation of HCA2 to

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In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Ma et al\(^15\) propose the transient receptor potential (TRP) channel TRPV1 as a new direct target of nicotinic acid, mediating nicotinic acid–induced flushing. TRPV1, also known as the capsaicin receptor 1, is a cation channel activated by temperatures >43°C and by low pH, as well as by several compounds including capsaicin, the pungent component of hot chili peppers.\(^16\) It is a central integrator of thermal and chemical signals on nociceptive neurons, and its sensitivity to noxious stimuli can be increased by inflammatory mediators such as prostaglandins and bradykinin through indirect intracellular signaling pathways mediated by activation of G-protein–coupled receptors.\(^9\) However, TRPV1 is also expressed on many non-neuronal cells including keratinocytes where its activation can regulate cell function.\(^17\) Ma et al\(^15\) now show that nicotinic acid–induced flushing is strongly reduced in mice lacking TRPV1. In addition, they demonstrate that nicotinic acid, when applied intracellularly, results in a left shift of the temperature dependence of TRPV1, causing a fraction of TRPV1 channels to be activated at normal body temperature. Although this study identifies an interesting new component of the nicotinic acid–induced flushing mechanism, several open questions remain. The authors used in their in vivo experiments a subcutaneous application route of nicotinic acid resulting in a rather delayed onset of the increase in cutaneous perfusion as measured with a laser Doppler probe. This approach is different from most other studies performed to date, and it would be interesting to see how mice lacking TRPV1 respond to nicotinic acid given orally or intraperitoneally. Also, it would be important to test whether flushing in response to other HCA2 agonists, including fumaric acid esters, is also affected in TRPV1-deficient mice. An inconsistency of the study arises from the observation that nicotinic acid showed rather low potency with regard to its TRPV1-activating activity in in vitro experiments. The intracellular nicotinic acid concentration required to activate mouse TRPV1 (EC\(_{50}=62\) mmol/L) is \(\approx 3\) orders of magnitude higher than the reported plasma concentrations in mice and men. One would have to postulate an active uptake mechanism to achieve high (millimolar) concentrations in cells. Given this low potency, it cannot be excluded that the regulation of TRPV1 in in vitro experiments is rather because of the physicochemical properties of nicotinic acid, and the authors report about a strong drop in the intracellular pH after addition of high doses of nicotinic acid, which by itself may alter TRPV1 activity. When studying the human TRPV1 channel in vitro, Ma et al\(^15\) however found that nicotinic acid has a higher potency toward the human TRPV1 and that intracellular application of nicotinic acid at concentrations that can be reached in the plasma of treated patients increases the temperature sensitivity of human TRPV1 in vitro. Although the mouse experiments in vivo and the extremely low potency of nicotinic acid toward the murine TRPV1 in vitro are difficult to reconcile, the higher sensitivity of the human TRPV1 makes it a potential target for nicotinic acid in treated patients. Given the central role of TRPV1 in sensing noxious stimuli, nicotinic acid–induced TRPV1 activation may, in particular, contribute to the sensory aspect of flushing induced by nicotinic acid and other agents, including fumaric acid esters. Given the evidence that nicotinic acid and similar flush-inducing drugs require activation of HCA2 to
induce full flushing and that this involves formation of prostanoids, it may be interesting to test whether HCA₂-mediated formation of prostanoids in cells of the epidermis results in the sensitization of TRPV1 on primary afferent nociceptors of the skin.

What are the potential clinical applications of the study? Clearly, additional work is required to determine the role of TRPV1 in the vascular and sensory component of the flushing response induced by drugs such as nicotinic acid and dimethyl fumarate. There are ongoing efforts to develop antagonists or negative modulators of TRPV1, and it would be interesting to see whether they affect flushing in animals and humans. If they do so, do they affect the vascular or the sensory component or both? In addition, it may be interesting to try TRPV1 antagonists in addition to existing flush inhibitors such as cyclooxygenase inhibitors or the DP receptor antagonist laropiprant to test whether their effects are additive or not. With nicotinic acid and dimethyl fumarate, 2 drugs are now in clinical practice, which cause similar flushing responses as unwanted effects. Any new insight into the mechanisms underlying, in particular, the unpleasant sensory component of flushing is of great importance to find new ways to mitigate flushing and to increase patient compliance. The work by Ma et al will certainly inspire studies to explore further the involvement of TRPV1 in drug-induced flushing and to search for new ways to blunt the flushing response.

Disclosures

None.

References

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