Role of keratinocytes GPR109A and COX-2 in nicotinic acid and mono-methyl fumarate induced flushing

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Abstract

The anti-dyslipidemic drug nicotinic acid and the anti-psoriatic drug mono-Methyl fumarate induce cutaneous flushing through the activation of the G-protein-coupled receptor GPR109A. Flushing is a troublesome side effect of nicotinic acid, but may be a direct reflection of the wanted effects of mono-Methyl fumarate. Here we analysed the mechanisms underlying GPR109A-mediated flushing and show that both Langerhans cells and keratinocytes express GPR109A. Using cell ablation approaches and transgenic cell type-specific expression of GPR109A in Gpr109a$^{-/-}$ mice, we provide evidence that the early phase of flushing depends on GPR109A expressed on Langerhans cells, whereas the late phase is mediated by GPR109A expressed on keratinocytes. Interestingly, the first phase of flushing is blocked by a selective cyclooxygenase-1 (COX-1) inhibitor, and the late phase is sensitive to a selective COX-2 inhibitor. Both, mono-Methyl fumarate and nicotinic acid, induce PGE_2 formation in isolated keratinocytes through activation of GPR109A and COX-2. Thus, early and late phases of the GPR109A-mediated cutaneous flushing reaction involve different epidermal cell types and prostanoid forming enzymes. These data will help to guide new efficient approaches to mitigate nicotinic acid-induced flushing and may help to exploit the potential anti-psoriatic effects of GPR109A agonists in the skin.