Pharmacology & Therapeutics 136 (2012) 1–7

Contents lists available at SciVerse ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Role of HCA_2 (GPR109A) in nicotinic acid and fumaric acid ester-induced effects on the skin

Julien Hanson [a,b,*], Andreas Gille [c,1], Stefan Offermanns [d,e]

[a] Molecular Pharmacology, GIGA-Signal Transduction Unit, University of Liège, CHU, B34 (+4), 4000 Liège, Belgium
[b] Medicinal Chemistry, Drug Research Center-CIRM, University of Liège, Belgium
[c] Institute for Experimental and Clinical Pharmacology and Toxicology, University of Heidelberg, Medical Faculty Mannheim, Maybachstrasse 14, 68169 Mannheim, Germany
[d] Department of Pharmacology, Max-Planck-Institute for Heart and Lung Research, Ludwigstrasse 43, 61231 Bad Nauheim, Germany
[e] Medical Faculty, Goethe University Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany

ARTICLE INFO

Keywords:
Nicotinic acid
Monomethyl fumarate
Flushing
Psoriasis
HCA_2
Keratinocytes
Cyclooxygenase

ABSTRACT

Nicotinic acid (NA) and fumaric acid esters (FAE) such as monomethyl fumarate or dimethyl fumarate are drugs that elicit a cutaneous reaction called flushing as a side effect. NA is used to reduce progression of atherosclerosis through its anti-dyslipidemic activity and lipid-independent mechanisms involving immune cells, whereas FAE are used to treat psoriasis via largely unknown mechanisms. Both, NA and FAE, induce flushing by the activation of the G-protein-coupled receptor (GPCR) Hydroxy-carboxylic acid receptor 2 (HCA_2, GPR109A) in cells of the epidermis. While the wanted effects of NA are at least in part also mediated by HCA_2, it is currently not clear whether this receptor is also involved in the anti-psoriatic effects of FAE. The HCA_2-mediated flushing response to these drugs involves the formation of prostaglandins D_2 and E_2 by Langerhans cells and keratinocytes via COX-1 in Langerhans cells and COX-2 in keratinocytes. This review summarizes recent progress in the understanding of the mechanisms underlying HCA_2-mediated flushing, describes strategies to mitigate it and discusses the potential link between flushing, HCA_2 and the anti-psoriatic effects of FAE.

Contents

1. Introduction

Nicotinic acid (NA) (Fig. 1) belongs to the B vitamin class (B_3) and has originally been used to treat pellagra, a disease caused by chronic deficiency of vitamin B_3. Rudolf Altschul et al. were the first to describe the effect of NA on human lipid metabolism (Altschul et al., 1955), and for almost 50 years NA has been used to treat dyslipidemia and to reduce cardiovascular risk. NA has beneficial effects on plasma levels of all major lipids decreasing total cholesterol, LDL-cholesterol, triglycerides and

Abbreviations: NA, nicotinic acid; FAE, fumaric acid ester; GPCR, G-protein-coupled receptor; HCA_2, hydroxy-carboxylic acid receptor 2; PG, prostaglandin; COX, cyclooxygenase; MMF, monomethyl fumarate; DMF, dimethyl fumarate; $cPLA_2$, cytosolic phospholipase A_2; GRK, GPCR kinase; FFA, free fatty acid.

* Corresponding author at: Molecular Pharmacology, GIGA-Signal Transduction, University of Liege, CHU, B34, Tour GIGA (+4), 1, av. de l'Hopital, B-4000 Liege, Belgium. Tel.: +32 43664748; fax: +32 43664362.
E-mail address: J.Hanson@ulg.ac.be (J. Hanson).
[1] Present address: CSL Limited, 45 Poplar Road, 3052 Parkville, Australia.

0163-7258/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2012.06.003

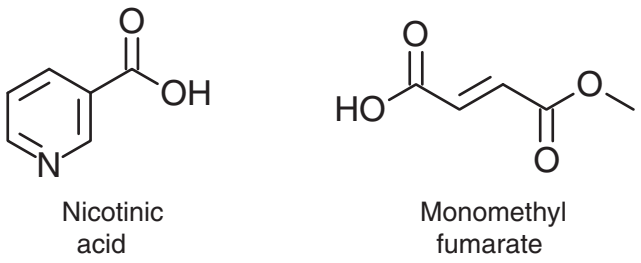

Fig. 1. Structures of nicotinic acid and monomethyl fumarate.

lipoprotein(a), while increasing HDL-cholesterol levels (Knopp et al., 1998; Goldberg et al., 2000; Carlson, 2006). Notably, NA is currently the most efficacious drug available to increase HDL-cholesterol levels (Brown & Zhao, 2008; Digby et al., 2009), and it was the first drug shown to reduce mortality in patients with coronary artery disease (Canner et al., 1986). The mechanism by which NA affects dyslipidemia and progression of atherosclerosis has been reviewed elsewhere (Gille et al., 2008; Kamanna & Kashyap, 2008; Lukasova et al., 2011a).

Monomethyl fumarate (MMF) (Fig. 1) has been used in combination with other fumaric acid esters (FAE) in the treatment of psoriasis and has been shown to reduce the keratinocytes proliferation and the infiltration of the dermis and epidermis by inflammatory cells in patients affected with psoriasis (Mrowietz & Asadullah, 2005). The German chemist Schweckendiek, who suffered from psoriasis himself, postulated that the cause of the disease was a defect in the citric acid cycle, of which fumaric acid is an intermediate, and he reported that FAE taken orally had an anti-psoriasis effect (Schweckendiek, 1959). Following subsequent studies supporting the anti-psoriatic activity of these preparations (Schäfer, 1984), FAE have been available since 1994 in German-speaking countries as a commercial preparation of which dimethyl fumarate (DMF) is the principal active component (Fumaderm®). Following oral application, DMF is rapidly converted by first-pass metabolism to the monoester, which is thought to be the active form (Rostami Yazdi & Mrowietz, 2008). Clinical trials have demonstrated that FAE reduce the psoriatic lesion area and the severity index after 12–16 weeks of treatment, and are considered to be safe as a long term treatment (Mrowietz et al., 1998; Gollnick et al., 2002; Hoefnagel et al., 2003; Reich et al., 2009; Wain et al., 2009).

It has recently been shown that skin flushing induced by MMF and NA occurs in both cases due to the activation of the G-protein-coupled receptor HCA_2 and involves identical cellular mechanisms (Hanson et al., 2010).

In this review, we summarize the mechanism of skin flushing and discuss the implication of the epidermal effects of the HCA_2 agonists NA and MMF with regard to their clinical use.

2. HCA_2

The receptor activated by NA and MMF, formerly named GPR109A or HM74a in humans and PUMA-G in mice, has recently been renamed by an IUPHAR nomenclature committee as hydroxy-carboxylic acid (HCA) receptor-2 (HCA_2) (Offermanns et al., 2011). HCA_2 belongs to the group of G-protein-coupled receptors and was listed as an orphan receptor after its cloning in 1993 (Nomura et al., 1993). In 2003, HCA_2 was shown to be a receptor for NA (Soga et al., 2003; Tunaru et al., 2003; Wise et al., 2003) and to mediate the antilipolytic effects of NA. Using mice lacking HCA_2, Benyó et al. subsequently showed that binding of NA to the receptor was also responsible for the cutaneous vasodilation observed during flushing (Benyó et al., 2005). Additionally, in 2008, Tang et al. showed in vitro that MMF was a potent full agonist of HCA_2 receptors whereas DMF was inactive (Tang et al., 2008). Whether the HCA_2 receptor is involved in the anti-psoriatic effects of FAE and whether NA has anti-psoriatic effects are still open questions (vide infra). HCA_2 is coupled to the G_i family of G-proteins (Aktories et al., 1980) and activates various downstream effectors depending on the cell type. In immune cells, activation of HCA_2 leads via the $G\beta\gamma$-complex to an activation of phospholipase C-β and an increase of intracellular Ca^{2+} (Exton, 1996; Rhee, 2001; Gille et al., 2008). In adipocytes, activation of the receptor results in $G\alpha_i$-mediated inhibition of adenylyl cyclase and subsequently of protein kinase A, resulting in reduced lipolysis and decreased release of free fatty acids into the circulation (Tunaru et al., 2003; Zhang et al., 2005). HCA_2 is expressed in white and brown adipose tissue, keratinocytes and various immune cells including monocytes, macrophages, neutrophils and dendritic cells including Langerhans cells (Soga et al., 2003; Wise et al., 2003; Maciejewski-Lenoir et al., 2006; Gille et al., 2008; Hanson et al., 2010). The most homologous protein to HCA_2 is HCA_3, which is found in humans but not in rodents and shares 96% homology with HCA_1. Reports suggest that this receptor is expressed in a pattern similar to HCA_1 in adipose tissue, neutrophils, monocytes and macrophages thus potentially providing an alternative therapeutic target (Bermudez et al., 2011; Offermanns et al., 2011).

3. HCA_2-mediated cutaneous effects

3.1. Flushing

Flushing in response to NA was first described by investigators who were treating patients with NA for pellagra (Smith et al., 1937; Spies et al., 1938). It is characterized by redness and warmth due to vasodilation of dermal blood vessels, and by various sensory phenomena such as tingling and burning. The flushing phenomenon lasts typically for an hour and usually starts in the head region thereafter expanding to the arms and trunk, and sometimes to legs and feet. In both humans and mice, the increase in dermal blood perfusion in response to nicotinic acid occurs in a biphasic fashion; a relatively short first phase is followed by a longer lasting second phase (Goldsmith & Cordill, 1943; Benyó et al., 2005). Although benign, the discomfort associated with flushing causes between 5% and 20% of patients taking NA to discontinue the treatment (Gray et al., 1994; Jacobson, 2010). Because the use of NA is greatly compromised by its major side effect, it is of clinical relevance to improve our understanding of the mechanism responsible for NA-induced flushing.

Although MMF has only recently been identified as an HCA_2 agonist (Tang et al., 2008), flushing is known as a side effect of FAE since early clinical studies and has led to the discontinuation of treatment in some patients (van Dijk, 1985; Nieboer et al., 1989; Nieboer et al., 1990). In a mouse model of flushing, MMF has been shown to elicit an HCA_2-mediated flushing response, with a mechanism identical to NA-mediated flushing (Hanson et al., 2010).

3.2. The epidermis as a site of flush initiation

The fact that local application of NA esters like methyl nicotinate or benzyl nicotinate to the skin surface produced a localized flushing response (Tur et al., 1983) indicates that the mechanism underlying the flushing response is confined to the skin. This hypothesis was supported by the finding that HCA_2 is expressed in the epidermis, in particular in keratinocytes (Tang et al., 2008; Dunbar & Gelfand, 2010; Hanson et al., 2010; Bermudez et al., 2011) and Langerhans cells (Benyó et al., 2006; Maciejewski-Lenoir et al., 2006). The epidermis is avascular and consists mainly of keratinocytes arranged in a stratified squamous epithelium. It is the interface between the environment and the organism, and is a first-line defense system in contact with potential pathogens. Langerhans cells are specialized epidermal dendritic cells that make up to 2–4% the total epidermal cell population. They establish dense networks within the basal and supra-basal layers of the epidermis and serve their function by uptake and presentation of antigens. Following antigen contact, Langerhans cells become activated and migrate from