Review

Nicotinic acid (niacin): new lipid-independent mechanisms of action and therapeutic potentials

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Nicotinic acid (niacin) has been used for decades to prevent and treat atherosclerosis. The well-documented antiatherogenic activity is believed to result from its antidyslipidemic effects, which are accompanied by unwanted effects, especially a flush. There has been renewed interest in nicotinic acid owing to the need for improved prevention of atherosclerosis in patients already taking statins. In addition, the identification of a nicotinic acid receptor expressed in adipocytes and immune cells has helped to elucidate the mechanisms underlying the antiatherosclerotic as well as the unwanted effects of this drug. Nicotinic acid exerts its antiatherosclerotic effects at least in part independently of its antidyslipidemic effects through mechanisms involving its receptor on immune cells as well as through direct and indirect effects on the vascular endothelium. Here, we review recent data on the pharmacological effects of nicotinic acid and discuss how they might be harnessed to treat other inflammatory diseases such as multiple sclerosis or psoriasis.

Nicotinic acid

Niacin, which refers to nicotinic acid and nicotinamide, is required at doses of 15–20 mg/day as a vitamin. However, when nicotinic acid, but not nicotinamide, is given in supraphysiological doses, it exerts a variety of pharmacological effects. Shortly after the introduction of nicotinic acid as a treatment of niacin deficiency (pellagra), it was observed that nicotinic acid induces a flush [1]. Later, Altschul *et al.* and Carlson showed that nicotinic acid also affects plasma levels of cholesterol, free fatty acids and triglycerides [2,3]. Thereafter, nicotinic acid has been established as a broad spectrum lipid-modulating drug which increases high-density lipoprotein (HDL) cholesterol levels and decreases plasma levels of triglycerides, low-density lipoprotein (LDL) cholesterol and lipoprotein(a) [4]. These lipid-modifying effects are accompanied by antiatherosclerotic effects. In fact, nicotinic acid was the first cholesterol-lowering drug shown to decrease cardiovascular events, cardiovascular mortality and all-cause mortality (The Coronary Drug Project [5,6]). The flush response has remained the major unwanted effect of nicotinic acid therapy. Although harmless, it can affect patients' adherence to therapy [7,8].

With the optimization of statin-based LDL cholesterol-lowering therapy during the past two decades and the realization that even under maximally decreased LDL cholesterol levels, a considerable cardiovascular risk remains [9], the search for drugs with an additional benefit to statins has been intensified. Nicotinic acid, which strongly increases HDL cholesterol levels and has a well-documented clinical efficacy, has attracted new interest. The discovery of the nicotinic acid receptor GPR109A, which has recently been renamed hydroxy-carboxylic acid (HCA) receptor 2 (HCA_2) [10] has led to new research activities into the mechanisms through which nicotinic acid exerts its pharmacological effects [7,11]. Recent studies have shown that the nicotinic acid receptor is expressed in various cells including adipocytes, several types of immune cells and keratinocytes. Evidence suggests that nicotinic acid has lipid-independent anti-inflammatory effects [12,13]. In addition, the anti-inflammatory drug monomethyl fumarate has been shown to be a full agonist of the nicotinic acid receptor [14]. These findings have initiated research activities to improve antiatherogenic therapeutic approaches with fewer unwanted effects and to explore the potential of the nicotinic acid receptor as a therapeutic target in other diseases involving inflammatory processes.

This review will summarize recent advances in the understanding of the pharmacological effects of nicotinic acid and will, in particular, focus on the pharmacological potential of nicotinic acid beyond its lipid-modifying activity.

Antidyslipidemic effects

Nicotinic acid has the remarkable ability to increase HDL cholesterol levels while decreasing triglyceride, LDL cholesterol and lipoprotein(a) levels, thereby improving the total plasma lipid profile. Although the mechanisms underlying the changes in plasma lipids in response to nicotinic acid have been studied for several decades, they have remained incompletely understood [7,9,11]. One of the well-studied activities of nicotinic acid is its antilipolytic

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effect mediated by the activation of the nicotinic acid receptor HCA_2 (GPR109A) on adipocytes and resulting in a decreased release of free fatty acids from fat tissue [3,15]. It has been suggested that the antilipolytic effect is involved in the modulation of the triglyceride and very-low-density lipoprotein (VLDL) metabolism by nicotinic acid. In this model, the reduced free fatty acid flux from adipocytes to the liver decreases VLDL-triglyceride production and subsequently results in decreased LDL cholesterol plasma levels [3,16] (Figure 1). There is also evidence that nicotinic acid enhances the clearance of triglyceride-rich lipoproteins such as VLDL [17]. Interestingly, the nicotinic acid-induced decrease in free fatty acid supply to the liver has recently been shown to suppress hepatic expression of PPARγ coactivator-1β (PGC-1β) and apolipoprotein C3 (APOC3), which is expected to reduce the production and to increase the turnover of VLDL [18] (Figure 1). It has also been shown *in vitro* that nicotinic acid can inhibit diacylglycerol acyltransferase 2, an enzyme involved in triglyceride synthesis [11]; however, it remains unclear whether this mechanism is of relevance *in vivo*.

Compared with the mechanism mediating nicotinic acid effects on triglyceride and VLDL/LDL, the processes underlying the elevation of HDL cholesterol activity by nicotinic acid are less clear. In humans, evidence has demonstrated that nicotinic acid decreases the clearance of HDL-apolipoprotein A1 (HDL-ApoAI) [19,20]. This is consistent with the observation that very high concentrations of nicotinic acid can reduce HDL uptake by a hepatic cell line *in vitro* [11]. More recently, nicotinic acid has been reported to upregulate ApoAI formation without affecting HDL-ApoAI clearance [17]. It is also possible that the decreased triglyceride content of ApoB-containing lipoproteins results in a decreased exchange of triglycerides for cholesteryl esters from HDL particles mediated by the cholesterol ester transfer protein (CETP) which would result in an increased HDL cholesterol level [9,21]. Consistent with this, the nicotinic acid-induced increase in HDL cholesterol levels has been shown to require the presence of CETP [22,23]. However, a partial agonist of the nicotinic acid receptor, MK0354, reduced plasma free fatty acid levels but did not induce an increase in HDL cholesterol levels [24]. This may be due to the lower efficacy of MK0354 compared with nicotinic acid, or it may indicate that a reduced free fatty acid supply to the liver is not a central mechanism involved in the modulation of HDL cholesterol plasma levels by nicotinic acid.

Although there is a strong inverse correlation between the plasma levels of HDL cholesterol and the risk for coronary heart disease [9,25], direct evidence for a beneficial role of an increase in HDL cholesterol plasma levels is still missing [26]. Recent experimental and clinical data indicate that the composition of HDL particles independent of its plasma concentration can affect the progression of chronic vascular diseases and that, for instance, the ability of HDL to promote cholesterol efflux from macrophages is a better predictor of atherosclerotic burden than the HDL cholesterol plasma concentration [27–29]. A recent study showed that HDL from nicotinic acid-treated patients moderately increased cholesterol efflux from macrophages, but nicotinic acid treatment did not improve the anti-inflammatory properties of HDL when tested *in vitro* [30]. HDL isolated from patients suffering from type 2 diabetes mellitus and treated with nicotinic acid showed improved endothelial-protective properties compared with HDL from untreated patients [31]. Future work has to clarify whether nicotinic acid can affect the functional

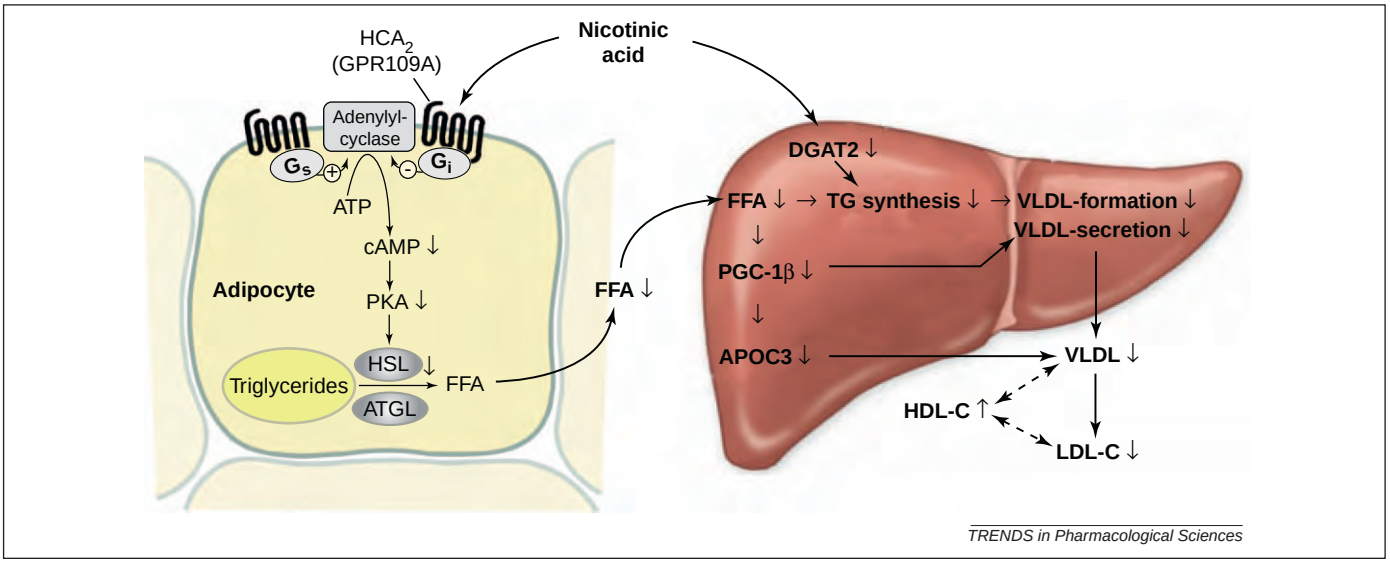

Figure 1. Potential mechanisms underlying the antidyslipidemic effects of nicotinic acid. Activation of the nicotinic acid receptor HCA_2 on adipocytes via the heterotrimeric G protein, G_i, leads to inhibition of adenylyl cyclase. Decreased cAMP levels via reduced activation of protein kinase A (PKA) results in an inhibition of lipolysis. Owing to this antilipolytic effect, free fatty acid (FFA) plasma levels drop, and triglyceride (TG) synthesis in the liver is reduced resulting in decreased very-low-density lipoprotein (VLDL) formation. A reduced supply of FFAs to the liver also suppresses hepatic expression of PPARγ coactivator-1β (PGC-1β) and of apolipoprotein C3 (APOC3). Decreased PGC-1β expression reduces VLDL formation and secretion. Under *in vitro* conditions, nicotinic acid has also been shown to inhibit triglyceride synthesis by a direct inhibitory effect on diacylglycerol acyltransferase 2 (DGAT2). The reduced expression of APOC3 may contribute to the decrease in VLDL levels by increasing VLDL turnover. Reduced VLDL levels result in reduced LDL cholesterol levels. How HDL cholesterol levels increase in unclear. This effect may be due to decreased expression of the cholesterol ester transfer protein (CETP) or the decreased exchange of triglycerides from VLDL and LDL particles against cholesterol esters of HDL particles. HSL, hormone sensitive lipase; ATGL, adipocyte triglyceride lipase. For details, see text.

properties of HDL particles and whether this contributes to the pharmacological effects of nicotinic acid.

Lipid-independent beneficial effects

Beneficial effects of nicotinic acid have historically been regarded as a result of its lipid-modifying activity. However, recent evidence in various *in vivo* animal models showed that nicotinic acid can also inhibit vascular inflammation and progression of atherosclerosis independently of changes in plasma lipids [12,13,32]. In these studies, treatment of atherosclerosis-prone mice with nicotinic acid reduced the progression of atherosclerosis in the absence of significant changes in plasma lipids. Similarly, in rats, nicotinic acid improved endothelial dysfunction and inhibited vascular inflammation independently of lipid changes. These antiatherosclerotic and anti-inflammatory effects were accompanied by a reduced infiltration of the vessel wall by immune cells such as macrophages and neutrophils, which both express the nicotinic acid receptor HCA_2 (GPR109A) [12,13,32]. An involvement of HCA_2 expressed by immune cells is suggested by the fact that the antiatherosclerotic effect of nicotinic acid in LDL receptor-deficient mice is absent in bone marrow chimeras which have received bone marrow from HCA_2-deficient mice, and that the recruitment of wild-type macrophages (but not HCA_2-deficient macrophages) to atherosclerotic lesions is inhibited by nicotinic acid [13].

In different *in vivo* animal models of acute and chronic vascular inflammation, nicotinic acid has been shown to reduce the expression of endothelial adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1) or of chemokines such as monocyte chemotactic protein 1 (MCP-1) [12,13], a phenomenon also observed in endothelial cells *in vitro* [12,33,34]. It has been suggested that the inhibition of VCAM-1 expression by nicotinic acid and the beneficial effects of nicotinic acid on acute vascular inflammation involve antioxidant effects of nicotinic acid due to its ability to elevate glutathione (GSH) levels via increased formation of nicotinamide adenine dinucleotide phosphate (NADPH) [12,33]. However, the nicotinic acid doses required to increase GSH levels and VCAM-1 expression *in vitro* (0.5–1 mM) were considerably higher than the peak plasma levels of nicotinic acid after oral administration [12,33,34]. It is also possible that changes in the expression of adhesion molecules and chemokines by nicotinic acid are mediated indirectly through activation of the nicotinic acid receptor HCA_2 on immune cells. This is suggested by the observation that the nicotinic acid-induced decrease in VCAM-1 and P-selectin mRNA levels in vessels of LDL receptor-deficient mice was not observed in mice transplanted with HCA_2-deficient bone marrow, and that inhibition of MCP-1 expression by nicotinic acid could be seen in wild-type peritoneal macrophages but not in macrophages from HCA_2-deficient mice [13].

There is also evidence that nicotinic acid may have antiatherosclerotic effects by direct activation of plaque macrophages that express the nicotinic acid receptor HCA_2 [13]. Nicotinic acid is able to increase the transcription and activity of PPARγ, the scavenger receptor CD36 and of the cholesterol transporter ABCA1 in monocyte/macrophage cell lines [35,36]. In addition, nicotinic acid has been shown to increase the expression of the ABCG1 transporter in macrophages from wild-type mice but not from HCA_2-deficient animals [13]. Both, ABCA1 and ABCG1, mediate the transport of cellular cholesterol to ApoAI-containing HDL particles for the reverse cholesterol transport pathway [37]. Consistent with this, isolated macrophages from wild-type mice treated with nicotinic acid showed an enhanced efflux of cholesterol to HDL particles, an effect not observed with macrophages from mice lacking HCA_2 [13]. Thus, there is evidence that nicotinic acid, by acting through its receptor on macrophages, can change the differentiation state of macrophages both *in vitro* and *in vivo*, and thereby enhance cholesterol transport out of plaque macrophages. Future work will be required to explore this effect in more detail.

Adipocytes have been shown to synthesize and secrete various mediators, collectively called adipokines. Among them are various proinflammatory mediators including tumor necrosis factor (TNF)-α, interleukins and chemokines, as well as anti-inflammatory mediators such as adiponectin. Adipokines are not only involved in the regulation of inflammatory processes in the adipose tissue but can also affect the progression of vascular diseases and atherosclerosis [38]. There is good evidence that nicotinic acid, by acting through its receptor on adipocytes, regulates the formation and release of adipokines. In humans as well as in mice, treatment with nicotinic acid has been shown to increase the plasma levels of the anti-inflammatory adipokine adiponectin [39,40], whereas the expression of proinflammatory chemokines such as MCP-1, fractalkine or RANTES (Regulated upon Activation, Normal T cell Expressed, and Secreted) in adipocytes is inhibited by nicotinic acid [41]. Thus, it is possible that the regulation of adipokine release from adipocytes by nicotinic acid contributes to the beneficial effects of this drug.

The fact that nicotinic acid can reduce the progression of atherosclerosis and vascular inflammation in various *in vivo* animal models without changing plasma lipid levels indicates that it has lipid-independent antiatherogenic effects (Figure 2). Based on well-described effects of nicotinic acid in vascular and immune cells, as well as on evidence indicating beneficial effects of nicotinic acid in lipid-independent diseases (see below), it will be of great interest to further explore these lipid-independent mechanisms and effects in the future, and to test whether they also occur in humans.

Unwanted effects

Flushing and gastrointestinal symptoms such as dyspepsia, diarrhea or nausea are the most common unwanted effects of oral nicotinic acid therapy. Although these effects are harmless, in particular the nicotinic acid-induced flushing can affect patients' compliance [8]. Flushing is a cutaneous reaction that lasts for ~1–2 h and is characterized by redness and warmth, as well as by tingling and burning sensations [8]. Twenty years ago, there was already evidence that skin-derived prostanoids are responsible for nicotinic acid-induced flushing [42]. Later, it was shown that HCA_2 mediates this phenomenon, and that Langerhans cells express HCA_2 and are required to elicit a complete flushing response in mice [43–45]. Recently,

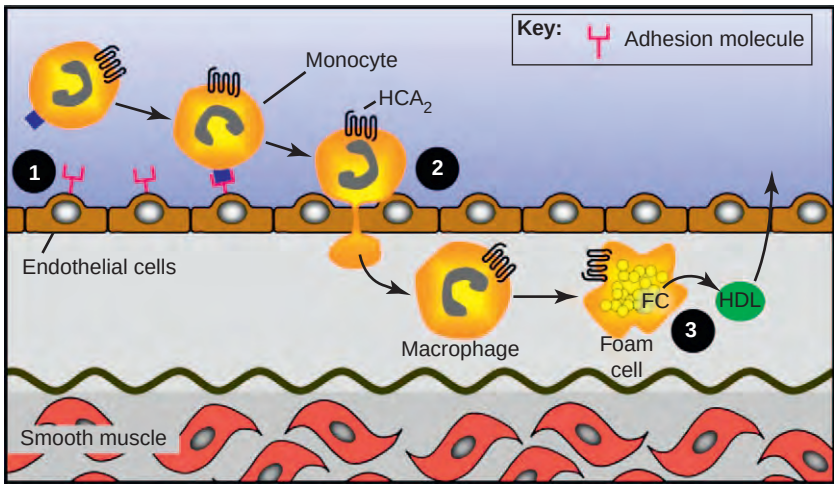

Figure 2. Potential mechanisms underlying lipid-independent antiatherogenic effects of nicotinic acid. Evidence has been provided that nicotinic acid can reduce the progression of atherosclerosis by direct lipid-independent effects on endothelial and immune cells. Shown is a simplified model of the recruitment of monocytes into atherosclerotic lesions of the arterial wall and formation of foam cells. Nicotinic acid has been suggested to affect this process via different mechanisms. **(i)** Nicotinic acid can reduce the expression of endothelial adhesion molecules involved in the binding and recruitment of immune cells. **(ii)** Via activation of HCA_2 on monocytes/macrophages, nicotinic acid inhibits the homing of cells to atherosclerotic lesions (e.g. through interaction with chemokine expression and/or signaling). **(iii)** Through activation of HCA_2 on macrophages, nicotinic acid increases the efflux of free cholesterol (FC) via cholesterol transporters onto HDL particles. For details, see text.

keratinocytes were also shown to express HCA_2 and to contribute to the flushing reaction [46]. Activation of HCA_2 on keratinocytes and Langerhans cells results in the formation and release of prostaglandin D_2 (PGD_2) and prostaglandin E_2 (PGE_2), which diffuse to the dermal layer and mediate the symptoms of flushing by activation of DP_1 and $EP_{2/4}$ receptors [43,47] (Figure 3). Whereas Langerhans cells use cyclooxygenase type 1 (COX-1) to produce PGE_2 and in particular PGD_2 [44–46], keratinocytes produce PGE_2 in a COX-2-dependent manner [46]. Interestingly, the acute first phase of flushing is mediated by Langerhans cells, whereas the continued and long-lasting vasodilation involves mainly keratinocytes, suggesting that both epidermal cell types respond with different kinetics to nicotinic acid during the flushing reaction [46] (Figure 3).

Other less frequent unwanted effects of nicotinic acid include a tendency to increase plasma levels of uric acid and to reduce glucose tolerance [48]. Both effects need to be considered when treating patients with nicotinic acid but are usually mild and occur preferentially in predisposed patients [48,49]. Older sustained-release formulations of nicotinic acid have been reported to occasionally increase plasma transaminase levels, suggesting a hepatotoxic effect due to increased hepatic metabolism [50].

New therapeutic potential

The development of HMG-CoA reductase inhibitors (statins) has dramatically improved the treatment of hypercholesterolemia. However, despite a reduction in cardiovascular risk achieved with statin therapy, a considerable risk for atherothrombotic cardiovascular disease remains. Nicotinic acid is one of the candidates currently under evaluation as an add-on therapy to statins, especially in patients with remaining cardiovascular risk factors [9,25]. First indications that nicotinic acid treatment in patients taking statins has an additional benefit came from the results of the HATS (HDL-Atherosclerosis Treatment Study) trial [51]. Using mainly surrogate parameters for the progression of atherosclerosis (e.g. noninvasive imaging of changes in intima-media thickness), it has recently been shown that nicotinic acid, if given in addition to statins in patients with existing coronary heart disease and low HDL cholesterol levels, has an additional atheroprotective effect and reduces major adverse cardiovascular events [52,53]. However, in patients with extremely low LDL cholesterol levels (average 1.8 mmol/l) under statin therapy with pre-existing cardiovascular disease, there is no additional benefit to nicotinic acid after 32 months of therapy, as recently demonstrated by the AIM-HIGH study [54]. A more definite answer to the question whether nicotinic acid therapy has additional benefits in statin-treated patients is expected from a much larger multicenter clinical outcome trial, the HPS2-THRIVE trial [55], which is expected to be completed in 2013.

Because flushing is the major unwanted effect of nicotinic acid therapy, there is a need for approaches that reduce flushing but do not affect the therapeutic effects of this drug. The use of extended-release formulation of nicotinic acid or taking nicotinic acid before bedtime and with meals reduces flushing and increases patients' compliance [56]. Also, COX inhibitors can be given to reduce flushing symptoms [57]. However, at the systemic concentrations required for this effect, COX inhibitors have multiple unwanted effects. A more specific inhibition of the nicotinic acid-induced flushing can be achieved with the PGD_2 receptor (DP_1) antagonist laropiprant [58], which in combination with nicotinic acid is approved for antidyslipidemic therapy in Europe. Finally, it has been proposed that the intracellular pathways activated via HCA_2 are different in adipose tissue and epidermal tissue in that the nicotinic acid-induced flushing response is mediated by β-arrestin1 and subsequent activation of extracellular signal-regulated kinase (ERK), whereas the supposedly beneficial lipolytic effect is independent of this pathway [59].

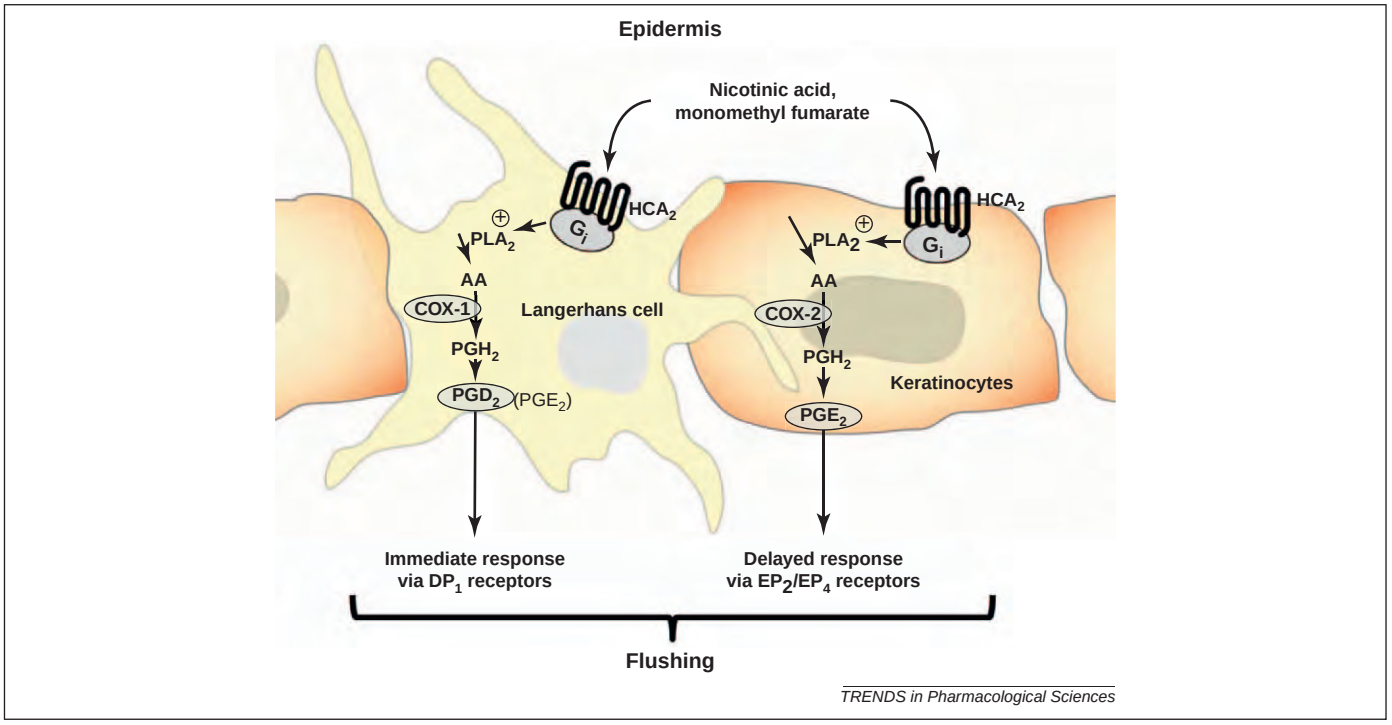

Figure 3. Mechanism mediating nicotinic acid-induced flushing. Nicotinic acid induces flushing by activation of HCA_2 on epidermal Langerhans cells as well as keratinocytes. Whereas activation of Langerhans cells and subsequent formation of prostaglandin D_2 (PGD_2) and prostaglandin E_2 (PGE_2) via cyclooxygenase-1 (COX-1) is responsible for the acute early phases of flushing, the COX-2-dependent activation of PGE_2 in keratinocytes underlies the late phases of flushing. Langerhans cell and keratinocyte-derived prostanoids act through PGD_2 (DP_1) and PGE_2 (EP_2 and EP_4) receptors to induce cutaneous vasodilation. AA, arachidonic acid; PLA_2, phospholipase A_2; PGH_2, prostaglandin H_2.

This would suggest that a biased HCA_2 agonist, which induces HCA_2 downstream signaling preferentially through a β-arrestin1-independent way, would still induce the anti-lipolytic effect but not the full flush response. In fact, MK-0354, a partial HCA_2 receptor agonist, which was shown to display strongly reduced flushing while retaining full antilipolytic activity, appears to act through a HCA_2-dependent biased signaling mechanism [60]. Unfortunately, MK-0354, when tested in humans, did not increase HDL cholesterol levels (see above).

The fact that the nicotinic acid receptor HCA_2 is expressed in various immune cells including macrophages, neutrophils, dendritic cells or epidermal Langerhans cells, as well as in keratinocytes (Table 1) together with recent evidence for lipid-independent beneficial effects raises the question whether nicotinic acid or synthetic HCA_2 (GPR109A) agonists can be used to treat other diseases. Interestingly, monomethyl fumarate, the active metabolite of the antipsoriatic drug dimethyl fumarate (Box 1) has been shown to be a selective full agonist of HCA_2 [14]. Nicotinic acid and monomethyl fumarate have common side effects, such as flush and gastrointestinal effects. The expression of HCA_2 in epidermal Langerhans cells and keratinocytes [44–46] strongly suggests that the receptor is involved in the antipsoriatic activity of fumaric acid esters. In animal models of neuroinflammation, both nicotinic acid and fumaric acid esters have been shown to improve neurological function, and this effect was accompanied by a significant reduction in inflammatory infiltrates [61,62]. After promising Phase II study results [63], fumaric esters have recently been evaluated in Phase III trials for multiple sclerosis with promising results regarding the efficacy and safety of this novel treatment [64,65]. Interestingly, nicotinic acid has recently been shown to have neuroprotective and anti-inflammatory activities also after acute ischemic stroke [66]. Beneficial effects of nicotinic acid were also reported in animal models of arthritis, chronic renal failure or sepsis [67–69]. Thus, agonists of the nicotinic acid receptor HCA_2 may have a broader spectrum of beneficial activities than currently appreciated; however, more work is required to explore this potential.

Table 1. Expression pattern of the nicotinic acid receptor HCA_2 (GPR109A)

Cell type	Effect resulting from receptor activation	Refs
Adipocyte	Inhibition of lipolysis, increased release of adiponectin	[15,39,71–73]
Neutrophil	Apoptosis	[45,74]
Monocyte/macrophage	Anti-inflammatory effects, increased expression of cholesterol transporter, increased transcription and activity of PPARγ	[13,35,36,75]
Langerhans cell	Increased formation of prostanoids (especially PGD_2)	[44–46]
Keratinocyte	Increased formation of prostanoids (especially PGE_2)	[14,45,46]
Intestinal epithelial cell	–	[76]
Retinal pigment epithelial cell	–	[77]

Box 1. Fumaric acid esters

Fumaric acid esters, in particular dimethyl fumarate (DMF), have been used for decades in Germany to treat psoriasis [70]. After promising clinical trials, a mixture of DMF and ethyl hydrogen fumarate was approved for the treatment of moderate to severe psoriasis, and DMF is also currently under investigation as a therapy for multiple sclerosis [64]. Orally administered DMF is rapidly absorbed and hydrolyzed by esterases to the active metabolite monomethyl fumarate (MMF), which is then further hydrolyzed to the inactive fumaric acid (Figure I, left). Interestingly, MMF has been shown to be an agonist of the nicotinic acid receptor HCA_2 [14]. Consistent with this, oral therapy with fumaric acid esters causes unwanted effects similar to those observed after nicotinic acid treatment such as cutaneous flushing and gastrointestinal effects.

There is evidence that MMF is the most active metabolite of fumaric acid esters, which correlates with its ability to activate HCA_2, whereas DMF is much less potent and fumarate is inactive ([14] Figure I, right).

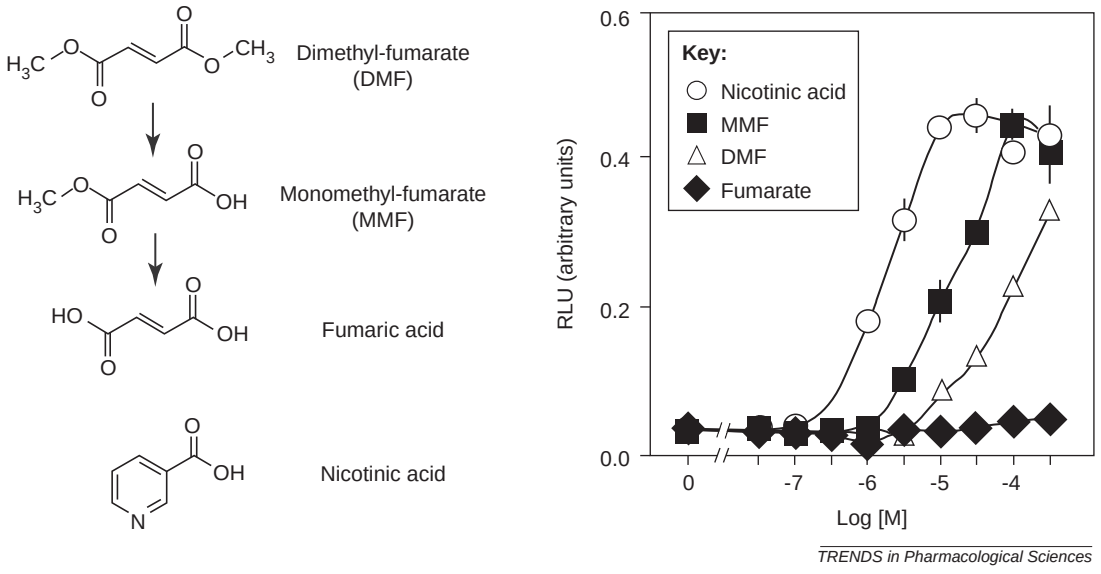

Figure I. Left panel: Structure of dimethyl-fumarate and its metabolites monomethyl-fumarate and fumaric acid as well as of nicotinic acid. Right panel: effect of increasing concentrations of nicotinic acid, monomethyl-fumarate (MMF), dimethyl-fumarate (DMF) and fumarate on $[Ca^{2+}]_i$ in CHO-K1 cells expressing HCA_2 (GPR109A) together with a Ca^{2+}-sensitive bioluminescent fusion protein and the promiscuous G-protein α-subunit $G\alpha_{15}$. RLU, relative light units.

Concluding remarks

Nicotinic acid was originally described by Altschul as an antiatherosclerotic drug believed to lower total cholesterol by increasing its oxidation. Later, the prevailing view was that nicotinic acid acts through a complex change in the plasma lipid profile involving a strong antilipolytic effect. In particular, the HDL cholesterol-elevating effect has been regarded as an important effect contributing to the antiatherosclerotic properties. Recent findings now indicate that nicotinic acid has other lipid-independent activities which are important for its clinical efficacy. Although there is a clear inverse relationship between the HDL cholesterol plasma concentration and the risk for coronary artery disease, the HDL plasma concentration is basically only a surrogate parameter and increases are not necessarily beneficial. Several studies have shown that nicotinic acid can have beneficial effects on acute and chronic vascular disease independently of its effects on plasma lipids. New strategies to reduce inflammation and to increase reverse cholesterol transport by regulating immune cells involved in the progression of atherosclerosis have been proposed as innovative approaches to prevent and treat atherosclerosis; it may well be that one of the oldest known antiatherosclerotic drugs in fact exerts its beneficial effects, at least in part, through mechanisms involving direct anti-inflammatory effects on leukocytes. This is certainly an area worth further research, as it may define new ways to prevent and treat atherosclerosis.

The discovery that monomethyl fumarate is a full agonist of the nicotinic acid receptor, its activity in treating inflammatory diseases such as psoriasis or multiple sclerosis, as well as first reports on anti-inflammatory activities of nicotinic acid in diseases other than atherosclerosis suggest that the nicotinic acid receptor is an interesting target for the treatment of a variety of diseases involving chronic inflammatory processes. Preclinical and clinical studies are already underway or will soon be initiated to explore the full potential of nicotinic acid receptor agonists.

References

1 Spies, T.D. *et al.* (1938) The use of nicotinic acid in the treatment of pellagra. *JAMA* 110, 622–627
2 Altschul, R. *et al.* (1955) Influence of nicotinic acid on serum cholesterol in man. *Arch. Biochem.* 54, 558–559
3 Carlson, L.A. (1963) Studies on the effect of nicotinic acid on catecholamine stimulated lipolysis in adipose tissue *in vitro*. *Acta Med. Scand.* 173, 719–722
4 Carlson, L.A. (2005) Nicotinic acid: the broad-spectrum lipid drug. A 50th anniversary review. *J. Intern. Med.* 258, 94–114
5 Canner, P.L. *et al.* (1986) Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J. Am. Coll. Cardiol.* 8, 1245–1255
6 Anonymous (1975) Clofibrate and niacin in coronary heart disease. *JAMA* 231, 360–381
7 Gille, A. *et al.* (2008) Nicotinic acid: pharmacological effects and mechanisms of action. *Annu. Rev. Pharmacol. Toxicol.* 48, 79–106
8 Kamanna, V.S. *et al.* (2009) The mechanism and mitigation of niacin-induced flushing. *Int. J. Clin. Pract.* 63, 1369–1377

9 Chapman, M.J. *et al.* (2010) Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. *Pharmacol. Ther.* 126, 314–345
10 Offermanns, S. *et al.* (2011) International Union of Basic and Clinical Pharmacology. LXXXII: nomenclature and classification of hydroxy-carboxylic acid receptors (GPR81, GPR109A, and GPR109B). *Pharmacol. Rev.* 63, 269–290
11 Kamanna, V.S. *et al.* (2009) Niacin: an old drug rejuvenated. *Curr. Atheroscler. Rep.* 11, 45–51
12 Wu, B.J. *et al.* (2010) Evidence that niacin inhibits acute vascular inflammation and improves endothelial dysfunction independent of changes in plasma lipids. *Arterioscler. Thromb. Vasc. Biol.* 30, 968–975
13 Lukasova, M. *et al.* (2011) Nicotinic acid inhibits progression of atherosclerosis in mice through its receptor GPR109A expressed by immune cells. *J. Clin. Invest.* 121, 1163–1173
14 Tang, H. *et al.* (2008) The psoriasis drug monomethylfumarate is a potent nicotinic acid receptor agonist. *Biochem. Biophys. Res. Commun.* 375, 562–565
15 Tunaru, S. *et al.* (2003) PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effect. *Nat. Med.* 9, 352–355
16 Wang, W. *et al.* (2001) Effect of nicotinic acid administration on hepatic very low density lipoprotein-triglyceride production. *Am. J. Physiol. Endocrinol. Metab.* 280, E540–E547
17 Lamon-Fava, S. *et al.* (2008) Extended-release niacin alters the metabolism of plasma apolipoprotein (Apo) A-I and ApoB-containing lipoproteins. *Arterioscler. Thromb. Vasc. Biol.* 28, 1672–1678
18 Hernandez, C. *et al.* (2010) Regulation of hepatic ApoC3 expression by PGC-1β mediates hypolipidemic effect of nicotinic acid. *Cell Metab.* 12, 411–419
19 Shepherd, J. *et al.* (1979) Effects of nicotinic acid therapy on plasma high density lipoprotein subfraction distribution and composition and on apolipoprotein A metabolism. *J. Clin. Invest.* 63, 858–867
20 Blum, C.B. *et al.* (1977) High density lipoprotein metabolism in man. *J. Clin. Invest.* 60, 795–807
21 Joy, T.R. and Hegele, R.A. (2008) Microsomal triglyceride transfer protein inhibition-friend or foe? *Nat. Clin. Pract. Cardiovasc. Med.* 5, 506–508
22 Hernandez, M. *et al.* (2007) Critical role of cholesterol ester transfer protein in nicotinic acid-mediated HDL elevation in mice. *Biochem. Biophys. Res. Commun.* 355, 1075–1080
23 van der Hoorn, J.W. *et al.* (2008) Niacin increases HDL by reducing hepatic expression and plasma levels of cholesteryl ester transfer protein in APOE*3Leiden.CETP mice. *Arterioscler. Thromb. Vasc. Biol.* 28, 2016–2022
24 Lai, E. *et al.* (2007) Abstract 190: A niacin receptor partial agonist, MK-0354, robustly reduces plasma free fatty acids and produces little flushing but fails to alter LDL-C, HDL-C, and triglycerides in humans. *Circulation* 116, II_16
25 Degoma, E.M. and Rader, D.J. (2011) Novel HDL-directed pharmacotherapeutic strategies. *Nat. Rev. Cardiol.* 8, 266–277
26 Briel, M. *et al.* (2009) Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. *BMJ* 338, b92
27 Olsson, A.G. (2009) Is high HDL cholesterol always good? *Ann. Med.* 41, 11–18
28 Nicholls, S.J. (2008) HDL: still a target for new therapies? *Curr. Opin. Investig. Drugs* 9, 950–956
29 Khera, A.V. *et al.* (2011) Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N. Engl. J. Med.* 364, 127–135
30 Yvan-Charvet, L. *et al.* (2010) Cholesterol efflux potential and anti-inflammatory properties of high-density lipoprotein after treatment with niacin or anacetrapib. *Arterioscler. Thromb. Vasc. Biol.* 30, 1430–1438
31 Sorrentino, S.A. *et al.* (2010) Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy. *Circulation* 121, 110–122
32 Holzhauser, E. *et al.* (2011) Nicotinic acid has anti-atherogenic and anti-inflammatory properties on advanced atherosclerotic lesions independent of its lipid-modifying capabilities. *J. Cardiovasc. Pharmacol.* 57, 447–454
33 Ganji, S.H. *et al.* (2009) Niacin inhibits vascular oxidative stress, redox-sensitive genes, and monocyte adhesion to human aortic endothelial cells. *Atherosclerosis* 202, 68–75
34 Tavintharan, S. *et al.* (2009) Effects of niacin on cell adhesion and early atherogenesis: biochemical and functional findings in endothelial cells. *Basic Clin. Pharmacol. Toxicol.* 104, 206–210
35 Knowles, H.J. *et al.* (2006) Niacin induces PPARγ expression and transcriptional activation in macrophages via HM74 and HM74a-mediated induction of prostaglandin synthesis pathways. *Biochem. Pharmacol.* 71, 646–656
36 Rubic, T. *et al.* (2004) Stimulation of CD36 and the key effector of reverse cholesterol transport ATP-binding cassette A1 in monocytoid cells by niacin. *Biochem. Pharmacol.* 67, 411–419
37 Yvan-Charvet, L. *et al.* (2010) Role of HDL, ABCA1, and ABCG1 transporters in cholesterol efflux and immune responses. *Arterioscler. Thromb. Vasc. Biol.* 30, 139–143
38 Gustafson, B. (2010) Adipose tissue, inflammation and atherosclerosis. *J. Atheroscler. Thromb.* 17, 332–341
39 Plaisance, E.P. *et al.* (2009) Niacin stimulates adiponectin secretion through the GPR109A receptor. *Am. J. Physiol. Endocrinol. Metab.* 296, E549–E558
40 Westphal, S. and Luley, C. (2008) Preferential increase in high-molecular weight adiponectin after niacin. *Atherosclerosis* 198, 179–183
41 Digby, J.E. *et al.* (2010) Anti-inflammatory effects of nicotinic acid in adipocytes demonstrated by suppression of fractalkine, RANTES, and MCP-1 and upregulation of adiponectin. *Atherosclerosis* 209, 89–95
42 Morrow, J.D. *et al.* (1992) Identification of skin as a major site of prostaglandin D2 release following oral administration of niacin in humans. *J. Invest. Dermatol.* 98, 812–815
43 Benyo, Z. *et al.* (2005) GPR109A (PUMA-G/HM74A) mediates nicotinic acid-induced flushing. *J. Clin. Invest.* 115, 3634–3640
44 Benyó, Z. *et al.* (2006) Nicotinic acid-induced flushing is mediated by activation of epidermal Langerhans cells. *Mol. Pharmacol.* 70, 1844–1849
45 Maciejewski-Lenoir, D. *et al.* (2006) Langerhans cells release prostaglandin D2 in response to nicotinic acid. *J. Invest. Dermatol.* 126, 2637–2646
46 Hanson, J. *et al.* (2010) Nicotinic acid- and monomethyl fumarate-induced flushing involves GPR109A expressed by keratinocytes and COX-2-dependent prostanoid formation in mice. *J. Clin. Invest.* 120, 2910–2919
47 Cheng, K. *et al.* (2006) Antagonism of the prostaglandin D2 receptor 1 suppresses nicotinic acid-induced vasodilation in mice and humans. *Proc. Natl. Acad. Sci. U.S.A.* 103, 6682–6687
48 Bodor, E.T. and Offermanns, S. (2008) Nicotinic acid: an old drug with a promising future. *Br. J. Pharmacol.* 153 (Suppl. 1), S68–S75
49 Goldberg, R.B. and Jacobson, T.A. (2008) Effects of niacin on glucose control in patients with dyslipidemia. *Mayo Clin. Proc.* 83, 470–478
50 Dalton, T.A. and Berry, R.S. (1992) Hepatotoxicity associated with sustained-release niacin. *Am. J. Med.* 93, 102–104
51 Brown, B.G. *et al.* (2001) Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N. Engl. J. Med.* 345, 1583–1592
52 Taylor, A.J. *et al.* (2009) Extended-release niacin or ezetimibe and carotid intima-media thickness. *N. Engl. J. Med.* 361, 2113–2122
53 Taylor, A.J. *et al.* (2006) The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. *Curr. Med. Res. Opin.* 22, 2243–2250
54 National Institutes of Health, (2011) NIH stops clinical trial on combination cholesterol treatment. *NIH News* May 16, 2011 (http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2792)
55 Armitage, J. *et al.* (2007) *Treatment of HDL to Reduce the Incidence of Vascular Events HPS2-THRIVE* July 19, 2010 (http://clinicaltrials.gov/ct2/show/NCT00461630?term=hps2-thrive&rank=1)
56 Davidson, M.H. (2008) Niacin use and cutaneous flushing: mechanisms and strategies for prevention. *Am. J. Cardiol.* 101, 14B–19B
57 Oberwittler, H. and Baccara-Dinet, M. (2006) Clinical evidence for use of acetyl salicylic acid in control of flushing related to nicotinic acid treatment. *Int. J. Clin. Pract.* 60, 707–715
58 Paolini, J.F. *et al.* (2008) Effects of laropiprant on nicotinic acid-induced flushing in patients with dyslipidemia. *Am. J. Cardiol.* 101, 625–630

59 Walters, R.W. *et al.* (2009) β-Arrestin1 mediates nicotinic acid-induced flushing, but not its antilipolytic effect, in mice. *J. Clin. Invest.* 119, 1312–1321
60 Semple, G. *et al.* (2008) 3-(1H-Tetrazol-5-yl)-1,4,5,6-tetrahydrocyclopentapyrazole (MK-0354): a partial agonist of the nicotinic acid receptor, G-protein coupled receptor 109a, with antilipolytic but no vasodilatory activity in mice. *J. Med. Chem.* 51, 5101–5108
61 Zhang, J. *et al.* (2008) Niaspan treatment improves neurological functional recovery in experimental autoimmune encephalomyelitis mice. *Neurobiol. Dis.* 32, 273–280
62 Schilling, S. *et al.* (2006) Fumaric acid esters are effective in chronic experimental autoimmune encephalomyelitis and suppress macrophage infiltration. *Clin. Exp. Immunol.* 145, 101–107
63 Kappos, L. *et al.* (2008) Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. *Lancet* 372, 1463–1472
64 Papadopoulou, A. *et al.* (2010) Dimethyl fumarate for multiple sclerosis. *Expert Opin. Investig. Drugs* 19, 1603–1612
65 Anonymous (2011) Trial watch: Phase III success for Biogen's oral multiple sclerosis therapy. *Nat. Rev. Drug Discov.* 10, 404
66 Shehadah, A. *et al.* (2010) Niaspan treatment induces neuroprotection after stroke. *Neurobiol. Dis.* 40, 277–283
67 Kwon, W.Y. *et al.* (2011) Niacin attenuates lung inflammation and improves survival during sepsis by downregulating the nuclear factor-κB pathway. *Crit. Care Med.* 39, 328–334
68 Cho, K.H. *et al.* (2009) Niacin ameliorates oxidative stress, inflammation, proteinuria, and hypertension in rats with chronic renal failure. *Am. J. Physiol. Renal Physiol.* 297, F106–F113
69 Mitrofanov, V.A. *et al.* (2005) Inflammatory degeneration of joint tissue in adjuvant arthritis after intraarticular treatment with the mixture of silver drug and nicotinic acid. *Bull. Exp. Biol. Med.* 140, 702–704
70 Rostami Yazdi, M. and Mrowietz, U. (2008) Fumaric acid esters. *Clin. Dermatol.* 26, 522–526
71 Soga, T. *et al.* (2003) Molecular identification of nicotinic acid receptor. *Biochem. Biophys. Res. Commun.* 303, 364–369
72 Wise, A. *et al.* (2003) Molecular identification of high and low affinity receptors for nicotinic acid. *J. Biol. Chem.* 278, 9869–9874
73 Tunaru, S. *et al.* (2005) Characterization of determinants of ligand binding to the nicotinic acid receptor GPR109A (HM74A/PUMA-G). *Mol. Pharmacol.* 68, 1271–1280
74 Kostylina, G. *et al.* (2008) Neutrophil apoptosis mediated by nicotinic acid receptors (GPR109A). *Cell Death Differ.* 15, 134–142
75 Schaub, A. *et al.* (2001) PUMA-G, an IFN-γ-inducible gene in macrophages is a novel member of the seven transmembrane spanning receptor superfamily. *Eur. J. Immunol.* 31, 3714–3725
76 Singh, N. *et al.* (2010) Blockade of dendritic cell development by bacterial fermentation products butyrate and propionate through a transporter (Slc5a8)-dependent inhibition of histone deacetylases. *J. Biol. Chem.* 285, 27601–27608
77 Martin, P.M. *et al.* (2009) Expression and localization of GPR109A (PUMA-G/HM74A) mRNA and protein in mammalian retinal pigment epithelium. *Mol. Vis.* 15, 362–372