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REVIEW

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Nicotinic acid: an old drug with a promising future

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Nicotinic acid has been used for decades to treat dyslipidaemic states. In particular its ability to raise the plasma HDL cholesterol concentration has led to an increased interest in its pharmacological potential. The clinical use of nicotinic acid is somewhat limited due to several harmless but unpleasant side effects, most notably a cutaneous flushing phenomenon. With the recent discovery of a nicotinic acid receptor, it has become possible to better understand the mechanisms underlying the metabolic and vascular effects of nicotinic acid. Based on these new insights into the action of nicotinic acid, novel strategies are currently under development to maximize the pharmacological potential of this drug. The generation of both flush-reducing co-medications of nicotinic acid and novel drugs targeting the nicotinic acid receptor will provide future therapeutic options for the treatment of dyslipidaemic disorders.
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Keywords: lipid-lowering drugs; HDL cholesterol; lipid metabolism; G-protein-coupled receptor; flushing

Abbreviations: CETP, cholesterol ester transfer protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very low-density lipoprotein

Introduction

The reduction of the plasma levels of cholesterol associated with proatherogenic 'low-density lipoprotein' (LDL) particles is one of the most important therapeutic measures to reduce cardiovascular morbidity and mortality. LDL cholesterol plasma levels can be pushed far below 100 mg per 100 ml by the inhibition of cholesterol synthesis, using HMG-CoA-reductase inhibitors (statins) alone or in combination with cholesterol-resorption inhibitors. Despite this very efficacious treatment, clinical studies have shown that even an aggressive reduction in LDL cholesterol reduces the occurrence of cardiovascular events by only 25–40% (Mahley and Bersot, 2006). This result is due to the fact that high LDL cholesterol levels are not the only risk factor for cardiovascular diseases. In addition to genetic factors, hypertension, age and cigarette smoking, low 'high-density lipoprotein' (HDL) cholesterol levels are also an independent risk factor (Gordon *et al*., 1977; Castelli *et al*., 1986). Currently, HDL cholesterol levels of $\leqslant$40–45 mg per 100 ml are regarded as a risk factor for coronary heart disease, whereas levels $>$60 mg per 100 ml are considered protective (Grundy *et al*., 2004). The development of new strategies to elevate HDL cholesterol plasma levels has therefore been intensified in recent years (Chapman, 2006; Rader, 2006). One of the most promising new approaches to raise HDL cholesterol levels, inhibition of the cholesterol ester transfer protein (CETP) (Le Goff *et al*., 2004), has recently suffered a setback when the CETP inhibitor torcetrapib failed in the phase III trials (Nissen *et al*., 2007). Currently, the oldest lipid-modifying drug, nicotinic acid (niacin), is attracting renewed attention as it has the strongest HDL cholesterol-elevating effect among the drugs currently approved for the treatment of lipid disorders (Table 1). In this review, we will summarize the pharmacology of nicotinic acid with particular focus on recent findings that have elucidated the mechanisms underlying some of the effects of nicotinic acid.

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Clinical use of nicotinic acid

Nicotinic acid has profound and unique effects on lipid metabolism and is thus referred to as a 'broad-spectrum lipid drug' (Carlson, 2005). In addition to elevating HDL cholesterol (Parsons and Flinn, 1959; Shepherd *et al*., 1979) as well as decreasing both LDL and total cholesterol (Altschul *et al*., 1955; Carlson *et al*., 1977), nicotinic acid also induces a decrease in the concentrations of both 'very-low-density lipoproteins' (VLDL) and plasma triglyceride (TG) (Table 1; Carlson *et al*., 1989). The plasma concentration of lipoprotein Lp(a), which has been suggested to play a role as an independent risk factor for coronary heart disease, is also decreased by nicotinic acid (Carlson *et al*., 1989; Berglund

and Ramakrishnan, 2004). Soon after the initial discovery of the lipid-modifying effect of high doses of nicotinic acid (Altschul *et al*., 1955), the water-soluble vitamin nicotinic acid was introduced into clinical therapy as the first lipid-modifying drug. In the Coronary drug project, conducted from 1966 to 1975, nicotinic acid administered as monotherapy at $3\,g\,day^{-1}$ was shown to lead to an efficient secondary prevention of myocardial infarction (Table 2) (Coronary Drug Project Research Group, 1975). A follow-up study of the Coronary Drug project revealed that nicotinic acid also reduced the mortality of patients who had been treated with nicotinic acid (Canner *et al*., 1986). The Stockholm ischaemic heart disease secondary prevention study came to similar findings (Carlson and Rosenhamer, 1988). With the introduction of cholesterol synthesis inhibitors (statins) in the therapy of hypercholesterolaemia during the late 1980s, interest in the therapeutic potential of nicotinic acid decreased. However, in recent years, several clinical studies have been conducted to test whether nicotinic acid provides a benefit to patients who are receiving treatment with statins but still display low HDL cholesterol levels. Both the HDL Atherosclerosis Treatment Study and the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol study indicate that patients with low HDL cholesterol levels benefit from a treatment with nicotinic acid in addition to statins (Brown *et al*., 2001; Taylor *et al*., 2004). However, both studies are relatively small and have some limitations, including the lack of an ideally designed control group in HDL Atherosclerosis Treatment Study or the evaluation of the intima-media thickness of the carotid artery as a surrogate parameter for the development of clinically relevant atherosclerosis in the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol study. In any case, there is good evidence supporting a therapeutic benefit of nicotinic acid (Brown, 2005), and randomized long-term studies to evaluate the effect of nicotinic acid in addition to statins in patients with low HDL cholesterol levels and increased cardiovascular risk have recently been initiated (Brown, 2006).

Table 1 Effect of various lipid-modifying drugs

	LDL-C	*HDL-C*	*TG*
Statins	20–55% ↓	5–10% ↑	7–30% ↓
Fibrates	5–20% ↓	10–20% ↑	20–50% ↓
Nicotinic acid	5–25% ↓	15–35% ↑	20–50% ↓
Anion exchange resins	10–20% ↓	3–5% ↑	—
Ezetemibe	15–20% ↓	(↑)	(↓)

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LCL-D, low-density lipoprotein cholesterol; TG, triglycerides.

Nicotinic acid effects on lipid metabolism

The most rapid effect of nicotinic acid on lipid metabolism is a decrease in plasma levels of free fatty acid , which can be observed within minutes upon administration of the drug. After a few hours, the plasma VLDL and TG levels are reduced, whereas the LDL and HDL cholesterol levels are changed only after several days of treatment (Carlson *et al*., 1968a). Soon after the discovery of the cholesterol-lowering effect of nicotinic acid, the still-prevailing hypothesis was formulated that the effects of nicotinic acid on LDL and HDL cholesterol levels are the result of a very rapid antilipolytic effect on adipocytes (Figure 1). This was based on studies *in vivo* as well as *in vitro* using isolated adipocytes (Carlson and Orö, 1962; Carlson, 1963; Butcher *et al*., 1968). The rapid decrease in plasma free fatty acid levels due to the antilipolytic effect of nicotinic acid is believed to result in reduced supply of substrate for the hepatic synthesis of TGs

Table 2 Clinical trials, which have evaluated the effect of nicotinic acid in the prevention of cardiovascular diseases

Study	*Method*	*Placebo*	*Nicotinic acid*	P-*value*
Coronary Drug Project (1975)	8341 patients after myocardial infarction	12.2%	8.9%	<0.05
	5 years, $3\,g\,day^{-1}$ myocardial infarctiontotal mortality	20.9%	21.2%	NS
Canner *et al*. (1986)	Coronary Drug Project follow-up after 15 years Total mortality	58.2%	52%	<0.005
Carlson and Rosenhammer (1988)	276 patients after myocardial infarction nicotinic acid + clofibrate Total mortality	29.7%	21.8%	<0.05
HATS[a], (58)	160 patients with coronary heart disease and low HDL cholesterol (males <35 mg per 100 ml; females <40 mg per 100 ml), 3 years nicotinic acid ($2–4\,g\,day^{-1}$) + simvastatin ($10–20\,mg\,day^{-1}$) Cardiovascular events	NT[b]	3%	
ARBITER 2[c], Taylor *et al*. (2004)	167 patients with coronary heart disease and low HDL cholesterol (<45 mg per 100 ml), 1 year nicotinic acid ($1\,g\,day^{-1}$) + simvastatin Increase in intima-media thickness of carotid artery	0.044 mm	0.014 mm	<0.08

Abbreviations: HDL, high-density lipoprotein; NS, not significant; NT, not tested.
[a]HDL Atherosclerosis Treatment Study (Brown *et al*., 2001).
[b]A placebo group (simvastatin only) was not studied in the HATS trial. The clinical and angiographic benefit of a combination treatment with simvastatin and nicotinic acid was, however, far higher than would have been expected with a simvastatin only treatment.
[c]Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (Taylor *et al*., 2004).

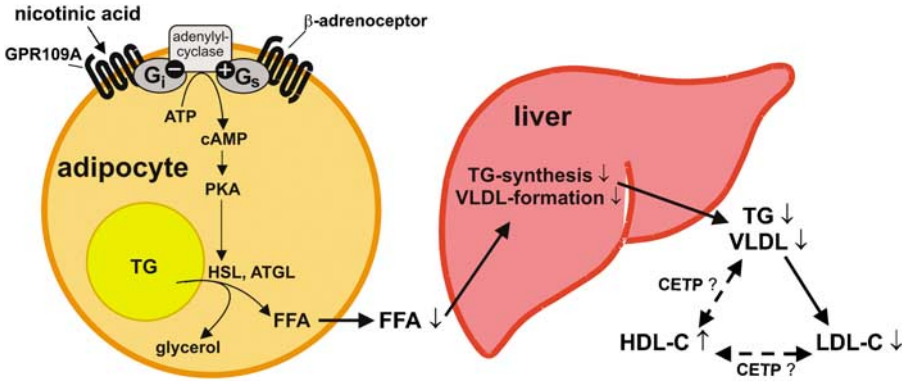

Figure 1 Mechanisms of nicotinic acid-induced changes in lipid metabolism. ATGL, adipocyte-triacylglycerol-lipase; CETP, cholesterol ester transfer protein; FFA, free fatty acid; HSL, hormone-sensitive lipase; PKA, protein kinase A; TG, triglyceride.

and VLDL particles (Lewis, 1997), which in turn leads to reduced formation of LDL particles (Figure 1). Recent studies in a hepatoblastoma cell line have suggested that nicotinic acid may have direct effects on hepatocytes, and may decrease hepatic VLDL and TG synthesis by the inhibition of diacylglycerol acyl transferase 2 and accelerating the intracellular degradation of apoprotein B (Jin *et al.*, 1999; Ganji *et al.*, 2004). However, these *in vitro* effects were observed only at nicotinic acid concentrations considerably higher than the plasma concentrations required for the *in vivo* effects on the plasma levels of TG and VLDL.

It is also not clear how nicotinic acid induces an increase in HDL cholesterol levels. The most plausible hypothesis is based on the well-established inverse correlation between TG levels and plasma HDL cholesterol concentrations (Szapary and Rader, 2001), which is primarily due to the exchange of TGs and cholesterol esters between apoprotein B-containing lipoproteins (especially VLDL and LDL) and HDL, which is mediated by CETP. According to this concept, the decrease in TG concentration in VLDL and LDL particles in response to nicotinic acid results in a reduced exchange of cholesterol esters and TGs and a subsequent increase in the plasma concentration of HDL cholesterol (Figure 1). This hypothesis is supported by the fact that inhibition of CETP has very similar effects to nicotinic acid treatment on the plasma concentration of HDL , in that both cause an elevation of the HDL_2 fraction (Le Goff *et al.*, 2004). Interestingly, in mice, which do not express CETP, the relatively high basal HDL cholesterol levels are rather decreased by nicotinic acid. Yet transgenic mice expressing the human CETP gene show lowered levels of basal HDL cholesterol and respond with an increase in HDL cholesterol levels to nicotinic acid treatment (Hernandez *et al.*, 2007). However, it has also been proposed that nicotinic acid increases plasma HDL levels by decreasing the catabolism of HDL (Blum *et al.*, 1977; Shepherd *et al.*, 1979). In addition, millimolar concentrations of nicotinic acid have been shown to decrease the uptake of HDL-apoprotein A-I by a hepatoma cell line *in vitro* (Jin *et al.*, 1997).

Recent studies have also suggested that some of the beneficial long-term effects of nicotinic acid may, at least in part, involve macrophages. Nicotinic acid has been shown to increase the expression of peroxisome proliferator-activated receptor-γ and to enhance peroxisome proliferator-activated receptor-γ transcriptional activity in macrophages (Rubic *et al.*, 2004; Knowles *et al.*, 2006). However, the mechanism underlying this effect and its pharmacological relevance are still unclear.

The nicotinic acid receptor

Over 25 years ago, a nicotinic acid receptor on adipocytes was postulated based on the observation that the strong and rapid antilipolytic effects of nicotinic acid are mediated by a G_i-dependent inhibition of adenylyl cyclase (Aktories *et al.*, 1980). Following the demonstration of specific binding sites for nicotinic acid on plasma membranes of adipocytes and spleen cells (Lorenzen *et al.*, 2001), the receptor for nicotinic acid was identified (Soga *et al.*, 2003; Tunaru *et al.*, 2003; Wise *et al.*, 2003) as the orphan receptor GPR109A, also referred to as HM74A in humans and protein up-regulated in macrophages by interferone-γ (PUMA-G) in mice. In addition to brown and white adipose tissue, GPR109A is also expressed in various immune cells, including monocytes, macrophages, dendritic cells and neutrophils (Yousefi *et al.*, 2000; Schaub *et al.*, 2001; Soga *et al.*, 2003; Tunaru *et al.*, 2003; Wise *et al.*, 2003; Maciejewski-Lenoir *et al.*, 2006). GPR109A is coupled to G_i type G proteins, and its activation by nicotinic acid results in a G_i-mediated inhibition of adenylyl cyclase, resulting in a decrease in intracellular cyclic AMP levels. This cyclic nucleotide is the principal mediator of adipocyte lipolysis (Figure 1). Lipolysis is increased when cAMP levels are elevated due to increased adenylyl cyclase activity, for example, by β-adrenergic receptor activation or by decreased phosphodiesterase-mediated cAMP degradation (Duncan *et al.*, 2007). Thus, the nicotinic acid-induced, GPR109A-mediated adenylyl cyclase inhibition counteracts the prolipolytic effects of elevated intracellular cAMP levels. The relevance of the nicotinic acid receptor GPR109A as a mediator of the pharmacological effects of nicotinic acid could be demonstrated in mice lacking GPR109A. In these animals, the nicotinic acid-induced antilipolytic effects on fat cells as well as the decrease in the plasma levels of free fatty acid and TG in response to nicotinic acid are abrogated (Tunaru *et al.*, 2003). Thus, strong evidence exists that at

least the initial steps of the nicotinic acid-induced changes in lipid metabolism are mediated by GPR109A.

The closest homologue of the human GPR109A is GPR109B, which is not found in rodents and clearly represents the result of a relatively recent gene duplication (Zellner *et al.*, 2005). Interestingly, nicotinic acid and related drugs with comparable pharmacological effects, such as acipimox (Fuccella *et al.*, 1980; Tornvall and Walldius, 1991), bind to GPR109A but not to GPR109B (Soga *et al.*, 2003; Tunaru *et al.*, 2003; Wise *et al.*, 2003). However, the furan carboxylic acid acifran is able to activate both receptors (Wise *et al.*, 2003; Figure 2). Several heterocyclic small molecules have been shown to act as selective agonists of GPR109A, however, none of them appear to surpass nicotinic acid with regard to potency (Wang and Fotsch, 2006; Gharbaoui *et al.*, 2007; Jung *et al.*, 2007; Soudijn *et al.*, 2007). Recently, a variety of 1- and 2-substituted benzotriazole-5-carboxylic acids, such as 1-isopropyl-benzotriazole-5-carboxylic acid, have been reported to be selective and relatively potent agonists at GPR109B (Semple *et al.*, 2006). Nicotinamide, which shares with nicotinic acid its function as a vitamin but has no pharmacological effects comparable to nicotinic acid, does not activate any of the receptors (Soga *et al.*, 2003; Tunaru *et al.*, 2003; Wise *et al.*, 2003).

a

	EC_{50} (μM)	
	GPR109A	GPR109B
nicotinic acid	0,1	>100
acipimox	5,1	>100
3-hydroxybutyrate	750	25 000
1-IPBT-5-CA	>1000	0,4
acifran	1,2	7
nicotinamide	inactive	inactive
acetoacetate	>25 000	25 000

b

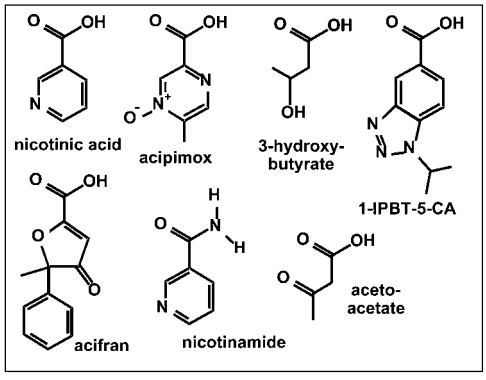

Figure 2 Properties (**a**) and structures (**b**) of various ligands of GPR109A and GPR109B. EC_{50} values were determined by measuring binding of GTPγS to membranes or by measuring adenylyl cyclase inhibition. 1-IPBT-5-CA, 1-isopropyl-benzotriazole-5 carboxylic acid.

Under physiological conditions, nicotinic acid concentrations in the plasma are relatively low, thus nicotinic acid is unlikely to be the endogenous ligand for GPR109A. Recently, the endogenous ketone body β-hydroxybutyrate was shown to selectively activate GPR109A (Taggart *et al.*, 2005). The potency of β-hydroxybutyrate is relatively low ($EC_{50} = 750\,\mu M$) yet does fall within its physiological concentrations in the plasma, which range from 50 to 400 μM under normal conditions to as high as 6–8 mM under starvation conditions. Thus, GPR109A appears to mediate the known antilipolytic effect of high concentrations of β-hydroxybutyrate, a negative feedback mechanism that may contribute to metabolic homoeostasis during starvation (Senior and Loridan, 1968).

All known agonists of the nicotinic acid receptor GPR109A have in common that they are relatively small molecules, which contain a carboxylic acid moiety. Intensive mutagenesis studies of the nicotinic acid receptor suggest that the binding pocket is formed by transmembrane helices 2, 3 and 7 (Figure 3), and that an arginine residue (Arg111) in the transmembrane helix 3 represents the anchor point for the carboxylic acid group of nicotinic acid and other receptor agonists (Tunaru *et al.*, 2005). Other important contacts of the pyridine ring of nicotinic acid with the

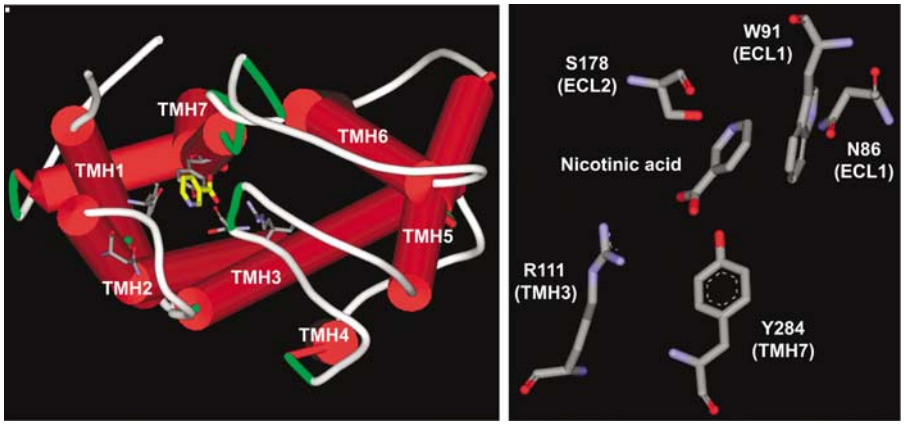

Figure 3 Model of GPR109A-binding nicotinic acid. (left panel) View on the extracellular site of the receptor, which binds nicotinic acid (yellow) in its binding pocket from transmembrane helices 2, 3 and 7. (right panel) Model of the most important interactions of nicotinic acid with amino-acid residues of the receptor. TMH, transmembrane helix; ECL, extracellular loop. The coordinates used to draw the model were generated by J Lättich and G Krause (FMP, Berlin) (Tunaru *et al.*, 2005).

receptor have been suggested to be localized at the extracellular junction of transmembrane helix 2, the extracellular loop 1 and the transmembrane helix 7. A serine residue (Ser178) in the extracellular loop 2 is essential for binding nicotinic acid to the receptor and may mediate the interaction with the nitrogen of the pyridine ring (Tunaru *et al.*, 2005).

Pharmacokinetics

After oral administration, nicotinic acid is absorbed rapidly and maximal plasma concentrations are reached after 30–60 min. The plasma half-life after administration of 1 g nicotinic acid is around 1 h (Carlson *et al.*, 1968b; Svedmyr and Harthon, 1970). Nicotinic acid is in part metabolized by the liver and in part excreted unchanged by the kidney. At low doses, a considerable fraction of nicotinic acid is metabolized via nicotinamide to *N*-methyl-nicotinamide, which is then further metabolized to *N*-methyl-2-pyridon-5-carboxamide and *N*-methyl-4-pyridon-5-carboxamide and are then renally excreted (Stern *et al.*, 1992). At intermediate and high pharmacological doses (1–3 g), an increasing fraction of nicotinic acid is conjugated with glycin and then excreted as nicotinuric acid by the kidney. With increasing doses, the direct renal excretion of nicotinic acid predominates (Petrack *et al.*, 1966).

The nicotinic acid-induced flushing response

Nicotinic acid, when given at pharmacological doses, has several unwanted yet harmless effects. The most common and most prominent unwanted effect of nicotinic acid is a cutaneous vasodilation, most prominently in the upper half of the body and in the face, which lasts for 1–2 h after an oral dose of nicotinic acid (Goldsmith and Cordill, 1943). This cutaneous reaction, called flushing, is relatively unpleasant and therefore negatively influences patients' compliance. This dilatory effect on dermal blood vessels is also the basis of the local effects of some dermatic formulations of nicotinic acid esters, including propyl-, benzyl- or methyl-nicotinate. In contrast to the nicotinic acid effects on lipid metabolism that are stable over long periods of treatment with nicotinic acid, the nicotinic acid-induced flushing response is subject to some tolerance, resulting in a reduced flushing response in the course of weeks (Stern *et al.*, 1991).

Recent studies in GPR109A-deficient mice have shown that the nicotinic acid-induced flushing response is mediated by the nicotinic acid receptor (Benyó *et al.*, 2005). The failure of GPR109A-deficient mice to respond to nicotinic acid with cutaneous vasodilation can be rescued by transplanting wild-type bone marrow to irradiated GPR109A-deficient animals (Benyó *et al.*, 2005), strongly suggesting that the receptor on bone marrow-derived cells and not on adipocytes mediates the flushing response. This finding, along with the fact that topical application of skin-permeable nicotinic acid esters results in a cutaneous reaction indistinguishable from the response induced by systemic application of nicotinic acid, suggests that the nicotinic acid-induced flushing response is a local phenomenon induced by activation of the receptor on dermal or epidermal immune cells. Strong evidence has been provided that epidermal Langerhans cells are critically involved in the nicotinic acid-induced flushing response (Benyó *et al.*, 2006; Maciejewski-Lenoir *et al.*, 2006). This is based on the observation that Langerhans cells express GPR109A and respond to nicotinic acid with an increase in intracellular Ca^{2+} as well as the formation of prostanoids (Maciejewski-Lenoir *et al.*, 2006). In addition, nicotinic acid does not induce a flushing response in mice, which are depleted of Langerhans cells (Benyó *et al.*, 2006).

It has long been known that treatment with COX inhibitors can reduce the nicotinic acid-induced flushing response while having no effect on the beneficial effects of nicotinic acid (Andersson *et al.*, 1977; Eklund *et al.*, 1979; Kaijser *et al.*, 1979). Indeed, prostanoids, especially prostaglandin D_2 (PGD_2) or their metabolites, have been shown to be produced after administration of nicotinic acid (Morrow *et al.*, 1989; Stern *et al.*, 1991). Pharmacological and genetic evidence from studies in mice clearly indicates that the nicotinic acid-induced flushing response is mediated by PGD_2 and prostaglandin E_2, which dilate dermal blood vessels via the activation of DP_1 and EP_2/EP_4 receptors (Benyó *et al.*, 2005; Cheng *et al.*, 2006). From these and other data, a model of the nicotinic acid-induced flushing response has emerged. Nicotinic acid induces an increase in intracellular Ca^{2+} via activation of GPR109A on epidermal Langerhans cells. This results in the activation of a Ca^{2+}-sensitive phospholipase A_2 and the formation of arachidonic acid, which is further metabolized to PGD_2 and prostaglandin E_2. Both prostanoids are then able to induce the dilation of blood vessels in the upper layer of the dermis by activation of their G_s-coupled receptors (Figure 4).

Several strategies have been proposed to reduce nicotinic acid-induced flushing. It is, for example, generally recommended to gradually increase the daily dose over a period of 1–4 months. As the onset of flushing rapidly follows the increase in nicotinic acid plasma levels after oral ingestion, slow-release formulations of nicotinic acid have been generated, which result in a delay and decrease of the peak plasma concentration of nicotinic acid and hence lead to fewer flushing events (Knopp *et al.*, 1998). The fact that the antilipolytic effects of nicotinic acid as well as the flushing response are mediated by GPR109A makes it difficult to

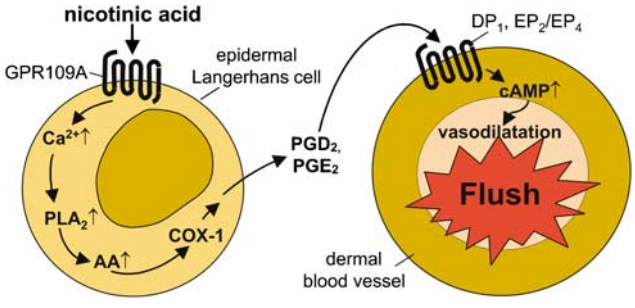

Figure 4 Proposed mechanism of the nicotinic acid-induced flushing response. AA, arachidonic acid; COX-1, cyclooxygenase-1; PGD_2, prostaglandin D_2; PGE_2, prostaglandin E_2; PLA_2, phospholipase A_2.

dissociate these two effects by generating new synthetic agonists of GPR109A. However, recent data indicate that partial agonists of GPR109A may have a reduced efficacy with regard to the induction of flushing while retaining mainly their antilipolytic activity (Richman *et al*., 2007). An alternative approach to reduce the unwanted flushing response could be the co-application of drugs that interfere with the downstream mechanisms of the nicotinic acid-induced flushing response. COX inhibitors including aspirin have been shown to reduce the flush response to nicotinic acid (Oberwittler and Baccara-Dinet, 2006), however, their side effects preclude long-term administration. Based on the recent elucidation of the mechanisms underlying nicotinic acid-induced flushing (see above), the specific inhibition of PGD_2 and prostaglandin E_2 formation or action appears to be a very promising strategy. In fact, it has recently been shown that the DP_1 receptor antagonist laropiprant (MK-0524) inhibits the nicotinic acid-induced flushing response in humans (Cheng *et al*., 2006; Lai *et al*., 2007).

Other unwanted effects

In some cases, the application of nicotinic acid has been reported to result in gastrointestinal effects, such as dyspepsia, diarrhoea or nausea. The mechanisms of these unwanted effects are unclear. Increases in plasma transaminase activity indicating a hepatotoxic effect have been reported in patients treated with nicotinic acid. This effect appears to be more frequently observed when sustained-release formulations of nicotinic acid are given, suggesting that an increased hepatic metabolism underlies this hepatotoxic effect (Etchason *et al*., 1991; Dalton and Berry, 1992). Patients predisposed to hyperuricaemia and gout have been reported to display a tendency towards elevated plasma levels of uric acid in response to nicotinic acid, which is likely due to a competition of nicotinic acid and uric acid for the same renal excretion mechanism (Anzai *et al*., 2007).

Patients suffering from type II diabetes mellitus often have dyslipidaemic changes characterized by an increase in TG levels as well as a decrease in HDL cholesterol levels. Given the characteristic profile of the pharmacological effects of nicotinic acid on lipid metabolism, nicotinic acid should counteract the dyslipidaemic changes in diabetic patients. However, several reports have been published indicating that nicotinic acid increases insulin resistance (Garg and Grundy, 1990; McCulloch *et al*., 1991). The mechanisms of this unwanted effect remain unclear. Recent analyses have, however, indicated that the risk–benefit ratio of nicotinic acid therapy in diabetic patients was similar to that of patient with normal glucose tolerance (Grundy *et al*., 2002; Canner *et al*., 2005). A final assessment of the effects of long-term nicotinic acid treatment in patients with diabetes mellitus is currently not possible, and rigid glycemic control should be ensured in diabetic or prediabetic patients treated with nicotinic acid.

Conclusions

Nearly 50 years ago, nicotinic acid was introduced into clinical practice as the first lipid-modifying drug. Its status among the growing number of antidyslipidaemic drugs has changed over the years. With the increased awareness of the role low HDL cholesterol levels play as a risk factor for cardiovascular diseases, the strong HDL cholesterol-elevating effect of nicotinic acid has resulted in an increased interest in the pharmacological properties of this drug. The clinical use of nicotinic acid, however, has been hampered by harmless but unpleasant side effects, primarily the flushing phenomenon. With the recent discovery of a specific receptor for nicotinic acid, the molecular mechanisms underlying the pharmacological effects of nicotinic acid have become clearer. In the upcoming years, it will be important to fully understand which of the effects are mediated by the receptor and which are not. Research on the mechanisms of nicotinic acid has already strongly influenced the development of new drugs for the treatment of dyslipidaemic states. New agents acting via the nicotinic acid receptor are currently being developed in various pharmaceutical companies. In addition, new co-medications, which aim to suppress the nicotinic acid-induced flushing response without affecting the wanted effects of nicotinic acid, are being tested.

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Conflict of interest

SO has been a consultant to Merck; ETB states no conflict of interest.

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