Nicotinic Acid: Pharmacological Effects and Mechanisms of Action

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Key Words

atherosclerosis, nicotinic acid receptor, flushing, dyslipidemia, coronary heart disease, G protein–coupled receptor

Abstract

Pharmacological doses of nicotinic acid induce a profound change in the plasma levels of various lipids and lipoproteins. The ability of nicotinic acid to strongly increase the plasma concentration of high-density lipoprotein (HDL) cholesterol has in recent years led to an increased interest in the pharmacological potential of nicotinic acid. There is increasing evidence that nicotinic acid alone or in addition to LDL cholesterol–lowering drugs can reduce the progression of atherosclerosis and reduce the risk of cardiovascular events. The clinical use of nicotinic acid is, however, hindered by harmless but unpleasant side effects, especially by a strong cutaneous vasodilation called flushing. The recent discovery of the G protein–coupled receptor GPR109A (HM74A or PUMA-G) as a receptor for nicotinic acid has allowed for better understanding of the mechanisms underlying the metabolic and vascular effects of nicotinic acid. On the basis of recent progress in understanding the pharmacological effects of nicotinic acid, new strategies are in development to better exploit the pharmacological potential of nicotinic acid. New drugs acting via the nicotinic acid receptor or related receptors, as well as new co-medications that suppress unwanted effects of nicotinic acid, will most likely be introduced as new therapeutic options in the treatment of dyslipidemia and the prevention of cardiovascular diseases.

INTRODUCTION

LDL: low-density lipoprotein

HDL: high-density lipoprotein

FFA: free fatty acid

Nicotinic acid and nicotinamide (collectively termed niacin) serve as precursors of coenzymes NAD and NADP and are water-soluble vitamins of the vitamin B complex. The pioneering work of Rudolf Altschul 50 years ago demonstrated that supraphysiological doses of nicotinic acid, but not of nicotinamide, have additional biological effects unrelated to those as a vitamin. The administration of gram quantities of nicotinic acid reduces total cholesterol plasma levels in healthy human volunteers and to an even greater extent in patients suffering from pathologically high levels of cholesterol (1). Shortly after this discovery, nicotinic acid was introduced into clinical practice to treat dyslipidemia by decreasing low-density lipoprotein (LDL)-cholesterol levels while raising high-density lipoprotein (HDL)-cholesterol levels. Nicotinic acid, in fact, was the first drug shown to have an effect on total mortality in long-term treatment of coronary heart disease (2). Administration of pharmacological doses of nicotinic acid is accompanied by unwanted effects, primarily a cutaneous reaction called flushing, which is characterized by strong vasodilation and sometimes a burning sensation. With the increasing awareness of the important role that low HDL-cholesterol levels play as a cardiovascular risk factor, the interest in the HDL-cholesterol-elevating effects of nicotinic acid has recently greatly increased. Despite a significant body of clinical evidence for the beneficial effect of nicotinic acid in preventing the progression of atherosclerosis and the occurrence of cardiovascular events (3), the mechanisms by which pharmacological doses of nicotinic acid exert their effects have been elusive. With the recent discovery of a G protein–coupled receptor that mediates many effects of nicotinic acid on adipocytes and immune cells (4–6), research into the mechanisms underlying the wanted and unwanted effects of nicotinic acid has gained momentum. In this review, we summarize the pharmacological effects of nicotinic acid and discuss the role of its recently discovered receptor in the pharmacological actions of nicotinic acid.

THE NICOTINIC ACID RECEPTOR

After the seminal discovery by Altschul and coworkers, the work of Carlson and colleagues in the early 1960s provided further insight into the mechanism of action of nicotinic acid. Following stimulation of lipolysis by catecholamines in adipose tissue as well as in isolated adipocytes, nicotinic acid treatment inhibited the hydrolysis of triglycerides, reducing the production of free fatty acids (FFAs), resulting in a decrease in FFA plasma concentration (7, 8). In addition, [^{3}H]nicotinic acid was found to distribute almost exclusively to adipose tissue, further supporting the role of nicotinic acid in regulating lipolysis (9). One possible mechanism of the antilipolytic effect of nicotinic acid was proposed to be the inhibition of cAMP accumulation in adipocytes (10). Later it was shown that nicotinic acid reduced cAMP levels in fat cells via the inhibition of adenylyl cyclase activity, and Aktories and colleagues provided the first evidence that nicotinic acid might act via a G_i-coupled receptor to inhibit adenylyl cyclase activity and lower cAMP levels (11, 12). This was supported by the demonstration of specific binding of [^{3}H]nicotinic acid to membranes prepared from

adipocytes and spleen (13). Ultimately, the nicotinic acid receptor was identified as the orphan receptor GPR109A (also referred to as HM74A in humans and PUMA-G in mice) and, through the use of mice lacking the gene coding for the receptor GPR109A, was shown to be the receptor mediating the lipid-lowering effects of nicotinic acid (4–6).

HSL: hormone-sensitive lipase

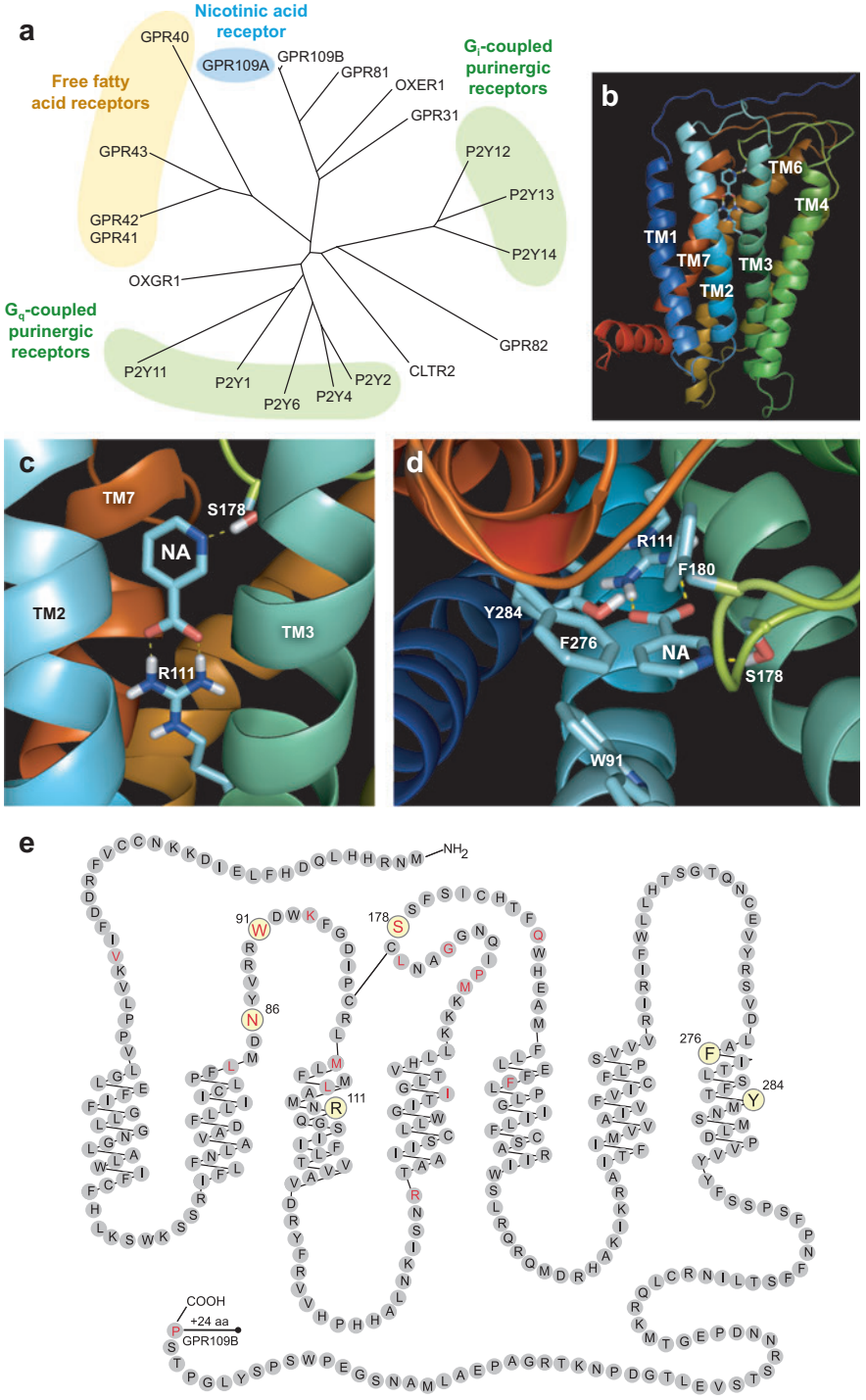
TAG: triacylglycerol

Basic Characteristics and Functions of the Nicotinic Acid Receptor GPR109A

GPR109A is a member of the class A rhodposin-like GPCRs (**Figure 1**) and contains the prototypical DRY motif. Quantitative reverse transcriptase-PCR on mRNA from various tissues showed that in addition to white and brown adipose tissue, GPR109A is also expressed at significant levels in the spleen and immune cells, such as monocytes, macrophages, dendritic cells, and in neutrophils (4–6, 14). The physiological role of GPR109A in immune cells is unclear. Interestingly, GPR109A expression in immune cells appears to be regulated by various cytokines. GPR109A expression can be upregulated by GM-CSF in neutrophils (15), whereas IFNγ increases GPR109A expression in monocytes, macrophages and Langerhans cells (14, 16).

Consistent with reports showing that the actions of nicotinic acid are pertussis toxin sensitive (17), GPR109A has been shown to couple to members of the G_i family of G proteins. Activation of G_i-type G proteins leads to different cellular effects depending on the cell type. In immune cells, for instance, G_i activation primarily results in the stimulation of β-isoforms of phospholipase C or of phosphoinositide 3-kinase γ via G protein $\beta\gamma$-subunits released from activated G_i. In many other cells, including adipocytes, activation of G_i preferentially results in the inhibition of the activity of adenylyl cyclases, resulting in a decrease in intracellular cyclic AMP levels. In adipocytes, the nicotinic acid–induced inhibition of adenylyl cyclase activity via GPR109A counteracts the activity of receptors, such as β-adrenergic receptors that via activation of G_s stimulate adenylyl cyclase activity, increase cellular cAMP levels, and stimulate protein kinase A (PKA). PKA phosphorylates a number of proteins, most notably hormone-sensitive lipase (HSL) and perilipin, which are required for triacylglycerol (TAG) hydrolysis. Phosphorylation of perilipin allows access to the TAG-containing lipid droplets by the now activated HSL and another lipase, adipose triacylglycerol lipase (ATGL), which hydrolyzes the TAGs into FFA and glycerol (18). Thus, the antilipolytic effect of nicotinic acid is likely mediated by activation of the G_i-coupled nicotinic acid receptor, impeding the cAMP/PKA signaling cascade thereby decreasing lipolysis and the subsequent release of FFA into the circulation (**Figure 2**).

The most homologous protein to GPR109A is GPR109B, which is found in humans but not in rodents and shares nearly 96% homology with GPR109A. Both genes are located in close proximity to one another on chromosome 12 in humans and GPR109B probably represents the result of a relatively recent gene duplication (19). GPR109B has an extension of 24 amino acids at the carboxy terminus relative to GPR109A, in addition to a change in 17 amino acids primarily located in the first two extracellular loops (**Figure 1**). A physiological relevance for GPR109B has yet



to be described; however, reports suggest that the receptor is expressed in a pattern similar to GPR109A, thus potentially providing an alternative therapeutic target to GPR109A. In addition to GPR109B, another closely related GPCR is the orphan receptor GPR81, whose chromosome location is also close to GPR109A (chromosome 5 in mice). Found in rodents and in humans, GPR81 is almost exclusively expressed in adipose tissue; however, the relevance of this receptor has yet to be determined (4). Based on homology, GPR109A falls into a subfamily of GPCRs, including the aforementioned receptors and the 5-oxo-eicosatetraenoic acid (5-oxo-ETE) receptor OXER1 (20) and the orphan receptor GPR31 (**Figure 1**).

Nicotinic Acid Receptor Pharmacology

A variety of nicotinic acid derivatives have been generated that selectively activate GPR109A, including acipimox, a drug with pharmacological effects similar to those of nicotinic acid (21, 22), and other carboxylic acids of nitrogen heterocyclics (23, 24) (**Table 1**, **Figure 3**). A number of pharmaceutical companies have reportedly developed selective agonists for GPR109A that do not resemble nicotinic acid and, in some cases, exclude the carboxylic acid group. Within the patent literature, Arena Pharmaceuticals has developed various GPR109A agonists, including 5-substituted pyrazole-3-carboxylic acid derivates with reported EC_{50} values in the lower micromolar range (25). This also includes tetrazole derivatives, which lack a carboxylic group (26). In addition, SmithKline Beecham Corporation reported on anthranilic acid derivatives and xanthine derivatives as GPR109A agonists (27, 28). Interestingly, Lorenzen, IJzerman, and coworkers recently described derivatives of pyrazole-3-carboxylic acids as partial agonists for GPR109A (29). Selective agonists for GPR109B have also been reported. Connolly and coworkers described a variety of 1- and 2-substituted benzotriazole-5-carboxylic acids, most notably 1-isopropyl-benzotriazole-5-carboxylic acid, as selective and relatively potent agonists at GPR109B (30). Aventis Pharmaceuticals has reportedly also developed GPR109B modulators in the form of furosemide and

Figure 1

GPR109A and related receptors. Snake and three-dimensional model of the nicotinic acid receptor. (*a*) Phylogenetic tree representing the relatedness of GPR109A and most closely related G protein–coupled receptors. Sequences were aligned using CLUSTALX, and the dendrogram was generated using PHYLIP 3.6. (*b*) Model of the nicotinic acid receptor GPR109A with bound ligand. The coordinates are based on the model of Lättich & Krause (36). Indicated are the transmembrane helices (TM). The binding pocket is formed by the transmembrane helices 2, 3, and 7, as well as by the extracellular loop 2. (*c*) Close-up view of the nicotinic acid (NA) binding pocket in the model shown in (*b*). The binding pocket is built by arginine 111 (TM3), serine 178 (extracellular loop 2), as well as several other residues in TM2 and TM7. Proposed hydrogen bonding is indicated by yellow dashed lines. (*d*) View on the nicotinic acid (NA)-binding pocket of GPR109A from the extracellular side. (*e*) Secondary structure of the human nicotinic acid receptor GPR109A. Red amino acid symbols indicate residues in GPR109A that differ from GPR109B. In addition, GPR109B has a C terminus that is extended by 24 amino acids. Shown in yellow circles are those residues that are required for nicotinic acid binding and most likely participate in forming the binding pocket.

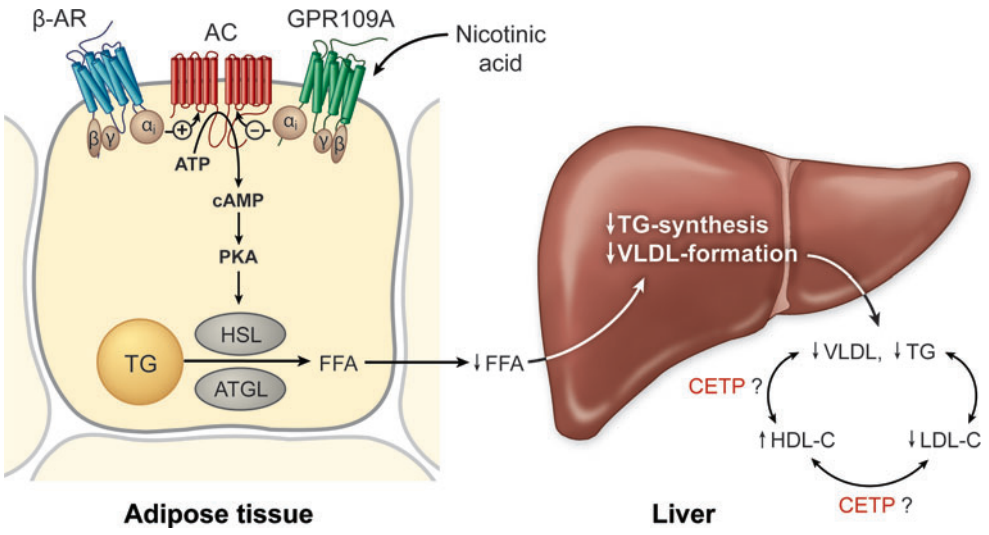


Figure 2

Metabolic effects of nicotinic acid at pharmacological doses. Activation of the nicotinic acid receptor GPR109A on adipocytes induces a G_i-mediated inhibition of adenylyl cyclase (AC) activity resulting in a decrease of cAMP levels. This leads to a decrease in lipolysis, as cAMP is the main intracellular mediator of prolipolytic stimuli, such as sympathetic stimuli acting through the β-adrenoceptor (β-AR). cAMP activates protein kinase A (PKA), which increases lipolysis by phosphorylation of various proteins, including perilipin and hormone-sensitive lipase (HSL). The decrease in free fatty acid (FFA) levels induced by nicotinic acid results in a substrate shortage for hepatic triglyceride (TG) synthesis. Consequently, less triglycerides and less VLDL are produced by the liver, and as a result, triglyceride and VLDL as well as LDL plasma levels drop. The mechanism of the nicotinic acid–induced increase in HDL cholesterol levels is less clear. Most likely, the decrease in triglyceride levels in ApoB-containing lipoproteins (LDL/VLDL) results in a decreased exchange between cholesterol esters carried by HDL particles and triglycerides in VLDL and LDL particles mediated by CETP, resulting in an increase in HDL cholesterol plasma concentrations. ATGL, adipocyte triglyceride lipase.

oxydecahydronaphthalene derivatives (31, 32). As noted above, no ligands have yet been reported for the closely related receptor GPR81.

Despite the high degree of sequence homology between GPR109A and GPR109B, there is a surprising disparity in the pharmacology of the two receptors (**Table 1**, **Figure 3**). Nicotinic acid has an EC_{50} in the high nanomolar range at GPR109A, whereas nearly a 1000-fold higher concentration is required to elicit activation of GPR109B, indicating that GPR109B is unlikely to be involved in the pharmacological effects of nicotinic acid. In fact, only the synthetic compound acifran, which has effects similar to those of nicotinic acid on lipid metabolism (33), has been identified as having near equipotency at the two receptors, with an EC_{50} of approximately 1 μM at GPR109A and 7 μM at GPR109B (4). Recently, it was reported that synthetic analogues of acifran in which the phenyl ring was replaced by a thiophene group have an increased potency at GPR109A. In particular, the (+)-enantiomer of

Table 1 EC_{50} values (μM) for ligands of GPR109A and GPR109B

Ligand	GPR109A	GPR109B	Reference
Nicotinic acid	0.10[b]	>100	(35)
Nicotinamide	Inactive	Inactive	(4, 5)
D-β-hydroxy-butyrate	770[b]	>25,000[b]	(35)
Acipimox	5.0[c]	>100	(5)
1-isopropyl-benzotriazole-5-CA	>1000[d]	0.4[d]	(30)
Acifran	1.13[b]	7.04[b]	(35)
(+)-5-Cl-3-thienyl acifran derivative	0.066[d]	0.69[d]	(34)
5-MSM-2H-pyrazole-3-CA	4.3[c]	NR	(25)
5-propyl-1H-pyrazole-3-CA	6.1[b]	NR	(29)
Tetrazole derivatives[a]	≤1[b]	NR	(26)
Anthranilic acid derivatives[a]	≥10	NR	(27)
Xanthine derivatives[a]	≥12.6[b]	NR	(28)

[a]Nonspecified derivatives.
[b]GTPγS binding assay.
[c]Ca^{2+} assay.
[d]cAMP assay.
Abbreviations: 5-MSM-2H-pyrazole-3-CA, 5-[(methylsufanyl)methyl]-2H-pyrazole-3-carboxylic acid; NR, not reported.

5-Cl-3-thienyl substitutions is more than 20-fold more potent than acifran at GPR109A, whereas the potency at GPR109B increases approximately tenfold (34).

Whereas pharmacological agents are in development to target these receptors, efforts to identify the endogenous ligands have been intense. Nicotinic acid is unlikely to be the endogenous ligand of GPR109A, as plasma concentrations are approximately 0.1–0.4 μM. A recent report demonstrates the activation of GPR109A by β-hydroxybutyrate, a ketone body produced during starvation (35). Although other ketone bodies, such as acetone and acetoacetate, have no activity at the receptor, β-hydroxybutyrate activates the receptor with an EC_{50} of approximately 750 μM. Whereas basal levels of β-hydroxybutyrate are in the range of 50–400 μM, plasma concentrations increase to levels in the lower millimolar concentration range under fasting conditions and can reach levels of 6–8 mM after prolonged starvation. As the formation of ketone bodies in the liver during starvation conditions depends on the delivery of FFA released from adipocytes after formation through lipolysis, the antilipolytic effect exerted by millimolar concentrations of β-hydroxybutyrate via activation of GPR109A on adipocytes most likely functions as a negative feedback regulatory mechanism (**Figure 4**). In this way, ketone bodies may counter-regulate the activity of prolipolytic stimuli during starvation, and the antilipolytic effects mediated by GPR109A would be required to maintain metabolic homeostasis to conserve energy when fasting.

The carboxylic acid moiety of ligands plays a critical role in the activation of the receptor, a conclusion that is strikingly evident when comparing nicotinic acid with its vitamin counterpart, nicotinamide, which has no activity at either GPR109A or

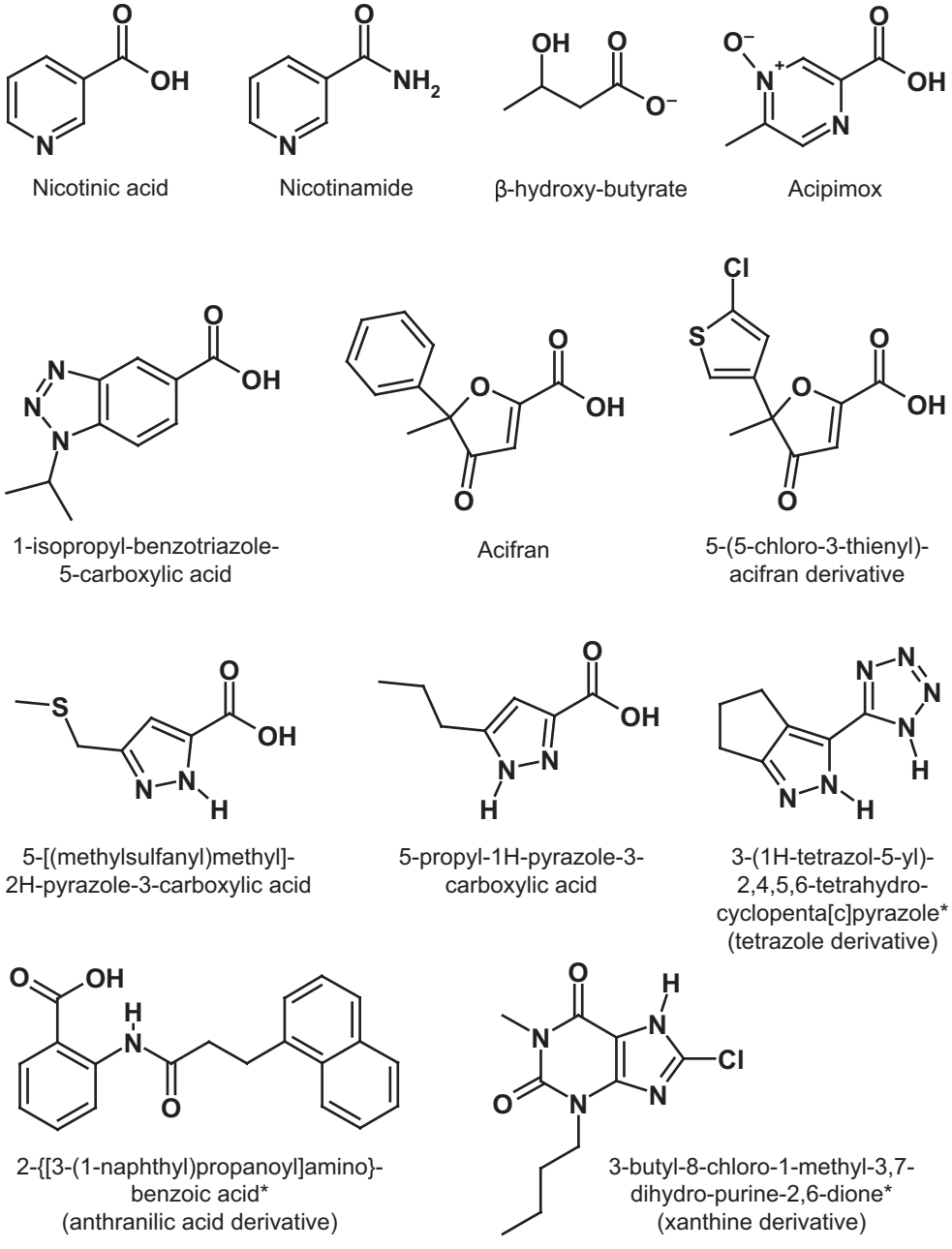


Figure 3

Ligands of GPR109A and GPR109B. *Examples of generally described derivatives.

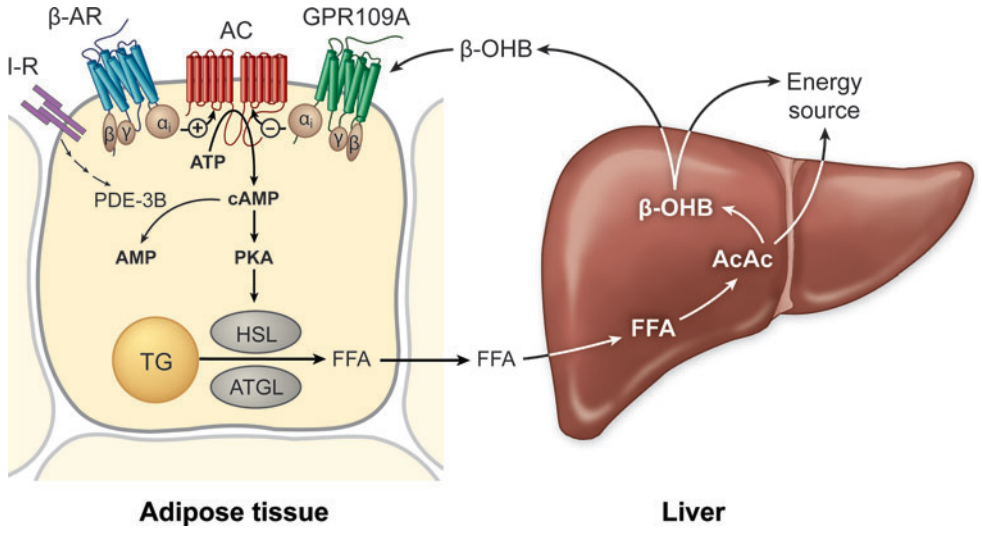


Figure 4

Potential physiological role of the nicotinic acid receptor GPR109A under starvation. Under such conditions, sympathetic stimulation of adipose cells via β-adrenoceptors (β-AR) is high and insulin levels are low, resulting in increased intracellular cAMP levels that stimulate lipolysis. FFAs that are released from fat cells are then metabolized in the liver to ketone bodies, including β-hydroxybutyrate (β-OHB) and acetoacetate (AcAc), which serve as important energy sources, e.g., for the brain. Plasma concentrations of β-OHB, which activates GPR109A with an EC_{50} of 750 μM, are in the upper micromolar and lower millimolar range under starvation conditions. The ability of millimolar concentrations of β-OHB to inhibit lipolysis via activation of GPR109A may represent an important negative feedback regulatory mechanism that helps to adjust an optimal lipolytic activity with starvation. GPR109A-mediated inhibition of adenylyl cyclase (AC) activity and the resultant decrease in cAMP synthesis would counteract the increased β-AR-mediated cAMP formation and the decreased cAMP degradation by phosphodiesterase 3B (PDE-3B) under starvation conditions. I-R, insulin-receptor.

GPR109B (4, 5). The high homology, yet stark pharmacological contrast, between GPR109A and GPR109B has allowed the determination of critical residues involved in ligand binding. By systematically employing site-directed mutagenesis, generating GPR109A/GPR109B receptor chimeras, and taking advantage of the pharmacological selectivity of the two receptors, the transmembrane helices 2, 3, and 7, the extracellular loop 2, and the junction of TM2/ECL1 were identified as being directly involved in nicotinic acid binding to GPR109A (36) (**Figure 1**). These binding properties of GPR109A are rare, although not altogether unique, among the class A receptors. Within the identified critical regions of GPR109A, amino acid residues Asn86, Trp91, Ser178, Phe276, and Tyr284 are absolutely required for nicotinic acid binding. Additionally, Arg111, which is conserved in GPR109B and GPR81, seems to be the positively charged residue involved in forming a salt bridge with the carboxylic acid group found in receptor agonists (36) (**Figure 1**).

USE OF NICOTINIC ACID IN THE PREVENTION OF ATHEROSCLEROSIS

VLDL: very-low-density lipoprotein

Atherosclerosis is characterized by the accumulation of cholesterol, various other lipids, extracellular matrix, and various inflammatory cells in the subendothelium, resulting in the narrowing of the vessel lumen (37, 38). The atherosclerotic lesion may eventually become unstable and rupture, exposing a highly prothrombotic surface that leads to arterial thrombosis. As a chronic progressive disorder of arterial blood vessels, atherosclerosis represents the predominant cause of multiple cardiovascular diseases. One of the major risk factors for atherosclerosis is a dyslipidemic state characterized by elevated levels of cholesterol in apolipoprotein B (apoB)-containing lipoproteins, including LDL and very-low-density lipoproteins (VLDLs), but with low cholesterol levels in the HDL fraction. The accumulation of cholesterol-rich LDL particles in the intima of arterial blood vessels and their subsequent modification has been shown to be an integral part of the initial phase of atherogenesis (39). In contrast, HDL particles have anti-atherogenic properties due to their ability to take up cholesterol from nonhepatic cells and transport them back to the liver via what has been termed the reverse cholesterol transport pathway (40). In addition, HDL appears to have anti-inflammatory and anticoagulatory properties (41, 42).

The lowering of the plasma levels of cholesterol associated with proatherogenic LDL particles is one of the most important therapeutic measures that have been used to reduce cardiovascular morbidity and mortality. Through the inhibition of cholesterol synthesis by HMG-CoA reductase inhibitors (statins) and inhibitors of cholesterol absorption, the concentration of LDL-cholesterol in the plasma can be reduced to relatively low levels. Despite this large therapeutic effect, even the aggressive lowering of LDL cholesterol levels reduces the occurrence of cardiovascular events only by 25%–40% (43). The insufficient efficacy of the lowering of LDL-cholesterol levels with regard to the reduction of cardiovascular events can be explained by the fact that high LDL-cholesterol levels are only one of several risk factors for the initiation and progression of atherosclerosis. In addition to various other risk factors, such as arterial hypertension, age, cigarette smoking, and genetic factors, low HDL cholesterol levels have been found to be an independent risk factor for cardiovascular diseases (44–47). The increased awareness of the role of low HDL-cholesterol levels as a risk factor for cardiovascular diseases as well as the optimization of strategies aimed at the lowering of LDL-cholesterol levels have recently shifted the focus of research toward innovative approaches to raise HDL-cholesterol levels (48, 49). Although there are several novel strategies being pursued, the oldest lipid-modifying drug, nicotinic acid, has recently enjoyed a renaissance owing to its strong HDL-cholesterol-elevating effect, which is unique among the drugs currently approved for clinical use (2).

Clinical Use of Nicotinic Acid

The spectrum of changes in lipid metabolism induced by nicotinic acid is broad. In addition to a decrease in both LDL-cholesterol and total cholesterol (1, 50), as well as

Table 2 Effects of nicotinic acid (>1,5 g day^{-1}) on plasma concentrations of lipids and lipoproteins

VLDL ↓ (25–40%)
LDL-cholesterol ↓ (6–22%)
HDL-cholesterol ↑ (18–35%)
Total cholesterol ↓ (4–16%)
Triglyceride ↓ (21–44%)
Lipoprotein Lp(a) ↓ (16–36%)

Data from References 53, 96, 97, 122.

an increase in HDL-cholesterol (51, 52), the VLDL plasma concentration drops, and with it the concentration of triglycerides (53) (**Table 2**). Interestingly, treatment with nicotinic acid also results in a decrease in lipoprotein Lp(a) levels (53), an independent risk factor for coronary heart disease (54). Within a few years after the discovery that nicotinic acid induces profound changes in plasma lipid concentrations, the drug was introduced into clinical therapy and the therapeutic efficiency was studied in clinical trials (**Table 3**). In the Coronary Drug Project (1966–1975), monotherapy with nicotinic acid at doses of 3 g day^{-1} was shown to improve secondary prevention of myocardial infarction (55). Interestingly, a follow-up study of the Coronary Drug Project revealed that all-cause mortality in the nicotinic acid group was significantly lower than in the placebo group, although most participants had discontinued drug treatment after the original trial period. The decreased mortality was primarily attributed to a reduction in occurrence of coronary heart disease (56). Similar results were obtained in the Stockholm Ischemic Heart Disease Secondary Prevention Study (57). The subsequent introduction of cholesterol synthesis inhibitors (statins) in the pharmacotherapy of hypercholesterolemia, as well as the unwanted effects of nicotinic acid (see below), resulted in a reduced interest in the therapeutic utility of nicotinic acid in the following years. Recently, however, several clinical studies have evaluated the therapeutic potential of nicotinic acid in statin-treated patients with low HDL-cholesterol levels and revealed that such patients may benefit from treatment with nicotinic acid in addition to standard statin therapy (**Table 3**). In the HDL Atherosclerosis Treatment Study (HATS) trial, patients with coronary heart disease and low HDL-cholesterol levels were treated for three years with 2–4 g day^{-1} nicotinic acid and simvastatin (10–20 mg day^{-1}). This treatment resulted in a reduction in major coronary events by 90% compared with placebo (58). Although an ideal control group treated with simvastatin alone was not tested, the reduction in cardiovascular events in patients treated with simvastatin and nicotinic acid was much larger than would have been expected from simvastatin treatment alone. In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2) trial, patients with coronary heart disease and low HDL cholesterol levels who received standard statin therapy were also treated with either placebo or nicotinic acid (1 g day^{-1}). Atherosclerosis, measured as carotid intima-media thickness, progressed in the placebo/statin group but not in the nicotinic acid/statin group (59). Both studies were conducted with a relatively small number of patients and their

Table 3 Clinical studies on the effect of nicotinic acid in the prevention of cardiovascular diseases

Study	Method	Placebo	Nicotinic acid	p-value
Coronary Drug Project (55)	8341 patients after myocardial infarction 5 years, 3 g day^{-1}			
	myocardial infarction	12.2%	8.9%	<0.05
	total mortality	20.9%	21.2%	ns
Canner et al. (56)	Coronary Drug Project follow-up after 15 years			
	total mortality	58.2%	52%	<0.005
Carlson & Rosenhamer (57)	276 patients after myocardial infarction nicotinic acid + clofibrate			
	total mortality	29.7%	21.8%	<0.05
FATS[1] (123)	146 patients with coronary artery disease 2.5 years, 4 g day^{-1} + colestipol 30 g day^{-1}			
	lesion progression	46%	25%	?
	lesion regression	11%	39%	<0.005
	cardiovascular events	10/52	2/48	<0.01
HATS[2] (58)	160 patients with coronary heart disease and low HDL cholesterol (males < 35 mg dl^{-1}; females < 40 mg dl^{-1}), 3 years nicotinic acid (2–4 g day^{-1}) + simvastatin (10–20 mg day^{-1})			
	cardiovascular events	nt[4]	3%	
ARBITER 2[3], Taylor et al. (59)	167 patients with coronary heart disease and low HDL cholesterol (<45 mg dl^{-1}), 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

[1]Familial Atherosclerosis Treatment Study (123).
[2]HDL Atherosclerosis Treatment Study (58).
[3]Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (59).
[4]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.
ns, not significant; nt, not tested.

value is limited owing to the lack of an optimal control group in the HATS trial and the analysis of a surrogate parameter in the ARBITER 2 trial. Nevertheless, together with the older studies, they clearly point to a therapeutic benefit of nicotinic acid (3) and represent a basis on which randomized long-term studies analyzing the effect of nicotinic acid added to statins in patients with low HDL-cholesterol levels and an increased risk for cardiovascular events have been initiated (60).

Mechanisms of Nicotinic Acid Effects on Lipid Metabolism

Within minutes, oral administration of nicotinic acid causes a decrease in FFA plasma levels, followed by a reduction in the concentration of VLDL triglycerides. Plasma triglyceride levels start to drop approximately 2 h after oral administration of a single dose of nicotinic acid, and reach a maximum reduction after 4 h (61). In contrast, levels of LDL-cholesterol are significantly lowered only after 4–5 days of treatment with nicotinic acid (61). Because the hepatic VLDL production appears to be primarily substrate-driven (62), the rapid decrease in the plasma concentration of FFA induced by nicotinic acid and the reduced FFA supply for the synthesis of triglycerides in the liver results in a reduced formation of VLDL and, in turn, of LDL particles (**Figure 2**). This is consistent with the observation that in mice lacking nicotinic acid receptors, not only the decrease in FFA plasma levels but also a subsequent decrease in plasma triglyceride levels in response to nicotinic acid is abrogated (5). This strongly suggests that the nicotinic acid receptor–mediated antilipolytic effect of nicotinic acid is required for the decrease in FFA and triglyceride levels observed after administration of nicotinic acid.

CETP: cholesterol ester transfer protein

Recently, an alternative mechanism for the nicotinic acid–induced reduction in ApoB-containing lipoproteins, such as VLDL and LDL, has been suggested. Studies in a human hepatoblastoma cell line showed that nicotinic acid accelerated the intracellular degradation of ApoB by inhibiting triglyceride synthesis, which results in a decreased formation of ApoB-containing VLDL (63). In addition, it has been postulated that nicotinic acid decreases hepatic triglyceride synthesis through the inhibition of diacylglycerol acyl transferase 2 (DGAT2) (64). However, inhibition of ApoB secretion and of DGAT2 was only observed at nicotinic acid concentrations of 0.25–3.0 mM, which are approximately 100-fold higher than the plasma concentrations associated with maximal pharmacological effects of nicotinic acid on FFA and VLDL-triglyceride levels (65). Thus, it is rather unlikely that the inhibition of hepatic ApoB secretion strongly contributes to the lipid-lowering effects of nicotinic acid observed at therapeutic doses. If nicotinic acid has direct effects on hepatocytes, they are not mediated by the nicotinic acid receptor, which is not expressed in the liver (4–6).

It is currently not clear how nicotinic acid increases HDL-cholesterol plasma levels. The prevailing hypothesis is based on the exchange of triglycerides and cholesterol esters between ApoB-containing lipoproteins (especially VLDL and LDL) and HDL, which is mediated by the cholesterol ester transfer protein (CETP). After treatment with nicotinic acid, a decrease of the triglyceride content in VLDL and LDL particles caused by the antilipolytic effect of nicotinic acid is expected to result in a decreased exchange of triglycerides and cholesterol esters between VLDL/LDL and HDL particles, resulting in an increase in HDL-cholesterol levels (**Figure 2**). This is supported by a strong negative correlation between triglyceride levels and plasma HDL-cholesterol concentrations (66). An inhibition of the CETP enzyme results in similar effects on HDL-cholesterol plasma levels, with an increase especially in the HDL_2 fraction (67). A critical role of CETP in nicotinic acid-induced elevation of HDL cholesterol levels is also suggested by recent data obtained in mice. Wild-type animals do not express CETP and have relatively high HDL-cholesterol levels, which

PPAR: peroxisome proliferator activator receptor

are decreased by nicotinic acid treatment. However, mice transgenically expressing the human CETP gene have lowered HDL cholesterol levels that are increased after 2 weeks of nicotinic acid treatment (68). An involvement of GPR109A in the nicotinic acid–induced increase in HDL-cholesterol levels is indicated by the correlation of agonism of GPR109A with the *in vivo* ability to increase HDL-cholesterol. Acipimox, for instance, which reduces FFA plasma levels by inhibition of adipocyte lipolysis via activation of GPR109A, also increases HDL-cholesterol levels (69); whereas nicotinamide, which is not an agonist of GPR109A, has no effect on the plasma levels of cholesterol (70).

It has also been proposed that nicotinic acid increases HDL-cholesterol levels by decreasing the catabolism of ApoA-I-containing lipoproteins (52, 71). Incubation of a hepatoma cell line with nicotinic acid at millimolar concentrations has been shown to decrease the uptake of HDL-ApoA-I, whereas the uptake of labeled cholesterol from HDL was unaffected (72, 73). Again, these in vitro studies are hampered by the fact that effects were observed at relatively high nicotinic acid concentrations (0.25–3.0 mM), which are far higher than the therapeutic plasma concentrations.

Another potential mechanism by which nicotinic acid increases HDL-cholesterol and decreases the progression of atherogenesis may involve macrophages that express the nicotinic acid receptor (16). Evidence has been provided showing that nicotinic acid increases peroxisome proliferator-activated receptor γ (PPARγ) expression and enhances PPARγ transcriptional activity in macrophages (74, 75). Although there is evidence that this effect involves the nicotinic acid receptor (74), the mechanism linking the receptor to the regulation of PPARγ expression and activity is less clear. It has been speculated that this involves the formation of the PPARγ activator 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) (74). Given the above data and the well-documented expression of the nicotinic acid receptor in peripheral macrophages, it remains an attractive hypothesis that nicotinic acid exerts its beneficial effects, at least in part, by enhancing the removal of cholesterol from peripheral macrophages and macrophage foam cells of atherosclerotic lesions and subsequent stimulation of reverse cholesterol transport.

UNWANTED PHARMACOLOGICAL EFFECTS OF NICOTINIC ACID

Common unwanted side effects of orally administered nicotinic acid are flushing and gastrointestinal symptoms, such as nausea and diarrhea (76). Although these effects can be regarded as relatively harmless, they strongly affect patients' compliance. Other less common unwanted effects, such as a decrease in glucose tolerance or an increase in plasma uric acid levels, can usually be well controlled but need to be taken into consideration in patients with additional diseases, such as diabetes or hyperuricemia.

Nicotinic Acid–Induced Flushing

The most common side effect of nicotinic acid is a cutaneous vasodilatation called flushing. A dose of 50–100 mg of nicotinic acid is sufficient to elicit flushing of the

face and upper body (77, 78). Higher doses (500–1000 mg) lead to a much stronger vasodilatation that also affects the rest of the body. The flush lasts for 30–90 min and is associated with intense erythema, tingling, itching, and elevation in skin temperature. The symptoms are often described as being similar to a sunburn but shorter lasting. Flushing is subject to tolerance as it markedly decreases after several weeks of continuous treatment with nicotinic acid. Therefore, flushing is seen primarily in the beginning of therapy. Some patients are prone to more severe skin reactions, with additional burning sensation, urticaria, periorbital edema, conjunctivitis, or nasal congestion. Up to one third of patients treated with nicotinic acid discontinue the drug mainly owing to intolerable flushing (55).

PGE_2: prostaglandin E_2

PGD_2: prostaglandin D_2

Mechanism of Nicotinic Acid–Induced Flushing

Pretreatment with inhibitors of cyclooxygenase reduces the nicotinic acid–induced flushing response but does not affect the desirable therapeutic effects of nicotinic acid (79–82). This strongly suggests that prostanoids are involved in the flushing phenomenon. This hypothesis was supported by the finding that increased levels of the vasodilatory prostanoids prostacyclin (PGI_2), prostaglandin E_2 (PGE_2), and prostaglandin D_2 (PGD_2) and their metabolites could be found after administration of nicotinic acid (79–81, 83–85). The strongest increases were of the PGD_2 metabolite 9α,11β-PGF_2 (85). The flushing response is subject to some tolerance, whereas the antidyslipidemic effects of nicotinic acid are not (86). Interestingly, the formation of PGI_2 and PGD_2 in response to nicotinic acid decreased after continuous administration of nicotinic acid with a time course that paralleled the development of tolerance to nicotinic acid–induced flushing (83, 87). This further supports a critical role of prostanoids in nicotinic acid–induced flushing and points to a mechanism upstream of prostanoids underlying the tolerance phenomenon.

The discovery of the nicotinic acid receptor GPR109A, which is expressed not only on adipocytes but also in immune cells such as macrophages (4–6, 16), raised the question whether the flushing is mediated by the receptor and which cells are involved. This question was addressed by studying nicotinic acid–induced changes in cutaneous blood flow in wild-type mice and mice deficient in GPR109A through the use of laser Doppler flowmetry. In contrast to wild-type animals, mice deficient in GPR109A did not display flushing in response to nicotinic acid. Bone marrow transplantation from wild-type mice to lethally irradiated GPR109A deficient mice, however, rescued the flushing response (88). Thus, activation of GPR109A on bone marrow–derived cells is necessary to induce flushing. The involvement of prostanoids in nicotinic acid–induced flushing was recently also demonstrated by studies in mice lacking cyclooxygenase type 1 (COX-1) that fail to respond with flushing to nicotinic acid (88). Of the three potential vasodilatory prostanoids, PGI_2, PGD_2, and PGE_2, the latter two appear to be involved in nicotinic acid–induced cutaneous vasodilation. In mice lacking the prostaglandin E_2 receptors EP_2 and EP_4 or the prostaglandin D_2 receptor DP_1, the flushing response to nicotinic acid was reduced, whereas the response was unaffected in mice lacking the PGI_2 receptor IP (88). In addition, a specific DP_1 receptor antagonist strongly reduces the flushing in mice and in humans (89).

The topical application of skin-permeable nicotinic acid esters causes local cutaneous reactions very similar to those evoked by the systemic application of nicotinic acid (90–92). This finding and studies indicating that nicotinic acid induces local formation of prostanoids in the skin (93) strongly suggest that the nicotinic acid–induced flushing response is a local cutaneous phenomenon. Transplantation of wild-type bone marrow to irradiated GPR109A-deficient mice can rescue the nicotinic acid–induced flushing response, indicating that the receptor on bone marrow-derived cells of the skin mediates the flushing phenomenon. It has been reported that mast cells are not involved in flushing (85, 88), and depletion of macrophages or dendritic cells had no effect on nicotinic acid–induced flushing (94). Recently, strong evidence has been provided that Langerhans cells are critically involved in the nicotinic acid–induced flushing phenomenon (14, 94). Langerhans cells were shown to express GPR109A and to respond with an increase in intracellular Ca^{2+} to nicotinic acid. In addition, Langerhans cells express PGE_2 and PGD_2 synthases, and high concentrations of nicotinic acid are able to induce PGD_2 formation in isolated Langerhans cells (14, 94). When mice are depleted of Langerhans cells, the nicotinic acid–induced flushing response is abolished (94). From these data and additional reports indicating that nicotinic acid can induce the PLA_2-mediated formation of arachidonic acid by an increase in intracellular Ca^{2+} (95), the following model for the nicotinic acid–induced flushing response has emerged. Nicotinic acid induces an increase in intracellular Ca^{2+} via its receptor on epidermal Langerhans cells. A Ca^{2+}-sensitive PLA_2 becomes activated, and the subsequently formed arachidonic acid is further metabolized to the active prostanoids PGD_2 and PGE_2, which via their G_s-coupled receptors (DP_1, EP_2, and EP_4) induce vasodilation in the upper layer of the dermis (**Figure 5**).

Pharmacological Strategies to Decrease Flushing

General recommendations to decrease the intensity of flushing after administration of nicotinic acid include the gradual increase of the daily dose over a 1- to 4-month period and the avoidance of hot beverages. Flushing has also been reported to be less severe when high peak plasma levels are avoided. One gram of nicotinic acid given orally will result in a peak plasma concentration of 15–30 $\mu g\ ml^{-1}$ within 30–60 min. Almost 90% of the administered nicotinic acid is rapidly eliminated by the kidney as unchanged drug or nicotinuric acid, and the plasma elimination half-life of nicotinic acid ranges from 20–45 min. Because the onset of the flush is closely related to the rapid increase in plasma levels, one approach to ameliorate this unwanted effect is to reduce the peak plasma concentrations. To achieve this, slow-release formulations of nicotinic acid (e.g., Niaspan®) have been generated. The slow intestinal release of nicotinic acid from this formulation delays and decreases the peak in the plasma concentration compared with plain nicotinic acid and causes fewer flushing events and fewer gastrointestinal side effects (96). The discontinuation rate of extended release formulations is smaller than that of plain nicotinic acid in short-term trials (97–99). A similar mechanism most likely underlies the lower intensity and frequency of flushing observed in response to acipimox, which also functions as an agonist on GPR109A but is absorbed significantly slower after oral administration and has a considerably longer plasma

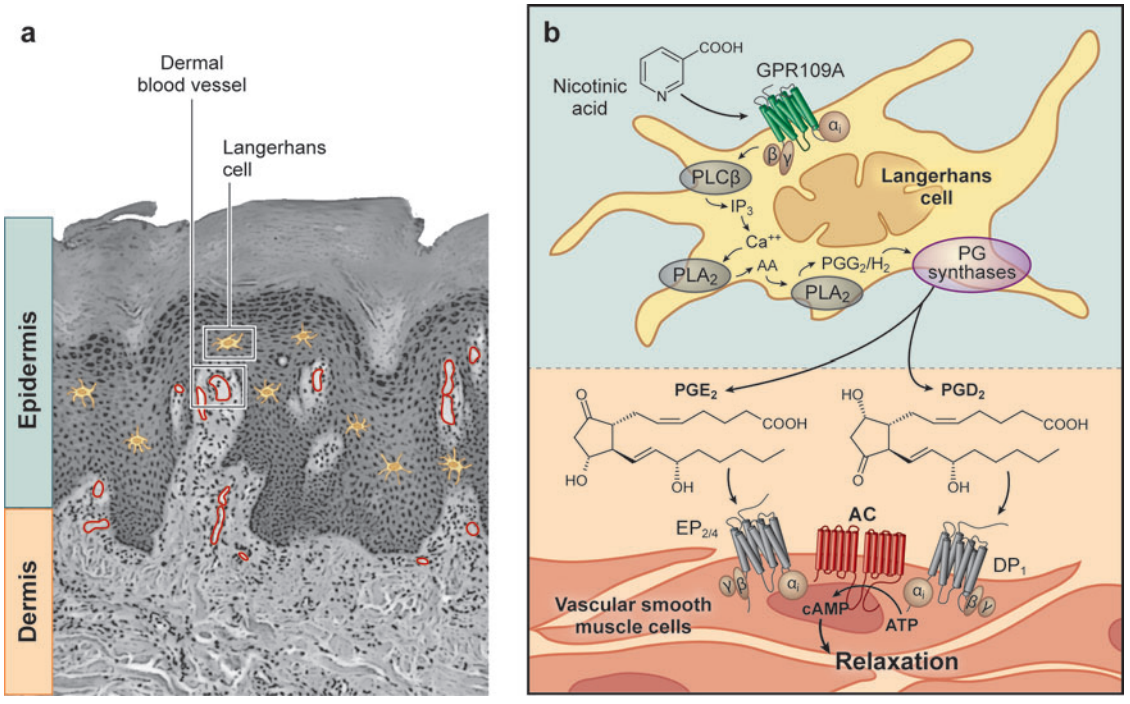


Figure 5

Potential mechanism of nicotinic acid–induced flushing. (*a*) Section of the skin with the epidermal and dermal layer containing Langerhans cells (*yellow*) and blood vessels (*red*), respectively. (*b*) Nicotinic acid induces the cutaneous flushing reaction by activation of GPR109A on cutaneous immune cells, most likely epidermal Langerhans cells. Activation of GPR109A on Langerhans cells results in an activation of β-isoforms of phospholipase C (PLCβ) via Gβγ-subunits. The consecutive inositol-1,4,5-trisphosphate (IP_3)-mediated release of intracellularly stored Ca^{2+} induces an activation of phospholipase A_2 (PLA_2) and the formation of arachidonic acid (AA). AA is then further metabolized via cyclooxygenase-1 (COX-1) to prostaglandin G_2 and prostaglandin H_2 (PGG_2/H_2) and subsequently via prostaglandin D_2 and prostaglandin E_2 synthases to the vasodilatory prostanoids prostaglandin D_2 (PGD_2) and prostaglandin E_2 (PGE_2). PGD_2 and PGE_2 are then acting on subepidermal blood vessels to induce a vasodilation via activation of DP_1 and EP_2/EP_4 receptors. These receptors have in common that they couple to G_s and lead to a stimulation of adenylyl cyclase (AC) activity and an increase in intracellular cAMP, which relaxes vascular smooth muscle.

half-life (100). Recent evidence suggests that synthetic partial agonists of GPR109A may induce much less flushing while retaining full antilipolytic activity (100a).

In addition, flushing can be reduced by the inhibition of cyclooxygenase (COX). COX inhibitors, such as acetylsalicylic acid (aspirin) and indomethacin, applied before administration of nicotinic acid have been used to prevent flushing (101, 102). Aspirin used to reduce the flush initially can be discontinued after tolerance has developed. A novel approach to reduce flushing in response to nicotinic acid is to antagonize the vasodilatory effects of prostanoids by blocking the DP_1 receptor (89). In humans, the DP_1 receptor antagonist laropiprant (MK-0524) reduced nicotinic acid–dependent

increases in malar skin blood flow and lowered flushing symptom scores (103). The practical problem, i.e., that COX-inhibitors and DP_1 antagonist have to be administered before nicotinic acid, may be overcome by the combination with a slow-release formulation of nicotinic acid.

Metabolic Effects of Nicotinic Acid in Patients with Metabolic Syndrome and/or Diabetes

Many diabetic or prediabetic patients show a dyslipidemic profile characterized by elevated triglyceride and low HDL-cholesterol plasma levels, while total cholesterol and LDL-cholesterol plasma concentrations are often in the normal range. This dysregulation of lipid metabolism is believed to contribute to the increased cardiovascular risk associated with diabetes (104–106). Thus, the spectrum of changes in lipid metabolism induced by nicotinic acid appears to be ideal to treat dyslipidemic states in diabetic or prediabetic patients. In addition, the antilipolytic effects of nicotinic acid that result in the lowering of plasma FFA levels would be expected to benefit patients with insulin resistance because increased circulating FFA levels have been shown to decrease insulin sensitivity (107). However, based on reports indicating that nicotinic acid may increase insulin resistance, concerns have been raised regarding the use of nicotinic acid in diabetic patients (108, 109). It had been speculated that the nicotinic acid–induced decrease in insulin sensitivity is due to the rebound increase in FFA levels observed when nicotinic acid blood levels fall. However, insulin resistance could also be observed when plasma nicotinic acid levels were kept in a therapeutic range (108). On the other hand, the nicotinic acid analog acipimox, which is also an agonist of GPR109A but does not induce a rebound increase in FFA levels, has been reported to have no effect on insulin sensitivity (21, 22). Thus, it is unclear whether the nicotinic acid–induced increase in insulin resistance is a class effect of agents acting via GPR109A or whether it represents a specific side effect of nicotinic acid. Despite the unclear mechanism of nicotinic acid effects on glucose tolerance, several studies have addressed the risk-benefit ratio of nicotinic acid therapy in diabetic patients. A post-hoc analysis of the Coronary Drug Project revealed that the benefit of nicotinic acid treatment in patients with decreased glucose tolerance was similar to that of patients with normal glucose tolerance (110). Two recent clinical studies demonstrated that in well-controlled type 2 diabetic patients, the administration of nicotinic acid is relatively safe, having no or only marginal effects on plasma levels of glucose and glycosylated hemoglobin (Hb_{A1c}) (111, 112). Although nicotinic acid has a well-documented potential to increase insulin resistance, there is good evidence that the beneficial effects of this drug on lipid metabolism associated with decreased cardiovascular risk outweigh the potential risk owing to the impairment of glucose tolerance, provided that patients at risk are identified and that tight glycemic control is implemented.

Other Unwanted Effects

Oral administration of nicotinic acid can have gastrointestinal effects, such as heartburn, indigestion, nausea, diarrhea, or stomach pain. Whether these unwanted effects

result from nonspecific local effects of nicotinic acid that is given in gram quantities or whether they involve the local activation of GPR109A-expressing cells, such as macrophages, is not known. Unwanted effects affecting the gastrointestinal system can be blunted by taking nicotinic acid with meals.

Occasionally, treatment with nicotinic acid causes hepatotoxicity accompanied by an increase in plasma transaminase activities (113, 114). Hepatic side effects appear to occur more often when nicotinic acid is given in a sustained-release form (113, 115). It has been speculated that this is due to the increased hepatic metabolism of slow-release forms of nicotinic acid 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 (115a).

The oral administration of nicotinic acid has been reported to occasionally induce hyperuricemia and gout (116), which is likely due to a decrease in uric acid excretion (117). Nicotinic acid can increase urate reabsorption in the kidney, where nicotinate functions as a counter-ion for the main uric acid transporter URAT1 (118, 119).

FUTURE DEVELOPMENTS

During the past two decades, the lipid-modifying therapies to prevent cardiovascular diseases have primarily focused on the lowering of LDL-cholesterol plasma levels. Despite the impressive success made in achieving low LDL-cholesterol levels through pharmacotherapy, a residual 60%–80% risk remains that requires alternative approaches. Among them, the increase in HDL-cholesterol levels, especially in patients with low levels, is one of the major strategies currently pursued. One of the promising new approaches to elevate HDL-cholesterol levels has been the inhibition of the CETP. However, the recent failure of the CETP inhibitor torcetrapib in Phase III trials (120, 121) has been a setback for this approach. Currently, the oldest antidyslipidemic drug, nicotinic acid, remains the best choice for increasing HDL-cholesterol plasma levels. However, despite promising clinical data indicating a beneficial effect of nicotinic acid, large outcome trials that evaluate the effect of nicotinic acid as an add-on therapy to statins in comparison with a statin monotherapy have only recently been initiated; results of these studies are expected several years from now.

The recent discovery of a receptor for nicotinic acid has allowed new insight into the mechanisms underlying the pharmacological effects of nicotinic acid. In the upcoming years it will be of particular interest to understand in which aspects of the pharmacology of nicotinic acid the receptor is involved. It is conceivable that some of the effects of nicotinic acid are not mediated by the receptor. Furthermore, receptors related to GPR109A, such as GPR109B and GPR81, which are also expressed in adipocytes, will be explored as potential new drug targets. The work on the mechanism underlying nicotinic acid pharmacology will be promoted by the development of new agents that act as agonists, antagonists, or modulators on the nicotinic acid receptor GPR109A and which can be used as tools to study the role of the receptor in physiology and pharmacology. One of the principal objectives would be that new GPR109A agonists have superior pharmacokinetic and pharmacodynamic

properties to nicotinic acid. A major goal will be to retain the anti-dyslipidemic effects of nicotinic acid while reducing the intensity of unwanted effects, especially the flushing response. Reducing the unwanted effects will certainly be aided by the recent progress made in deciphering the mechanism underlying the prostanoid-mediated cutaneous vasodilatory effect of nicotinic acid.

SUMMARY POINTS

1. Nicotinic acid at pharmacological doses has unique effects on the plasma lipid profile.
2. Nicotinic acid is the most efficacious HDL-cholesterol-elevating drug currently in clinical use.
3. GPR109A (HM74A/PUMA-G) is a G_i-coupled receptor that is activated by nicotinic acid and related drugs.
4. GPR109A mediates the antilipolytic effects of nicotinic acid.
5. GPR109A is expressed in adipocytes and immune cells.
6. The nicotinic acid–induced flushing response is mediated by GPR109A.
7. Vasodilatory prostanoids, such as PGD_2 and PGE_2, most likely generated by Langerhans cells, are critically involved in the nicotinic acid–induced flushing phenomenon.

FUTURE ISSUES

1. The therapeutic benefit of nicotinic acid as an add-on therapy to statins must be evaluated in large clinical trials.
2. The mechanism underlying the nicotinic acid-induced increase in plasma HDL-cholesterol levels needs to be elucidated.
3. We need a better understanding of the physiological role of the nicotinic acid receptor GPR109A in lipid metabolism and immune functions.
4. Are there other endogenous ligands that regulate metabolic or immune functions via GPR109A?
5. Agonists, antagonists, or modulators of GPR109A and related receptors must be developed and evaluated.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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