Mechanism of Action of Niacin

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Nicotinic acid (niacin) has long been used for the treatment of lipid disorders and cardiovascular disease. Niacin favorably affects apolipoprotein (apo) B–containing lipoproteins (eg, very-low-density lipoprotein [VLDL], low-density lipoprotein [LDL], lipoprotein[a]) and increases apo A-I–containing lipoproteins (high-density lipoprotein [HDL]). Recently, new discoveries have enlarged our understanding of the mechanism of action of niacin and challenged older concepts. There are new data on (1) how niacin affects triglycerides (TGs) and apo B–containing lipoprotein metabolism in the liver, (2) how it affects apo A-I and HDL metabolism, (3) how it affects vascular anti-inflammatory events, (4) a specific niacin receptor in adipocytes and immune cells, (5) how niacin causes flushing, and (6) the characterization of a niacin transport system in liver and intestinal cells. New findings indicate that niacin directly and noncompetitively inhibits hepatocyte diacylglycerol acyltransferase–2, a key enzyme for TG synthesis. The inhibition of TG synthesis by niacin results in accelerated intracellular hepatic apo B degradation and the decreased secretion of VLDL and LDL particles. Previous kinetic studies in humans and recent in vitro cell culture findings indicate that niacin retards mainly the hepatic catabolism of apo A-I (vs apo A-II) but not scavenger receptor BI–mediated cholesterol esters. Decreased HDL–apo A-I catabolism by niacin explains the increases in HDL half-life and concentrations of lipoprotein A-I HDL subfractions, which augment reverse cholesterol transport. Initial data suggest that niacin, by inhibiting the hepatocyte surface expression of β-chain adenosine triphosphate synthase (a recently reported HDL–apo A-I holoparticle receptor), inhibits the removal of HDL–apo A-I. Recent studies indicate that niacin increases vascular endothelial cell redox state, resulting in the inhibition of oxidative stress and vascular inflammatory genes, key cytokines involved in atherosclerosis. The niacin flush results from the stimulation of prostaglandins D_2 and E_2 by subcutaneous Langerhans cells via the G protein–coupled receptor 109A niacin receptor. Although decreased free fatty acid mobilization from adipose tissue via the G protein–coupled receptor 109A niacin receptor has been a widely suggested mechanism of niacin to decrease TGs, physiologically and clinically, this pathway may be only a minor factor in explaining the lipid effects of niacin. **(Am J Cardiol 2008;101[suppl]:20B–26B)**

In a landmark study in 1955, Altschul et al[1] reported that nicotinic acid (niacin) lowered plasma cholesterol in normal as well as hypercholesterolemic subjects. In view of the recognition of plasma cholesterol as an independent risk factor for coronary artery disease, this important clinical observation by Altschul et al[1] formed the basis for the development of lipid-based therapies for coronary artery disease. Several subsequent clinical studies established the use of niacin as a broad-spectrum lipid-regulating medication and the first lipid-based intervention to prevent cardiovascular disease and death.[2,3] In pharmacologic doses, niacin reduces total cholesterol, triglyceride (TG), very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and lipoprotein(a) (Lp[a]) levels and increases high-density lipoprotein (HDL) levels.[2,3] Niacin is the most potent available lipid-regulating agent to increase HDL levels.[2,4] Additionally, niacin was shown to increase larger HDL_2 subfractions and decrease atherogenic small, dense LDL particles.[5–10] We have shown that niacin selectively increases apolipoprotein (apo) A-I–containing (vs apo A-II–containing) HDL particles (lipoprotein A-I, Lp[A-I]), a cardioprotective subfraction and an efficient mediator of the reverse cholesterol transport pathway.[11] Several clinical trials have indicated that treatment with niacin, alone or in combination with other lipid-lowering agents, significantly reduces total mortality and coronary events and retards the progression of and induces the regression of coronary atherosclerosis.[2,3,12,13]

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After 50 years of successful clinical use of niacin for the treatment of dyslipidemia and atherosclerosis, new discoveries regarding its mechanism of action have emerged during the past 10 years. These new findings include (1) data on the regulatory role of niacin on lipid and lipoprotein metabolism in the liver and (2) the characterization of niacin receptors in adipocytes and immune cells and their role in adipocyte TG lipolysis and niacin flush. In addition to findings regarding niacin's lipid-regulating role, new discoveries are emerging that suggest vascular anti-inflammatory and antioxidative properties of niacin that may shed light on its pleiotropic role in reducing atherosclerosis. Recent studies have characterized the existence of a specific niacin transport system in human liver and intestinal epithelial cells.[14,15] Specific characteristics of the niacin transport system in human liver cells include the following: the rate of niacin transport is dependent on acidic pH, temperature, and energy, but transport is sodium independent. Data also suggest the involvement of Ca^{2+}-calmodulin-mediated pathways in niacin transport in liver cells.[14]

This review is focused specifically on the current understanding of the mechanism of action of niacin to modulate lipoproteins and atherosclerosis. To present an integrated overview of the mechanism of action of niacin, the review is divided into 4 sections covering (1) the basic mechanisms of niacin to decrease lipids and apo B–containing lipoproteins (eg, LDL, VLDL), (2) mechanisms of niacin to increase apo A-I and HDL, (3) novel non-lipid-related action of niacin to influence vascular inflammatory and oxidative processes involved in atherogenesis, and (4) the mechanism of action of niacin to induce an adverse flush response.

Basic Mechanisms of Niacin to Decrease Lipids and Apolipoprotein B–Containing Lipoproteins

Studies from our and other laboratories have indicated that niacin, mainly by 2 mechanisms, influences plasma TGs and the secretion of apo B–containing lipoproteins, including VLDL and LDL particles, in the liver. These include (1) the modulation of liver TG synthesis, resulting in increased intracellular apo B degradation, and (2) the modulation of TG lipolysis in adipose tissue.

Mechanism of action of niacin to modulate TG synthesis and secretion of VLDL and LDL particles by liver: The liver is a major organ for the production and secretion of apo B, its associated lipids, and subsequently VLDL, LDL, and Lp(a) particles. The hepatic intracellular processing of apo B (the major protein of VLDL and LDL) plays a central role in regulating apo B–containing lipoprotein secretion. The rate of TG synthesis and the availability to lipidate apo B specifically play a critical role in the translocation of apo B, resulting in either secretion or intracellular degradation before secretion.[16,17]

Using plasma turnover kinetic studies in humans, Grundy et al[18] showed that niacin decreased the synthetic rate (transport) of VLDL-TGs by 21%. These studies suggested TG synthesis as a major target of niacin's effect to influence VLDL and LDL secretion. To gain further insight into the hepatocellular mechanism of action of niacin on TG synthesis and VLDL and LDL metabolism, studies in our laboratory focused on the effect of niacin on a key enzyme involved in TG synthesis and the regulatory processes associated with intracellular apo B degradation and secretion in the human hepatocyte cell line (Hep G2 cells). The data indicated that niacin increased apo B intracellular degradation and decreased the subsequent secretion of apo B into the culture media of Hep G2 cells.[19] Additionally, we have shown that niacin decreases the inhibition of oleate-mediated apo B degradation, suggesting that niacin-induced apo B degradation may be dependent on the pathways involving the synthesis and association of TG before apo B processing. In subsequent studies, we reported that niacin directly and noncompetitively inhibited the activity of hepatocyte microsomal diacylglycerol acyltransferase–2 (DGAT2), a key enzyme that catalyzes the final reaction in TG synthesis.[20] The half maximal inhibitory concentration for DGAT2 inhibition by niacin was 0.1 mmol/L.[20] The lipid-lowering effects of niacin were observed with peak plasma concentrations of niacin in the range of 0.05–0.3 mmol/L, achieved after pharmacologic doses of niacin in humans. Thus, the similar range of effective plasma niacin concentrations seen for lipid-lowering effects and hepatocyte DGAT2 inhibition suggest that hepatic DGAT2 plays a role in the pharmacologic effect of niacin in vivo. These data define DGAT2 as a major site of niacin's action (Figure 1).

As summarized in Figure 1, our data indicate that niacin, by inhibiting hepatic DGAT2, decreases TG synthesis and its availability for VLDL assembly, resulting in increased posttranslational intrahepatic apo B degradation. Increased hepatocyte apo B degradation by niacin would decrease the number of VLDL particles and their catabolic product, LDL particles, which explains the lower apo B and LDL concentrations observed clinically after niacin treatment. Additionally, the niacin-mediated inhibition of TG synthesis may produce decreased concentrations of large, TG-rich $VLDL_1$ particles, which in turn may result in decreased formation of small, dense LDL particles.

Mechanism of action of niacin to modulate TG lipolysis in adipose tissue: Adipose tissue cells are specialized for the synthesis and storage of TGs and for their mobilization to the liver as a fuel in the form of free fatty acids (FFAs) and glycerol. Carlson[3] extensively studied the involvement of adipocyte TG lipolysis as a mechanism of action of niacin to decrease plasma TGs. Carlson and Oro[21] showed that within minutes, niacin lowered plasma concentrations of FFAs in humans, and this reduction in FFAs was followed by a rebound within 1 hour. Additionally, in vitro studies with rat epididymal fat pads showed that niacin decreased the release of FFAs from adipose tissue by inhibiting TG lipolysis.[22]

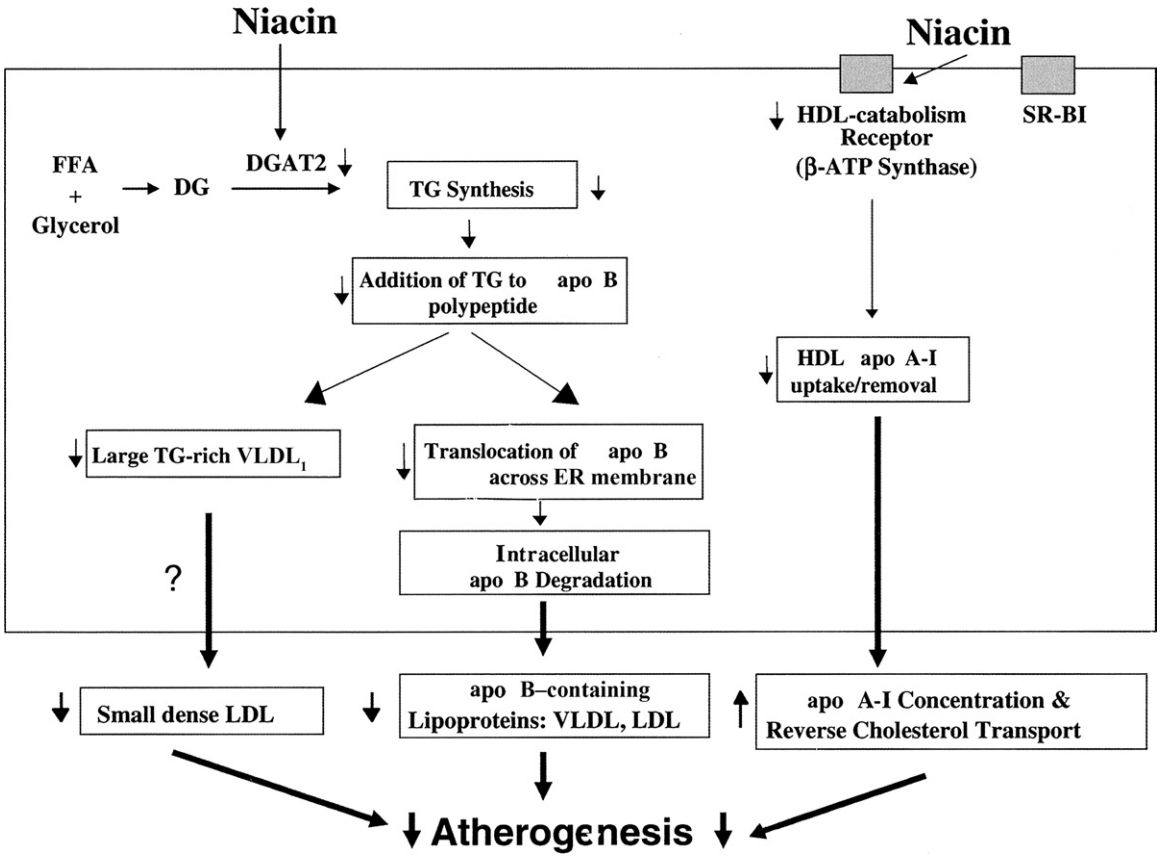

Figure 1. Mode of action of niacin on low-density lipoprotein (LDL) and high-density lipoprotein (HDL) metabolism in the liver. In hepatocytes, niacin directly and noncompetitively inhibits diacylglycerol acyltransferase–2 (DGAT2), resulting in decreased triglyceride (TG) synthesis. The niacin-mediated inhibition of TG synthesis may decrease the lipidation of apolipoprotein (apo) B and translocation through endoplasmic reticular (ER) membrane, leading to increased intracellular apo B degradation and decreased secretion of very-low-density lipoprotein (VLDL) and LDL particles. Conceptually, the niacin-mediated inhibition of TG synthesis may produce decreased levels of large, TG-rich $VLDL_1$ particles, which in turn may result in the decreased formation of small, dense LDL particles. Niacin, by inhibiting the putative hepatocyte HDL catabolism receptor—potentially β-chain adenosine triphosphate (ATP) synthase but not scavenger receptor BI (SR-BI)—may inhibit the removal of HDL–apo A-I. These mechanisms of decreased HDL–apo A-I catabolism by niacin would increase HDL half-life and concentrations of lipoprotein A-I HDL, thereby augmenting reverse cholesterol transport. Taken together, niacin, through these collaborative intracellular metabolic processes, favorably modulates LDL and HDL levels, resulting in decreased atherosclerotic coronary artery disease. DG = diglyceride; FFA = free fatty acid; ? = mechanisms not clearly understood.

The recent discovery of G protein–coupled receptor (GPR) 109A and GPR109B (HM74A and HM74, respectively) as niacin receptors in adipocytes and immune cells has advanced understanding of niacin's actions on adipocyte TG lipolysis and niacin flush. In this regard, 3 groups independently identified GPR109A (protein upregulated in macrophages by interferon-γ [PUMA-G] in mice) as a specific and high-affinity receptor for niacin.[23–25] Another member of this receptor family, GPR109B, has also been reported as a low-affinity receptor for niacin.[24] The half-maximal effective concentration and binding affinity of niacin for GPR109A were 250 and 96 nmol/L, respectively.[24] Using PUMA-G-deficient mice (PUMA-G in mice is equivalent to GPR109A in humans), Tunaru et al[23] showed that niacin had no effect on plasma FFA levels in PUMA-G-deficient mice. PUMA-G-deficient mice on a high-fat diet for 2 weeks showed no decrease in TG levels on treatment with niacin, whereas wild-type mice showed a 30% decrease in TG levels. These studies suggest evidence in mice for the involvement of PUMA-G in niacin's effect on adipocyte fatty acid mobilization and the subsequent decreased availability of fatty acid substrate for TG synthesis. However, as indicated later, whether this mechanism operates in humans is controversial.

Although niacin's effect on adipocyte lipolysis and fatty acid mobilization is widely recognized, physiologically and clinically, this mechanism may be only minor and may not provide a full explanation of all lipid effects of niacin in humans. In humans, evidence indicates that niacin subacutely causes a profound rebound in lipolysis, such that serum FFA levels are actually increased over 24 hours. This rebound in lipolysis and elevated FFA levels may in part mediate the insulin resistance induced by long-term niacin therapy.[26] Decreased adipocyte lipolysis by niacin would theoretically increase adipose tissue TGs and could result in obesity. Clinically, niacin has not been reported to influence obesity. Niacin-induced modulation of TG synthesis occurs during the acute decrease in FFAs, but the rebound in FFAs

would reverse this. Moreover, there is no evidence that the longer term transport (flux rate) of nonesterified fatty acids is decreased after niacin treatment. Additionally, the nanomolar range of reported half maximal effective concentrations for the stimulation of guanosine-5′-O-(γ-thio)-triphosphate binding (250 nmol/L) and niacin binding affinity (96 nmol/L) with GPR109A[24] are small fractions of the pharmacologic concentrations of niacin required for lipid effects in humans. On the basis of these considerations, GPR109A may not have a major role in niacin's effect on lowering VLDL and LDL in humans. Our data (as discussed earlier) suggest that niacin mainly affects the liver's ability to synthesize TGs by the direct inhibition of DGAT2.[20] In fact, the inhibition of DGAT2 in mice with antisense oligonucleotide has been shown to markedly reduce TG synthesis, suggesting a critical regulatory role of DGAT2 in TG synthesis.[27]

Mechanisms of Niacin to Increase Apolipoprotein A-I and High-Density Lipoprotein

The liver and intestine are major organs for the synthesis and secretion of apo A-I and HDL. Previous plasma turnover studies in humans have indicated that niacin primarily decreases the fractional catabolic rate of HDL–apo A without altering apo A synthesis rates.[28,29] Using human hepatocytes (Hep G2 cells) as an in vitro modeling system, we investigated the effect of niacin on apo A-I–HDL synthetic and catabolic pathways. Our findings indicated that niacin selectively inhibited the uptake of HDL–apo A-I but not HDL cholesterol esters without affecting the de novo synthesis of apo A-I in Hep G2 cells.[30] As a negative control, nicotinamide (a niacin analog with no effect on lipid profile) did not affect HDL–apo A-I uptake (L. Zhang, V. S. Kamanna, and M. L. Kashyap, unpublished data, 2006). Because nicotinamide had no effect on plasma levels of lipids and lipoproteins and in vitro HDL–apo A-I uptake, the inhibition of HDL–apo A-I uptake by niacin would be a relevant mechanism of action to increase apo A-I–containing HDL particles. On the basis of these data, we have suggested that niacin inhibits the removal of HDL–apo A-I at the level of the putative "HDL holoparticle catabolism receptor" or pathways, but not scavenger receptor BI–mediated events, which are selective to HDL cholesterol esters.[31]

To address the role of niacin in the HDL holoparticle catabolic receptor pathway, we recently initiated studies on β-chain adenosine triphosphate synthase, which has been implicated in mediating hepatic HDL holoparticle (protein plus lipids) endocytosis.[32] Specifically, we examined the effects of niacin on cell surface expression of the β-chain in Hep G2 cells, a key step in this receptor pathway. Preincubation with niacin reduces the surface expression of the β-chain in Hep G2 cells.[33] These data suggest that niacin downregulates cell surface expression of β-chain adenosine triphosphate synthase, leading to reduced hepatic removal of HDL through holoparticle endocytosis, thus implicating a potential cellular receptor site for niacin's action to increase plasma HDL.

Because the HDL subfractions Lp(A-I) and lipoprotein A-I+A-II (Lp[A-I+A-II]) (HDL particles containing apo A-I and those containing apo A-I and apo A-II, respectively) have differential cardioprotective effects, we investigated the clinical effect of niacin on Lp(A-I) and Lp(A-I+A-II) levels in 139 patients with low HDL cholesterol.[11] The data indicated that during the 19-week treatment period, niacin dose-dependently and significantly increased Lp(A-I) levels by 24% above baseline. Gemfibrozil had no significant effect on Lp(A-I). The treatment of patients with niacin also significantly increased Lp(A-I+A-II) particles by 9.5% above baseline, similar to the effect of gemfibrozil, but the effect was less compared with Lp(A-I) levels. Additionally, we have shown that niacin significantly inhibited the uptake of radiolabeled Lp(A-I) particles by Hep G2 cells. However, niacin had no significant effect on the uptake of Lp(A-I+A-II) particles by Hep G2 cells. Lp(A-I) particles delivered cholesterol esters 70% more efficiently than Lp(A-I+A-II) particles into cultured Hep G2 cells.[11] These data suggest that niacin, by selectively inhibiting the hepatic removal and uptake of Lp(A-I) particles, may lead to the increased retention of Lp(A-I) particles in the circulation and a greater effect on reverse cholesterol transport function.

As summarized in Figure 1, niacin, by inhibiting the putative hepatocyte HDL catabolism receptor—potentially β-chain adenosine triphosphate synthase but not scavenger receptor BI—may inhibit the removal of HDL–apo A-I. These mechanisms of decreased HDL–apo A-I catabolism by niacin would increase HDL half-life and concentrations of Lp(A-I) HDL subfractions, thereby augmenting cholesterol efflux and reverse cholesterol transport. Increased residence time would also allow HDL size to increase (from HDL_2 to HDL_3) from peripheral tissue cholesterol uptake. Although these in vitro data provide a novel approach for the mechanism of action of niacin to increase Lp(A-I) HDL, additional direct plasma kinetic studies with these HDL subfractions in humans would be warranted to address the synthetic or catabolic aspects of these particles in controls and niacin-treated patients.

In addition to the effect of niacin on HDL catabolism in liver, recent studies have shown that niacin increases the expression of peroxisome proliferator–activated receptor–γ and conserved domain 36 (CD36) in monocyte and macrophage cells and stimulates adenosine triphosphate–binding cassette, subfamily A, member 1 transporter, a primary protein involved in the transport of cellular cholesterol to apo A-I–containing HDL particles for the reverse cholesterol transport pathway.[34] These data suggest an additional regulatory role of peroxisome proliferator–activated receptor–γ and responsive genes in niacin-mediated beneficial effects on monocyte and macrophage adenosine triphosphate–binding cassette, subfamily A, member 1 and the subsequent reverse cholesterol transport pathway.

Table 1
Sites of action of niacin: enzymes and receptors

Organ/Tissue	Cell	Target Enzyme/Receptor	Primary Effect	Clinical Effect
Adipose tissue	Adipocyte	↑ GPR109A (HM74A)	↓ Lipolysis ↓ FFA mobilization	↓ ? VLDL-TG
Liver	Hepatocyte	(1) ↓ DGAT2	↓ TG synthesis ↓ Apo B secretion	↓ VLDL-TG ↓ Apo B ↑ LDL particle size ↓ Lp(a)
		(2) ↓ ? β-chain ATP synthase	↓ HDL (apo A-I) catabolism	↑ Lp(A-I), HDL_2
Artery	(1) Endothelium	↑ NAD^+ phosphate ↓ Redox-sensitive genes	↓ LDL oxidation ↓ MCP-1 ↓ VCAM-1	↓ Vascular inflammation
	(2) Macrophage	Unknown	↑ Prostaglandin J2 ↑ PPAR-γ, ABCA1	↑ Cholesterol efflux ↑ HDL-C
Skin	Langerhans cell/macrophage	GPR109A	↑ Prostaglandin D2 and E2, acting on DP1, EP2, and EP4 receptors	Flushing

ABCA1 = adenosine triphosphate–binding cassette, subfamily A, member 1; apo = apolipoprotein; ATP = adenosine triphosphate; DGAT2 = diacylglycerol acyltransferase–2; FFA = free fatty acid; GPR = G protein–coupled receptor; HDL = high-density lipoprotein; HDL-C = HDL cholesterol; LDL = low-density lipoprotein; Lp(a) = lipoprotein (a); Lp(A-I) = lipoprotein A-I; MCP = monocyte chemoattractant protein; NAD^+ = nicotinamide adenine dinucleotide; PPAR-γ = peroxisome proliferator–activated receptor–γ; TG = triglyceride; VCAM = vascular cell adhesion molecule; VLDL = very-low-density lipoprotein; ↑ = increased; ↓ = decreased; ? = mechanisms not clearly understood.

Novel Non-Lipid-Related Action of Niacin to Influence Vascular Inflammatory and Oxidative Processes Involved in Atherogenesis

On the basis of the role of pyridine nucleotides in redox reactions, we proposed that niacin exhibits antioxidative and anti-inflammatory properties in aorta wall cells. In the Jurkat cell line (human T-cell lymphoma), previous studies have shown that niacin, as a precursor for the synthesis of nicotinamide adenine dinucleotide, increased cellular concentrations of nicotinamide adenine dinucleotide[35] and upregulated the expression of glucose-6-phosphate dehydrogenase, the rate-limiting enzyme in the pentose phosphate pathway and the principal source of cellular reduced nicotinamide adenine dinucleotide phosphate.[36] However, the roles of niacin in vascular endothelial cell reactive oxygen species formation and the subsequent oxidation of LDL and expression of oxidation-sensitive inflammatory genes involved in early atherosclerotic processes are not known.

Using human aortic endothelial cells as an in vitro modeling system, we have recently provided direct evidence for the antioxidative and anti-inflammatory properties of niacin. The findings from these studies demonstrate that niacin significantly increased nicotinamide adenine dinucleotide phosphate and reduced glutathione levels and inhibited (1) angiotensin II–induced reactive oxygen species production, (2) LDL oxidation, (3) tumor necrosis factor–α–induced redox-sensitive vascular cell adhesion molecule–1 and monocyte chemoattractant protein–1 messenger ribonucleic acid expression, and (4) tumor necrosis factor–α–induced and oxidized LDL–induced monocyte adhesion to endothelial cells.[37] These findings indicate for the first time that niacin inhibits vascular inflammation by decreasing endothelial reactive oxygen species production, LDL oxidation, and subsequent vascular cell adhesion molecule–1 and monocyte chemoattractant protein–1 expression, resulting in decreased monocyte and macrophage adhesion and accumulation, key events in early atherogenesis. These in vitro studies describe a novel anti-inflammatory mechanistic role for niacin in decreasing atherosclerosis, separate from its conventional role as a lipid-regulating agent.

Mechanism of Action of Niacin to Induce Adverse Flush Response

Although niacin favorably affects all class of lipoproteins and prevents cardiovascular disease, it is underused because of a major adverse vasocutaneous flushing reaction. Previous studies have suggested that the cutaneous production of prostanoids, including prostaglandin D_2 and prostaglandin E_2, mediates niacin flush.[38] Recent studies have shown that skin Langerhans cells are the primary cell types responsible for niacin-induced prostaglandin D_2 release and the flushing response.[39,40] Using in vitro cultures, we have shown that human macrophages (isolated from peritoneal fluid and THP-1 cells) can also produce prostaglandin D_2 in response to niacin treatment[41] and express GPR109A (L. Zhang, V. S. Kamanna, and M. L. Kashyap, unpublished data, 2005). Using gene-knockout animal models, new data have emerged to indicate the involvement of PUMA-G, cyclooxygenase type 1, prostaglandin D_2, and prostaglandin E_2 receptors in the niacin-induced vasodilatory flush response. The findings of these studies indicated that mice deficient in PUMA-G did not show a niacin-induced increase in ear blood flow, a measure of niacin flush.[42] Additionally, studies reported by these and other investigators showed that niacin flushing was also abrogated in the absence of cyclo-

oxygenase type 1, and mice lacking prostaglandin D_2 and prostaglandin E_2 receptors had reduced flushing responses.[42,43] These studies clearly suggest that GPR109A or PUMA-G indirectly mediates niacin-induced flushing through the production of prostaglandin D_2 and prostaglandin E_2 by immune cells such as Langerhans cells and macrophages.

Conclusion

As summarized in Table 1, current evidence indicates that niacin acts on multiple tissues and targets to beneficially modulate the lipid and lipoprotein profile, induce anti-inflammatory processes, and cause adverse flush reactions. On the basis of the physiologic considerations and recent published research, the liver appears to be the major target organ of niacin to increase HDL–apo A-I and decrease TGs and VLDL and LDL particles. The selective tissue distribution of GPR109A and GPR109B only in adipose tissue, the spleen, and immune cells but not in other major tissues, including the liver, kidneys, heart, intestine, and so on,[24,25] indicate that the niacin receptor GPR109A may not be involved in niacin's action on liver apo A-I–HDL catabolism, DGAT2 and apo B–bearing lipoprotein secretion, and vascular anti-inflammatory properties. In humans, physiologically PUMA-G- or GPR109A-mediated adipocyte TG lipolysis may be only a minor mechanism explaining TG lowering and other beneficial effects of niacin. Rather, PUMA-G and GPR109A receptors in Langerhans cells and macrophages are importantly involved in niacin-induced adverse flushing.

The direct effect of niacin to increase aortic endothelial cell redox potential and its vascular anti-inflammatory properties may additionally account for its proved effects in atherosclerotic cardiovascular disease beyond lipid regulation. The new concepts of niacin's mechanisms of action on TGs, apo A-I, vascular inflammation, and flushing need to be expanded to lay the foundation for new drug discovery to beneficially alter lipoproteins and atherosclerosis without adverse effects.

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