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Niacin: an old lipid drug in a new NAD$^+$ dress

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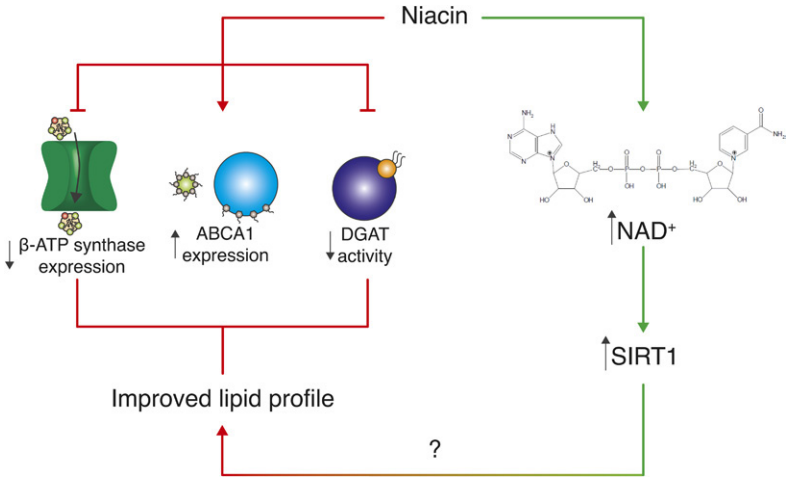
Abstract **Niacin, the first antidyslipidemic drug, has been at the center stage of lipid research for many decades before the discovery of statins. However, to date, despite its remarkable effects on lipid profiles, the clinical outcomes of niacin treatment on cardiac events is still debated. In addition to its historically well-defined interactions with central players of lipid metabolism, niacin can be processed by eukaryotic cells to synthesize a crucial cofactor, NAD$^+$. NAD$^+$ acts as a cofactor in key cellular processes, including oxidative phosphorylation, glycolysis, and DNA repair. More recently, evidence has emerged that NAD$^+$ also is an essential cosubstrate for the sirtuin family of protein deacylases and thereby has an impact on a wide range of cellular processes, most notably mitochondrial homeostasis, energy homeostasis, and lipid metabolism. NAD$^+$ achieves these remarkable effects through sirtuin-mediated deacetylation of key transcriptional regulators, such as peroxisome proliferator-activated receptor gamma coactivator 1-α, LXR, and SREBPs, that control these cellular processes. Here, we present an alternative point of view to explain niacin's mechanism of action, with a strong focus on the importance of how this old drug acts as a control switch of NAD$^+$/sirtuin-mediated control of metabolism.**—Romani, M., D. C. Hofer, E. Katsyuba, and J. Auwerx. **Niacin: an old lipid drug in a new NAD$^+$ dress.** ***J. Lipid Res.*** **2019.** 60: **741–746.**



Supplementary key words nicotinic acid • sirtuins • mitochondria • cholesterol • dyslipidemia • HDL • LDL • kidney disease • fatty acid oxidation • lipid synthesis

Nicotinic acid was identified in the beginning of the 20th century by Conrad Elvehjem (1) as an effective treatment for pellagra, which at that time was endemic in the United States. The name of nicotinic acid was replaced by niacin in the 1940s to avoid any association with nicotine (2), and a decade later, the lipid-modulating effects of this molecule were described in patients by Rudolf Altschul (3), making niacin the oldest lipid-lowering drug. Despite the fact that several of the molecular mechanisms underlying its remarkable effects on lipid metabolism have been elucidated since then, the molecular mechanism of how niacin works remains elusive.

NIACIN, KNOWN MECHANISMS OF ACTION

In pharmacological doses, niacin acts as a broad-spectrum lipid-modulating drug and increases the circulating levels of HDL (4) (**Fig. 1**). This class of lipoproteins, which is particularly enriched with ApoA-I and ApoA-II, are major players in reverse cholesterol transport. Most peripheral tissues indeed rely on HDL for cholesterol clearance and transport to the liver, where cholesterol is either processed or degraded (5). Thanks to this scavenging function, low HDL is considered, with few exceptions, an independent risk factor for coronary artery disease (6). Niacin increases

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Abbreviations: CKD, chronic kidney disease; DGAT2, diglyceride acyltransferase 2; ESRD, end-stage renal disease; NAM, nicotinamide; NAMPT, nicotinamide phosphoribosyltransferase; NNMT, nicotinamide *N*-methyltransferase; NR, nicotinamide riboside; PARP, poly(ADP-ribose)-polymerase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-α; SIRT1, sirtuin 1; TG, triglyceride.

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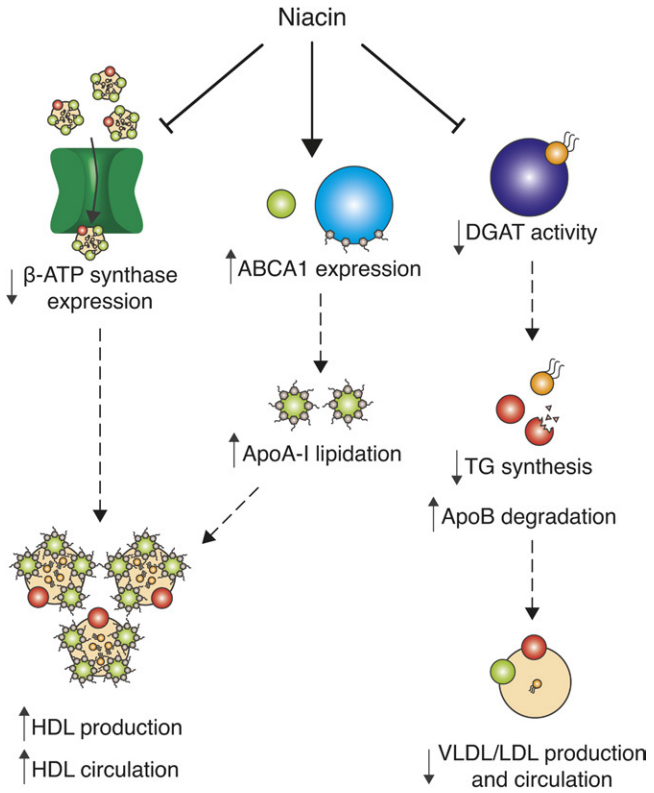

Fig. 1. Known mechanisms of action of niacin. Niacin increases circulating HDL particles for peripheral cholesterol scavenging by two described mechanisms: First, by reducing the surface expression of the hepatic HDL receptor β-ATP synthase, which is involved in the endocytosis of HDL particles in the liver, and, second, by increasing the expression of ABCA1, which promotes ApoA-I lipidation and stabilization and thus promotes HDL production. Moreover, niacin reduces the activity of DGAT, which leads to reduced TG synthesis, Apo B degradation, and reduced VLDL and LDL production and circulation.

HDL availability through different mechanisms (Fig. 1). First, it has a direct effect on ApoA-I stability and function. In fact, niacin boosts the expression of the membrane protein ABCA1, the main regulator of ApoA-I lipidation and consequent stabilization, through the LXR (7). Moreover, niacin prevents the surface expression of the hepatic HDL receptor β-chain ATP synthase (8). This inhibition decreases HDL uptake in the liver and consequently increases HDL availability for cholesterol scavenging in the blood (9).

The best-characterized effect of niacin on lipid metabolism is, however, the reduction of triglyceride (TG) and circulating FFA levels (Fig. 1). The first proposed mechanism explaining this outcome involves its inhibitory actions on adipocyte TG lipolysis, which would decrease FFA release and the availability of FFAs to stimulate liver TG synthesis (10). However, this hypothesis has been challenged when the niacin receptor, a G-protein-coupled receptor, termed GPR109A, was identified as the mediator of its antilipolytic effect. After niacin administration, *Gpr109a*-KO mice show the typical serum TG-lowering effect, despite the absence of adipocyte lipolysis. Moreover, GPR109A agonists were shown to inhibit lipolysis in patients with dyslipidemia in the absence of effects on circulating lipids (11), arguing that mechanisms independent from niacin's antilipolytic function via activation of GPR109A are responsible for its beneficial effects on lipid homeostasis. The most recent hypothesis identifies the liver as the main contributor in the niacin-mediated modulation of serum lipids. More specifically, in vitro evidence suggests that the hepatic lipid-lowering effects of niacin are mediated by a noncompetitive direct interaction of niacin with the final enzyme of TG synthesis, diglyceride acyltransferase 2 (DGAT2) (Fig. 1) (12). In support of this, patients on niacin display a lipid-lowering response influenced by genetic *DGAT2* polymorphisms (13). Moreover, the hepatic modulation of TG biosynthesis impacts on apo-B-containing VLDLs, and LDLs, the principal transporters of TG and cholesterol, respectively. These lipoproteins require TGs for their formation; therefore, reducing TG synthesis leads to destabilization of VLDL and LDL particles, decreasing circulating lipids. However, recent publications seem to quench the translation of these findings in humans, proving that the in vivo TG-lowering effects of DGAT2 inhibitors observed in murine models are not present in a primate model (14).

NIACIN, THE FIRST ANTIDYSLIPIDEMIC DRUG

The beneficial effects of niacin on lipid metabolism promoted several clinical trials in patients suffering from different cardiovascular conditions. However, the outcomes of these studies were controversial. The first large clinical study, the Coronary Drug Project, showed a reduced incidence of nonfatal reinfarction and all-cause mortality after 5 years in patients with documented myocardial infarction when compared with placebo (15). Following these initial positive results, niacin was tested in combination with other drugs to treat dyslipidemias. First, when it was coadministered with the bile acids sequestrant colestipol, niacin markedly increased HDL and atherosclerotic regression in two trials (16, 17). With the discovery of statins and their prominent beneficial effects on cholesterol metabolism, niacin has been investigated as a possible add-on to improve the therapeutic outcome of statins. In five different clinical trials, add-on of niacin to the statin treatment reduced the onset of cardiovascular events with a concomitant increase in HDL (18–22). The excitement for the potential application of niacin as an add-on to statin therapy has, however, been dampened when two recent, large clinical studies, the AIM-HIGH and the HPS2-THRIVE trials, failed in reproducing the benefits of previous studies. Niacin, in combination with simvastatin, did not improve the risk of major cardiovascular events; however, a significant improvement in HDL and TG levels remained (23, 24). The main difference from the previous clinical trials, besides the recruitment of a significantly larger group of patients (several thousand vs. hundreds), was the use of statins in the control conditions, as opposed to four out of the five prior studies in which no drug at all or double placebo were used. Interestingly, in AIM-HIGH, niacin treatment abolished the correlation between non-HDL cholesterol and cardiovascular

events (23). In control conditions, the levels of non-HDL cholesterol were predictors of cardiovascular complications—an association that is lost upon niacin treatment, suggesting the involvement of nonlipoprotein mechanisms. The results from the AIM-HIGH and HPS2-THRIVE studies have, however, resulted in marginalization of niacin in national guidelines for treatment of dyslipidemia and atherosclerotic CVD. To date, statin therapy remains the gold standard for treatment of these conditions due to its more potent effect on cholesterol levels (25). Niacin, however, is approved in many countries as therapy for patients with statin intolerance and as a broad lipid-lowering drug (26). Moreover, it has an off-target use in chronic kidney disease (CKD) and end-stage renal disease (ESRD), given its beneficial impact on factors affecting the glomerular filtration rate, including phosphate levels (27), oxidative stress (28, 29), inflammation (30–32), and HDL and TG levels (4, 33). Interestingly, HDL and TG levels have both been associated independently with CKD (34), indicating that niacin treatment may be relevant in these conditions, thus providing the rationale for future clinical trials to test the effects of niacin in CKD and ESRD patients.

NIACIN, ALSO A PRECURSOR FOR NAD^+

Although less studied than other mechanisms of niacin, niacin is also an important precursor for NAD^+ via the so-called Preiss-Handler pathway (**Fig. 2**). Hence, current literature on niacin's mechanism of action needs to be revisited from an NAD^+-centered point of view. Until very recently, NAD^+ was, together with its reduced counterpart, NADH, perceived as a redox couple, whose function seemed to be fully established since the 1930s (35). In 2000, however, the discovery that NAD^+ is a cosubstrate for the sirtuin family of deacylases, important longevity and metabolic regulators, heralded a whole new era in NAD^+ research (36). Raising NAD^+ levels was found to promote sirtuin 1 (SIRT1) activity, leading, among others, to the deacetylation and thus activation of the peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α), an important regulator of mitochondrial biogenesis (37, 38), thus putting sirtuins at the pinnacle of the control of mitochondrial homeostasis. In line with this, sirtuins were found to govern lipid and energy metabolism, acting as negative regulators of TG synthesis (39–41) and stimulating FA oxidation (42–44). The beneficial effects of niacin on serum TG and FFA levels might therefore at least in part be explained by raising NAD^+ levels, which promotes sirtuin activity, mitochondrial biogenesis, and thus enhanced mitochondrial FA oxidation and reduced TG synthesis (**Fig. 3**).

Further supporting the hypothesis of NAD^+-driven effects of niacin, SIRT1 was also shown to regulate the activity of important transcription factors that control lipid metabolism, including the LXR and SREBP families. More specifically, SIRT1-mediated deacetylation of LXR leads to its activation and subsequently to increased expression of its target genes, including *Abca1* and *Srebp-1c* (45). Thus, increases of NAD^+ levels after niacin administration might act upstream of the previously described effects of niacin on ABCA1-mediated cholesterol homeostasis (7) (Fig. 3). In line with this, *Sirt1*-KO mice show impaired cholesterol homeostasis and develop hepatic steatosis (45–47), whereas gain of SIRT1 function provides protection against hepatic steatosis (48). As LXR activation, however, also upregulates the expression of *Srebp-1c* (45), a key driver of FA and TG synthesis, the impact of SIRT1-LXR activation on lipid homeostasis is controversial. A possible explanation for this discrepancy could be the fact that SIRT1 not only deacetylates LXR, but also SREBP-1c itself and other members of

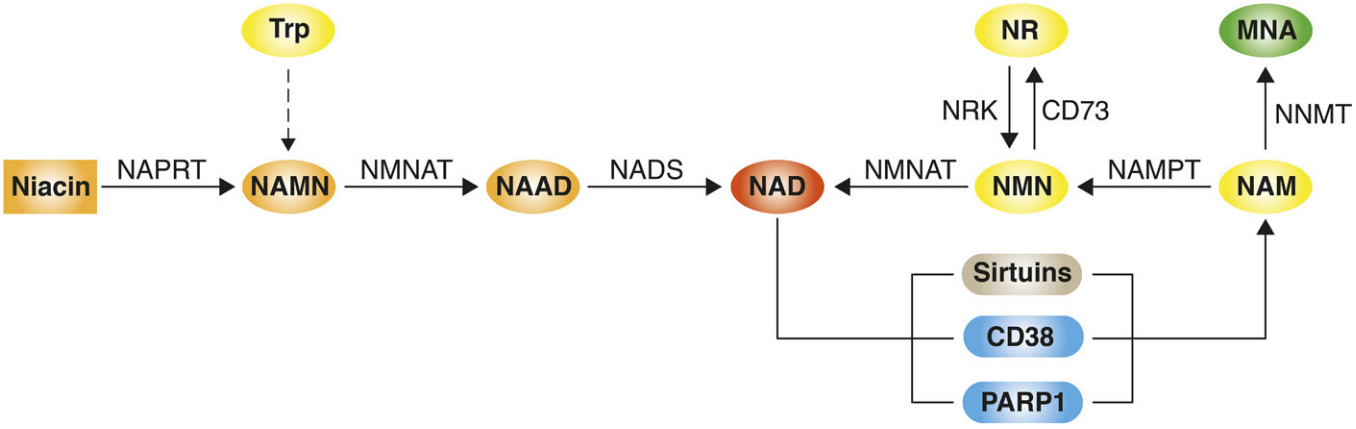

Fig. 2. Pathways modulating NAD^+ levels in mammals. NAD^+ can be synthesized either via salvage pathways from precursors such as niacin (nicotinic acid), nicotinamide (NAM), and nicotinamide riboside (NR) or de novo from tryptophan (Trp). In the first step of the Preiss-Handler pathway, niacin is converted into NA mononucleotide (NAMN) by nicotinate phosphoribosyltransferase (NAPRT). NAM mononucleotide adenylyltransferase (NMNAT) uses NAMN to generate NA adenine dinucleotide (NAAD), which gets converted into NAD^+ by NAD synthetase (NADS). NAD^+ synthesis from NAM and NR comprises their conversion into NAM mononucleotide (NMN) by NAM phosphoribosyltransferase (NAMPT) and NAM riboside kinase (NRK), respectively, and the subsequent conversion of NMN into NAD^+ by NMNAT. NMN can also be recycled back into NR by CD73. The de novo NAD^+ synthesis pathway from Trp consists of eight steps and merges with the Preiss-Handler pathway. Pathways that reduce NAD^+ availability include the conversion of NAM into methylnicotinamide (MNA) by N-methyltransferase (NNMT) and NAD^+ consumption by enzymes including the sirtuins, CD38, and PARP1.

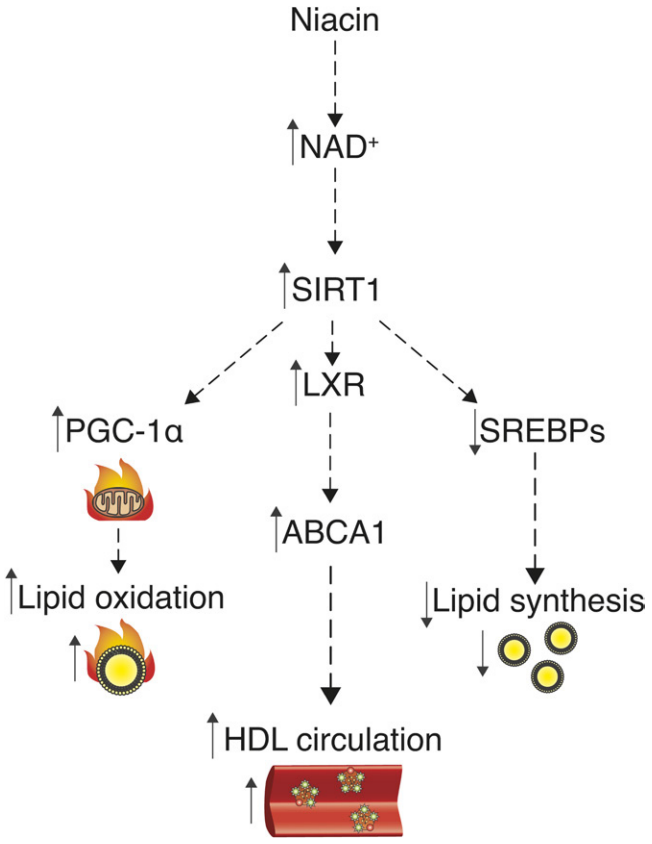

Fig. 3. Niacin's mechanism of action explained by raising NAD^+ levels? As a precursor for NAD^+, niacin can activate the deacylase SIRT1, which might explain niacin's beneficial effects on lipid homeostasis. First, SIRT1 activates PGC-1α, which leads to increased mitochondrial activity and FA oxidation. Moreover, SIRT1 activates LXR, which leads to increased expression of ABCA1, and thus increased circulating HDL particles. Furthermore, SIRT1 destabilizes SREBPs and thereby lowers SREBP-mediated FA, TG, and cholesterol synthesis and circulation.

the SREBP family, including SREBP-2, which governs cholesterol biosynthesis, and SREBP-1a, which is involved in FA, TG, and cholesterol biosynthesis (49). SIRT1-mediated deacetylation of these transcription factors leads to their destabilization and subsequently to decreased SREBP-mediated lipid synthesis (40, 50). Hence, activation of SIRT1 by NAD^+ seems to promote LXR-mediated improvements in cholesterol homeostasis, while at the same time abrogating detrimental SREBP-mediated lipid synthesis (Fig. 3). Future work focused on the sirtuin family as putative mediators of niacin's health benefits is therefore urgently needed.

Apart from niacin, NAD^+ can be produced from two other precursor molecules, nicotinamide (NAM) and nicotinamide riboside (NR), or synthesized de novo from tryptophan (Fig. 2). Studies exploring these alternative NAD^+-replenishing pathways provided further support for the hypothesis that niacin's beneficial effects involve NAD^+-mediated signaling.

For example, the expression of the rate-limiting enzyme for NAD^+ synthesis from NAM, NAM phosphoribosyltransferase (NAMPT), is decreased in adipose tissue in obesity (51–53). In line, adipocyte-specific KO of *Nampt* leads to increased plasma FFA and TG levels and adipose tissue dysfunction (54). Moreover, inactivation of NAMPT in mature macrophages induces lipid accumulation in these cells (55), and the inhibition of NAMPT enhances hepatic steatosis in mice challenged with high-fat diet (56).

Interestingly, NAD^+-consuming enzymes, including the poly(ADP-ribose)-polymerase (PARP) family, can be overactivated in some diseases by lipid overload and, hence, could be responsible for NAD^+ depletion, as observed in steatotic livers (57). In line, several different approaches to increase NAD^+ levels, including stimulation of NAD^+ biosynthesis, e.g., by administration of NR, as well as inhibition of PARPs, were shown to protect from hepatic lipid accumulation in the case of nonalcoholic fatty liver disease (57–60) and alcoholic liver disease (61). Although administration of NAM failed to reproduce the benefits of niacin due to end-product inhibition of sirtuin activity (62), NR potently increases the use of lipids as energy substrates and ameliorates cholesterol profiles in mice (63), reminiscent to what is seen upon niacin treatment. Furthermore, also knockdown of nicotinamide *N*-methyltransferase (NNMT), which is responsible for the conversion of NAM into methylnicotinamide (MNA) (Fig. 2), leads to increased NAD^+ levels and subsequently promotes SIRT1-target gene expression in adipose tissues and overall energy expenditure (64). Importantly, recent publications also highlighted that raising NAD^+ levels provides protection against acute kidney injury in mice (59, 65), which might explain in part the beneficial impact of niacin on kidney function in patients with CKD and ESRD (27–34). Despite the wealth of preclinical studies studying the effects of NAD^+ boosting on lipid metabolism, metabolic control, and longevity, large clinical trials focused on the consequences of NAD^+ boosting on lipid homeostasis and CVDs in humans are still pending.

CONCLUSION AND PERSPECTIVES

Niacin, the oldest antidyslipidemic drug, has been intensively studied in the past, revealing several mechanisms that might explain its significant health benefits. Through its interaction with important players in lipid metabolism, such as β-chain ATP synthase, ABCA1, and DGAT2, niacin is capable of increasing the levels of circulating HDL particles while decreasing TG levels. However, niacin also has the ability to raise levels of NAD^+ through the Preiss-Handler pathway. Interestingly, boosting NAD^+ levels recapitulates several of the initially observed effects of niacin on lipid metabolism. These NAD^+-driven effects are mainly mediated by SIRT1, which plays a key role in the modulation of important regulators of lipid metabolism such as PGC-1α, LXR, and SREBP. Although increasing evidence in literature points to the NAD^+/sirtuin-axis as a mediator of niacin's health benefits, future studies will be needed to tell whether niacin acts on its own or whether it should from now on be exclusively perceived as precursor for NAD^+. These studies could also uncover important mechanisms of action for other NAD^+ boosters, such as NR.

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