World Journal of Pharmacology

Online Submissions: http://www.wjgnet.com/esps/
wjpharmaco@wjgnet.com
doi:10.5497/wjp.v1.i3.50

World J Pharmacol 2012 June 9; 1(3): 50-54
ISSN 2220-3192 (online)

OBSERVATION

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Nicotinic acid: Do we know how it works after 55 years of clinical experience?

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Author contributions: Kei A and Elisaf MS contributed to the conception, design, acquisition and interpretation of data, revised the paper critically and gave their final approval of the version to be published.
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Received: August 26, 2011 Revised: December 27, 2011
Accepted: April 10, 2012
Published online: June 9, 2012

Abstract

Nicotinic acid (NA) comprises the oldest hypolipidemic drug, in use since 1955. Despite its established broad spectrum effect on lipid profile and the associated reduction in cardiovascular morbidity and mortality, the mechanisms by which NA achieves its beneficial effects remain elusive. Regarding the NA-associated reduction in triglyceride and low density lipoprotein cholesterol levels, data are controversial. The prevailing view which suggested that NA inhibits lipolysis and decreases free fatty acid (FFA) release both *via* activation of adipose tissue G-protein receptor-109A (GPR109A) and *via* inhibition of hepatic triglyceride synthesis is currently debated by the observation that the initially decreased FFA levels rebound during long-term NA treatment even though the beneficial NA effects on lipid metabolism are preserved, while other mechanisms involving modulation of transcription and translation pathways are emerging. In addition, NA has been demonstrated to affect high density lipoprotein (HDL) particles remodeling in a number of ways, including reducing cholesterol ester transfer protein levels and activity, increasing apolipoprotein A-I levels, eliminating HDL hepatic uptake, increasing cholesterol efflux *via* ATP-binding cassette A1, inhibiting hepatic lipase, thereby overall increasing the plasma residence time of HDL and apoA-I with retention of cholesterol esters in HDL. Focus of this article is to present the mechanisms by which NA exerts its broad spectrum hypolipidemic actions.

Key words: Dyslipidemia; Nicotinic acid; Niacin; Mechanisms; GPR109A; Free fatty acids

Peer reviewer: Josh Burk, Associate Professor, Department of Psychology, College of William and Mary, 540 Landrum Drive, Williamsburg, VA 23187, United States

Kei A, Elisaf MS. Nicotinic acid: Do we know how it works after 55 years of clinical experience? *World J Pharmacol* 2012; 1(3): 50-54 Available from: URL: http://www.wjgnet.com/2220-3192/full/v1/i3/50.htm DOI: http://dx.doi.org/10.5497/wjp.v1.i3.50

INTRODUCTION

Nicotinic acid (NA), also known as the water-soluble vitamin B3 (niacin), comprises the oldest hypolipidemic agent, being in use since 1955[1]. It decreases by 5%-25% and 20%-50% the levels of low density lipoprotein (LDL) cholesterol and triglycerides (TG), respectively, while NA remains the most effective currently available agent for raising high density lipoprotein (HDL) cholesterol levels (by 20%-25%) and decreasing the levels of lipoprotein (a) [Lp(a)] (by 28%-40%)[2,3]. Moreover, a number of clinical trials have demonstrated that NA may decrease cardiovascular events[4] and total mortality[5] in patients with coronary heart disease. Overall, NA comprises a hypolipidemic agent with unique broad-spectrum lipid-modifying properties and possible clinical benefits[6,7]. However, the mechanisms by which NA exerts its lipid-modifying

effects remain elusive. Focus of this paper is the presentation of these mechanisms. We searched PubMed up to 10 August 2011 using combinations of the following keywords: niacin, NA, mechanism, action, GPR109A, free fatty acids (FFA), dyslipidemia, hypolipidemic, liver, adipose tissue, macrophages and receptor. The references of these articles were scrutinized for relevant articles.

TG AND LDL CHOLESTEROL LEVEL REDUCTION

The mechanisms which contribute to the NA-associated TG and LDL cholesterol level reduction are not fully understood. However, the prevailing view holds that NA achieves TG and LDL cholesterol level reduction, primarily by affecting both adipose tissue's and liver's TG metabolism. (Figure 1).

NA's effect on adipose tissue

G-protein receptor-109A (GPR109A), also known as HM74A receptor in humans[8] is expressed in adipose tissue, spleen and immune cells[9-11]. NA binds and activates GPR109A in adipose tissue inducing a Gi-mediated inhibition of adenylyl cyclase activity, thereby resulting in a decrease of cyclic adenosine monophosphate (cAMP) intracellular levels[12]. This leads to decreased lipolysis, as cAMP is the main intracellular mediator of prolipolytic stimuli. cAMP normally activates protein kinase A (PKA) to phosphorylate various proteins, including perilipin and hormone-sensitive lipase (HSL), thereby promoting lipolysis[12]. The decrease in circulating FFA results in a substrate shortage for hepatic very low density lipoprotein (VLDL) production, consequently reducing plasma levels of LDL cholesterol and TG[13,14]. Paradoxically, it has been established that the initially decreased FFA levels rebound during long-term NA treatment even though the beneficial NA effects on lipid metabolism are preserved[15,16]. But how that happens? Phosphoenolopyruvate carboxykinase (PEPCK1) is a key enzyme in adipose tissue gluconeogenesis and its deficit leads to increased FFA release Recently, NA was associated with decreased expression of PEPCK1 in adipose tissue and thus increased FFA release, partly explaining the rebound phenomenon[17]. Another contributing mechanism to FFA rebound could also be the NA-induced up-regulation of tumor necrosis factor-α (TNF-α) transcription and the consequent increase of interleukin-6 (IL-6), as both of them comprise cytokines with lipolytic properties, thereby increasing FFA release[17]. Of note, MK-0354, a partial agonist of GPR109A which resulted in decreased plasma FFA concentrations, paradoxically failed to affect LDL cholesterol and TG levels[18]. Overall, it seems that the contribution of GPR109A activation to the long-term hypolipidemic effects of NA remains debatable.

NA's effect on liver

NA has been demonstrated to inhibit diacylglycerol acyl transferase 2 (DGAT2) which comprises a key enzyme

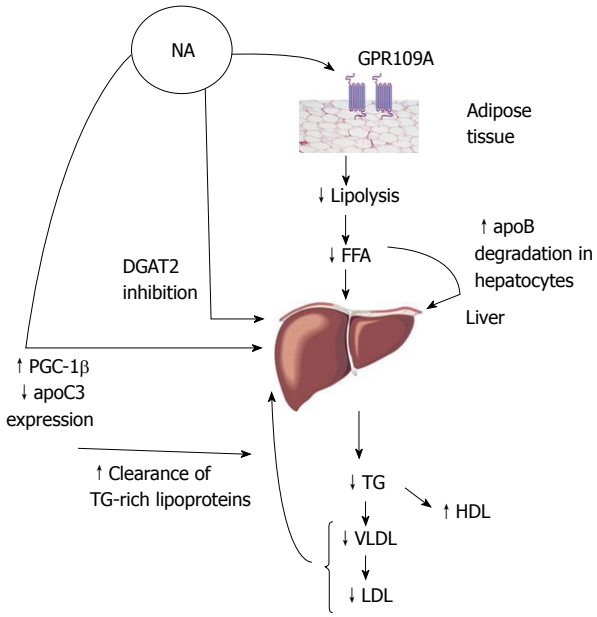

Figure 1 How nicotinic acid decreases triglycerides and low density lipoprotein cholesterol levels. NA: Nicotinic acid, TG: Triglycerides, LDL: Low density lipoprotein; FFA: Free fatty acids; VLDL: Very low density lipoprotein; DGAT2: Diacylglycerol acyl transferase 2; PGC-1β: Peroxisome proliferator-activated receptor γ coactivator-1β; apoC3: Apolipoprotein C3; apoB: Apolipoprotein B.

for the hepatic TG synthesis[19]. However, DGAT2 inhibition has been observed at NA concentrations 100-folder higher than those associated with maximal pharmacological effects of NA on FFA and TG levels[20].

Current evidence indicates that the post-translational apolipoprotein B (apoB) degradative processes regulate the hepatic assembly and secretion of VLDL and the subsequent generation of LDL particles. The availability of TG for the addition to apoB during intracellular processing appears to play a central role in targeting apoB for either intracellular degradation or assembly and secretion as VLDL particles. NA-induced TG synthesis inhibition has been demonstrated to create a favorable environment for protease-mediated intracellular apoB degradation in hepatocytes, thereby resulting in decreased apoB-containing VLDL and thus LDL particle formation[21,22]. In addition, stable isotope methodologies in dyslipidemic patients demonstrated NA-enhanced plasma clearance of TG-rich lipoproteins containing either apoB100 or apoB48, thereby implying that NA may affect both hepatic and intestinal TG-rich lipoproteins' metabolism[22]. Of note, NA failed to interact with hepatic LDL-receptors[23].

Further actions on TGs have been associated with the NA-induced inhibition of peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1β (PGC-1β). PGC-1β is a transcriptional co-activator that is regulated by FFA. Specifically, PGC-1β induces hypertriglyceridemia in response to dietary fats through activation of hepatic lipogenesis and lipoprotein secretion. Moreover, PGC-1β regulates plasma TG levels by stimulating apolipoprotein C3 (apoC3) expression, thereby inhibiting

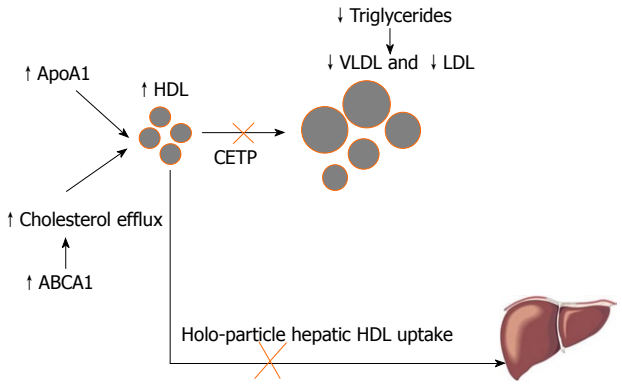

Figure 2 How nicotinic acid can increase high density lipoprotein cholesterol level. NA: Nicotinic acid; HDL: High density lipoprotein; VLDL: Very low density lipoprotein; LDL: Low density lipoprotein; CETP: Cholesterol ester transfer protein; ApoA1: Apolipoprotein A1; ABCA1: ATP-binding cassette protein A1.

apolipoprotein E (apoE) driven clearance of TG-rich lipoproteins[24]. Of note, both acute and chronic treatment with NA were associated with reduced hepatic expression of PGC-1β and apoC3, while knockdown of PGC-1β or APOC3 in mice liver recapitulated NA's hypolipidemic effect[24].

HDL CHOLESTEROL LEVEL ELEVATION

The mechanisms by which NA elevates HDL cholesterol level have not been fully elucidated. However, a number of mechanisms have been shown to contribute to the observed NA-induced HDL cholesterol level elevation. (Figure 2).

NA's effect on cholesterol ester transfer protein

The NA-induced decrease in TG levels in apoB-containing lipoproteins (LDL and VLDL) eliminates the exchange of TG for cholesteryl-esters from HDL particles mediated by cholesterol ester transfer protein (CETP), resulting in increased HDL concentration[25,26]. In fact, NA-associated HDL cholesterol elevation depended on the presence of CETP in mice[27]. However, the partial GPR109A agonist MK-0354 failed to raise HDL levels despite the reduction in plasma FFA[18]. NA has been also associated with reduced CETP activity per se as a result of reduced hepatic CETP gene expression and reduced release of CETP in plasma[28]. Of note, the reduction in CETP activity can also explain how NA promotes the maturation of HDL into large particles[22].

NA's effect on the holo-particle uptake pathway

NA has been associated with reduced hepatic uptake of HDL, potentially by the holo-particle uptake pathway. In fact, NA has been shown to inhibit the surface-expressed ATP-synthase β-chain which acts as a HDL holoparticle receptor leading to slower HDL catabolism[29].

NA's effect on apolipoprotein A-I metabolism

Data regarding the effect of NA on apolipoprotein A-I (apoA-I) metabolism are controversial. NA has been shown to increase production rate of apoA-I both in liver and intestinal cells[22,30]. In fact, NA activates both mitogen activated protein (MAP) kinase and the PPAR transcription factors pathways, which both affect hepatic apoA-I production[31-33]. On the contrary, other studies with hepatic cells and mice reported no effect of NA on apoA-I production rate, while NA administration was associated with decreased apoA-I hepatic removal[28,34].

NA's effect on ATP-binding cassette protein A1

NA, potentially *via* GPR109A activation, enhances transcription of cholesterol efflux transporters ATP-binding cassette protein A1 and G1 (ABCA1 and ABCG1, respectively). Thus, NA-induced cholesterol efflux from macrophages could also contribute to the reported increase in HDL cholesterol levels[23,35]. Moreover, NA dose-dependently stimulated PPARγ and ABCA1 expression and promoted ApoA-I-induced cholesterol efflux in adipocytes. In fact, treatment of PPARγ-selective antagonist GW9662 significantly abolished the NA-induced increase in ABCA1 mRNA expression and cholesterol efflux to ApoA-I[36]. Of note, NA had no effect in HDL cholesterol levels in GPR109A knock-out mice[36]. On the other hand, overexpression of GPR109A reduced hepatocyte ABCA1 expression and activity, thereby decreasing cholesterol efflux to nascent apoA-I and reducing HDL cholesterol levels in mice[37]. Overall, it seems that NA effect on ABCA1 is mediated *via* GPR109A and we can speculate that a phenomenon of tachyphylaxis may occur in case of GPR109A overstimulation.

NA's effect on hepatic lipase

In mice NA has been shown to inhibit hepatic lipase activity. This results in decreased remodeling of plasma HDL, thereby limiting HDL clearance[28].

Lp(a) REDUCTION

No particular mechanisms regarding the NA-induced reduction of Lp(a) have been reported. However, the NA-associated reduction in the circulating FFA by both GPR109A-mediated lipolysis and DGAT2 inhibition results in reduced VLDL and subsequently LDL levels[13,19]. As LDL particles comprise the substrate for Lp(a) it comes as no surprise that NA also reduces Lp(a) levels.

CONCLUSION

Overall, NA exerts broad spectrum effects on lipids through a number of elusive and even controversial mechanisms. Regarding the NA-associated reduction in TG and LDL cholesterol levels, the prevailing view which suggested that NA inhibits lipolysis *via* GPR109A activation is currently debated by both the rebound phenomenon and the failure of partial GPR109A agonist, MK-0354 to reduce TG and LDL cholesterol levels despite the decrease in plasma FFA. On the other hand,

the NA-associated DGAT2 inhibition was reported at NA levels much higher than those used in clinical setting. However, it can be argued that plasma levels of NA may not reflect its bioavailability at the liver. In addition, PGC-1β mediated increased clearance of TG-rich lipoproteins may also contribute to hypolipidemic effects of NA.

Similarly, data regarding the mechanisms by which NA increases HDL cholesterol level are scant. However, it seems that NA affects HDL particles remodeling in a number of ways, including reducing CETP levels and activity, increasing apoA-I levels, eliminating HDL hepatic uptake, increasing cholesterol efflux *via* ABCA1, inhibiting hepatic lipase, thereby overall increasing the plasma residence time of HDL and apoA-I with retention of cholesterol esters in HDL.

Conclusively, the mechanisms by which the oldest hypolipidemic drug exerts its lipid-modifying effects remain elusive even after 55 years of clinical experience. However, it is undebatable that NA targets a number of different receptors expressed in a variety of cells including hepatic, intestinal and adipose tissue cells in order to achieve its broad spectrum effect on lipid profile. More research effort especially with genetically modified animals which do not express or overexpress a number of receptors or transporters including GPR109A, ABCA1, PGC-1β is needed in order to decode how NA really works.

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