Niacin Metabolism:
Effects on Cholesterol

By
Julianne R. Edwards

For
Dr. William R. Proulx, PhD, RD
Associate Professor of Nutrition and Dietetics

In partial fulfillments for the requirements of
NUTR342 Advanced Nutrition II

May 1, 2012
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. INTRODUCTION</td>
<td>2</td>
</tr>
<tr>
<td>2. REVIEW OF LITERATURE</td>
<td>2</td>
</tr>
<tr>
<td>A. Niacin’s effect on LDL Cholesterol (apo B)</td>
<td>3</td>
</tr>
<tr>
<td>1. Lowering Mechanism 1</td>
<td>3</td>
</tr>
<tr>
<td>2. Lowering Mechanism 2</td>
<td>4</td>
</tr>
<tr>
<td>B. Niacin’s effect on HDL Cholesterol (apo A)</td>
<td>4</td>
</tr>
<tr>
<td>C. Side Effects</td>
<td>6</td>
</tr>
<tr>
<td>3. CONCLUSIONS</td>
<td>7</td>
</tr>
<tr>
<td>4. REFERENCE LIST</td>
<td>8</td>
</tr>
</tbody>
</table>
INTRODUCTION

Niacin is found in two forms: nicotinic acid and nicotinamide. Niacin is a precursor for two essential coenzymes, NAD and NADP. NAD and NADP can be reduced to NADH and NADPH, respectively. Both of these coenzymes are tightly bound to Apo enzymes (HDL, LDL, and VLDL.) In addition, both coenzymes are involved in oxidation-reduction reactions catalyzed by dehydrogenase and oxidoreductase enzymes. Nicotinic acid and nicotinamide have a plethora of differences, including structural differences. Nicotinic acid has a pyridine 3-carboxylic acid structure (COOH) and nicotinamide has a nicotinic acid amide structure (CONH$_2$).

Dyslipidemia is a disorder of lipoprotein metabolism. Dyslipidemia can be characterized by an elevation of total cholesterol, LDL, and TG levels and a decrease in HDL levels. Pharmacological doses of niacin have been previously used to regulate abnormalities in plasma lipid and lipoprotein metabolism thus niacin has been used in the treatment of dyslipidemia.

This paper will review niacin’s ability to exhibit lipid-modifying capacities in order to regulate abnormalities in plasma lipid and lipoprotein levels thus clarify why pharmacological doses of niacin can be used to treat dyslipidemia. Side effects of using pharmacological doses of niacin will also be discussed.

REVIEW OF LITERATURE

Niacin’s effect on LDL Cholesterol (apo B)

Pharmacological doses of niacin (nicotinic acid) of up to 6 g/day in divided doses has shown to be an effective way to treat dyslipidemia by lowering VLDL, LDL, triglyceride (TG),
and total serum cholesterol. Although all complex mechanisms of action are not fully understood, niacin has shown to be able to lower these levels through two mechanisms. (1) One mechanism is through decreasing fatty acid (FA) mobilization from adipose tissue. The second mechanism to lower levels other is inhibiting hepatocyte diacylglycerol acyltransferase and triglyceride synthesis leading to increased intracellular apo B degradation and thus decreased secretion of VLDL and LDL particles.

**LDL Lowering Mechanism I**

HM74A (GRP109A) is a niacin receptor which has been identified in humans on the distinct chromosome gene, 12.q.24.31. (2) Niacin is able to bind to G-protein-coupled receptor (GPCR), HM74A, due to its structural characteristic of the carboxylic acid group expressed in niacin in the form of nicotinic acid. The other form of niacin, nicotinamide, does not share the structural characteristic of a carboxylic acid group thus it can’t bind to the GPCR HM74A. Furthermore, HM74A is responsible for the majority of clinical effects on niacin and plasma lipids. This receptor is highly expressed in adipocyte tissues and is coupled to G\textsubscript{i} subunits. The activation of this receptor results in decreased adenylate cyclase activity with a succeeding reduction in the intracellular concentration of cyclic AMP. Cyclic AMP is the mediator of adipocyte lipolysis due to the subsequent protein kinase A activation which phosphorylates and activates hormone sensitive lipase.

As reviewed by Ganji et al, adipose cells are specialized for the synthesis and storage of TG and for their mobilization to the liver as a fuel in the form of FFA and glycerol. (1) Adipose tissue TG lipolysis is controlled by the cyclic AMP mediated activation of hormone sensitive lipase. Therefore, once nicotinic acid binds to the GPCR HM74A, there is a decrease in adenylate cyclase activity as well as concentration in cyclic AMP. The decrease in cyclic AMP
subsequently inhibits the activation of hormone sensitive lipase and decreases TG lipolysis. Release of FFA from adipose tissue is decreased. Mobilization of FA to the liver is thus decreased as well. A decrease in mobilization from FA to the liver results in a decrease of FA synthesis, a decrease in TG synthesis, a decrease in the addition of TG to Apo B polypeptides, a decrease in large TG rich VLDL. This process results in an overall decrease of LDL production and lower LDL levels are thus seen in human beings.

**LDL Lowering Mechanism II**

As previously stated, nicotinic acid decreases the hormone sensitive lipase which decreases mobilization of FA to the liver in through binding to its HM74A receptor in adipocyte tissues. In hepatocytes, niacin then inhibits FA synthesis and the esterification of diacylglycerol (DAG) to form TG mediated by direct non-competitive inhibition of diacylglycerol acyltransferase (DGAT). (1) DGAT is a key enzyme in FA synthesis thus inhibition of DGAT results in decreasing TG synthesis. A decrease in TG synthesis decreases the addition of TG to apo B polypeptide. A decrease in the addition of TG to Apo B polypeptide may then decrease lipidation of apo B and the translocation across the endoplasmic reticular membrane. Due to this process intracellular apo B degradation is increased and the number of VLDL and LDL particles produced decreases. This process is controversial and complex. Further studies and research is still necessary to completely explain all mechanisms of action.

**Niacin’s effect on HDL Cholesterol (apo A)**

Niacin’s ability to increase HDL levels is an emerging concept and topic. It has been suggested that niacin directly inhibits the uptake and catabolism of apo AI containing HDL particles therefore increasing plasma levels of HDL. (3) Additionally, a plethora of research has
drawn attention to the idea of niacin increase HDL levels through deficiency and/or inhibition of cholesteryl ester transfer protein (CETP.) CETP is also known as a plasma lipid transfer protein. (4) CETP is a hydrophobic glycoprotein that typically bound to HDL, secreted from the liver and circulated in plasma. CETP promotes the transfer of cholesteryl esters from HDL to VLDL, LDLs, and other apo B containing lipoproteins. A deficiency of CETP has been associated with increased HDL levels. Studies that experiment with inhibition of CETP typically have statistical data analysis supporting the idea that a deficiency and/or inhibition of CETP will result in increased HDL.

Haan et al, investigated for clarification of the mechanism of underlying niacin’s HDL-raising effect. (5) Haan et al, previously identified APOE*3Leiden (E3L) mice as having human-like lipoprotein profile with high plasma cholesterol and TG levels. TG levels were mainly confined to the VLDL-sized. Mice developed atherosclerosis on dietary cholesterol feeding and responded in human manner to drugs used in treatment of CVD (ie, statins, fibrates, calcium channel blockers.) E3L mice were cross-bread with hemizygous human cholesteryl ester transfer protein (CETP) transgenic mice. E3L.CETP type mice were produced. Both, E3L and E3L.CEPT mice obtained similar total cholesterol levels by being fed a semisynthetic cholesterol-rich diet for 3 weeks. Mice were matched 8 per group and received a Western-type diet without or with 36mg/kg/d (0.03%), 118mg/kg/d (0.1%), 360 mg/kg/d (0.3%), or 118 mg/kg/d (1%) niacin for three weeks. Considering mice have ten times faster metabolism than humans, doses of niacin have been proven to correspond. Statistical analysis revealed that in E3L.CETP mice, niacin increased HDL up to +87% (P<0.001) in a dose-dependent fashion. Additionally, apo AI was increased up to +72% (P<0.001) as well as the HDL particle size. Niacin showed to dose-dependently decrease the hepatic expression of CETP up to -88%
Plasma CETP mass was also decreased up to -45% (P<0.001) and CETP activity up to -52% (P<0.001). Lastly, niacin dose-dependently decreased the clearance of apo AI from plasma and reduced the uptake of apo AI by the kidney up to -90% (P< 0.01). On the other hand, evidence showed that in E3L mice not expressing CETP, HDL was not increased. Statistical findings provide evidence that niacin increases both HDL and apoAI although the effects of HDL at the various doses are semi-more pronounced than on apoAI thus suggesting that niacin increases the lipidation of apoAI. This study concludes that the HDL-increasing effect of niacin in E3L.CETP mice is dose-dependent and that niacin increased HDL in E3L.CETP mice due to the reduction of CETP activity. Therefore, the reduction of CETP due to dose-dependent niacin in humans, results in an increased HDL level. It is important to understand that this data is not conclusive and should continue to be studied.

Side Effects

Niacin being used in pharmacological doses for treatment is associated with a number of side effects both mild and severe. (2) Mild side effects include headache, itching, and gastrointestinal disturbances while a more severe side effect is flushing. Flushing is caused by production of PGD₂ which gives rise to endogenous ligands for PPARy. PPARy is a major regulator of adipocyte development. (6) PPARy controls genes involved in adipocyte differentiation and fat storage and inhibits genes involved in lipolysis and release of FFA from adipose tissue. Therefore, the flushing is considered to be beneficial in regards to the cardiovascular system. All side effects including mild and severe are short and have not been proven to be harmful to the body.
CONCLUSION

Niacin, in the form of nicotinic acid, can lower LDL levels in human beings through different mechanisms after binding to the GPCR HM74A located mainly in adipocyte tissues. Niacin has also been shown to increase HDL levels by through inhibiting the uptake and catabolism of apo AI containing HDL particles as well as through inhibiting the cholesteryl ester transfer protein which is secreted from the liver. Therefore through a plethora of complex mechanisms, niacin has the ability to decrease total cholesterol, TG, and LDL levels and increase HDL levels. Modifying lipid and lipoprotein levels in such a manor aids and emphasizes niacin’s ability to act in regulating abnormalities in plasma lipid and lipoprotein levels thus treat and prevent progression of dyslipidemia. The side effects which occur due to taking pharmacological doses of niacin to treat dyslipidemia are not considered to be harmful to the body.
REFERENCES


