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Dr. Pallavi Khajuria
College of Veterinary Science, Rampura Phul, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India

Dr. Gurpreet Singh
College of Veterinary Science, Rampura Phul, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India

Dr. Dawoud Aamir Nehru
College of Veterinary Science, Rampura Phul, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India

Dr. Inder Pal Singh
College of Veterinary Science, Rampura Phul, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India

Dr. Amit Challana
College of Veterinary Science, Rampura Phul, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India

Dr. Anavil Bhardwaj
College of Veterinary Science, Rampura Phul, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India

Corresponding Author:
Dr. Pallavi Khajuria
College of Veterinary Science, Rampura Phul, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India

A review: Role of niacin as antihyperlipidemic drug

Dr. Pallavi Khajuria, Dr. Gurpreet Singh, Dr. Dawoud Aamir Nehru, Dr. Inder Pal Singh, Dr. Amit Challana and Dr. Anavil Bhardwaj

Abstract
Niacin is frequently referred to as a 'broad spectrum anti-hyperlipidemic drug'. Niacin has been reported to reduce total plasma cholesterol, triglyceride, VLDL, and LDL concentrations and increases HDL concentration. This makes niacin ideal for treating a wide variety of lipid disorders, including the metabolic syndrome, diabetes mellitus, isolated low high-density lipoprotein cholesterol, and hypertriglyceridemia.

Keywords: Niacin, Nicotinic acid, Cholesterol, antihyperlipidemic

Introduction
Niacin is a broad-spectrum anti-hyperlipidemic drug (Ganji *et al.*, 2003) [1] and is one of the most potential agent which can be used in disorders of lipid metabolism. Niacin (nicotinic acid, vitamin B_3), is a water-soluble vitamin (Wadhera *et al.*, 2016) [2] which has potential to reduce plasma cholesterol levels along with triglyceride, VLDL (Very Low Density Lipoprotein), and LDL (Low Density Lipoprotein) concentrations and increases the levels of the levels of circulating HDL cholesterol which is considered as good cholesterol for the body along with a major protein ie. apo A-I. Activation of HCAR2 is one of the major ways by which niacin reduces very low density lipoprotein levels (VLDL). It also reduces the levels of an important protein ie. Cholesteryl ester transfer protein (CETP), which is required for reverse transport of cholesterol by HDL and is responsible for exchange of triglycerides in VLDL and LDL particles for cholesteryl esters in HDL particles. For syntheisis of reduced glutathione (GSH), reduced nicotinamide adenine dinucleotide phosphate (NADPH) is considered as important cofactor and this NADPH is coenzyme of the enzyme glutathione reductase (Ambrosio *et al.*, 1991) [3]. Glutathione peroxidase is an important antioxidant which fights against production of ROS (Reactive Oxygen Species) and this reduced GSH is required for action of for glutathione peroxidase (GPx), in the living system (Ambrosio *et al.*, 1991)[3]. Apart from this, this vitamin along with its coenzymes is found to have potential to play major role in metabolism of xenobiotics, energy metabolism, amino acid metabolism detoxification reactions for drugs, amino acid metabolism (Perumal *et al.*, 2005) [4].

Mechanism of action of niacin as hypolipidemic drug
Inhibition of lipolysis in adipose tissue, is the major pathway by which niacin acts as antihyperlipidemic drug in the body. Niacin acts on different lipoprotein fractions of the blood ie. LDL, VLDL and HDL which are required for transport of lipids in the blood. Lowering of VLDL fraction by the liver and rising HDL fraction is one of the mechanisms by which it acts as a potential source of drug to reduce lipids. (DiPalma and Thayer, 1991) [5].
Reverse cholesterol transport is the mechanism by which the cholesterol from tissues of the body is transported towards liver for metabolism and thus inhibits the deposition of excess cholesterol in the arteries and thereby reducing the chances of atherosclerosis and niacin raises the levels of this HDL fractions in the blood, thereby increasing the removal of excess cholesterol from the body. It also reduces the synthesis of cholesterol in the body. Cyclic adenosine monophosphate is also required for lipolysis and niacin reduces the levels of CAMP and thus inhibits lipolysis. (Birnbaumer, 1990) [6]. Free fatty acids in the liver are the major source of triglyceride synthesis and other lipoproteins (VLDL), reducing CAMP levels inhibits triglyceride synthesis by inhibiting CAMP. VLDL fractions leads to synthesis of LDL fraction, thus inhibition in VLDL synthesis automatically results in deacreased LDL fractions in the liver (Dipalma and Thayer, 1991) [5].

Niacin lowers triglyceride levels by reducing hepatic VLDL synthesis, thereby limiting the activity of cholesteryl ester transfer protein (CETP), which exchanges triglycerides in VLDL and LDL particles for cholesteryl esters in HDL particles (Digby *et al.*, 2009) [7]. Diacylglycerol O-acyltransferase 2 (DGAT2) is the major enzyme that catalyses triglyceride synthesis and its inhibition is the major cause for reduction of triglyceride synthesis in the body (Ganji *et al.*, 2004) [8]. DGAT2 inhibition thus reduced triglyceride synthesis, thereby reducing VLDL and LDL. ApoB catabolism is increased by niacin which results in reduced synthesis of apoB-containing lipoproteins (Jin *et al.*, 1999) [9]. The increased levels of HDL and HDL-associated cholesterol (Alderman *et al.*, 1989) [10] is one of the contributory factor for its action. Inhibition of Apo A1 which is required for enzyme LCAT that is required for removal of cholesterol from peripheral tissues also supports the antihyperlipidemic effects of niacin. (Dipalma and Thayer, 1991) [5].

Role of Niacin on blood vessels

Nicotinic acid is flound to have hypotensive effects in the body. (Bays and Radar, 2009) [11]. Some studies have also reported that acute niacin administration resulted in significant lowering of blood pressure in patients with hypertension but showed no effect in normotensive individuals (Bays and Radar, 2009) [11]. Acute vasodilation is the major cause for the lowering of blood pressure after administration of niacin. The role of niacin as an antihypertensive agent and its mechanism how it causes hypotensive effects is not known and more studies are needed to explore the therapeutic potential (Bays *et al*., 2009) [12].

Mechanism of action as antioxidant

NADPH which is important for various cellular metabolisms such as energy metabolism and metabolism of xenobiotics is part of niacin and thus plays an important role in antioxidant defense of the body (Perumal *et al.*, 2005) [4]. NADPH regenerates GSH from GSSG in the enzymatic reaction catalysed by glutathione reductase and this NADPH increases the levels of this GSH. Niacin administration results in increase levels of glutathione which is a major antioxidant enzyme in the body and reduces the level of free radical generation/ reactive oxygen production (Benavente and Jacobson, 2008) [13].

Several *in vivo* and *in vitro* studies have proved antioxidant potential of niacin (Ganji *et al.*, 2009) [14]. Tupe *et al.* (2011) [15] reported a significant increase in levels of SOD, CAT, GPx, glutathione and zinc, while, LPO level was lower in the niacin treated rat. Several studies have reported similar findings on the positive effects of niacin on GPx (Dou *et al.*, 2013) [16] and CAT (Dou *et al.*, 2013) [16] activities. A negative correlation between niacin and LPO/ROS production have also been observed (Ilkhani *et al.*, 2016) [17]. However, contrary reports are also available (Bernabucci *et al*., 2002) [18]. Niacin supplementation in animals is postulated to ameliorate metabolic stress by decreasing insulin resistance, reduce oxidative stress and reduce the chances of infection aby improving immunity. (Manat *et al.*, 2023) [19]

Adverse effects of niacin

Generalized pruritus is one of the major allergic reaction that is found after administration of niacin which results in burning sensations in chest and facial regions. Drugs such as Laropiprant, can used to counter such side effects of niacin (Parhofer, 2009) [20]. Niacin is also not recommended in patients with diabetes as it can result in more aggravated hyperglycemia Niacin therapy is thus not recommended in patients with metabolic syndrome or diabetes(Meyer-Ficca and Kirklad, 2016) [21]. Other side effects include generalised symptoms like nausea, rashes on the body vomiting, gastrointestinal disorders, increase in homocysteine levels, hypotension, and alterations in in liver enzyme (SGPT and SGOT). It is contraindicated in patients with active peptic ulcer disease as it can cause GIT disorders and also in patients with liver diseases its use is contraindicated as it results in alterations in liver specific enzymes.

Conclusion

Niacin is a pharmacotherapeutic pleiotropic agent but considering its side effects such as vomotion, nausea, generalized pruritis reaction such as its use has been limited. It also increases the risk of reduced blood pressure ie. Hypotension and increasing the blood uric acid levels in patients. One of the concerning effects is that its potential to rise blood glucose levels causing hyperglycemia is also limiting its use and more studies are needed to study such such side affects and it can be used as combination drugs to counter such side effects. More studies are needed in this concern to explore the role therapeutic effects of the nicotinic acid.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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