Journal of Biosciences and Medicines, 2023, 11, 233-238
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Mechanism of Niacin Induced Hot Flushes and Suppression of Cholesterol

Thirugnana Subramanian*

Department of Pediatric Hematology and Oncology, Washington University School of Medicine, Saint Louis, USA
Email: thirusubraman@gmail.com

How to cite this paper: Subramanian, T. (2023) Mechanism of Niacin Induced Hot Flushes and Suppression of Cholesterol. *Journal of Biosciences and Medicines*, **11**, 233-238.
https://doi.org/10.4236/jbm.2023.115016

Received: April 25, 2023
Accepted: May 19, 2023
Published: May 22, 2023

Abstract

Niacin or nicotinic acid is a form of B3 vitamin prescribed at higher concentrations for the suppression of cholesterol levels. Supplemental doses may cause very little or no side effects. However, higher concentrations of niacin cause hot flushes for most people. Here we propose a biochemical mechanism of niacin induced hot flushes. Orally taken prescription doses of niacin are converted to NAD with the liberation of excess pyrophosphate which in turn releases energy in the form of heat (hot flushes through capsaicin receptor) by the action of pyrophosphatases. The excess pyrophosphate may suppress cholesterol biosynthesis through feedback mechanism. The pathways of NAD and cholesterol biosynthesis were discussed with refence to the production and function of pyrophosphate.

Keywords

Cholesterol Biosynthesis, NAD, Niacin, Niacinamide, Pyrophosphate

1. Introduction

Niacin, or nicotinic acid, is a water-soluble B3 vitamin. The other forms of B3 are niacinamide or nicotinamide and nicotinamide riboside. Among the B3 vitamins niacin is an important precursor of NAD and most of the NAD is synthesized from niacin. Besides from B3 vitamins very little NAD is synthesized from amino acid, tryptophane. Niacin is prescribed at higher doses (500 to 2000 mg/day) to help control cholesterol levels. Normal supplemental doses (10 to 25 mg/day) have minimal side-effects, whereas prescription doses cause hot flushes: characterized by cutaneous vasodilation with redness and warmth of the skin accompanied by tingling, burning and itching. It is a nonallergic form of response that lasts within an hour producing discomfort to patients. It has been shown that prescription doses of niacin suppress serum levels of total cholesterol

*Retired Staff Scientist.

as well as low-density lipoprotein, while raising high-density lipoprotein [1]. This leads to reduced risk of mortality from cardiovascular disease. While it may cause flushing, statin-intolerant individuals may have to use niacin as their primary medication for dyslipidemia. The mechanism by which niacin induces flushing and suppressing cholesterol levels is not well understood. I collected literature, analyzed niacin and cholesterol metabolism, and proposed a mechanism for its function as an inducer of hot flushes as well as regulator of cholesterol biosynthesis and presented here.

2. Methods

I collected literature using key words niacin, niacinamide, niacin metabolism, NAD, niacin supplemental and prescription doses, cholesterol metabolism and the effects of niacin on cholesterol levels as well as its side effects of inducing hot flushes through PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Google (https://www.google.com/).

Initially, a total of 35 related articles (including reviews) with a coverage of years 1958 to 2022 were selected in a preliminary search. From the initially selected articles, the important articles which are more relevant to this study were further analyzed for their exclusion and inclusion criteria. Only 13 articles were finally used in this study to support the newly proposed mechanism of niacin induced hot flushes and suppression of cholesterol biosynthesis. My search was limited to the papers in English only.

3. Results and Discussion

Pyrophosphates (PPi) are high energy inorganic polyphosphates liberated from nearly 200 biochemical reactions, including biosynthesis of DNA, RNA, proteins, lipids and coenzymes [2]. Pyrophosphatases are enzymes present throughout the cell and extracellular space, with the exception of mitochondria, which hydrolyze PPi into phosphates and maintain PPi homeostasis. Abundance of PPi is detrimental so it must be eliminated. During DNA and RNA synthesis, the polymerase activity is coupled to pyrophosphatase activity that eliminates pyrophosphates making the reactions irreversible [3]. The PPi formed during cholesterol biosynthesis serves as feedback to control cholesterol levels. The locations and numbers of PPi synthesis during NAD biosynthesis from niacin and cholesterol biosynthesis from acetate are shown in **Figure 1**. The PPi formed during NAD synthesis is transported out of mitochondria into the cytosol since there is no pyrophosphatase activity within the mitochondria and more than 70% of NAD is synthesized inside the mitochondria [4]. For each molecule of NAD synthesis from niacin there are three PPi molecules formed inside the cell as shown in **Figure 1(a)**. Since the pyrophosphatase reaction is exothermic, it releases the energy as heat into the cell and there will be minimal adverse effects under normal physiological concentrations of the substrates. At prescription doses (500 to 2000 mg/day) of niacin, large amounts of PPi are liberated and

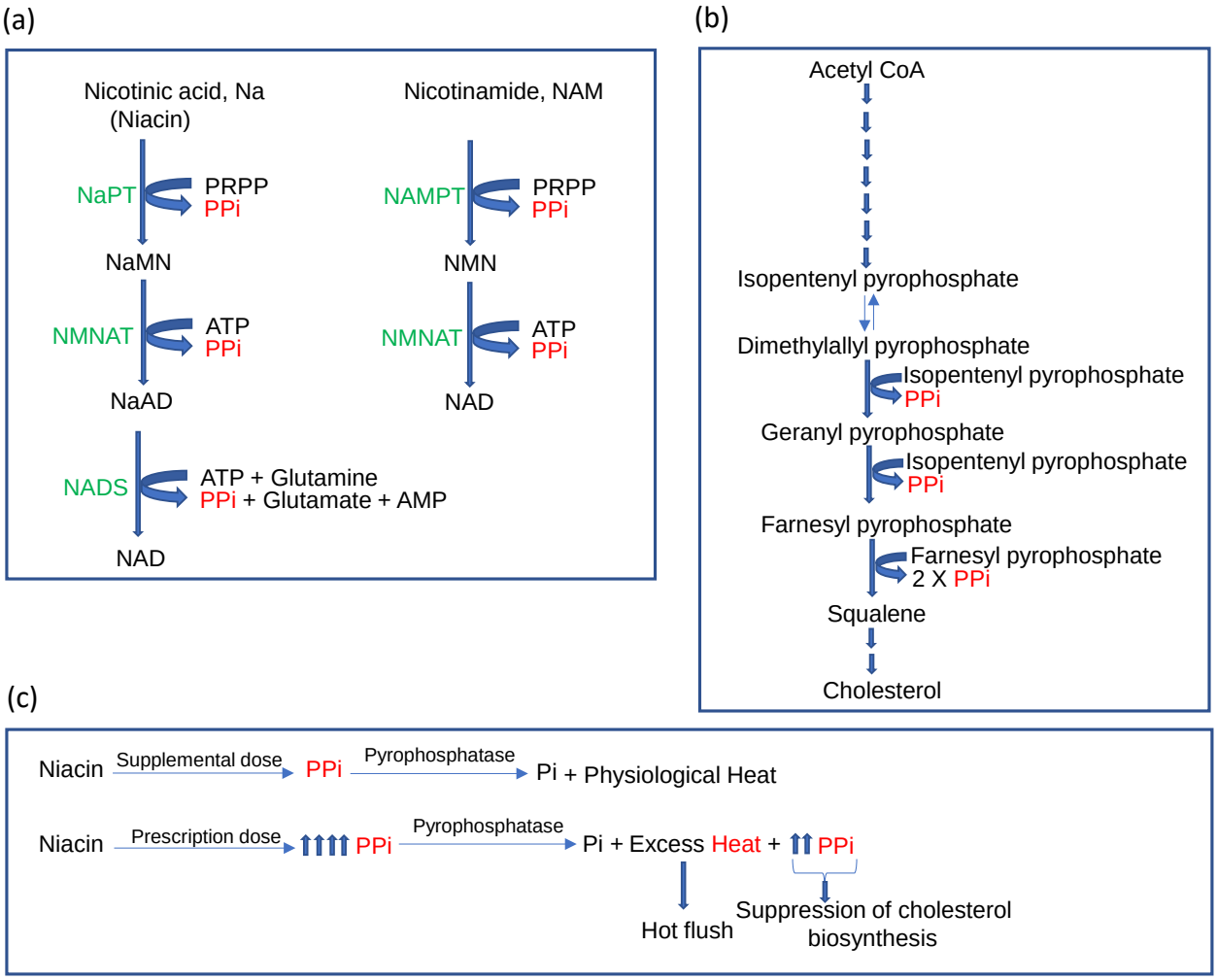

Figure 1. Formation of PPi during the biosynthesis of NAD (a), cholesterol (b) and its effect (c). (a) In mammals, Na enters the cell and is converted to NaMN by the enzyme NaPT using PRPP as co-substrate, with the formation of one molecule of PPi. The enzyme NMNAT then converts NaMN to NaAD using ATP as co-substrate, with the formation of a second molecule of PPi. Finally, NaAD is converted to NAD by the enzyme NADS using ATP and glutamine as co-substrates, with the formation of a third molecule of PPi and AMP. For comparison NAD synthesis from niacinamide is shown. This pathway produces only two molecules of PPi. In total, three molecules of PPi are formed for each molecule of NAD synthesized from Na. (b) Pathway of cholesterol biosynthesis from acetyl CoA; only the PPi forming reactions are mentioned. After several reactions, acetyl CoA is converted to isopentenyl pyrophosphate which then isomerizes to dimethylallyl pyrophosphate. Each one molecule of isopentenyl pyrophosphate and dimethylallyl pyrophosphate condenses to form geranyl pyrophosphate with the formation of one molecule of PPi. Again, isopentenyl pyrophosphate condenses with geranyl pyrophosphate to yield farnesyl pyrophosphate, with the formation of a second molecule of PPi. Two molecules of farnesyl pyrophosphate condense to form squalene with the formation of two molecules of PPi. Squalene undergoes further reactions to form cholesterol. During cholesterol biosynthesis four molecules of PPi are formed. The pyrophosphate has to be eliminated by pyrophosphatases to make the cholesterol biosynthesis irreversible. If there is excess PPi, it can push back the reaction and halt cholesterol biosynthesis. (c) At supplemental doses of niacin, only limited amount of PPi is formed that can be hydrolyzed by the pyrophosphatase to Pi with the liberation of a physiological amount of heat. At prescription doses of niacin, large amounts of PPi are formed which are then hydrolyzed to Pi with the liberation of excess heat resulting in hot flushes. The available pyrophosphatase is unable to hydrolyze all of the PPi produced, so in turn, this excess PPi makes the cholesterol biosynthesis reaction reversible and inhibits cholesterol synthesis. NaPT: Nicotinic acid phosphoribosyl transferase; PRPP: Phosphoribosyl pyrophosphate; PPi: inorganic pyrophosphate; NaMN: Nicotinic acid mononucleotide; NMNAT: Nicotinic acid (nicotinamide) mononucleotide adenylyl transferase; ATP: Adenosine triphosphate; NaAD: Nicotinic acid adenine dinucleotide; NADS: NAD synthase; AMP: Adenosine monophosphate; NAD: Nicotinamide adenine dinucleotide; NAMPT: nicotinamide phosphoribosyl transferase; NMN: nicotinamide mononucleotide; Pi: inorganic phosphate.

their hydrolysis releases large amounts of heat that cause hot flushes through the activation of capsaicin receptor,TRPV1 [5]. Capsaicin has been reported to induce upregulation of oxidative phosphorylation uncoupling proteins like UCP-1 and produce heat [6]. This liberated heat activates TRPV1 which is a heat sensing protein that induces pain sensation and thermoregulatory responses such as sweating and vasodilation. The induction of hot flushes by niacin and capsaicin may be similar, but the mechanism may be different. Capsaicin induces heat through uncoupling of oxidative phosphorylation by upregulating uncouplers whereas niacin induces heat through the production of PPi and its hydrolysis by pyrophosphatases.

It has been shown that increasing intracellular levels of NAD enhances survival by boosting energy production and upregulating cellular repair system [7]. It is well known that vitamin B3 is a precursor and building block of NAD. Vitamin B3 includes niacin, nicotinamide and nicotinamide riboside. Besides these three precursors of NAD, nicotinamide mononucleotide (NMN) has been shown to increase the intracellular level of NAD without hot flush [8]. It should be noted (**Figure 1(a)**) that for each molecule of NAD synthesis the PPi formed from nicotinamide is two molecules and only one molecule from NMN compared to three molecules from niacin. Since nicotinamide and NMN formed lower PPi, they should produce less or no hot flushes when compared to niacin. Our hypothesis is supported by the previous report [9] that nicotinamide didn't induce hot flushes or reduce cholesterol levels like niacin. In addition, NMN is safe even at a high concentration of 1000 mg/day without producing hot flush and several manufacturers are selling as an antiaging supplement. Taken together all these observations suggest that excess PPi produced by niacin during NAD synthesis cause hot flush.

During cholesterol biosynthesis there are four PPi molecules formed from each molecule of cholesterol (**Figure 1(b)**) which can serve as a feedback mechanism for cholesterol biosynthesis, making PPi a key regulator [10]. Still, it is not clear where the PPi goes and whether they produce heat. During DNA, RNA synthesis also one molecule of PPi is formed for each addition of nucleotide into the growing chain of DNA or RNA. Here the polymerases are coupled to pyrophosphatase activity and eliminate the PPi formed [3]. But there is no evidence that during DNA and RNA synthesis heat is liberated. Further work is needed to show where the energy goes during DNA, RNA or cholesterol synthesis. However, the excess PPi produced during NAD synthesis can produce heat through pyrophosphatase hydrolysis and the PPi escaped from pyrophosphatase can suppress cholesterol synthesis.

The mechanism of prescription-dose niacin-induced hot flushes and suppression of cholesterol biosynthesis is shown in **Figure 1(c)**. High doses of niacin lead to the synthesis of large quantities of NAD that can prevent aging and subsequently PPi. Large quantities of PPi are hydrolyzed by pyrophosphatase that produce excess heat resulting in hot flushes. The level of pyrophosphatase

present inside the cell may not be sufficient to hydrolyze that large amount of PPi and the remaining PPi inhibits the biosynthesis of cholesterol in a feedback manor. Although high doses of niacin produce hot flushes, it is good for reducing cholesterol synthesis with the production of large amount of NAD which aids preventing aging. It is important to note that supplemental doses of nicotinamide or other precursors of NAD will not produce hot flush and will not reduce cholesterol biosynthesis. In a recent study it has been shown that 500 mg of nicotinamide given to patients did not produce hot flush [11]. In addition, a non-flush form of niacin, inositol hexanicotinate has not been shown to have any beneficial effects on lipid levels [12]. According to our hypothesis and the previous report [9], the cholesterol reducing effect of niacin may be through the excess PPi production that escapes from pyrophosphatases. So, it can be advisable to take prescription doses of niacin along with aspirin to reduce flushing [13] for lowering cholesterol.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Vosper, H. (2009) Niacin: A Re-Emerging Pharmaceutical for the Treatment of Dyslipidemia. *British Journal of Pharmacology*, **158**, 429-441. https://doi.org/10.1111/j.1476-5381.2009.00349.x

[2] Ferjani, A. and Maeshima, M. (2016) Editorial: Multiple Facets of H^+-Pyrophosphatase and Related Enzymes. *Frontiers in Plant Science*, **7**, Article 1265. https://doi.org/10.3389/fpls.2016.01265

[3] Lapenta, F., Silva A.M., Brandimarti, R., Lanzi, M., Gratani, F.L., Gonzalez, P.V., Perticarari, S. and Hochkoeppler, A. (2016) *Escherichia coli* DNAE Polymerase Couples Pyrophosphatase Activity to DNA Replication. *PLOS ONE*, **11**, e0152915. https://doi.org/10.1371/journal.pone.0152915

[4] Nikiforov, A., Dolle, C., Niere, M. and Ziegler, M. (2011) Pathways and Subcellular Compartmentation of NAD Biosynthesis in Human Cells. From Entry of Extracellular Precursors to Mitochondrial NAD Generation. *Journal of Biological Chemistry*, **286**, 21767-21778. https://doi.org/10.1074/jbc.M110.213298

[5] Ma, L., Lee, B.H., Mao, R., Cai, A., Jia, Y., Clifton, H., Schaefer, S., Xu, L. and Zheng, J. (2014) Nicotinic Acid Activates the Capsaicin Receptor TRPV1—A Potential Mechanism for Cutaneous Flushing. *Arteriosclerosis Thrombosis and Vascular Biology*, **34**, 1272-1280. https://doi.org/10.1161/ATVBAHA.113.303346

[6] Masuda, Y. (2004) Upregulation of Uncoupling Proteins by Oral Administration of Capsiate, a Nonpungent Capsaicin Analog. *Journal of Applied Physiology*: *Respiratory*, *Environmental and Exercise Physiology*, **95**, 2408-2415. https://doi.org/10.1152/japplphysiol.00828.2002

[7] Schultz, M.B. and Sinclair, D.A. (2016) Why NAD+ Declines during Aging: It's Destroyed. *Cell Metabolism*, **23**, 965-966. https://doi.org/10.1016/j.cmet.2016.05.022

[8] Johnson, S. and Imai, S. (2018) NAD+ Biosynthesis, Aging, and Disease. *F1000-*

Research, **7**, 132. https://doi.org/10.12688/f1000research.12120.1

[9] Walter, A.A. (1992) Megavitamin and Megamineral Therapy in Childhood. *Canadian Medical Association Journal*, **146**, 2140.

[10] Wimmer, J.L.E., Kleinermanns, K. and Martin, W. F. (2021) Pyrophosphate and Irreversibility in Evolution, or Why PPi Is Not an Energy Currency and Why Nature Chose Triphosphates. *Frontiers in Microbiology*, **12**, Article 759359. https://doi.org/10.3389/fmicb.2021.759359

[11] Allen, N.C., Martin, A.J., Snaidr, V.A., Eggins, R., Chong, A.H., Fernandez-Penas, P., *et al.* (2023) Nicotinamide for Skin-Cancer Chemoprevention in Transplant Recipients. *The New England Journal of Medicine*, **388**, 804-812. https://doi.org/10.1056/NEJMoa2203086

[12] Norris, R.B. (2006) Flush-Free Niacin: Dietary Supplement may Be Benefit-Free. *Preventive Cardiololy*, **9**, 64-65. https://doi.org/10.1111/j.1520-037X.2006.04736.x

[13] Kamanna, V.S., Ganji, S.H. and Kashyap, M.L. (2009) The Mechanism and Mitigation of Niacin-Induced Flushing. *The International Journal of Clinical Practice*, **63**, 1369-1377. https://doi.org/10.1111/j.1742-1241.2009.02099.x