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Original article

Comparison of the effects of nicotinic acid and nicotinamide degradation on plasma betaine and choline levels

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SUMMARY

Aim: The present study was to compare the effects of nicotinic acid and nicotinamide on the plasma methyl donors, choline and betaine.

Methods: Thirty adult subjects were randomly divided into three groups of equal size, and orally received purified water (C group), nicotinic acid (300 mg, NA group) or nicotinamide (300 mg, NM group). Plasma nicotinamide, N^1-methylnicotinamide, homocysteine, betaine and choline levels before and 1.5-h and 3-h post-dosing, plasma normetanephrine and metanephrine concentrations at 3-h post-dosing, and the urinary excretion of N^1-methyl-2-pyridone-5-carboxamide during the test period were examined.

Results: The level of 3-h plasma nicotinamide, N^1-methylnicotinamide, homocysteine, the urinary excretion of N^1-methyl-2-pyridone-5-carboxamide and pulse pressure (PP) in the NM group was 221%, 3972%, 61%, 1728% and 21.2% higher than that of the control group ($P < 0.01$, except homocysteine and PP $P < 0.05$), while the 3-h plasma betaine, normetanephrine and metanephrine level in the NM group was 24.4%, 9.4% and 11.7% lower ($P < 0.05$, except betaine $P < 0.01$), without significant difference in choline levels. Similar but less pronounced changes were observed in the NA group, with a lower level of 3-h plasma N^1-methylnicotinamide (1.90 ± 0.20 μmol/l *vs.* 3.62 ± 0.27 μmol/l, $P < 0.01$) and homocysteine (12.85 ± 1.39 μmol/l *vs.* 18.08 ± 1.02 μmol/l, $P < 0.05$) but a higher level of betaine (27.44 ± 0.71 μmol/l *vs.* 23.52 ± 0.61 μmol/l, $P < 0.05$) than that of the NM group.

Conclusion: The degradation of nicotinamide consumes more betaine than that of nicotinic acid at identical doses. This difference should be taken into consideration in niacin fortification.

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1. Introduction

Nicotinic acid and nicotinamide, collectively known as niacin, are the precursors of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are essential coenzymes involved in cellular redox reactions [1]. Nicotinic acid and nicotinamide are derived from different sources: the former is from plant-based foods, and the latter is from animal-based foods. Moreover, there are differences between the degradation of nicotinic acid and nicotinamide. N-methylation, catalysed by nicotinamide *N*-methyltransferase (NNMT), is the key enzyme first degrades nicotinamide to N^1-methylnicotinamide (NMN). NMN is further oxidized to N^1-methyl-2-pyridone-5-carboxamide (2-Py) and N^1-methyl-4-pyridone-5-carboxamide (4-Py) by aldehyde oxidase 1 (Fig. 1). On the other hand, a considerable amount of nicotinic acid is converted to nicotinuric acid. Since methylation is a methyl-group-consuming reaction, accompanied by the production of homocysteine (Hcy), it is assumed that nicotinic acid and nicotinamide at the same doses may have different effects on the pool size of labile methyl groups, which is also a prerequisite for the methylation of numerous other substrates, including DNA and catecholamines (epinephrine and norepinephrine).

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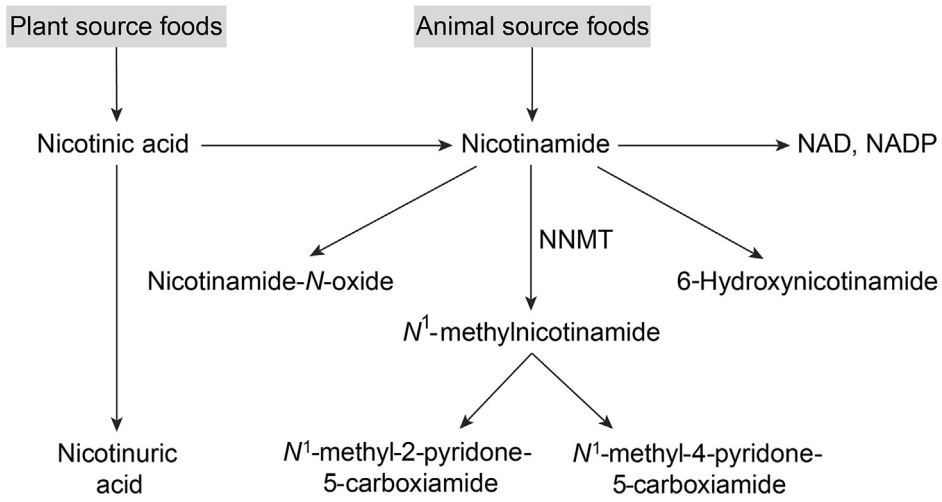

Fig. 1. Degradation pathways of nicotinic acid and nicotinamide in the body. Nicotinic acid is derived from plant-based foods, and nicotinamide is derived from animal-based foods. N-methylation, catalysed by nicotinamide *N*-methyltransferase (NNMT), is a major pathway in the degradation of nicotinic acid and nicotinamide in the body. Alternatively, nicotinic acid can also be eliminated in a non-methylated metabolite nicotinuric acid, which is also a major way in nicotinic acid degradation. NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate.

Although both dietary niacin deficiency and excess have dramatic effects on cellular function and health [1], niacin excess is a major health concern in developed countries. Since the early 1940s, niacin has been widely used in food fortification and supplementation [2]. Daily intake of niacin ranges from a few tens of milligrams to up to 2.0 g or more (e.g. in the prevention of cardiovascular disease [3,4], diabetes [5] and skin cancers [6]). It is noteworthy that both low-dose supplementation (fortification doses) [7] and high-dose nicotinic acid (lipid-lowering doses) [3,4] are found to be associated with increased risk for type 2 diabetes. Niacin fortification is associated with increased prevalence of diabetes with a lag time of 26 years [7], while high-dose nicotinic acid therapy is found to be associated with a rapid increase in diabetes rates (within years) [3,4]. Moreover, it is also found that some human diseases, such as obesity, type 2 diabetes [8,9] and cancer [10,11], show enhanced niacin metabolism. It has been reported in animal studies that excess nicotinamide causes DNA hypomethylation, an important epigenetic alteration in diseases [12,13]. It is therefore of significance to investigate the effects of high niacin intake on the methyl pool in the human body. The aim of this study is to compare the degradation of nicotinic acid and nicotinamide and their effects on the levels of plasma choline, betaine, Hcy, the methylated metabolites of catecholamines and blood pressure.

2. Materials and methods

2.1. Reagents and solvents

Nicotinamide, Hcy, betaine, cystamine dihydrochloride, 4-fluoro-7-sulfobenzofurazan ammonium salt, tris (2-carboxyethyl) phosphine hydrochloride and 18-crown-6, 4-bromophenacyl bromide were from Sigma (St. Louis, MO, USA). Both nicotinic acid and nicotinamide tablets (50 mg/tablet) were purchased from Lisheng Pharma (Tianjin, China). NMN was purchased from Takeda Chemical Industries (Osaka, Japan). 2-Py was kindly synthesized by Professor ZN Li [14]. Acetonitrile and methanol were chromatography grade. All other chemicals and reagents were of analytical grade.

2.2. Participants

This study was conducted according to the Declaration of Helsinki and all human subjects procedures were approved by the local Ethics Committee of Dalian University. All the participants gave their written informed consent. Thirty healthy male subjects, aged 20–23 years, were recruited for this study. All participants did not receive any dietary intervention or vitamin supplements before study. All participants were non-smokers and did not drink alcohol and consume caffeinated products for at least 6 days before the study.

2.3. Study protocol

The participants were divided into three groups randomly (n = 10 each): a control group with 30 ml purified water (C group), a single oral dose of nicotinic acid (300 mg) intake with 30 ml purified water group (NA group) and a single oral dose of nicotinamide (300 mg) intake with 30 ml purified water group (NM group). The experiments were conducted after fasting overnight and completed at 3 h after dosing (this design is based on the understanding that the absorption and biotransformation of niacin occur rapidly [15]). All the participants lay in bed quietly throughout the tests. Antecubital venous blood (4 ml) was collected into EDTA-anticoagulated tubes before, and at 1.5 h and 3 h intervals after dosing. The blood samples were kept on ice and then centrifugated (1500*g*, 10 min) immediately after sampling. Urine from participants was collected 3-h after the oral administration of the assigned load. Plasma and urine samples were directly frozen in liquid nitrogen and subsequently transferred to −80 °C for subsequent analyses. Blood pressure was measured before and 3-h after loading tests.

2.4. Determination of plasma nicotinamide, NMN, 2-Py, Hcy and betaine

High-performance liquid chromatography (HPLC) system, includes an LC-9A pump (Shimadzu, Kyoto, Japan), a Rheodyne 7725i sample injector with a 20 μl sample loop (Rheodyne LLC, Rohnert Park, CA, USA), a Hypersil ODS C18 column (Thermo, Bellefonte, PA,

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