9. Niacin

Physiology and metabolism

Two related compounds, nicotinic acid and nicotinamide, have the biological activity of niacin. Niacin is not strictly a vitamin, and there is no absolute requirement for a source of preformed nicotinic acid or nicotinamide in the diet; nicotinamide can be synthesised from the essential amino acid tryptophan. Requirements for tryptophan and niacin must therefore be considered together, and are generally expressed as 'niacin equivalents' – the sum of preformed niacin plus that provided by endogenous synthesis from tryptophan.

The metabolic function of niacin is as the precursor of the nicotinamide nucleotide coenzymes, NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate), which are involved in a wide variety of oxidation and reduction reactions.

In addition to its role in such reactions, NAD is the source of ADP-ribose for the DNA repair mechanism which is activated by a variety of DNA-breaking mutagens and other toxins. Much of the nicotinamide released by this poly-(ADP)-ribosyl transfer reaction is metabolised further and excreted, so it is likely that heavy exposure to such toxins will increase niacin requirements. There is little evidence that this is nutritionally significant, although toxins have been implicated in the aetiology of pellagra in people whose intake of tryptophan and niacin is marginal.

Most of the dietary preformed niacin is present in foods as the nicotinamide nucleotide coenzymes. These are hydrolysed by intestinal enzymes, and the resultant nicotinamide is absorbed either unchanged or as nicotinic acid after deamidation. The niacin in cereals is largely present as a glycoside of nicotinic acid, niacytin. A small proportion of this is hydrolysed by gastric acid, and more free niacin may be liberated in cooking, but 90% of the apparent niacin content of cereals cannot be utilised, and hence is biologically unavailable. The preformed niacin of cereals is usually ignored in calculating intakes.

Tissues can take up either nicotinic acid or nicotinamide from the circulation, and utilise them for the synthesis of the nicotinamide nucleotide coenzymes. The liver has only a very limited capacity for niacin uptake, and functions mainly to release nicotinamide and nicotinic acid synthesised from tryptophan, into the circulation for use by other tissues.

Tryptophan which is not required for net new protein synthesis or the synthesis of specialised metabolites (i.e. both 'surplus' tryptophan derived from the diet and that released by the turnover of tissue proteins) is oxidised in the liver. This is the fate of about 99% of the total dietary intake of tryptophan of an adult in nitrogen balance [1].

The oxidative pathway of tryptophan metabolism leads either to complete oxidation or to the synthesis of the nicotinamide ring of the coenzymes. Therefore, the amount of nicotinamide coenzymes formed from tryptophan changes with the amount of tryptophan available. At normal intakes of tryptophan, about 60 mg dietary tryptophan is equivalent to 1 mg preformed niacin, although there is considerable variation around this figure. The ratio of 60 mg tryptophan equivalent to 1 mg preformed niacin is an over-estimate of the mean requirement, including a 'safety margin' to cover individual variation [2,3]. By convention, the total niacin equivalence of a diet is taken to be the sum of preformed niacin (neglecting that in cereals) plus 1/60 of the tryptophan content.

Nicotinamide arising from the breakdown of the coenzymes which is not required for the synthesis of new coenzyme, and surplus nicotinamide from the diet, are mainly converted to N^1-methyl nicotinamide in the liver. N^1-Methyl nicotinamide may be either excreted unchanged or may undergo further metabolism to methyl pyridone carboxamide before excretion.

Deficiency and excess

An inadequate intake of both tryptophan and preformed niacin leads to the development of the deficiency disease pellagra. Diseases involving impairment of the oxidative metabolism of tryptophan, drugs which inhibit enzymes in the pathway or deficiency of riboflavin and vitamin B_6, both of which are required for the synthesis of nicotinamide nucleotides from tryptophan, can also result in the development of pellagra.

Pellagra is characterised by a photosensitive dermatitis resembling severe sunburn, normally restricted to areas of the skin directly exposed to the sun, although physical pressure on the knees and elbows, and abrasion by clothes around the wrists and ankles, can lead to similar skin lesions in deficient subjects. Advanced pellagra also involves a characteristic depressive psychosis or dementia. The psychosis may also develop in the absence of skin lesions in subjects not exposed to sunlight. Untreated pellagra is fatal because of the severe impairment of nicotinamide nucleotide-requiring reactions in energy metabolism.

Nicotinic acid in modest doses causes a marked vasodilatation, with flushing, burning and itching of the skin. Very large single doses of nicotinic acid may cause sufficient vasodilatation to lead to hypotension; after the administration of 3-6 g of nicotinic acid daily for several days the effect wears off. Nicotinamide does not have this effect.

Doses of nicotinic acid, but not nicotinamide, of 3-6 g/day have a modest, but potentially useful, hypocholesterolaemic and hypolipidaemic effect. At this level of intake there is evidence of liver damage and even clinical liver dysfunction. Use of sustained release preparations of nicotinic acid providing more modest intakes of the vitamin (500 mg/day) may also result in liver damage as a result of prolonged high concentrations in blood and tissues [4].

Requirements

Adults

The only data available on which to base estimates of niacin requirements are the results of depletion-repletion studies in which the amount of preformed niacin or tryptophan required to restore 'normal' excretion of N^1-methyl nicotinamide and methyl pyridone carboxamide was determined [2,3].

In subjects receiving 1 mg niacin equivalents /MJ, the urinary excretion of N^1-methyl nicotinamide fell to the upper limit of that seen in pellagrins, although none of the subjects showed clinical signs of deficiency. Adequate excretion of N^1-methyl nicotinamide is seen in subjects receiving 1.3 mg niacin equivalents /MJ. Allowing for individual variation, the Population Reference Intake is based on 1.6 mg niacin equivalents /MJ energy expenditure.

For people on low energy diets, niacin will be required for the metabolism of tissue reserves of metabolic fuels. It is possible that the requirement for those habitually on intakes below 8 MJ/d also may not be covered by 1.6 mg niacin equivalents /MJ. For such groups a PRI of 13 mg niacin equivalents /d is suggested.

It is likely that there is no requirement for any preformed niacin in the diet under normal conditions, and that endogenous synthesis from tryptophan will meet requirements. Average protein intakes in the EC are about 15% of energy intake. On the assumption that dietary protein provides 14 mg tryptophan /g (a conservative estimate), this represents 2 mg niacin equivalents /MJ energy intake from dietary tryptophan, greater than the Population Reference Intake without any preformed dietary niacin.

Other age groups

There is no evidence that any other group of the population has a requirement for niacin different from that for adult men, other than on the basis of energy expenditure.

Pregnancy and lactation

The hormonal changes associated with pregnancy increase the efficiency of the synthesis of nicotinamide nucleotides from tryptophan. There is thus no increased requirement for niacin in pregnancy. In lactation the Population Reference Intake is for 2 mg niacin equivalents /d above that calculated on the basis of energy intake to allow for the vitamin secreted in milk.

Summary

There is no absolute requirement for preformed niacin in the diet, since endogenous synthesis from normal intakes of tryptophan is more than adequate to meet requirements. There is a requirement for an adequate intake of tryptophan plus niacin, apart from the requirement for tryptophan as an essential amino acid for the maintenance of nitrogen balance. Population Reference Intakes are based on the ratio of 60 mg dietary tryptophan equivalent to 1 mg preformed niacin (i.e. total niacin equivalents = preformed niacin + 1/60 x tryptophan), and assume that intakes of riboflavin and vitamin B_6 are adequate.

Average Requirement	1.3 mg niacin equivalents /MJ
Population Reference Intake	1.6 mg niacin equivalents /MJ
Lowest Threshold Intake	1.0 mg niacin equivalents /MJ

These can be expressed for average energy expenditures as mg niacin equivalents/d.

Adults	*Males*	*Females*
Average Requirement	15	11
Population Reference Intake	18	14
Lowest Threshold Intake	11	9
Pregnancy		14
Lactation		16
Harmful effects	>500 mg/day as preformed nicotinic acid	

Population Reference Intakes for younger age groups

Age Group		PRI (mg niacin equivalents /d)
	6 - 11 m	5
	1 - 3 y	9
	4 - 6 y	11
	7 -10 y	13
Males	11-14 y	15
	15-17 y	18
Females	11-14 y	14
	15-17 y	14

References

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