Nicotinic Acid, Nicotinamide, and Nicotinamide Riboside: A Molecular Evaluation of NAD^+ Precursor Vitamins in Human Nutrition

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Abstract

Although baseline requirements for nicotinamide adenine dinucleotide (NAD^+) synthesis can be met either with dietary tryptophan or with less than 20 mg of daily niacin, which consists of nicotinic acid and/or nicotinamide, there is growing evidence that substantially greater rates of NAD^+ synthesis may be beneficial to protect against neurological degeneration, *Candida glabrata* infection, and possibly to enhance reverse cholesterol transport. The distinct and tissue-specific biosynthetic and/or ligand activities of tryptophan, nicotinic acid, nicotinamide, and the newly identified NAD^+ precursor, nicotinamide riboside, reviewed herein, are responsible for vitamin-specific effects and side effects. Because current data suggest that nicotinamide riboside may be the only vitamin precursor that supports neuronal NAD^+ synthesis, we present prospects for human nicotinamide riboside supplementation and propose areas for future research.

Contents

INTRODUCTION

Deficiency of niacin and/or tryptophan (Trp) causes pellagra, which is characterized by a darkly pigmented skin rash and the three D's of dermatitis, diarrhea, and dementia. A century ago, pellagra was common among the rural poor in the southern United States and was thought to be an infectious disease. However, in 1914, Joseph Goldberger tested the hypothesis that pellagra might be caused by a dietary deficiency and discovered that substituting corn-based diets with fresh milk, eggs, and meat cured and prevented the condition (29). Twenty-three years later, Conrad Elvehjem obtained a nicotinamide (Nam) fraction from deproteinized liver and a sample of crystalline nicotinic acid (Na) and showed that these compounds have an antipellagragenic "antiblack tongue" activity on malnourished dogs (20). Subsequent biochemical studies identified Nam as a component of NAD^+ and nicotinamide adenine dinucleotide phosphate (NADP) and showed that animals with pellagra have a significant decrease in muscle and liver NAD^+ and NADP (5). Today pellagra occurs rarely in cases of extreme alcoholism and anorexia, or as a seasonal malady in underdeveloped parts of the world.

As schematized in **Figure 1**, the reason that a poor diet can produce a requirement for Na and Nam is that Trp, Na, and Nam are all NAD^+ precursors (7). Trp is converted to NAD^+ through an eight-step de novo pathway (**Figure 2**), so termed because the Nam base is essentially made from scratch. In contrast, Na and Nam are considered "salvageable precursors" that require only three steps and two steps, respectively, to rebuild NAD^+. Nicotinamide riboside (NR) is an additional salvageable NAD^+ precursor vitamin with a two-step pathway (14) and a three-step pathway (8) to form NAD^+. As schematized in **Figures 1** and **2**, cells require ongoing NAD^+ synthesis because NAD^+ and NADP are not only coenzymes, which are recycled back and forth between oxidized (NAD^+ and NADP) and reduced (NADH, NADPH) forms by hydride transfer enzymes, but are also substrates of NAD^+-consuming enzymes that break the glycosidic bond between the Nam moiety and the ADPribose moiety. NAD^+-consuming enzymes transfer ADPribose and/or ADPribose polymers, form signaling compounds from NAD^+ and NADP, and reverse the acetyl modification of protein lysine residues. Each of these reactions consumes an NAD^+ equivalent to a salvageable Nam product plus an ADPribosyl product (7).

NAD^+-consuming enzymatic activities are induced, in part, by stresses such as DNA damage and inflammation. Many of these stresses are accompanied by specifically induced biosynthetic pathways, which appear to function to maintain NAD^+ homeostasis. The term NAD^+ homeostasis should be used cautiously, however, because it is not clear that cells are always in NAD^+ homeostasis. Mammalian NAD^+ biosynthesis is not

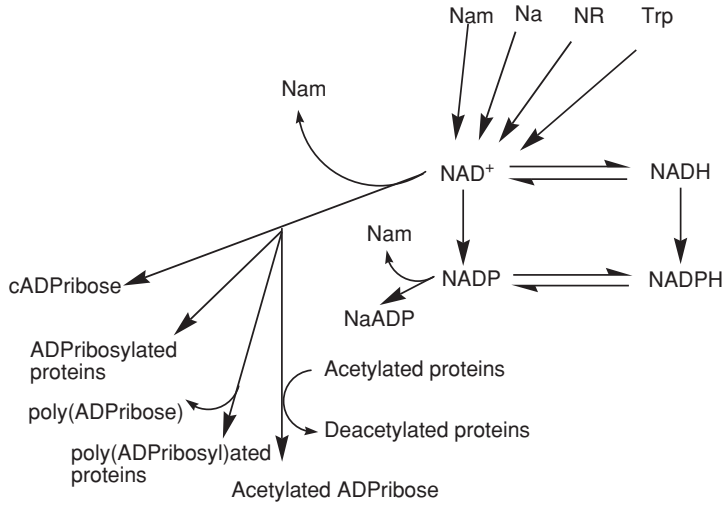

Figure 1

NAD^+ is both a coenzyme for hydride transfer enzymes and a substrate of NAD^+-consuming enzymes. NAD^+ is interconverted between oxidized and reduced states by NAD^+/NADH-requiring hydride transfer enzymes. Both NAD^+ and NADH can be phosphorylated by NAD^+/NADH kinases. NADP and NADPH are interconverted by NADP/NADPH-requiring hydride transfer enzymes. These reactions are performed without net coenzyme consumption. In contrast, NAD^+ is consumed to nicotinamide (Nam) and multiple forms of ADPribose by at least three types of NAD^+-consuming enzymes. cADPribose synthases cyclize the ADP-ribose moiety of NAD^+ and form NaADP from NADP with production of Nam. These enzymes also hydrolyze cADPribose and NaADP. ADPribosyltransferases (ARTs) post-translationally modify proteins with an ADPribosyl group, and polyADPribosyltransferases (PARPs) form a polymer of ADPribose from multiple NAD^+ molecules. Sirtuins use the ADPribose moiety of NAD^+ to accept the acetyl modification of a protein lysine, forming deacetylated protein plus Nam and acetylated ADPribose. NAD^+ breakdown necessitates Nam salvage. Nicotinamide (Nam), nicotinic acid (Na), nicotinamide riboside (NR), and tryptophan (Trp) are the dietary precursors of NAD^+.

a closed, cell-autonomous system, and there appear to be situations in which cells actively increase and/or reduce the concentration of NAD^+ and NAD^+ metabolites to promote vital and/or regulatory functions, including cell death.

RECOMMENDED DAILY REQUIREMENTS OF THE NAD^+ PRECURSORS

Despite the fact that the biosynthetic pathways are not the same, in the literature of human and animal nutrition, Nam and Na are collectively termed niacin and/or vitamin B_3. To protect against pellagra that can develop with Trp deficiency, recommended daily allowances (RDAs) of niacin are 16 and 14 mg per day for adult men and women, respectively (79). Because all plant, animal, and fungal inputs in our diet contain cellular NAD^+ and NAD^+ metabolites, foods provide NAD^+, NADH, NADP, and NADPH, which are considered nutritional "niacin equivalents," in addition to Nam and Na. Whereas Nam and Na are the fully broken down NAD^+ metabolites from animals and plants/fungi/bacteria respectively, NR and nicotinic acid riboside (NaR) can be considered partly broken down niacin equivalents. In the genetically tractable yeast system, all of the salvageable precursors (Na, Nam, NR, and NaR) support the growth of cells inactivated for de novo NAD^+ synthesis (83).

A single yeast cell deficient in de novo synthesis or undergoing a biological process

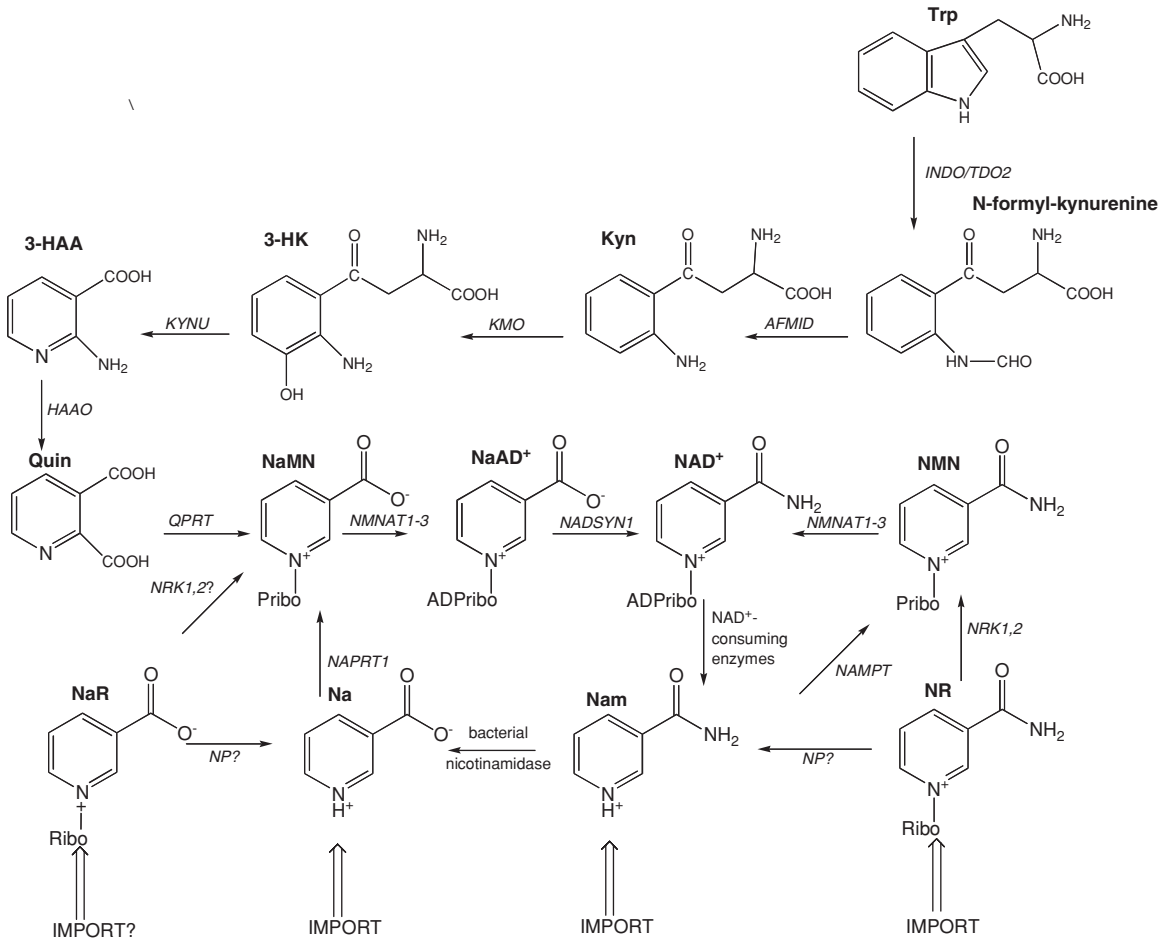

Figure 2

Intracellular NAD^+ metabolism in humans. Tryptophan (Trp), nicotinic acid (Na), nicotinamide (Nam), nicotinamide riboside (NR), and possibly nicotinic acid riboside (NaR) are utilized through distinct metabolic pathways to form NAD^+. Tryptophan (Trp) is converted to NAD^+ in the eight-step de novo pathway. First, Trp is converted to *N*-formylkynurenine by the gene products of either indoleamine dioxygenase (*INDO*) or tryptophan dioxygenase (*TDO2*). The product of the arylformamidase gene (*AFMID*) forms kynurenine (Kyn) from N-formylkynurenine. Kynurenine is used as a substrate of kynurenine monooxygenase (*KMO*) and forms 3-hydroxykynurenine (3-HK). Kynureninase (*KYNU*) then forms 3-hydroxyanthranilate (3-HAA), which is converted to 2-amino-3-carboxymuconate semialdehyde (not shown) by 3-hydroxyanthranilate dioxygenase (*HAAO*). The semialdehyde undergoes a spontaneous condensation and rearrangement to form quinolinate (Quin), which is converted to nicotinic acid mononucleotide (NaMN) by quinolinate phosphoribosyltransferase (*QPRT*). NaMN is then adenylylated by the products of the *NMNAT1-3* genes to form nicotinic acid adenine dinucleotide ($NaAD^+$), which is converted to NAD^+ by glutamine-dependent NAD^+ synthetase (*NADSYN1*). Nicotinic acid (Na) is utilized in the three-step Preiss-Handler pathway. Nicotinic acid phosphoribosyltransferase (*NAPRT1*) forms NaMN by addition of the 5-phosphoribose group from 5-phosphoribosyl-1-pyrophosphate to Na. In two steps shared with the de novo pathway, NaMN is then converted to $NaAD^+$ and NAD^+ via activity of *NMNAT1-3* and *NADSYN1*. Nam is utilized via nicotinamide phosphoribosyltransferase (Nampt), encoded by the *PBEF1 (NAMPT)* gene. Nampt catalyzes the addition of a phosphoribose moiety onto Nam to form nicotinamide mononucleotide (NMN). NMN is subsequently converted to NAD^+ by the products of *NMNAT1-3*. Nam is produced by NAD^+-consuming enzymes. Nam can be converted to Na by bacterial nicotinamidase in the gut for subsequent Preiss-Handler salvage. Nicotinamide riboside (NR) is phosphorylated by the products of nicotinamide riboside kinase genes (*NRK1* and *NRK2*) to form NMN, which is converted to NAD^+ by *NMNAT1-3*. NR may also be utilized by the product of the *NP* gene, purine nucleoside phosphorylase, for subsequent Nam salvage. NaR is utilized in yeast via the Nrk and NP pathways. The enzymes of human NAD^+ biosynthesis are summarized in **Table 1**.

Table 1 Enzymes of human NAD^+ biosynthesis

Enzyme	Gene	Gene ID
Indoleamine-pyrrole 2-3 dioxygenase	*INDO*	3620
Tryptophan 2,3-dioxygenase	*TDO2*	6999
Arylformamidase	*AFMID*	125061
Kynurenine 3-monooxygenase	*KMO*	8564
Kynureninase	*KYNU*	8942
3-hydroxyanthranilate 3,4-dioxygenase	*HAAO*	23498
Quinolinate phosphoribosyltransferase	*QPRT*	23475
Nicotinamide nucleotide adenylyltransferase 1	*NMNAT1*	64802
Nicotinamide nucleotide adenylyltransferase 2	*NMNAT2*	23057
Nicotinamide nucleotide adenylyltransferase 3	*NMNAT3*	349565
NAD synthetase 1	*NADSYN1*	55191
Nicotinamide riboside kinase 1	*NRK1*	54981
Nicotinamide riboside kinase 2	*ITGB1BP3 (NRK2)*	27231
Nicotinamide phosphoribosyltransferase	*PBEF1 (NAMPT)*	10135
Nicotinate phosphoribosyltransferase 1	*NAPRT1*	93100
Purine nucleoside phosphorylase	*NP*	4860

that requires more than the minimum vital concentration of NAD^+ must convert an available vitamin precursor to NAD^+ in a cell-autonomous fashion. In contrast, humans exhibit the complexity of systemic NAD^+ metabolism in which particular cells may utilize an NAD^+ precursor to produce an excess of NAD^+ and export salvageable precursors to other cells. Accordingly, dietary Trp is also classified as a niacin equivalent. However, because of the protein and other biosynthetic uses of Trp, 60 mg of Trp is considered the equivalent of 1 mg of niacin (79). This physiological fact, that high levels of dietary Trp result in circulation and excretion of Na (9, 10, 60, 70), has resulted in claims in textbooks and reviews that Na is derived from Trp. Whereas this is true in vertebrate organisms, there may not be a vertebrate intracellular pathway that is responsible. As illustrated in **Figure 2**, Trp can be converted to Nam but not Na in any vertebrate cell expressing a de novo pathway and an NAD^+-consuming enzyme such as poly(ADPribose)polymerase (PARP) or a sirtuin. Nam can then be converted in the intestinal lumen by bacterial nicotinamidase to Na. The most reasonable pathway by which a single vertebrate cell might convert Trp to Na was depicted by Magni and coworkers (53). Magni's scheme of human NAD^+ metabolism depicts the activity of Na phosphoribosyltransferase (*NAPRT1* gene product) and several other enzymes as bidirectional. Indeed, if there is sufficient pyrophosphate and NaMN in cells, then Naprt1 could catabolize nicotinic acid mononucleotide (NaMN) to Na, thereby creating a cell-autonomous route from Trp to Na. This is an interesting possibility that has not been demonstrated in vivo.

NR is a newly discovered salvageable precursor of NAD^+ that occurs in cow's milk (14). Studies in *Saccharomyces cerevisiae* have shown that, like Na and Nam, NR is an NAD^+ precursor that contributes to maintaining intracellular NAD^+ concentration and improves NAD^+-dependent activities in the cell including Sir2-dependent gene silencing and longevity (8, 14). NR can either be converted to NAD^+ by the Nrk pathway (14), which is induced by axotomy in dorsal root ganglion (DRG) neurons (71), or by the action of nucleoside

phosphorylase and nicotinamide salvage (8). It has also been shown that the same two pathways required for NR salvage in yeast cells can also be used for NaR salvage (83). In yeast cells, NR clearly qualifies as a vitamin by virtue of rescuing growth of strains deficient in de novo synthesis (14, 83), improving Sir2 functions (8), and utilizing a dedicated transporter (8a). Additionally, because cells deleted for the NR/NaR salvage enzymes have a significant deficiency in intracellular NAD^+ when not supplemented with these compounds, it appears that NR and/or NaR are also normal metabolites (8).

Five lines of reasoning support designation of NR as an authentic NAD^+ precursor vitamin in vertebrates. First, *Haemophilus influenza*, a flu-causing bacterium, which has no de novo pathway and cannot utilize Na or Nam, is strictly dependent on NR, NMN, or NAD^+ for growth in the host bloodstream (22). Second, milk is a source of NR (14). Third, NR protects murine DRG neurons in an ex vivo axonopathy assay via transcriptional induction of the nicotinamide riboside kinase (NRK) 2 gene (71). Fourth, exogenously added NR and derivatives increase NAD^+ accumulation in a dose-dependent fashion in human cell lines (94). Fifth, *Candida glabrata*, an opportunistic fungus that depends on NAD^+ precursor vitamins for growth, utilizes NR during disseminated infection (51).

It should be realized that not every cell is capable of converting each NAD^+ precursor to NAD^+ at all times. Expression of the eight-step de novo pathway is required to utilize trp. Expression of the Nampt pathway is required to utilize Nam. Expression of either the Nrk pathway or nucleoside phosphorylase and the Nampt pathway is required to utilize NR. Finally, expression of the Preiss-Handler pathway is required to utilize Na. Because tissue and cell-type specific enzyme expression differences exist, the precursors are differentially utilized in the gut, brain, blood, and organs. Understanding the unique aspects of metabolism of each precursor is necessary to define the mechanisms underlying the physiological effects and side effects of each.

NAD^+ FUNCTIONS AND THE REQUIREMENT FOR NAM SALVAGE

NAD^+ is classically known as a coenzyme for hydride-transfer enzymes. As a coenzyme, NAD^+ is essential to a variety of diverse biological processes including energy production and synthesis of fatty acids, cholesterol, and steroids. NAD^+ participates in oxidation-reduction (redox) reactions as hydride donor (NADH and NADPH) and acceptor (NAD^+ and NADP). NAD^+ most commonly functions in energy-producing catabolic reactions, such as the degradation of carbohydrates, fats, proteins, and alcohol, whereas NADP functions in anabolic reactions, such as the synthesis of cellular macromolecules including fatty acids and cholesterol. As depicted in **Figure 1**, coenzymatic activities of NAD^+ and its reduced and phosphorylated derivatives interconvert but do not alter total cellular levels of NAD^+.

In recent years, multiple enzyme-mediated, nonredox roles for NAD^+ have been discovered. NAD^+-consuming enzymes break down NAD^+ to Nam and an ADPribosyl product (7). These enzymes fall into three classes. The first class consists of ADPribose transferases (ARTs) and PARPs, which transfer and/or polymerize NAD^+-derived ADPribose, frequently as a post-translational modification. PARP activity, which is upregulated by DNA strand breaks (54), may be the major source of intracellular NAD^+ consumption. The second class of NAD^+-consuming enzymes consists of cADPribose synthases, which are membrane-bound ecto-enzymes also known as CD38 and CD157, that produce and hydrolyze the Ca^{2+}-mobilizing second messenger cADPribose from NAD^+ (38, 39, 43). Additionally, CD38 catalyzes a base exchange between NADP and Na to form nicotinic acid adenine dinucleotide phosphate (NaADP) (1), which is also a hydrolytic substrate (30). The products of these reactions have distinct and important roles in Ca^{2+} mobilization and signaling. The third class of NAD^+-consuming enzymes consists of sirtuins, named for their

sequence similarity to the yeast Sir2 gene-silencing protein. Sirtuins exhibit protein lysine deacetylase and, occasionally, ADPribose transferase activities. Sirtuin deacetylation reactions proceed by binding an acetyl-modified lysine on a target protein and NAD^+ in distinct pockets. Deacetylation of the modified lysine side chain is coupled to the cleavage of the glycosidic bond in NAD^+ such that the products are the deacetylated lysine, acetylated ADPribose, and Nam (72). Sirtuin-dependent deacetylation of histones and other proteins results in reprogrammed gene expression, mitochondrial synthesis and function, cell survival, and longevity (91). Sirtuins have been recently reviewed as master switches of metabolism (18a).

Nam regulates the activity of NAD^+-consuming enzymes both by direct enzyme inhibition and by its role as an NAD^+ precursor. Nam inhibits NAD^+-consuming enzymes by binding a conserved pocket that participates in NAD^+ binding and catalysis (4). Recycling of Nam back to NAD^+ raises NAD^+ levels, increasing substrate availability and relieving Nam inhibition. In systems such as yeast in which NAD^+ concentration has been determined carefully, basal intracellular NAD^+ concentration is approximately 0.8 mM and can be elevated with vitamin precursors by 1 mM or more (8). At first glance, it would seem that 0.8 mM NAD^+ should be saturating for virtually all sirtuins, which exhibit K_m values for NAD^+ between 5 μM and 500 μM (72). However, the first 0.8–1 mM of intracellular NAD^+ concentration may largely be bound by redox enzymes such that salvage-derived synthesis of NAD^+ may generate the majority of free NAD^+ to drive sirtuin functions.

The first step in Nam salvage is catalyzed by Nam phosphoribosyltransferase (Nampt), which is encoded by the *PBEF1* gene. This polypeptide, first identified as an extracellular protein termed pre B-cell colony enhancing factor (PBEF), was characterized as cytokine that enhances the maturation of B-cell precursors in the presence of IL-7 and stem cell factor (69). The same polypeptide was also termed Visfatin, due to reported insulin mimetic functions and regulation of systemic metabolism (26). However, the intracellular form of the molecule was shown to be induced in activated lymphocytes and function simply as Nampt (68).

Because of the disparate functions ascribed to the same polypeptide, it had been assumed that intracellular Nampt functions as an NAD^+ biosynthetic enzyme, whereas extracellular Nampt has cytokine and insulin-mimetic roles. However, it has now been reported that both intra- and extracellular Nampt exhibit robust phosphoribosyltransferase activities and that inhibiting NAD^+ biosynthesis through the Nampt pathway, either genetically or pharmacologically, causes impaired glucose tolerance and reduced insulin secretion in mice, a defect that can be corrected by administering nicotinamide mononucleotide (NMN) (66). Moreover, murine plasma contains high concentrations of Nampt and NMN, which are reduced in *nampt* heterozygous animals. These new findings strongly indicate that the primary role for extracellular PBEF/Visfatin/Nampt is to catalyze NMN production from Nam, and that NMN has an important role in maintaining β-cell function (66). In a recent review, we speculated that a partially extracellular NAD^+ cycle might consist of a Nampt step, followed by extracellular dephosphorylation of NMN to NR, intracellular transport of NR, and conversion of NR to NAD^+ (7).

NAD^+ PRECURSORS IN FOODS

Consistent with Goldberger's studies (29), niacin is abundant in meat, eggs, fish, dairy, some vegetables, and whole wheat. Notably, corn contains abundant Na and Nam, largely present in bound forms that are not bioavailable. Treatment with alkali is used to increase bioavailability, a practice that protected native and South American populations from deficiency. Untreated corn is considered "pellagragenic," causing increased sensitivity to low dietary niacin concentrations in animal studies (46, 47). Milk, now known to be a natural

source of NR (14), was shown to counteract the growth defect seen in corn-fed animals (46). In meats, Na and Nam are scarce and NAD^+ and NADP are the abundant sources of niacin (34, 86). Nam is produced by mucosal enzymes that cleave NAD^+ (86), and Na is produced from Nam by deamination by bacterial nicotinamidase in the gut (13). Both Na and Nam are absorbed from the alimentary canal and enter the bloodstream for distribution to tissues (40, 82, 86). Studies indicate that Nam is the dominant absorbed form of niacin when the dietary sources are NAD^+ and NADP (16, 35, 36, 81). However, it has also been reported that NAD^+ is digested by pyrophosphatases to NMN and hydrolyzed to NR, which was found in the lumen of the upper small intestine (32). We surmise that NR is incorporated into the cellular NAD^+ pool via the action of Nrk pathway (14) or via Nam salvage after conversion to Nam by phosphorolysis (8).

SYSTEMS ANALYSIS OF NAD^+ BIOSYNTHESIS

Qprt, Nampt, Naprt1, and Nrk1,2 are the committed enzymes in the synthesis of NAD^+ from Trp, Nam, Na, and NR. As such, by examining the expression of each enzyme and by following the metabolic fates of dietary inputs, one can describe tissue-specific pathways of NAD^+ biosynthesis.

Animals on diets containing sufficient amounts of both Trp and niacin have a measurable concentration of each in liver (9, 10). Nam and Na, however, are thought to supply only a fraction of the NAD^+ produced in the liver, with much niacin circulating to other tissues. Trp is thought to be the principal NAD^+ precursor utilized in liver (9). In addition to producing quinolinate for entry into NAD^+ biosynthetic pathways, Trp is incorporated into protein, utilized to generate energy through total oxidation, and utilized to form kynurenic acid. Inducible enzymes of Trp utilization regulate the flux of Trp through different pathways depending on diet and cellular metabolic state. Under conditions of low Trp consumption, circulating levels of Trp decrease and enzymes that direct Trp to non-NAD^+ biosynthetic routes are down-regulated, suggesting a shift of all possible Trp catabolism to NAD^+ generation (75). Supplementing high amounts of Trp allows more flux to the oxidative branch and allows increased levels of Nam to be released into the vasculature (6, 9, 10). All Trp that reaches quinolinate in the liver is thought to be converted to NAD^+ via subsequent enzyme reactions of Qprt, Nmnat1-3, and Nadsyn1, which are highly expressed in liver (24, 58).

In addition to liver (27), Qprt is expressed in human and rat brain and plays a critical role in protection against the neurotoxic effects of quinolinate (23, 45, 58, 93). Quinolinate is a potent endogenous neurotoxin, and elevated levels in brain are associated with neurodegenerative disorders including epilepsy and Huntington's disease (73, 74). The normal concentration of quinolinate in the brain was found to be in the low- to mid-nanomolar range (37), and Qprt activity increases in response to increased levels of quinolinate (25), suggesting a protective role. The highest levels of quinolinate are found in spleen, lymph nodes, thymus, and many specific immune cell types and are increased following stimulation by immune activators (57).

Activated lymphocytes induce expression of Nampt (68), which is also expressed in smooth muscle cells with loss of expression in senescence (87). In the mouse, Nampt has been shown to circulate and to be highly expressed intracellularly in brown adipose tissue, liver, and kidney, with fat as the source of extracellular Nampt. Human fat is also a source of circulating Nampt (66). From classical feeding studies, the testes were found to utilize Nam rather than Na or quinolinate (50), and blood and liver were also found to be major sites of Nam utilization (41). Nam crosses the blood-brain barrier and is converted to NAD^+ in brain, though it is not known whether Nam is a precursor of NAD^+ in neuronal or non-neuronal cells (78). Studies with DRG neurons suggest that Nampt is not neuronally expressed (71). Nam and NR

are also taken up by intestinal epithelial cells and both are utilized by Nam salvage (15).

By global analysis of mRNAs, Naprt1 is expressed in most tissues of the adult mouse, including colon, heart, kidney, and liver, suggesting the presence and utilization of the substrate Na as an NAD^+ precursor in these tissues (21). Classical feeding studies showed that exogenously added Na is a better NAD^+ precursor than Nam in liver, intestine (16), and kidney (50). Similarly, rats fed Na showed elevated levels of NAD^+ in the heart and kidney in addition to blood and liver, which are sites of Na and Nam utilization (41). Classical studies have been corroborated by a recent report that mouse Naprt1 is expressed in intestine, liver, kidney, and heart. In addition, human kidney cell lines are able to use Na to increase intracellular NAD^+ concentration in a manner that depends on the *NAPRT1* gene. Moreover, Naprt1 expression decreases vulnerability to oxidative damage from NAD^+ depletion. The use of Na as an NAD^+ precursor in normal and stress conditions implicates the presence of Na as a normal cellular metabolite in humans (33). As discussed earlier, we consider the bacterial flora of the intestinal lumen to be the first major site in a vertebrate for production of Na, though bacterial and fungal degradation of cellular NAD^+ in food and direct Na supplementation will also produce supplies of Na in the alimentary canal for distribution to tissues through the vasculature. True intracellular production of Na in a vertebrate cell (53) would require high levels of Trp and/or NAD^+ and substantial reverse flux through what are usually considered anabolic pathways.

The use of NR as a precursor in mammalian cell types was first demonstrated in DRG neurons, which induce the *NRK2* transcript when damaged by axotomy (71). The ubiquitous expression of Nrk1 in mammalian tissues (80) suggests utilization of NR and/or NaR (83) in a diverse array of cell types. However, Nrk2 is present in heart, brain, and skeletal muscle, and is notably absent in kidney, liver, lung, pancreas, and placenta (48, 71). The fact that DRG neurons cannot be protected from damage-induced neuropathy by Na or Nam without concurrent gene expression of Na or Nam salvage genes suggests that NR is a uniquely useful precursor to the nervous system (71) when de novo synthesis of NAD^+ from Trp is not sufficient.

Available data summarizing the system-wide use of NAD^+ precursors are summarized in **Figure 3**. The data are more static than one would like, such that it will be important to determine how gene expression and precursor utilization changes as a function of nutrition, age, stress, and disease state. It is particularly striking that two enzymes, namely Nampt and Nrk2, were first identified as highly regulated proteins involved in immune cell (69) and muscle cell (48) development. Thus, developmental regulation of NAD^+ synthesis and utilization remains on the forefront of NAD^+ biology.

ALTERATION OF NAD^+ METABOLISM BY CALORIC RESTRICTION

Caloric restriction (CR) is the most effective intervention to extend the lifespan of multiple model organisms including mammals. CR is defined as a 20% reduction versus ad libitum feeding without compromising adequate nutrition (56). Although the mechanisms of CR remain elusive, it is thought that CR modulates fat and carbohydrate metabolism, attenuates oxidative damage, and activates a stress-induced hormetic response that mediates improved vitality and disease resistance (55). Among these three major mechanisms, modulation of fat and carbohydrate utilization is the most direct response to reduced dietary inputs, and hormesis is potentially the mechanism most influenced by the "signaling" aspect of CR.

The hormetic theory is supported by experiments in which model organisms exhibit extended lifespan when placed in a variety of sublethal stress conditions including high temperature, high salt, or osmotic stress. In yeast, such conditions increase expression of nicotinamidase, thereby altering NAD^+ metabolism

in a manner that favors Sir2 activity (2). The principal mechanism by which Sir2 extends lifespan in a wild-type yeast cell is repression of formation of aging-associated extrachromosomal ribosomal DNA circles (76). Though this mechanism is unique to yeast, there are substantial data showing that sirtuins are conserved from fungi to metazoans to mediate some of the beneficial effects of CR (77). Sir2 is not the only mediator of CR-induced lifespan extension in yeast (42), nor are sirtuins necessarily the only targets of nicotinamide inhibition (84). Nonetheless, there is excellent evidence that NAD^+ metabolism is altered in vertebrate systems by CR and that increased activity of sirtuins may mediate beneficial brain and liver physiology under CR conditions.

In CR-treated mice, brain NAD^+ levels are increased and Nam levels are decreased, and these changes accompany neuronal Sirt1 activation, which reduces Alzheimer's neuropathology (63). In fasted mice, NAD^+ levels are increased in liver, which is accompanied by Sirt1 activation, PGC1α deacetylation, and increased mitochondrial biogenesis (67). The mechanisms by which lower food inputs increase NAD^+ levels in brain and liver are completely unknown. Two potential mechanisms that may account for this phenomenon are systemic mobilization of NAD^+ precursors to the brain and liver and reduced NAD^+ breakdown. Among the potential precursors that could mediate this phenomenon, Na and Trp seem unlikely because one would expect that increased food consumption would be required to increase their availability. Analysis of CR-induced systemic metabolites should permit the detection of either Nam or NR as candidate mediators of increased brain and liver NAD^+ levels. Reduced NAD^+ breakdown is another mechanism by which CR might increase NAD^+ levels in particular tissues. This could occur if an NAD^+-consuming activity such as PARP is negatively regulated by CR. The pathways that produce NR or NaR at the expense of NAD^+ (8) are not known. These, too, might be negatively regulated by CR in order to elevate brain and liver NAD^+.

LESSONS FROM THE *wlds* MOUSE

Wallerian degeneration refers to the ordered process of axonal degeneration. Wallerian degeneration occurs when an axon is severed from the cell body, and proceeds via characteristic fragmentation of cellular components initiated by a factor or factors intrinsic to the neuron (28, 31). The distal part of a severed or damaged axon usually undergoes Wallerian degeneration within 24–48 hours of injury (88). This type of axonopathy is thought to be a critical, early event in neurodegenerative conditions including multiple sclerosis, Alzheimer's, and Parkinson's diseases and in polyneuropathies associated with diabetes and acute chemotherapy use (64, 90). Remarkably, a mouse mutant, termed *wlds*, with delayed Wallerian degeneration has been identified in the C57BL/6 background. Axons from the *wlds* mouse survive several weeks after transection (61, 62).

The dominant neuroprotective gene in the *wlds* mouse is an in-frame fusion of the N-terminal 70 amino acids of a ubiquitin assembly factor (Ube4b/Uf2a) with the entire coding sequence of Nmnat1 (17). Transgenic mice expressing the Ube4b/Nmnat fusion gene showed that the nuclear protein protected from axonopathy in a manner that depended on the level of protein expression, indicating the activity of a nuclear-derived factor (52). Although Nmnat in flies can protect against degeneration of optic neurons in an active site-independent manner (95, 96), the protective factor for DRG neurons appears simply to be NAD^+. The evidence is as follows. Lentiviral expression of Nmnat1 protects DRG neurons from axonopathy in an active site-dependent manner (3). Overexpression of *wlds* or Nmnat1 prevents NAD^+ and ATP decline in response to mechanical and chemical damage (89). Nam and Na also protect against axonopathy as long as Nampt or Naprt1 are concomitantly expressed in DRG neurons, whereas NR protects without engineered gene expression of a biosynthetic gene (71). Nrk2 mRNA levels following

axonopathy are induced approximately 20-fold, indicating a preferential use of NR as a precursor in maintaining intracellular NAD^+ levels in DRG neurons (71). Whether sufficient oral NR supplementation might protect against diabetic or chemotherapy-induced neuropathy or protect against age-associated neurodegenerative conditions remains to be determined.

NAD^+ SYNTHESIS IN *CANDIDA GLABRATA*

Candida glabrata, the second leading cause of candidiasis, does not encode genes for de novo synthesis of NAD^+, such that it is a Na auxotroph. Because the *C. glabrata* Sir2 homolog represses transcription of a set of adhesin genes, Na limitation leads to adhesin gene expression and host colonization (19). Recent data establish that NR is also utilized by *C. glabrata* as the primary vitamin precursor in disseminated infection in mouse (51). The Nrk pathway (14) and NR to Nam salvage (8) are both components of NR utilization in *C. glabrata* (51).

NICOTINIC ACID MECHANISMS OF ACTION IN DYSLIPIDEMIA

Na has been used to treat dyslipidemias in humans since the 1950s. Gram dosages reduce triglycerides and low-density lipoprotein (LDL, i.e., "bad") cholesterol and raise high-density lipoprotein (HDL, i.e., "good") cholesterol levels. As a monotherapy, Na is one of the most effective means to improve cardiovascular risk factors and, in combination with statins and bile acid treatments, can enhance therapeutic effects (18). In addition to lowering circulating cholesterol levels, Na prevents establishment of lipid deposits and the progression of atherosclerosis in a cholesterol-fed rabbit model (59). However, high-dose Na utilization produces a painful flushing response that limits use.

The mechanism of action of Na in treatment of dyslipidemias is not clear. Na is an agonist of the G-protein-coupled receptor Gpr109A (PUMAG in mice) (85, 92). However, it is not clear that activation of this receptor, which is not expressed in the liver, can account for the clinical efficacy of Na. Activation of Gpr109A in adipocytes inhibits the liberation of free fatty acids from stored triglycerides. However, activation of GPR109A in epidermal Langerhans cells is directly responsible for flushing (11). The lack of expression of Gpr109A in the liver and the finding that Gpr109A mediates flushing cast serious doubt on the receptor model of Na function in dyslipidemia.

We have hypothesized that the beneficial effects of high-dose Na derive simply from NAD^+ biosynthesis (7, 14). The fact that Nam is not beneficial in promoting reverse cholesterol transport can be explained in two ways. First, Na is a better NAD^+ precursor than Nam in liver (16). Second, if the requirement for elevated NAD^+ biosynthesis for improved reverse cholesterol transport depends on sirtuin function, one would expect Nam to be inhibitory.

Sirt1 has been identified as a positive regulator of liver X receptor (LXR), which in turn is a regulator of cholesterol and lipid homeostasis. Sirt1 deacetylates LXR at conserved lysine residues, resulting in LXR activation. *sirt1*−/− animals show reduced expression of LXR target genes, *SREBP1*, and *ABCA1*, in macrophages and in liver, which play important roles in HDL biogenesis (49). These data would appear to make the simple model of Na as an NAD^+ precursor highly reasonable.

PROSPECTS FOR NR AS A SUPPLEMENT

The most fundamental use of NAD^+ precursor molecules, Na and Nam, is in the prevention of pellagra. Like Na and Nam, NR is a natural product found in milk (14), which is incorporated into the intracellular NAD^+ pool (94), and thus could be used as a general supplement, potentially for people who have adverse reactions to Na or Nam. More significantly, however, the specific utilization of NR by neurons may provide qualitative advantages over niacins in promoting function in the central and peripheral nervous system.

NR may also find uses related to the pharmacological uses of Na or Nam, which are limited by the side effects of each. Because Gpr109A is specific for the acid and not the amide (85, 92), one would not expect NR to cause flushing. Similarly, the side effects associated with high-dose use of Nam in the prevention and treatment of diabetic disorders (65) raise substantial health and safety concerns (44). In light of the inhibitory effects of Nam on sirtuins and the protective roles of sirtuins in normal cellular metabolism (18a, 91), NR may represent an alternative supplement. Though uncertainties as to the mechanisms of action of therapeutic doses of Na and Nam exist, positive results with NR would clarify the mechanisms of action of Na and Nam.

Because of the prevalence of PARP activation in neuropathies, inflammation, and neurodegeneration and the association of *C. glabrata* adherence with low NAD^+, NR has great potential as a supplement or therapeutic agent that would elevate or maintain NAD^+ in specific tissues. Future work will evaluate the pharmacokinetics, safety, and efficacy in animal and human systems to maintain health and to prevent disease.

DISCLOSURE STATEMENT

C.B. is an inventor of intellectual property related to nutritional and therapeutic uses of nicotinamide riboside.

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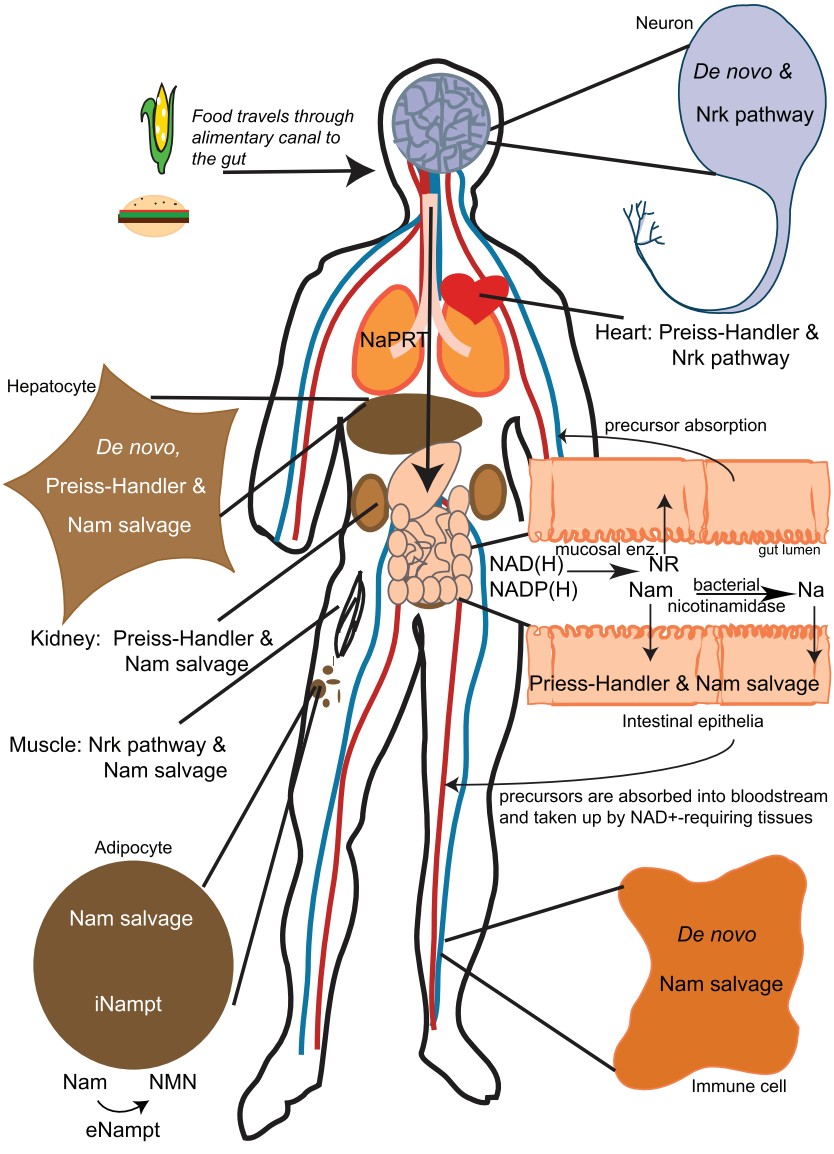

Figure 3

Tissue specificity of nicotinamide adenine dinucleotide (NAD^+) metabolism. Tissue distributions for key pathway enzymes Qprt, Nampt, Naprt1, and Nrk1/2 are represented by pathway identifiers *De novo*, Nam salvage, Preiss-Handler, and Nrk pathway, respectively. Food is broken down in the alimentary canal to NAD(H), NADP(H), Nam, Na, NR, and Trp. Salvageable precursors Nam, Na, and NR are absorbed by intestinal epithelia and transported to the bloodstream. Mucosal enzymes break NAD(H) and NADP(H) into Nam and NR, and bacterial nicotinamidase in the intestinal lumen produces Na from Nam. The intestine conducts Preiss-Handler and Nam salvage. Circulating precursors are taken up by various tissues. The de novo pathway is active in liver, neuronal, and immune cells. Intracellular Nam salvage is active in adipose tissue, liver and kidney, and immune cells in addition to intestine. Extracellular Nampt is produced by adipocytes and circulates in plasma. Naprt1 is most highly expressed in liver, kidney, and heart in addition to the intestine. The Nrk pathway is expressed in neurons and in cardiac and skeletal muscle.

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Errata

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