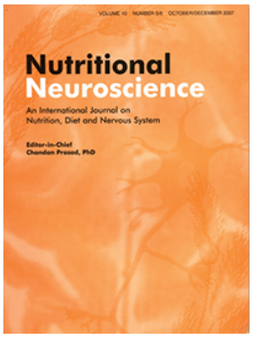

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Review

Nicotinamide and neurocognitive function

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Nicotinamide, or vitamin B3, is a precursor of nicotinamide adenine dinucleotide (NAD^+) and is involved in a multitude of intra- and inter-cellular processes, which regulate some of the cell's metabolic, stress, and immune responses to physiological or pathological signals. As a precursor of NAD^+, which is a key coenzyme in the production of adenosine triphosphate or cellular energy, nicotinamide has been investigated for potential neuroprotective effects in cellular, animal, and human studies.

Objectives: We aimed to summarize the current evidence on the effect of dietary and supplemental nicotinamide on cognitive function.

Methods: A literature review was conducted on the effects of nicotinamide and its derivatives as a preventive and therapeutic agent for disorders of neurocognitive function. Specific conditions examined include age-related cognitive decline, Alzheimer's disease, Parkinson's disease, and ischaemic and traumatic brain injury.

Results: Data from animal and human interventional studies and epidemiological research suggests that nicotinamide may be beneficial in preserving and enhancing neurocognitive function.

Discussion: Nicotinamide is non-toxic, inexpensive and widely available, and interventional studies in humans, using supplemental doses of nicotinamide, are now warranted.

Keywords: Vitamin B3, Niacinamide, Memory

Nicotinamide in health and disease

Nicotinamide is an amide form of vitamin B3. Other forms of vitamin B3 include nicotinic acid (niacin), more complex amides, and esters. Nicotinamide is a precursor to nicotinamide adenine dinucleotide (NAD^+), and both it and its metabolic products are critical in essential cellular functions such as energy production and maintenance of genomic stability.[1] Nicotinamide has a wide range of dietary sources including meats, fish, legumes, nuts, grains, coffee, tea, and niacin fortified cereals.[2] Nicotinamide can also be synthesized from dietary tryptophan, an essential amino acid that constitutes ~1% of the total dietary protein.[1] Oral nicotinamide has good bioavailability, distributes well throughout all tissues in the body, and is metabolized in the liver and renally excreted.[3] The recommended dietary intake of nicotinamide is approximately 15 mg/day.[3] Vitamin B3 deficiency causes pellagra, which is characterized by photo-distributed dermatitis, diarrhoea, dementia, and death.[1]

Nicotinamide has anti-inflammatory effects and has been used in clinical dermatology at doses of ~1.5 g/day as a steroid-sparing agent in autoimmune blistering dermatoses such as bullous pemphigoid.[4,5] It has also shown some efficacy in acne and rosacea, atopic dermatitis, and skin photoageing.[5] Nicotinamide also has a range of photoprotective effects on the skin. Repair of ultraviolet (UV)-induced DNA damage in skin is a highly energy-intensive process, and nicotinamide enhances DNA repair in cultured human keratinocytes and *ex vivo* human skin.[6] A likely mechanism of action in this setting is that nicotinamide replenishes adenosine triphosphate (ATP) or cellular energy in keratinocytes after UV exposure.[7] DNA damage is also a key trigger of the immune suppressive, and hence tumour-promoting, effects of UV radiation on the skin,[8] and nicotinamide has been found to prevent UV-induced immune suppression in the skin of healthy volunteers.[9] Two randomized, double-blinded controlled trials have found that nicotinamide at doses of 500 or 1000 mg daily reduces premalignant

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actinic keratoses ($P = 0.0006$ and $P = 0.005$) and may prevent non-melanoma skin cancers in humans.[10]

Nicotinamide has a well-established safety profile with few or no side effects at these doses.[11,12] At doses beyond ~3.5 g/day, however, there are isolated reports of reversible hepatotoxicity.[3] The vasodilatory side effects seen with nicotinic acid, such as flushing, hypotension, and headache, are not observed with nicotinamide.[3,13]

Nicotinamide and cellular energy status

Nicotinamide, as the primary precursor of NAD^+, is involved in many fundamental cellular processes. Dietary or pharmacological nicotinamide is preferentially used to synthesize NAD^+ in most tissues with nicotinamide mononucleotide as an intermediary utilizing the enzymes nicotinamide mononucleotide adenylyltransferase (NMNAT).[14,15] NAD^+ can also be recycled forming nicotinamide and other ADP-related products via poly ADP-ribose polymerases (PARPs) or sirtuins.[1] The regulation of these synthetic and recycling pathways may explain the variability observed in clinical outcomes with nicotinamide supplementation, as the regulation of NMNAT is closely controlled during cellular stress, and PARPs and sirtuins are linked to various signalling pathways of metabolism, endocrine regulation, cellular proliferation, DNA repair, senescence, and apoptosis.[1,16]

The key metabolic pathways associated with nicotinamide include the reduction of NAD^+ to NADH in the citric acid cycle and subsequently the oxidation of NADH in oxidative phosphorylation, driving ATP synthesis. Nicotinamide is also important in the biosynthesis of purines and pyrimidine nucleotides via the utilization of the phosphorylated form of NAD^+, i.e. $NADP^+$, in the pentose phosphate pathway. The reduced form of $NADP^+$ from this pathway, i.e. NADPH, is further involved in the reduction of glutathione, which interacts with and neutralizes pro-oxidant species, therefore also implicating nicotinamide in anti-oxidant pathways,[1] although we found that nicotinamide itself does not have measurable antioxidant effects in the skin.[7] Further, nicotinamide is associated with metabolism regulation, for instance in NAD^+ utilization of sirtuins.[16]

Both inflammation and immunity are highly energy-dependent processes, and here the role of nicotinamide seems to be part of a complex balance between adequate cellular responses to injury and excessive intracellular resource expenditure which may prove detrimental. On the one hand, nicotinamide has anti-inflammatory effects, which are thought to be partly due to its effect as a PARP inhibitor. Inhibition of PARP leads to inhibition of inducible nitric oxide synthase, suppression of intercellular adhesion molecule-1 expression on endothelial cells, inhibition of tumour necrosis factor secretion, and inhibition of Ia antigen expression on major histocompatibility Class II molecules.[17–19] On the other hand, nicotinamide utilization via the regulation of nicotinamide phosphoribosyltransferase in times of cellular stress leads to increased cellular proliferation, increased survival following genotoxicity, promotion of myeloid and lymphoid differentiation, and increased cytokine production via the sirtuins.[20] These latter events can lead to a heightened inflammatory response and even cell death.

Nicotinamide and cognitive function

In the context of nicotinamide's central roles in cellular metabolism, the high metabolic demand of neuronal tissue, as well as the neurodegenerative effects of vitamin B3 deficiency, there has been increasing research on the effects of nicotinamide and its metabolites in neurocognitive function. In particular, it has been noted that in a long-standing model of neuronal differentiation, the NADP-derived substance nicotinic acid adenine dinucleotide phosphate evoked the differentiation of a rat pheochromocytoma cell line (PC12 cells) into neuronal cells,[21] suggesting a role for nicotinamide metabolites in neuronal development. Nicotinamide may also be protective against damage to existing neuronal tissue. In the presence of nuclear NAD^+, damaged neuronal axons have been shown to be more resilient to degeneration.[22] A recent study of the transcriptional regulation of brain-derived neurotrophic factor (BDNF), which is involved in neuronal generation and survival, and is necessary for learning memory and cognition, has implicated age-related decreases in NAD levels to decreased BDNF transcription.[23] There has been suggestion of an association between neuronal loss and NMNAT, which forms NAD from both nicotinamide and nicotinic acid mononucleotide.[24,25] The mechanism behind the possible neuro-protective properties of NMNAT may be related to its role as a chaperone for neuronal protection, given there is a lack of increased NAD in mice with increased NMNAT-1 expression.[26–28]

The role of nicotinamide in cognitive function is seen most dramatically in settings of overt deficiency. Pellagra-induced dementia is rarely seen in developed countries today, except in the setting of excessive alcohol use, drug dependency, dietary restriction, malabsorptive disorders, HIV infection or carcinoid syndrome,[29] or in long-term institutionalized patients.[30] However with the ageing population and associated cognitive decline, attempts are being made to understand whether there is a place for nicotinamide supplementation in preservation or enhancement of cognition. Neurocognitive decline in the elderly is often multi-factorial. The elderly are not uncommonly undernourished, especially those residing in long-term

care settings, and it is known that better nutrition correlates with improved cognitive performance.[31,32] The elderly are also less likely to be able to utilize nutrients effectively. An observational study with 75 long-term care patients, however, did not find that patients who had niacin deficiency, defined as a niacin ratio (NAD/NADP) of less than or equal to 1, were significantly different to non-deficient patients on cognitive function based on the standardized mini-mental state examination.[30] Thus, attempts have been made to determine whether nicotinamide supplementation can influence cognitive function in animal models.

Peripheral nicotinamide or NADH administration in rats correlates with central nervous system NAD^+ or NADH concentrations, respectively.[33,34] Studies conducted by Koppen *et al.*[35] and Young *et al.*[34] found that young rats given oral nicotinamide were found to have either no effect or actually a worsening of spatial learning ability; however, these studies did contain confounders such as reduced or increased overall feed intake settings occurring in conjunction with decreased or increased nicotinamide supplementation, respectively. Further, younger rats tend to have an accelerated learning curve compared to older rats, which may have influenced the results.[36] In older rats, Koppen *et al.*[35] found a difference in spatial learning, where lower dosing (100 mg/kg; still ~6–8 times the relative dose given to humans) did not affect spatial learning, while very high doses (1000 mg/kg) impaired spatial learning. The spatial learning ability of rats was assessed by the Morris water maze test, which required the rats to use distant spatial cues to recall the location of a submerged escape platform in a pool of water. In this study, nicotinamide supplementation was associated with sedative effects in the rats at high doses, which might have affected their spatial learning ability.[37] The studies by Koppen *et al.* and Young *et al.* used short-term nicotinamide administration only. In the Young *et al.*[34] experiment, dietary modification began 2–3 weeks prior to Morris water maze testing, which was continued for another 1 week, and in the Koppen *et al.*[35] experiment water maze testing was performed 1 hour prior to nicotinamide administration and continued for 5 days. In relation to nicotinamide metabolites, short-term NADH supplementation at various concentrations (10, 50, or 100 mg/kg) resulted in improved spatial learning and memory in older Wistar rats but not younger rats.[38]

Apart from physiological ageing, key causes of decreased neurocognitive function are neurodegenerative disorders including Alzheimer's disease (AD) and vascular dementia, as well as frank ischaemic and infarction events.[39] Although the precise aetiology of dementia under various clinical settings is unclear at present, it is associated with a decreased cerebral metabolic rate, which can be illustrated by imaging studies, mitochondrial function studies, or assays of specific metabolites, including NAD^+.[40–42]

In AD there is neurodegeneration and cognitive decline, and the characteristic pathological manifestations of the disease are the accumulation of Aβ amyloid protein and tau neuro-fibrillary tangles. It is theorized that AD is associated with an inflammatory process involving oxidative imbalance leading to the formation of reactive oxygen species (ROS).[43] Sources of ROS have been identified as coming from the reaction of Aβ aggregates in neuronal membranes generating H_2O_2, the reduced activity of mitochondrial enzymes alpha-ketoglutarate dehydrogenase, and pyruvate dehydrogenase leading to increased O_2 available for ROS formation, and up-regulation of the L-tryptophan catabolism pathway leading to NAD^+ and quinolinic acid production, the latter producing ROS.[43] ROS result in decreased cellular protection mechanisms, including superoxide dismutase activity, raised intracellular calcium, inhibition of glutamate synthase, decreased glucose uptake, lipid peroxidation, protein cross-linking, DNA damage, PARP activation, and NAD^+ depletion[43] as well as reduction in neuronal NADH diaphorase, which catalyses NAD^+ production from NADH.[44] Oxidative stress signalling and the cell's energy state regulate lysosomal organelle turnover and protein aggregation. Suppression of this lysosomal system leads to neuro-degeneration,[45–47] but it is not known whether dysregulation of this system in AD leads to the disease or is a consequence of some other cause of neuronal death.[48] Specifically, Blass[40] described the mitochondrial spiral in relation to AD which involves a relationship between energy inefficiency, production of ROS, and changes in calcium metabolism, all of which are influenced by the metabolic products of nicotinamide. It is thought that mitochondrial dysfunction leads to the formation of a mitochondrial permeability transition pore which allows mitochondrial matrix solutes, including NAD^+ and H^+, to escape into the cytosol where the former molecule eventually leads to intra-cellular calcium release and the latter molecule to H^+ gradient failure and mitochondrial swelling.[49] The resulting decrease of NAD^+ is likely to be detrimental, based on a neuro-degenerative mouse model that has shown the presence of nuclear NAD^+ to be protective.[22]

AD is also associated with increased intra-cellular redox active transition metals, Fe^{2+} and Cu^{2+}, which cause DNA damage and NAD^+ depletion.[49] The production of NAD from the kynurenin pathway also forms quinolinic acid, which increases cellular ROS and nitric oxide, leading to cellular dysfunction, partly through increased PARP activity and decreased NAD^+; and it has been observed that PARP and p53 are increased in AD.[49]

In murine models of AD there is evidence of reduced cognitive deficit and decreased Aβ amyloid protein and tau neuro-fibrillary tangle accumulation with nicotinamide supplementation.[50–52] A study by Green *et al.*[50] looked at the effect of long-term oral nicotinamide supplementation on AD transgenic mice and non-transgenic mice. The mice were given nicotinamide (200 mg/kg/day) or vehicle in their drinking water from birth until 4 months of age when the tests were carried out. Vehicle-treated AD transgenic mice reached the pre-defined criterion of less than 25 seconds to escape the Morris water maze in 6 days on repeat attempts. However, nicotinamide-treated AD transgenic mice reached the criterion in only 4 days ($P < 0.05$), suggesting improved spatial learning ability. In non-transgenic mice, nicotinamide treatment made no difference to the escape latency. Spatial reference memory probe trials were also conducted at 1.5 and 24 hours after the last training trial to assess short- and long-term memory. Nicotinamide improved both the short- and long-term memory in the AD transgenic mice ($P < 0.05$). Nicotinamide also improved the short-term memory ($P < 0.05$), although not the long-term memory, in non-transgenic (control) mice.

Contextual learning, an amygdala and hippocampal-dependent task, was assessed by evaluating whether the AD transgenic mice avoided a dark, shock-associated compartment at 1.5 and 24 hours after training. Nicotinamide-treated AD transgenic mice showed a trend to improvement at 1.5 hours and a statistically significant improvement ($P < 0.05$) at 24 hours. These improvements have been attributed to increased NAD concentrations and decreased mitochondrial oxidative stress. In addition, nicotinamide was found to enhance autophagy-lysosomal activity, for instance as an NAD-dependent Class III histone deacetylase inhibitor by selectively reducing phosphorylated tau protein which is involved in the depolymerization of neuronal microtubules and hence neuronal dysfunction.[50] Nicotinamide has also been found to up-regulate p25 levels and decrease p35 levels which lead to improved learning and memory.[53]

An alternative form of vitamin B3, nicotinamide ribose, has also been investigated in AD models given it was found that neurons prefer this form of the vitamin to maintain NAD^+ levels[54] and that it led to greater increases in NAD^+ levels in mice.[55] Nicotinamide ribose has been found to prevent mitochondrial membrane depolarization in oxidative stress and to regulate Aβ amyloid generation via proliferator-activated receptor-gamma coactivator 1α.[56]

Evidence of improvements in human cognitive and disability assessments with NADH supplementation in AD patients is equivocal with the subjects having been found to show improvements on both of these measures in some studies,[57] while in one study there was no improvement over time, as summarized in Table 1.[58,59] The Birkmayer open label study[58] used 10 mg of NADH per day for 8–12 weeks and showed improvement on the Mini-Mental State Examination (MMSE) and Global Deterioration Scale (GDS) for 17 AD patients. The Rainer open label study[59] used the same dosage of NADH for 12 weeks and showed no statistically significant change from baseline on MMSE, GDS, or the Alzheimer's Disease Assessment Scale for 19 dementia patients. Both of these studies lacked controls and had small sample sizes. An observational study reported a decreased relative risk of AD as well as decreased levels of cognitive decline with increased dietary intake of vitamin B3.[60] In this study, intake of

Table 1 Summary of human studies looking at the general cognitive effects and effects on AD of nutritional vitamin B3 and derivatives

Study	Subjects (*N*)	Intervention	Duration	Results
Birkmayer[58]	AD (17)	NADH 10 mg/day	8–12 weeks	Improved MMSE and GDS scores
Rainer *et al.* [59]	AD, vascular dementia, FTLD (19)	NADH 10 mg/day	8–12 weeks	No significant change on MMSE, GDS, and ADAS
Morris *et al.* (2004)[60] AD risk reduction	Residents aged 65 years and older in a geographically defined Chicago community participating in the Chicago Health and Aging Project population (815)	Comparison between median niacin intakes ranging from 15.2 mg/day (lowest quintile) to 22.4 mg/day (highest quintile)	Mean follow up 3.9 years	Basic adjusted relative risk reduction of AD of 0.4 per 7.2 mg/day increase in dietary niacin
Morris *et al.* (2004)[60] Association with cognitive decline	Residents aged 65 years and older in a geographically defined Chicago community participating in the Chicago Health and Aging Project population (3718)	Comparison between median niacin intakes of 12.6–22.1 mg/day	Median follow up 5.5 years	44% reduction in cognitive decline

NADH, nicotinamide adenine dinucleotide; MMSE, Mini-Mental State Examination; GDS, Global Deterioration Scale; ADAS, Alzheimer's Disease Assessment Scale; AD, Alzheimer's disease; FTLD, fronto-temporal lobe dementia.

vitamin B3 was determined for 3718 subjects from the Chicago Health and Aging Project using a Food Frequency Questionnaire and people were stratified into quintiles of niacin intake, the lowest having a median of 12.6 mg/day and the highest 22.1 mg/day. Clinical assessment for AD was carried out by a neurologist for 815 of the 3718 subjects. It found a basic adjusted relative risk for AD of 0.4 per 7.2 mg/day increase in dietary niacin. For the entire 3718 subjects, an association between increased food intake of niacin and decreased cognitive decline was found, as assessed by the East Boston Test of Immediate and Delayed Recall, the MMSE, and the Symbol Digit Modalities tests with a median follow up of 5.5 years. As a Food Frequency Questionnaire was used to assess niacin intake, the study was limited by reliance on patient recall.

Cerebrovascular ischaemia can also result in cognitive impairment, and murine models have shown beneficial effects with nicotinamide treatment.[51] Pre-ischaemic intravenous nicotinamide administration has been shown to increase nicotinamide concentration in the ischaemic core and penumbra while apparently increasing NAD^+ concentration in the penumbra alone.[61] These findings were accompanied by a decreased volume of infarcted tissue. In this study there was also increased cerebral blood flow at higher nicotinamide concentration, i.e. 250 mg/kg, which may be a confounder in the study.[61] Active and passive learning capacity was significantly improved in mice given high-dose nicotinamide shortly after cerebrovascular insult.[62] An associated model of cerebral ischaemia investigated for the potential protective effects of nicotinamide is that of perinatal asphyxia. In these models it is again clear that nicotinamide has a complex association in the repair mechanisms of neurons, which appears to be specific to a given part of the brain and type of neuron or neuronal process. For instance, Klawitter *et al.*[63] discovered that nicotinamide decreased nitric oxide synthase activity in the neostriatum but not in the substantia nigra, while Morales *et al.*[64] found that nicotinamide decreased neuronal apoptosis but had no effect on abnormal axonal growth in the hippocampus despite an associated decrease in both non-spatial working memory deficiency and anxiety.

In trying to explain the above-mentioned cerebral hypoxic-associated phenomena, *in vitro* analysis of the effect of nicotinamide on the formation of reactive oxygen and nitrogen species has found that nicotinamide decreases lactate dehydrogenase and caspase 3 cleavage activity, calcium influx and nuclear condensation, the presence of ROS, and markers of early post-ischaemic cell activation and transcription regulation factors.[65] It has also been suggested that the beneficial effects of nicotinamide are due to improvements in ATP utilization under ischaemic conditions.[66] Translation of the use of neuroprotectants, such as nicotinamide, from experimental animal models to human clinical trials is subject to certain inherent difficulties, such as experimental animal models consisting of homogeneous populations which also lack comorbidities commonly seen in older stroke patients.[67]

Several short-term traumatic brain injury models in young rodents have indicated structural, somatosensory, and cognitive improvements with the administration of nicotinamide,[68] although differences between the studies suggest the significance of dosing regimens on efficacy.[69–72] For example, the experiments of Vonder Haar *et al.*[70] and Hoane *et al.*[69] had similar designs but better cognitive outcomes were seen with continuous and prolonged administration of nicotinamide. Interestingly, Swan *et al.*[73] performed a similar experiment to those cited above with the exception that the rats were middle-aged (14 months) and subsequently found no improvement in cognitive performance in lower dose (50 mg/kg) nicotinamide administration following traumatic brain injury and even a reduced cognitive performance in rats administered a higher dose (500 mg/kg). These findings mirror those of Koppen *et al.*[35] who described that older healthy rats are more prone to the sedative effects of nicotinamide than younger rats, suggesting that for older rats the benzodiazepine-like effects of high-dose nicotinamide may counteract the potential neuro-protective effects in the setting of traumatic brain injury.

Further studies have tried to elucidate the aetiology of the beneficial effects of nicotinamide in traumatic brain injury models. Holland *et al.*[74] structurally assessed brain tissue at 24 hours and 7 days post fluid perc-ssion injury in a rodent model and discovered that nicotinamide-treated animals expressed lower levels of a neuro-degeneration marker, Fluoro-Jade B, at both time intervals and decreased levels of cortical loss at 7 days compared to controls. Interestingly, they also discovered an acute (at 24 hours) decrease in astrocytic activity, assessed with glial fibrillary acidic protein labelling, and a subsequent rise at 7 days, suggesting an acute suppression of astrocytic activity with the initial inflammatory response and a subsequent activation at 7 days limiting tissue loss and facilitating recovery of function. Although using different dosing regiments to the previous study, Anderson *et al.*[75] explored genetic expression characteristics in a similar traumatic brain injury model. Anderson *et al.* discovered that, compared to controls, nicotinamide-treated animals had 150 differentially expressed genes at 24 hours post-injury, most of which were down-regulated and involved in inflammatory signalling pathways, and 119 differentially expressed genes at 72 hours, most of which were up-regulated and involved in neuron

metabolism, development, differentiation, and plasticity including genes associated with cell signalling, neurotransmitters, neuropeptides, growth factors, and ion channels. At day 7, however, there were only five differentially expressed genes suggesting an acute temporal benefit of nicotinamide administration post-brain trauma and a complex time-dependent relationship between nicotinamide and the natural repair process. It will require experiments with a post-injury follow-up design of higher resolution and length, as well as more focused gene-phenotyping designs, to clarify this relationship.

Nicotinamide might also have benefit in Parkinson's disease, in which cognitive impairment as well as motor deficits may occur. An animal (*drosophila*) model of Parkinson's disease has demonstrated improved motor function with high-dose nicotinamide, the mechanism of which is likely due to decreased oxidative damage to mitochondria.[76] A suggestion of potential clinical benefit from NADH, a nicotinamide metabolite, in neurodegenerative disorders was found in a large open label trial, consisting of 885 Parkinsonian patients, who were given oral and parenteral NADH. The patients were found to be improved on the Birkmayer and Neumayer disability scale, which includes measures of mobility, posture, speech, writing, and facial expression.[77] However, a small double-blind study with nine patients failed to show a significant improvement with NADH.[78]

Conclusion

Nicotinamide plays a crucial role in cellular function. However, due to the integrated nature of its metabolic products and the fine balance within which all cellular processes occur, manipulations of nicotinamide in healthy and pathological neurological states are currently not well understood. There is now sufficient evidence to support further, interventional studies into the effects of nicotinamide and its metabolites on neurocognitive function, especially in the preventive setting.

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