NEURAL REGENERATION RESEARCH
August 2014, Volume 9, Issue 16
www.nrronline.org

INVITED REVIEW

The biochemical pathways of central nervous system neural degeneration in niacin deficiency

Linshan Fu[1], **Venkatesh Doreswamy**[2], **Ravi Prakash**[2]

1 Department of Neurosurgery, the First People's Hospital of Yancheng, Yancheng, Jiangsu Province, China
2 Department of Physiology, M.S. Ramaiah Medical College, Bangalore, India

Corresponding author:
Ravi Prakash, M.D., D.P.M., Tutor of Department of physiology, M.S. Ramaiah Medical College, Bangalore, India, drravi2121@gmail.com.

doi:*10.4103/1673-5374.139475*
http:*//www.nrronline.org/*

Accepted: *2014-08-10*

Abstract

Neural degeneration is a very complicated process. In spite of all the advancements in the molecular chemistry, there are many unknown aspects of the phenomena of neurodegeneration which need to be put together. It is a common sequela of the conditions of niacin deficiency. Neural degeneration in Pellagra manifests as chromatolysis mainly in pyramidal followed by other neurons and glial cells. However, there is a gross lack of understanding of biochemical mechanisms of neurodegeneration in niacin deficiency states. Because of the necessity of niacin or its amide derivative NAD in a number of biochemical pathways, it is understandable that several of these pathways may be involved in the common outcome of neural degeneration. Here, we highlight five pathways that could be involved in the neuraldegeneration for which evidence has accumulated through several studies. These pathways are: 1) the tryptophan-kyneurenic acid pathway, 2) the mitochondrial ATP generation related pathways, 3) the poly (ADP-ibose) polymerase (PARP) pathway, 4) the BDNF-TRKB Axis abnormalities, 5) the genetic influences of niacin deficiency.

Key Words: *Niacin deficiency; neural degeneration; chromatolysis; biochemical pathways of degeneration; kyneurenic acid; BDNF-TRKB pathway*

Fu LS, Doreswamy V, Prakash R. The biochemical pathways of central nervous system neural degeneration in niacin deficiency. Neural Regen Res. 2014;9(16):1509-1513.

Introduction

Niacin is chemically synonymous with nicotinic acid although the term is also used for its amide derivative (nicotinamide). Nicotinamide is the form of the vitamin, which does not have the pharmacological action of the acid. It is the amide form that exists within the redox-active co-enzymes, nicotinamide adenine dinucleotide (NAD) and its phosphate (NADP), which function in dehydrogenase-reductase systems requiring transfer of a hydride ion (McCormick, 1996, 1997). In the chemical form of NAD, niacin is involved in a number of biochemical processes, including energy metabolism (redox reactions), protein modification by mono and poly (ADP-ribose) polymerases and synthesis of intracellular calcium signaling molecules (McCormick, 1988). NAD is also required for non-redox adenosine diphosphate-ribose transfer reactions involved in DNA repair (Berger, 1985) and calcium mobilization. It also participates in intracellular respiration along with enzymes involved in the oxidation of fuel substrates such as glyceraldehyde 3-phosphate, lactate, alcohol, 3-hydroxybutyrate, and pyruvate. NADP mainly functions in reductive biosynthesis such as fatty acid and steroid synthesis and in the oxidation of glucose-6-phosphate to ribose-5-phosphate in the pentose phosphate pathway.

Neurodegenerative pathology in niacin deficiency is well-known. However, this degeneration has to be distinguished from the pathological conditions occurring in primary neurodegenerative disorders like Alzheimer's and Parkinson's diseases. Whereas these primary neurodegenerative diseases occur due to accumulation of intraneuronal pathogens usually due to inherent genetic problems, Niacin deficiency on the other hand is an example of environmental factor deficiency leading to neural degenerative process. However, the specific biochemical mechanisms and pathways underlying this neural degeneration in Niacin deficiency are not well understood. However, over past few years, some prominent biochemical pathways which are disturbed in niacin deficiency and possibly contribute to the neurodegenerative events have been identified. However, we could not find any literature where these pathways have been reviewed together. Purpose of present review is to compile these pathways together so that a more comprehensive picture could be created.

Methodology

A general search of Internet using Google and specific medical indexing databases like Pubmed, Science-direct *etc*. were carried out for selecting the articles relevant to present review, specifically regarding the neural degenerative process in Pellagra. All the relevant articles were referred, and these included the original as well as review articles. All the articles were reviewed for the descriptions of biochemical pathways involved in the phenomenon of neural degeneration. Five biochemical pathways most commonly implicated in these articles were

identified, these five pathways will be the center of this review and will be described individually in subsequent sections.

Neuropathology of pellagra

Few studies have been conducted for exploring the neuropathology of Pellagra *per se*. In human pellagra, neuropathologic abnormalities consistently observed are chromatolysis in motor neurons, such as Betz cells in the motor cortex, nuclei of brain stem, and anterior horn cells of the spinal cord (Langworthy, 1931; Zimmermann et al., 1934). Neuronal chromatolysis is characterized by cytological features of cytoplasmic swelling, disappearance of Nissl granules and displacement of flattened nucleus to the periphery of the cell body. These changes have also been described in the anterior horn cell and hypoglossal nuclei following axonal injury and have been termed as axonal reactions (Torvik, 1976). Apart from chromatolysis in the anterior horn cells, other striking microscopic changes seen in the central nervous system (CNS) of the mice treated with 6-AN were swelling and vacuolation of ependymal and glial cells (Aikawa and Suzuki, 1986).

Biochemical pathways of neural degeneration in pellagra

Although describing the details of all the molecular mechanisms is out of scope of this review, we proceed to provide an overview of the common and most studied pathways at present. Overall, alterations in five major biochemical pathways have been studied so far in the context of Pellagra:

1) The tryptophan-kyneurenic acid pathway;
2) The mitochondrial ATP generation related abnormality;
3) The poly (ADP-ribose) polymerase (PARP) pathway;
4) The BDNF-TRKB Axis abnormalities;
5) The genetic consequences of niacin deficiency.

The tryptophan-kyneurenic acid pathway

The kyneurenic pathway (KP) is the principle route of L-tryptophan (TRP) metabolism, producing several neurotoxic and neuroprotective metabolic precursors before complete oxidation to yield the essential pyridine nucleotide, nicotinamide adenine dinucleotide (NAD^+) (5). It is thus the principal route of L-tryptophan catabolism, resulting in the production of NAD. This metabolic pathway of the amino acid L-tryptophan is a highly regulated physiological process leading to the generation of several neuroactive compounds within the central nervous system. These compounds include the aminergic neurotransmitter serotonin (5-hydroxytryptamine, 5-HT), products of the kyneurenine pathway of tryptophan metabolism (including 3-hydroxykyneurenine, 3-hydroxyanthranilic acid, quinolinic acid and kyneurenic acid), the neurohormone melatonin, several neuroactive kyneuramine metabolites of melatonin, and the trace amine, tryptamine. Inhibition of KP holds therapeutic potential in modulating the inflammation of central nervous system (CNS) by reducing the production of excitotoxins such as quinolinic acid (QUIN) (Ruddick et al., 2006). It has been proposed that the generation of nicotinamide, and the subsequent restoration or maintenance of NAD levels is a major function of the kyneurenic pathway acting paradoxically as a pathway for cellular protection.

However, in the conditions of deficiency of exogenous nicotinamide and subsequently NAD, there is a loss of nicotinamide related negative feed-back of KP, resulting in its over-activation and thus release of more of neurotoxic intermediate metabolites. The pathway is regulated by the immune-factor responsive enzyme indoleamine-2,3-dioxygenase (IDO) in most cells and by tryptophan-2,3-dioxygenase (TDO) in the liver which is modulated by tryptophan and glucocorticoids. Several intermediate products of the KP are known to be neurotoxic. Among them, the N-methyl-D-aspartate (NMDA) receptor agonist and neurotoxin, quinolinic acid (QA) is likely to be the most important in terms of biological activity (Stone, 2001; Davies et al., 2010). QA can cause stimulation of NMDA receptors independent of its agonistic action by inhibiting glutamate uptake by astrocytes, increasing synaptosomal release and reducing its catabolism by astrocytes through inhibition of glutamine synthase activity (Ting et al., 2009). Alternative routes causing neurotoxicity include production of reactive oxygen species, mitochondrial dysfunction and lipid peroxidation (Vu et al., 1997; Jacobson et al., 1999). This is supported by the observation that free radical scavengers and antioxidants reduce QA-induced neurotoxicity. Anthranilic acid (AA), 3-hydroxyanthranilic acid (3-HAA), and 3-hydroxykyneurenine (3-HK) have been shown to generate free radicals leading to neuronal damage similar to QUIN (Stone, 2001; Davies et al., 2010).

Poly(ADP-ribose) polymerase (PARP) pathway

More recently NAD^+ has been identified as a primary substrate for several other important enzymes including poly (ADP-ribose) polymerase (PARP). PARP is a nuclear enzyme, activated by breaks of DNA strand that are involved in DNA repair and in maintenance of genomic integrity. Several members of the PARP family have been identified, of which PARP-1 is the most reported. PARP uses up NAD^+ to produce ADP ribose polymers. An increase in DNA damage (often due to oxidative stress) can rapidly deplete the cell of NAD^+ resulting in reduced ATP production and cell death (Pacher and Szabo, 2007; Braidy et al., 2008). Consistent with this finding, cellular NAD^+ status has actually been increasingly demonstrated to alter the cell susceptibility to genotoxic damage (Jacobson et al., 1999). In fact, one of the major causes of cell death due to genotoxic stress is hyperactivation of the NAD^+ dependent enzyme poly(ADP-ribose) polymerase-1 (PARP-1), which depletes nuclear and cytoplasmic NAD^+ causing the translocation of apoptosis inducing factor (AIF) from the mitochondrial membrane to the nucleus (Bürkle, 2005; Cipriani et al., 2005). In the presence of nicotinamide, an essential precursor to NAD^+, cellular NAD^+ stores are more effectively replenished and damaged DNA is more effectively repaired (Ayoub et al., 1999; Maiese and Chong, 2003). Nicotinamide improves neuronal survival

following a variety of insults, including free radical exposure and oxidative stress (Mukherjee et al., 1997; Klaidman et al., 2001). However, its protective function is thought to be based on its numerous and diverse pharmacological effects, in addition to the inhibition of PARP-1. These mechanisms include prevention of ATP depletion (Yang et al., 2002; Klaidman et al., 2003), lipid peroxidation, anti-inflammatory activity, and prevention of apoptosis (Klaidman et al., 2001; Ungerstedt et al., 2003). Recent study has reported that a fraction of PARP-1 is also localized in mitochondria, which leads to speculation about the potential for mitochondrial NAD^+ to determine fate of the cell (Du et al., 2003). This dimension of PARP related cell injury will be discussed in later section.

In addition to the genotoxic damage, PARP pathways have also been implicated in Pellagra related symptoms. It was thought that the clinical manifestations of pellagra arise from the deficient NAD^+ and $NADP^+$ levels in maintaining energy for cellular functions (Hendricks, 1991). However, understanding of these multiple symptoms has progressed with the finding of NAD^+ acting as a substrate for poly(ADP-ribose) polymerases (PARPs) (Chambon et al., 1963). PARP has been recognized to play a multitude of roles in DNA damage including DNA repair, maintenance of genomic stability, transcriptional regulation, signaling pathways involving apoptosis, and telomere functions (Oliver et al., 1999). NAD^+ has been shown to be a free radical scavenger (Yamada et al., 1982; Wilson et al., 1984; Kamat and Devasagayam, 1996; Vincent et al., 2005; Abdallah, 2010) and is directly used for the synthesis of cyclic ADP-ribose. It may be thus involved in calcium signaling pathways leading to apoptosis or necrosis (Vu et al., 1997, Vu et al., 1997).

The mitochondrial ATP pathway

Mitochondria maintain relatively high NAD^+ concentrations which does not readily leak across the inner mitochondrial membrane (Di and Ziegler, 2001). Depletion of the mitochondrial NAD results in impairment of respiration and ATP synthesis resulting in energy crisis ultimately causing cell death. A major mechanism of depletion of cellular NAD seems to be by activation of the enzyme ADP-ribose.

DNA damage activates a nuclear enzyme poly(ADP-ribose) synthetase that facilitates DNA repair and this enzyme activity can provide an early index of DNA damage following neurotoxic insults (Zhang et al., 1995). As mentioned before, NAD is required for the non-redox adenosine diphosphate-ribose transfer reaction. Excessive activation of this enzyme can thus, deplete tissue stores of NAD, leading to cell death with the depletion of ATP (Pieper et al., 1999). Pharmacological experiments have found that Poly (ADP-ribose) synthetase inhibitors and poly (ADP-ribose) synthetase gene deletion induces dramatic neuroprotection in experimental animals (Boulu et al., 2001). On the other hand nitric oxide stimulates auto-ADP-ribosylation of glyceraldehyde-3-phosphate dehydrogenase (*via* hydroxyl radical) (Dimmeler and Brune, 1992; Zhang and Snyder, 1992; Brune et al., 1994) causing free-radical mediated cellular injury. Several researchers have in fact attempted to attenuate free radical mediated cerebral damage by inhibition of poly(ADP-ribose) synthetase (Lo et al., 1998; Takahashi et al., 1999) or by supplementation of niacin (Hageman et al., 1998). These studies have found that poly(ADP-ribose) synthetase activation mediates MPTP neurotoxicity (Mandir et al., 1999), and its inhibitors protect against MPTP-induced depletion of striatal dopamine (Schapira et al., 1990) or brain NAD and ATP (Cosi and Marien, 1998).

Poly ADP-ribosylation also results in the release from NAD of nicotinamide, which is methylated to MNA in the body.

Brain derived neurotrophic factor-tropomyosin related kinase B (BDNF-TrkB) axis

In the mature nervous system, BDNF/TrkB is crucial for regulating neuronal migration, morphological and biochemical differentiation, and controlling synaptic function as well as synaptic plasticity, along with modulation of neuronal survival (Bibel and Barde, 2000; Huang and Reichardt, 2001). Also, it is a well known fact that the expression of Brain derived neurotrophic factor (BDNF) and its receptor tropomyosin-related kinase B (TrkB) supports neuron survival and axon growth after neuronal injury (Gordon, 2009; Li et al., 2009). For example, after injury of somatosensory cortex, BDNF is up-regulated in these regions (Josephson et al., 2003; Endo et al., 2007).

Recent evidences suggest that niacin administration may up-regulate the expression of BDNF-TrkB. In a recent study, it has been found that niacin treatment increased synaptic plasticity and axon growth in rats. They observed that the treatment with niacin for stroke significantly increased BDNF/TrkB expression both in the ischemic brain and in PCN cultures. Although the study did not elaborate all the molecular mechanisms leading to this upregulation of BDNF-TrkB by Niacin, their results indicated that it was mediated by HDL (Cui et al., 2010). They came to this conclusion because in their results, the TrkB inhibitor (K252a, 200 nmol/L, Calbiochem, Cat# 480354) significantly decreased the neuritic growth in the primary cultured neurons (PCNs) group treated with HDL and niacin together in comparison to the group with treated niacin alone. Cui et al. (2010) concluded that this finding was an indication that the HDL involvement was at least partially responsible for the TrkB inhibitor mediated inhibition of neuritic growth in such neurons. Additionally, they also found an increased expression of mRNA of the BDNF-TrkB factors, indicating that the net effect is mediated by at least some genetic mechanisms. However, more well planned and detailed studies are needed to further elaborate these biochemical mechanisms. If closer attention is paid to this scenario the evidences for both the facts that (a) niacin increases HDL-C levels (Elam et al., 2000) and that (b) HDL increases neuritic growth (Anne et al., 1996) have been well supported by scientific results. Infact, niacin is presently the most potent enhancer of HDL-C levels (Elam et al., 2000). However, it is still not known whether HDL induces this

neuronal growth by increasing TrkB levels. Therefore, this seems to be a potent area of future researches. At present, we can safely raise the possibility that niacin-mediated neural growth by the BDNF-TrkB pathway could be at least partially mediated by enhanced HDL-C levels.

Gene-level effects of niacinamide

In addition to these biochemical pathways, there are various effects at genetic-level which are possible contributors to the niacin or NAD-deficient neural degeneration.

Recently, Nmnat genes (Nmnat1, 2, and 3) have been studied as potential targets based on their ability to delay Wallerian degeneration after axonal damage (Coleman and Freeman, 2010). All the members of Nmnat family can catalyze the synthesis of NAD^+ both in the *de novo* pathway as well as in the recycling pathway (Sorci et al., 2007). Nmnat1 is ubiquitously expressed and localized to the nucleus. Nmnat3 shows a more restricted expression pattern and localizes to mitochondria (Berger et al., 2005). Nmnat2 is expressed predominantly in neurons (Berger et al., 2005; Mayer et al., 2010). Its protein product has been shown to localize to the trans-Golgi complex (Berger et al., 2005; Mayer et al., 2010) where it is packaged and transported down axons to the synapse (Gilley and Coleman, 2010). In addition to the differences in tissue expression and intracellular localization, there is an isoform-specific domain on each of the Nmnat genes (Braidy et al., 2008). In Nmnat2, this region is palmitoylated at two cysteine residues and when cleaved, the NAD^+ synthesis activity of the enzyme increases significantly (Mayer et al., 2010). This provides a mechanism to increase the cytosolic pool of NAD^+ quickly in response to a stimulus like cell stress.

Nmnat2, *in vitro*, has been associated with axonal survival in primary sensory and sympathetic nerve cell injury models (Gilley and Coleman, 2010; Yan et al., 2010). Historically, aberrant or exogenous overexpression of the Wldsprotein (a fusion protein containing Nmnat1) or Nmnat1 itself, has been used to protect axons from Wallerian degeneration after injury (Coleman and Freeman, 2010). But more recent studies suggest that the endogenous Nmnat isoform required for the normal maintenance of healthy axons is actually Nmnat2 (Gilley and Coleman, 2010; Conforti et al., 2011). Significant overexpression of this isoform can also delay Wallerian degeneration (Feng et al., 2010; Gilley and Coleman, 2010; Yan et al., 2010). Studies on the d-Nmnat ortholog in Drosophila indicate that it has a protective function analogous to the mouse Nmnat2 gene (Zhai et al., 2006; Ali et al., 2011). Using a unique mouse mutant, these studies produced *in vivo* data indicating that during embryogenesis, Nmnat2 plays an essential role in axonal growth and/or survival. In its absence, major organs and muscles are not functionally innervated resulting in peri-natal lethality, which is likely due to failure of respiratory function at birth.

Genes required for axonal development and neuronal survival may provide targets for the treatment of neurodegenerative disorders also like Alzheimer's and Parkinson's diseases, and for the re-innervation of tissues after injury. They may also be used to promote innervations of tissues and organs created using tissue engineering techniques.

References

Abdallah DM (2010) Nicotinamide alleviates indomethacin induced gastric ulcers: a novel antiulcer agent. Eur J Pharmacol 627:276-280.

Aikawa H, Suzuki K (1986) Lesions in the skin, intestine, and central nervous system induced by an antimetabolite of niacin. Am J Pathol 122:335-342.

Ali YO, Ruan K, Zhai RG (2011) NMNAT suppresses Tau-induced neurodegeneration by promoting clearance of hyperphosphorylated Tau oligomers in a Drosophila model of tauopathy. Hum Mol Genet 21:237-250.

Anne M. Fagan, Guojun Bu, Yuling Sun, Alan Daughertyi, David M. Holtzman (1996) Apolipoprotein E-containing high density lipoprotein promotes neurite outgrowth and is a ligand for the low density lipoprotein receptor-related protein. J Biol Chem 271:30121-30125.

Ayoub IA, Lee EJ, Ogilvy C, Flint BM, Maynard KI (1999) Nicotinamide reduces infarction up to two hours after the onset of permanent focal cerebral ischemia in wistar rats. Neurosci Lett 259:21-24.

Berger F, Lau C, Dahlmann M, Ziegler M (2005) Subcellular compartmentation and differential catalytic properties of the three human nicotinamide mononucleotide adenylyltransferase isoforms. J Biol Chem 280:36334-36341.

Berger NA. Poly (ADP-ribose) in the cellular response to DNA damage. Radiat Res 101:4-15.

Bibel M, Barde YA (2000) Neurotrophins: Key regulators of cell fate and cell shape in the vertebrate nervous system. Genes Dev 14:2919-2937.

Boulu RG, Mesenge C, Charriaut-Marlangue C, Verrecchia C, Plotkine M (2001) Neuronal death: potential role of the nuclear enzyme, poly (ADP-ribose) polymerase. Bull Acad Natl Med 185: 555-563.

Braidy N, Guillemin G, Grant R (2008) Promotion of cellular NAD̲Anabolism: therapeutic potential for oxidative stress in ageing and Alzheimer's disease. Neurotox Res 13:1-12.

Brune B, Dimmeler S, Molina Y, Vedia L, Lapetina EG (1994) Nitric oxide: a signal for ADP-ribosylation of proteins. Life Sci 54:61-70.

Bürkle A (2005) Poly(ADP-ribose). The most elaborate metabolite of NAD+. FEBS J 272:4576-4589.

Chambon P, Weill JD, Mandel P (1963) Nicotinamide mononucleotide activation of a new DNA-dependent polyadenylic acid synthesizing nuclear enzyme. Biochem Biophys Res Commun 11:39-43.

Cipriani G, Rapizzi E, Vannacci A, Rizzuto R, Moroni F, Chiarugi A (2005) Nuclear poly(ADP-ribose) polymerase-1 rapidly triggers mitochondrial dysfunction. J Biol Chem 280:17227-17234.

Coleman MP, Freeman MR (2010) Wallerian degeneration, wld(s), and nmnat. Annu Rev Neurosci 33:245-267.

Conforti L, Janeckova L, Wagner D, Mazzola F, Cialabrini L, Di Stefano M, Orsomando G, Magni G, Bendotti C, Smyth N, Coleman M (2011) Reducing expression of NAD+ synthesizing enzyme NMNAT1 does not affect the rate of Wallerian degeneration. FEBS J 278:2666-2679.

Cosi C, Marien M (1998) Decreases in mouse brain NAD^+ and ATP induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): prevention by the poly(ADP-ribose) polymerase inhibitor, benzamide. Brain Res 809:58-67.

Cui X, Chopp M, Zacharek A, Roberts C, Buller B, Ion M, Chen J (2010) Niacin treatment of stroke increases synaptic plasticity and axon growth in rats. Stroke 41:2044-2049.

Davies NW, Guillemin G, Brew BJ (2010) Tryptophan, neurodegeneration and HIV-associated neurocognitive disorder. Int J Tryptophan Res 3:121-140.

Di Lisa F, Ziegler M (2001) Pathophysiological relevance of mitochondria in NAD(+) metabolism. FEBS Lett 492:4-8.

Dimmeler S, Brune B (1992) Characterization of a nitric-oxidecatalysed ADP-ribosylation of glyceraldehyde-3-phosphate dehydrogenase. Eur J Biochem 210:305-310.

Du L, Zhang X, Han YY, Burke NA, Kochanek PM, Watkins SC, Graham SH, Carcillo JA, Szabó C, Clark RS (2003) J Intra-mitochondrial poly(ADP-ribosylation) contributes to NAD+ depletion and cell death induced by oxidative stress. Biol Chem 278:18426-18433.

Elam MB, Hunninghake DB, Davis KB, Garg R, Johnson C, Egan D, Kostis JB, Sheps DS, Brinton EA (2000) Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: The admit study: A randomized trial. Arterial disease multiple intervention trial. JAMA 284:1263-1270.

Endo T, Spenger C, Tominaga T, Brene S, Olson L (2007) Cortical sensory map rearrangement after spinal cord injury: Fmri responses linked to nogo signalling. Brain 130:2951-296.

Feng Y, Yan T, Zheng J, Ge X, Mu Y, Zhang Y, Wu D, Du JL, Zhai Q (2010) Overexpression of Wld(S) or Nmnat2 in mauthner cells by single-cell electroporation delays axon degeneration in live zebrafish. J Neurosci Res 88:3319-3327.

Gilley J, Coleman MP (2010) Endogenous Nmnat2 is an essential survival factor for maintenance of healthy axons. PLoS Biol 8:e1000300.

Gordon T (2009) The role of neurotrophic factors in nerve regeneration. Neurosurg Focus 26:E3.

Hageman GJ, Stierum RH, van Herwijnen MH, van der Veer MS, Kleinjans JC (1998) Nicotinic acid supplementation: effects on niacin status, cytogenetic damage, and poly(ADP-ribosylation) in lymphocytes of smokers. Nutr Cancer 32:113-120.

Hendricks WM (1991) Pellagra and pellagralike dermatoses: etiology, differential diagnosis, dermatopathology, and treatment. Semin Dermatol 10:282-292.

Jacobson EL, Shieh WH, Huang AC (1999) Mapping the role of NAD metabolism in prevention and treatment of carcinogenesis. Mol Cell Biochem 193:69-74.

Josephson A, Trifunovski A, Scheele C, Widenfalk J, Wahlestedt C, Brene S, Olson L, Spenger C (2003) Activity-induced and developmental downregulation of the nogo receptor. Cell Tissue Res 311:333-342.

Kamat JP, Devasagayam TP (1996) Methylene blue plus light-induced lipid peroxidation in rat liver microsomes: inhibition by nicotinamide (vitamin B3) and other antioxidants. Chem Biol Interact 99:1-16.

Klaidman L, Morales M, Kem S, Yang J, Chang ML, Adams JD Jr (2003) Nicotinamide offers multiple protective mechanisms in stroke as a precursor for NAD^+, as a PARP inhibitor and by partial restoration of mitochondrial function. Pharmacology 69:150-157.

Klaidman LK, Mukherjee SK, Adams JD (2001) Oxidative changes in brain pyridine nucleotides and neuroprotection using nicotinamide. Biochim Biophys Acta 1525:136-148.

Langworthy OR (1931) Lesions of the central nervous system characteristic of pellagra. Brain 54:291-302.

Li F, Li L, Song XY, Zhong JH, Luo XG, Xian CJ, Zhou XF (2009) Preconditioning selective ventral root injury promotes plasticity of ascending sensory neurons in the injured spinal cord of adult rats-possible roles of brain-derived neurotrophic factor, trkb and p75 neurotrophin receptor. Eur J Neurosci 30:1280-1296.

Lo EH, Bosque-Hamilton P, Meng W (1998) Inhibition of poly(ADP-ribose) polymerase: reduction of ischemic injury and attenuation of N-methyl-D-aspartate-induced neurotransmitter dysregulation. Stroke 29:830-836.

Maiese K, Chong ZZ (2003) Nicotinamide: necessary nutrient emerges as a novel cytoprotectant for the brain. Trends Pharmacol Sci 24:228-232.

Mandir AS, Przedborski S, Jackson-Lewis V, Wang ZQ, Simbulan-Rosenthal CM, Smulson ME, Hoffman BE, Guastella DB, Dawson VL, Dawson TM (1999) Poly(ADP-ribose) polymerase activation mediates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism. Proc Natl Acad Sci U S A 96:5774-5779.

Mayer PR, Huang N, Dewey CM, Dries DR, Zhang H, Yu G (2010) Expression, localization, and biochemical characterization of nicotinamide mononucleotide adenylyltransferase 2. J Biol Chem 285:40387-40396.

McCormick DB (1988) Niacin. In: Modern Nutrition in Health and Disease, 6th edition (Shils ME., Young VR, eds), pp370-375. Philadelphia: Lea & Febiger.

McCormick DB (1996) Co-enzymes, Biochemistry of. In: Encyclopedia of Molecular Biology and Molecular Medicine (Meyers RA, ed), pp396-406. Weinheim: VCH.

McCormick DB (1997) Co-enzymes, Biochemistry. In: Encyclopedia of Human Biology 2nd edition (Dulbecco R ed.-in-chief). p. 847-864 San Diego: Academic Press.

Mukherjee SK, Klaidman LK, Yasharel R, Adams JD (1997) Increased brain NAD prevents neuronal apoptosis in vivo. Eur J Pharmacol 330:27-34.

Oliver FJ, Menissier-de Murcia J, De Murcia G (1999) Poly(ADP-Ribose) polymerase in the cellular response to DNA damage, apoptosis, and disease. Am J Hum Genet 64:1282-1288.

Pacher P, Szabo C (2007) Role of poly(ADP-ribose) polymerase 1 (PARP-1) in cardiovascular Diseases: the therapeutic potentia of PARP inhibitors. Cardiovasc Drug Rev 25:235-260.

Pieper AA, Verma A, Zhang J, Snyder SH (1999) Poly(ADP-ribose polymerase, nitric oxide and cell death. Trends Pharmacol Sci 20:171-181.

Ruddick JP, Evans AK, Nutt DJ, Lightman SL, Rook GA, Lowry CA. (2006) Tryptophan metabolism in the central nervous system: medical implications. Expert Rev Mol Med 8:1-27.

Schapira AH, Mann VM, Cooper JM, Dexter D, Daniel SE, Jenner P, Clark JB, Marsden CD (1990) Anatomic and disease specificity of NADH CoQ 1 reductase (complex I) in Parkinson's disease. J Neurochem 5:2142-2145.

Sorci L, Cimadamore F, Scotti S, Petrelli R, Cappellacci L, Franchetti P, Orsomando G, Magni G (2007) Initial-rate kinetics of human NMN-adenylyltransferases: substrate and metal ion specificity, inhibition by products and multisubstrate analogues, and isozyme contributions to NAD^+ biosynthesis. Biochemistry 46:4912-4922.

Stone TW (2001) Endogenous neurotoxins from tryptophan. Toxicon 39:61-73.

Takahashi K, Pieper AA, Croul SE, Zhang J, Snyder SH, Greenberg JH (1999) Post-treatment with an inhibitor of poly(ADPribose) polymerase attenuates cerebral damage in focal ischemia. Brain Res 829:46-54.

Ting K, Brew B, Guillemin G (2009) Effect of quinolinic acid on human astrocytes morphology and functions: implications in Alzheimer's disease. J Neuroinflammation 6:1186-1136.

Torvik A (1976) Central chromatolysis and the axon reaction: A reappraisal. Neuropathol Appl Neurobiol 2:423-432.

Ungerstedt JS, Blomback M, Soderdtom T (2003) Nicotinamide is a potent inhibitor of proinflammatory cytokines. Clin Exp Immunol 131:48-52.

Vincent AM, Stevens MJ, Backus C, Mclean LL, Feldman EL (2005) Cell culture modeling to test therapies against hyperglycemia-mediated oxidative stress and injury. Antioxid Redox Signal 7:1494-1506.

Vu CO, Coyle DL, Jacobson EL, Jacobson MK (1997) Intracellular signaling by cylic ADP-Ribose in oxidative cellinjury. FASEB J 11:A1116 (Abstract).

Vu CQ, Coyle DL, Tai HH, Jacobson EL, Jacobson MK (1997) " Intramolecular ADP-ribose transfer reactions and calcium signalling," In ADP-Ribosylation in Animal Tissue: Structure, Function, and Biology of Mono-DPRibosyltransferases and Related Enzymes (F. Haag and F. Koch- Nolte, eds), pp381-388. Plenum Press, New York, NY, USA.

Wilson GL, Patton NJ, McCord JM (1984) Mechanisms of streptozotocin- and alloxan-induced damage in the rat Bcells. Diabetologia 27:587-591.

Yamada K, Nonaka K, Hanafusa T, Miyazaki A, Toyoshima H, Tarui S (1982) Preventative and therapeutic effects of large-dose nicotinamide injections on diabetes associated with insulitis-an observation in non-obese diabetic (NOD) mice. Diabetes 31:749-753.

Yan T, Feng Y, Zheng J, Ge X, Zhang Y, Wu D, Zhao J, Zhai Q (2010) Nmnat2 delays axon degeneration in superior cervical ganglia dependent on its NAD synthesis activity. Neurochem Int 56:101-106.

Yang J, Klaidman LK, Nalbandian A, Oliver J, Chang ML, Chan PH, Adams JD Jr (2002b) The effects of nicotinamide on energy metabolism following transient focal cerebral ischemia in Wistar rats. Neurosci Lett 333:91-94.

Zhai RG, Cao Y, Hiesinger PR, Zhou Y, Mehta SQ, Schulze KL, Verstreken P, Bellen HJ (2006) Drosophila NMNAT maintains neural integrity independent of its NAD synthesis activity. PLoS Biol 4:e416.

Zhang J, Pieper A, Snyder SH (1995) Poly(ADP-ribose) synthetase activation: an early indicator of neurotoxic DNA damage. J Neurochem 65:1411-1414.

Zhang J, Snyder SH (1992) Nitric oxide stimulates auto-ADPribosylaton of glyceraldehyde-3-phosphate dehydrogenase. Proc Natl Acad Sci U S A 89:9382-9385.

Zimmermann HM, Cohen LH, Gildea EF (1934) Pellagra in association with chronic alcoholism. Arch Neurol Psychiat (Chicago) 31:290-309.