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Nicotinamide as a Foundation for Treating Neurodegenerative Disease and Metabolic Disorders

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Abstract

Neurodegenerative disorders impact more than one billion individuals worldwide and are intimately tied to metabolic disease that can affect another nine hundred individuals throughput the globe. Nicotinamide is a critical agent that may offer fruitful prospects for neurodegenerative diseases and metabolic disorders, such as diabetes mellitus. Nicotinamide protects against multiple toxic environments that include reactive oxygen species exposure, anoxia, excitotoxicity, ethanol-induced neuronal injury, amyloid (Aß) toxicity, age-related vascular disease, mitochondrial dysfunction, insulin resistance, excess lactate production, and loss of glucose homeostasis with pancreatic β-cell dysfunction. However, nicotinamide offers cellular protection in a specific concentration range with dosing outside of this range leading to detrimental effects. The underlying biological pathways of nicotinamide that involve the silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1), the mechanistic target of rapamycin (mTOR), AMP activated protein kinase (AMPK), and mammalian forkhead transcription factors (FoxOs) may offer insight for the clinical translation of nicotinamide into a safe and efficacious therapy through the modulation of oxidative stress, apoptosis, and autophagy. Nicotinamide is a highly promising target for the development of innovative strategies for neurodegenerative disorders and metabolic disease, but the fruits of this foundation depend greatly on gaining further understanding of nicotinamide's complex biology.

Keywords

Alzheimer's disease; AMP activated protein kinase (AMPK); autophagy; apoptosis; dementia; diabetes mellitus; forkhead transcription factors; FoxO; mechanistic target of rapamycin (mTOR); oxidative stress; silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1); sirtuin; stem cells

1. Nicotinamide

Nicotinamide is the amide form of the vitamin B_3 (niacin). Nicotinamide is obtained in the body either as a dietary source and supplement, such as from animal sources or plants, or through synthesis in the body [1]. Nicotinic acid is the alternative form of the water-soluble vitamin B_3 [2]. The primary form of niacin in dietary plant sources is nicotinic

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acid that is rapidly absorbed through the gastrointestinal epithelium [3]. Nicotinamide is then obtained through the conversion of nicotinic acid in the liver or through the hydrolysis of the coenzyme ß-nicotinamide adenine dinucleotide (NAD^+). Once present in the body, nicotinamide is a precursor for the coenzyme NAD^+ [4, 5]. Nicotinamide also is required for the synthesis of nicotinamide adenine dinucleotide phosphate ($NADP^+$) [6]. Nicotinamide is changed to its mononucleotide form (NMN) with the enzyme nicotinic acid/nicotinamide adenylyltransferase. NMN is converted to the dinucleotides NAD^+ and $NAAD^+$. $NAAD^+$ yields NAD^+ through NAD^+ synthase [7]. NAD^+ also can be synthesized through nicotinamide riboside kinase that phosphorylates nicotinamide riboside to NMN [8, 9].

Nicotinamide through NAD^+ can be directly utilized by cells to synthesize NAD^+ [1, 5, 10–12]. Nicotinamide participates in energy metabolism through the tricarboxylic acid cycle by utilizing NAD^+ in the mitochondrial respiratory electron transport chain for the production of ATP, DNA synthesis, and DNA repair [13–15]. These cellular pathways are critical for energy metabolism and can impact normal physiology as well as disease processes [12, 16–19]. For example, lack of nicotinamide can lead to fatigue, loss of appetite, pigmented rashes of the skin, and oral ulcerations. Severe states of deficiency lead to pellagra that is characterized by cutaneous rashes, oral ulcerations, gastrointestinal difficulties, and cognitive disability [16, 20, 21]. Pellagra can occur as a result of conditions that lead to depressed nicotinamide levels or during the inability to absorb nicotinamide. The inability to absorb tryptophan that causes Hartnup's disease, isoniazid treatment, or carcinoid syndrome also can be associated with pellagra. Excessive alcohol consumption with poor dietary intake can result in severe nicotinamide loss and insufficient gastrointestinal absorption [22, 23].

2. Nicotinamide and Oxidative Stress

Nicotinamide can affect cellular survival and longevity through different pathways that involve oxidative stress, apoptosis, and autophagy [24]. Reactive oxygen species (ROS) are generated during oxidative stress [18, 25]. These include nitrogen based free radical species, such as nitric oxide and peroxynitrite, and oxygen derivatives involving superoxide free radicals, hydrogen peroxide, and singlet oxygen [26–28]. One source of ROS are mitochondria. Mitochondria yield adenosine triphosphate (ATP) through the oxidation of glucose, pyruvate, and NAD^+ that exist in the cytosol. In the tricarboxylic acid cycle, NAD^+ and flavin adenine dinucleotide (FAD) are reduced to NADH and $FADH_2$. The redox energy from NADH and $FADH_2$ is transferred to oxygen through the electron transport chain. This process facilitates protons to be transferred from respiratory complexes I, III, and IV in the inner membrane to the intermembrane space with a subsequent proton gradient that is formed across the inner membrane. Complex V (ATP synthase) then accumulates the energy from this gradient to produce ATP from adenosine diphosphate (ADP) and inorganic phosphate (P_i). With the aerobic production of ATP, the generation of ROS occurs [29–36].

Some studies suggest that ROS may be necessary for the promotion of extended lifespan [37]. This may require a careful balance in ROS generation that appears necessary for the generation of ROS to limit cell injury and extend lifespan. Moderate levels of ROS may be required for the tolerance against metabolic, mechanical, and oxidative stressors [38]. The

generation of brief periods of ROS during ischemia-reperfusion models may limit cellular injury [39, 40] through several different pathways such as those that involve the mechanistic target of rapamycin (mTOR) [29, 41–46] or Wnt signaling [47–49]. However, at increased levels, ROS through oxidative stress can result in mitochondrial and other organelle injury, DNA damage, protein misfolding, cell demise, and the promotion of aging [50–54].

Depletion of NAD^+ has been associated with aging. The maintenance of adequate NAD^+ stores has been linked to a reduction in the aging process and increased resistance to oxidative stress [19]. As a result, nicotinamide through NAD^+ generation may reduce ROS and prevent cellular senescence [1]. Pathways associated with nicotinamide can limit oxidative stress to increase life span [55], limit vascular disease [11, 20], alleviate mitochondrial stress [56, 57], ischemic injury [58], drug toxicity [59], and neurodegenerative disorders [60–62].

3. Nicotinamide, Apoptosis, and Autophagy

Apoptosis can ensue at elevated levels of ROS generation and involve mitochondrial dysfunction during oxidative stress [63–67]. Apoptosis has both an early and late phase [68, 69]. The early phase consists of phosphatidylserine (PS) asymmetry loss on the plasma membrane [70–72]. The later phase results in genomic DNA degradation [72, 73]. Apoptosis begins through a cascade of nuclease and protease activation that leads to caspase activation [35, 68, 74]. Mitochondrial dysfunction leads to the opening of the mitochondrial membrane permeability transition pore, release of cytochrome c, and apoptotic caspase activation [75–77]. Loss of cellular membrane PS asymmetry activates inflammatory cells to seek out cells with membrane asymmetry and remove them through engulfment [71, 78]. If this process can be prevented, then cells remain functional despite externalization of membrane PS residues [68, 72]. However, the destruction of cellular DNA is usually not considered to be a reversible process [68].

Apoptosis leads to cell death in multiple disease processes. Suppression of cellular apoptosis can increase cell survival in Alzheimer’s disease (AD) [79–82], epilepsy [79, 83, 84], retinal disease [85, 86], Parkinson’s disease (PD) [68, 81, 87], trauma [88], spinal cord injury [89, 90], and neuronal, renal, lung, and vascular cells [45, 91–93]. Apoptotic injury also can lead to long-term disability through progressive neuronal loss such as during subarachnoid hemorrhage [94, 95].

Nicotinamide can influence both phases of apoptotic cell death. Nicotinamide can prevent exposure of plasma membrane PS residues [70–72, 96–99] to prevent inflammatory cell activation [4, 24, 100–102]. Nicotinamide can limit cardiovascular injury by blocking membrane PS exposure in vascular cells [5, 101], since membrane PS residue externalization in vascular cells can lead to hypercoagulation states [103] and cellular inflammation [104, 105]. Nicotinamide can reverse a previously sustained insult. Post-treatments studies with nicotinamide that can follow apoptotic injury in “real-time” show that early cellular apoptotic injury can be reversed [5, 61, 100–102, 106].

Interestingly, it appears that a reduction in nicotinamide levels during nicotinamidase expression can sometimes lead to increased cellular survival and longevity [55, 62]. Nicotinamide can inhibit silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1) by intercepting an ADP-ribosyl-enzyme-acetyl peptide intermediate with the regeneration of NAD^+ (transglycosidation) [107]. Nicotinamidase expression prevents both apoptotic early PS membrane exposure and late DNA degradation. In addition, inhibition of SIRT1 activity either by pharmacological methods or siRNA gene silencing is detrimental to cell survival during oxidative stress and blocks nicotinamidase protection, further supporting that SIRT1 activity may be necessary for nicotinamidase protection during oxidative stress. It has been hypothesized that sirtuins also may prevent nicotinamide from assisting with DNA repair by altering the accessibility of DNA damaged sites for repair enzymes [108].

Other pathways of programmed cell death, such as autophagy, also may be involved during oxidative stress [12, 44, 109–114]. Autophagy can impair endothelial progenitor cells, and lead to mitochondrial oxidative and endoplasmic reticulum stress [63, 115]. However, autophagy also may be necessary for the removal of misfolded proteins and to eliminate non-functioning mitochondria [112] that has been shown to maintain β-cell function and prevent the onset of diabetes mellitus [116]. Autophagy recycles cytoplasmic organelles and components for tissue remodeling [68, 117] and can remove non-functional organelles [41, 111, 118]. Macroautophagy recycles organelles and sequesters cytoplasmic proteins into autophagosomes within cells. Autophagosomes subsequently combine with lysosomes to become degraded and begin a course for recycling [68]. Microautophagy is a process for lysosomal membrane invagination. Components of the cell cytoplasm are sequestered and digested. Chaperone-mediated autophagy is a process that depends upon cytosolic chaperones to move components of the cytoplasm across lysosomal membranes.

Autophagy also plays a significant role with several disease processes. Autophagy activation that can eliminate or sequester intracellular accumulations that lead to cell death may influence disease progression, such as in PD [79, 119–123], cognitive impairment and AD [68, 122, 124, 125], amyotrophic lateral sclerosis [126–128], Huntington's disease (HD) [68, 129], and traumatic brain injury [79, 130, 131].

Nicotinamide is linked to SIRT1 to oversee cellular function and autophagy [30, 132–138]. SIRT1 through the transfer of the acetyl residue from the acetyllysine residue of histones to the ADP-ribose moiety of NAD^+ can lead to the production of nicotinamide. SIRT1 is a histone deacetylase that can transfer acetyl groups from ε-N-acetyl lysine amino acids to the histones of deoxyribonucleic acid (DNA) to control transcription [68, 127, 135, 136, 138–148]. Physiological concentrations of nicotinamide noncompetitively inhibit SIRT1, suggesting that nicotinamide is a physiologically relevant regulator of SIRT1 enzymes [149]. As a result, in relation to cell longevity, it is the lower concentrations of nicotinamide that can function as an inhibitor of sirtuins that are necessary for the promotion of increased lifespan and cellular survival [55, 61, 62, 100, 101, 106, 150], at least in yeast and metazoans [10, 151, 152].

Nicotinamide and SIRT1 function through autophagic pathways that necessitate a tight oversight of SIRT1 activity [69, 76, 79, 111, 112, 153]. Nicotinamide can promote the delayed induction of autophagy and subsequently decreased survival in cancer cells [154]. During nicotinamide administration, mitochondrial autophagy (mitophagy) can lead to an increased NAD^+/NADH ratio [18, 155, 156]. Chronic administration of nicotinamide can lead to skeletal muscle lipotoxicity and glucose intolerance during autophagy activation [156]. As an inhibitor of SIRT1, nicotinamide through autophagy can limit cancer cell growth and in combination with chemotherapeutic agents lead to apoptotic cell death [154, 157–160]. Through SIRT1 inhibition, nicotinamide may exert anti-inflammatory properties, promote SIRT activity as a result of the cellular conversion of nicotinamide to NAD^+, and affect the transcriptional regulation of inflammatory genes [161]. As a result, nicotinamide has been shown to be cytoprotective through SIRT1 to prevent palmitate-induced hepatotoxicity through SIRT1-dependent induction of autophagy [162].

Nicotinamide maintains a significant relationship with the mechanistic target of rapamycin (mTOR) pathways and autophagy to influence cellular survival [30, 43, 45, 46, 52, 93, 117, 163–166]. mTOR, a 289-kDa serine/threonine protein kinase, is a vital pathway for nicotinamide to control cellular metabolism [12, 30, 41, 46, 52, 165, 167–169]. mTOR is the principal component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) [170–172]. mTORC1 and mTORC2 are further divided into subcomponents. mTORC1 consists of Raptor, the proline rich Akt substrate 40 kDa (PRAS40), Deptor (DEP domain-containing mTOR interacting protein), and mammalian lethal with Sec13 protein 8, termed mLST8 (mLST8) [173]. mTORC1 activity can be controlled through multiple pathways, such as through PRAS40, by preventing the association of p70 ribosomal S6 kinase (p70S6K) and the eukaryotic initiation factor 4E (eIF4E)-binding protein 1 (4EBP1) with Raptor [174, 175]. mTORC2 consists of Rictor, mLST8, Deptor, the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1) [174, 176]. mTORC2 controls cytoskeleton remodeling through PKCα and cell migration through the Rac guanine nucleotide exchange factors P-Rex1 and P-Rex2 and through Rho signaling [177].

Nicotinamide can lead to the activation of autophagy and inhibit mTOR. During the enhanced activation of autophagy, nicotinamide can limit ß-amyloid (Aß) toxicity and improve cognition [2, 178], reduce metabolic dysfunction through the maintenance of mitochondria [12, 16, 56, 179], maintain metabolic homeostasis [31, 180, 181], block neuronal ischemic injury [182] and endothelial injury [92], and increase survival of hypoxic myocardial cells [183]. Yet, limits in autophagy activation may be necessary. Interneuron progenitor growth in the brain requires mTOR activity with the inhibition of autophagy [184]. Autophagy activation also can lead to injury of endothelial progenitor cells, result in mitochondrial oxidative stress, and block new blood vessel formation during elevated glucose exposure [185]. Inhibition of autophagy can limit infarct size and rescue cerebral neurons during stroke and oxidative stress [186].

4. Nicotinamide and Neurodegenerative Disease

Acute and chronic neurodegenerative diseases affect a large number of individuals throughout the globe [119, 187–190]. Neurodegenerative disorders can impact more than one billion individuals. This number represents approximately fifteen percent of the world's population. Approximately seven million die each year from neurodegenerative disorders [41]. Nervous system diseases comprise over six hundred disorders that can progressively lead to death and disability [119, 190, 191]. Furthermore, neurodegenerative disorders are expected to increase in prevalence throughout the globe. For example, sporadic cases of AD are increasing in the world with dementia now ranked as the 7th leading cause of death [190]. Dementia occurs in all countries throughout the world at a significant financial burden [192]. Greater than five million people suffer with cognitive disorders in the US and most of these cases, at least sixty percent, are from AD [41]. Currently, fifty million people in the world, or five percent of the global population, have dementia. By 2030, dementia will affect eighty-two million individuals, and by 2050, one hundred fifty-two million individuals will suffer with dementia. In addition, caring for dementia is considered a significant cost factor with more than $800 billion USD a year required for dementia care at the present time [192].

In addition, metabolic disorders also can lead to neurodegeneration and affect all cellular systems [168]. In the peripheral nervous system, at least seventy percent of individuals with diabetes mellitus (DM) can develop diabetic peripheral neuropathy. DM can lead to autonomic neuropathy [193] and peripheral nerve disease [42, 194–197]. In the central nervous system, DM can result in insulin resistance and loss of cognition [41, 124, 147, 168, 190, 198–200]. DM can affect several cellular pathways that lead to cognitive loss and dementia [138, 201–206]. DM also has been linked to mental illness [207, 208], cerebral vascular injury [63, 138, 209–212], impairment of microglial activity [124, 190, 198, 199], and impairment of stem cell development [30, 138, 201–205, 213]. DM leads to vascular endothelial dysfunction [138, 147, 214–216], cardiovascular disease [49, 215, 217–224], retinal disease [48, 225, 226], and immune and infectious disorders [52, 137, 227–231].

Nicotinamide provides cellular protection for both neuronal [61, 232, 233] and vascular cells [4, 5, 10, 11]. In neuronal cells, nicotinamide protects against free radical injury [102], anoxia [106], excitotoxicity [234], homocysteine toxicity [235], ethanol-induced neuronal injury [23], oxygen-glucose deprivation [61, 236], and Aß toxicity [138, 237]. Nicotinamide can protect against ultraviolet light in endothelial corneal cells [92], age-related vascular dysfunction [20], endothelial mitochondrial dysfunction [101], and vascular mimicry during cancer [238].

Nicotinamide prevents oxidant-induced apoptotic neuronal injury in a specific concentration range [4]. As a result, limited concentrations of nicotinamide and NAD^+ are critical for neuronal survival [11, 156, 239]. Administration of nicotinamide in a range of 5.0 – 25.0 mmol/L can significantly protect neurons during oxidative stress injuries and apoptosis. This concentration range is similar to other injury paradigms in both animal models [240] and in cell culture models [5, 101, 102]. Nicotinamide improves cognitive function and neuronal cell survival following cortical trauma [241], limits axonal degeneration [242], prevents

spinal cord injury [243, 244], blocks neuronal death during toxic agent exposure [245] and lessens disability in models of PD [246–248].

Nicotinamide has been shown to also utilize pathways of mammalian forkead transcription factors to block apoptotic neuronal cell death [1, 10, 166, 249, 250]. Mammalian forkhead transcription factors (FoxOs) can affect multiple neurodegenerative disorders [69, 127, 251, 252]. Since the discovery of the *Drosophila melanogaster* gene *forkhead*, over one hundred forkhead genes and nineteen human subgroups have been identified that range from *FOXA* to *FOXS* [127, 201, 253]. The mammalian FOXO proteins of the O class have important relevance to neurodegenerative disorders and include the members FOXO1, FOXO3, FOXO4, and FOXO6 [109, 127, 143, 146, 201, 252, 254–261]. Forkhead proteins are also known as forkhead in rhabdomyosarcoma (FKHR) (FOXO1), FKHRL1 (forkhead in rhabdomyosarcoma like protein 1) (FOXO3a), the *Drosophila* gene *forkhead* (*fkh*), Forkhead RElated ACtivator (FREAC)-1 and -2, and the acute leukemia fusion gene located in chromosome X (*AFX*) (*FOXO4*) [127]. FoxO proteins are transcription factors that bind to deoxyribonucleic acid (DNA) through the FoxO-recognized element in the C-terminal basic region of the forkhead DNA binding domain [69]. Post-translational changes include FoxO protein phosphorylation or acetylation change the binding of the C-terminal basic region to DNA to prevent transcriptional activity and block FoxO activity [262]. Additional factors may affect forkhead binding to DNA. These include N-terminal region of the recognition helix variations, electrostatic distribution changes, and sequestering FoxO proteins in the nucleus of cells [263].

Nicotinamide has been shown to inhibit FoxO protein activity [61] and is protective through two separate mechanisms of post-translational modification of FoxO3a [201, 253, 257]. Nicotinamide not only can maintain phosphorylation of FoxO3a and inhibit its activity to potentially block caspase 3 activity [61], but also can reduce caspase activity and preserve the integrity of the FoxO3a protein to block FoxO3a proteolysis. During oxidative stress, an initial inhibitory phosphorylation of FoxO3a at the regulatory phosphorylation sites (Thr^{32} and Ser^{253}) occurs [61, 264]. Loss of phosphorylated FoxO3a integrity can subsequently ensue by caspase activity that can increase the vulnerability of neurons to apoptotic injury [61] since FoxO3a proteolysis results in pro-apoptotic amino-terminal (Nt) fragments that can become biologically active and lead to cellular injury [265]. Nicotinamide, through the phosphorylation of FoxO3a at regulatory sites that possess high affinity for protein kinase B (Akt) can prevent apoptotic cell injury [61]. In addition, decrease of caspase 3 activity by nicotinamide appears to be tied to a unique regulatory mechanism that blocks the proteolytic degradation of phosphorylated FoxO3a by caspase 3. Since FoxO3a has been shown to be a substrate for caspase 3-like proteases at the consensus sequence $DELD^{304}A$ [265], inhibition of caspase 3 activity prevents the destruction of phosphorylated FoxO3a during oxidative stress [61], suggesting that nicotinamide maintains a regulatory loop through the modulation of caspase 3 and the preservation of phosphorylated FoxO3a integrity.

5. Nicotinamide and Metabolic Disease

Metabolic disease that includes DM affects a broad spectrum of the world's population [41, 113, 168, 190, 259, 266–270]. Approximately five hundred million individuals have

DM [26, 138, 271–274]. An additional four hundred million individuals either suffer from metabolic disease or are at risk for developing DM [63, 221, 274, 275]. The number of individuals with DM is expected to rise to seven hundred million individuals by the year 2045 [274]. At least thirty-five million individuals are diagnosed with DM [268]. Seven million individuals over the age of eighteen remain undiagnosed with DM and almost thirty-five percent of adults in the US had prediabetes based on their fasting glucose and hemoglobin A1c (HbA_{1c}) levels in the year 2018 [276]. Obesity and excess body fat can increase the risk for developing DM in young individuals [57] and can affect stem cell proliferation, aging, inflammation, oxidative stress injury, and mitochondrial function [249, 277–283]. The care for patients with DM equals approximately $760 billion USD and consumes more than seventeen percent of the Gross Domestic Product in the US [274, 284].

Nicotinamide has a vital role during metabolic dysfunction and DM [1, 5, 10, 12, 57, 179, 285]. Nicotinamide reduces insulin resistance and glucose release with additional pathways to prevent the development and progression of DM [286–288]. Nicotinamide (niacin) blocks skeletal muscle atrophy during DM [289] and reduces brain inflammation during DM [290]. In animal models, nicotinamide can maintain normal fasting blood glucose with streptozotocin-induced DM [291, 292] and prevent oxidative stress pathways that lead to cell death and apoptosis [22, 100, 101, 293, 294]. Nicotinamide also can improve glucose utilization, block excess lactate production, and enhance electrophysiologic capacity in ischemic animal models [295]. Oral nicotinamide administration at a dose of 1200mg/m^2/day has been shown to protect pancreatic β-cell function and limits clinical disease in islet-cell antibody-positive first-degree relatives of type-1 DM [296]. Patients with recent onset type-1 DM receiving nicotinamide (25mg/kg) in combination with intensive insulin therapy for up to two years demonstrate significantly reduce HbA_{1c} levels [297]. Yet, prolonged exposure of nicotinamide has been reported to result in impaired pancreatic β-cell function and cell growth [298, 299]. Nicotinamide also may block cytochromes P450 and hepatic metabolism [300]. As a result, the duration of nicotinamide administration may influence efficacy of treatment since long-term administration also has been reported to support glucose intolerance in some animal models [156].

Nicotinamide is reliant upon mTOR pathways to offer cellular protection during metabolic disease and DM. Nicotinamide has a fine control over cellular metabolism through mTOR pathways such as p70S6K, 4EBP1, and AMP activated protein kinase (AMPK). Both p70S6K and 4EBP1 in the mTOR pathway are required by nicotinamide to protect against radiation-induced apoptosis [301]. p70S6K and 4EBP1 activation also can enhance insulin secretion in pancreatic β-cells and increase resistance to β-cell streptozotocin toxicity and obesity in mice [302]. With nicotinamide, mTOR activity plays a significant role to maintain metabolic homeostasis. During the loss of mTOR activity, reduced β-cell function, insulin resistance, and decreased insulin secretion can result and lead to DM progression [303]. Decreased activity of mTOR has been shown to increase mortality in a mouse model of DM [304]. Translocation of glucose transporters to the plasma membrane in skeletal muscle can be blocked in the absence of mTOR activity [305].

Yet as previously described, nicotinamide can lead to the activation of autophagy with mTOR inhibition to reduce metabolic dysfunction through the maintenance of mitochondria

[12, 16, 56, 179] and also maintain metabolic homeostasis [31, 180, 181]. These observations suggest that a careful balance of mTOR activity is required for the efficacy of nicotinamide. As an example, if mTOR activity becomes elevated, mTOR and p70S6K can lead to glucose intolerance by inhibiting the insulin receptor substrate 1 (IRS-1) [306]. At times, mTOR inhibition may be required to reduce stroke infarct size during models of DM [307], block cardiac hypertrophy [308], protect vascular cells from oxidative stress [45], prevent retinal degeneration [133], and maintain a balance between pancreatic β-cell proliferation and cell size [309].

Nicotinamide employs AMPK to oversee cellular metabolism [190, 219, 310, 311]. AMPK prevents mTORC1 activity through the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex that blocks mTORC1 [145, 312]. Nicotinamide can reduce intracellular mitochondrial stress in hypoxic cardiomyocytes through the activation of AMPK [56]. Pathways of nicotinamide also may be necessary with AMPK to allow skeletal muscle cells to sense and react to nutrient availability [313]. Nicotinamide in conjunction with AMPK recently has been shown to decrease metabolic abnormalities in polycystic ovary syndrome [314]. AMPK activation during metabolic disease can promote insulin sensitivity, fatty acid oxidation, and mitochondrial biogenesis that results in the generation of ATP and serves to limit oxidative stress [12, 41]. In line with the endothelial protective properties of nicotinamide that can rely potentially upon AMPK [61, 101, 315], AMPK can limit insulin resistance [316] and protect endothelial progenitor cells during periods of hyperglycemia [219]. AMPK activation also can strengthen memory retention in models of AD and DM [310], may assist with Aß elimination in the brain [317], foster tau clearance [318], and reduce chronic inflammation in the nervous system [79, 144, 312].

With AMPK signaling, nicotinamide may not always yield cellular protection during metabolic disorders. AMPK and autophagy pathways may require oversight during metabolic disease and DM [52, 113, 124, 168, 198, 229, 319]. For example, increased activity of autophagy has been shown to result in the loss of cardiac and liver tissue in diabetic rats [320]. Toxic advanced glycation end products (AGEs) during metabolic disorders can yield autophagy activation and vascular smooth muscle proliferation that may lead to in atherosclerosis [321] as well as cardiomyopathy [322]. During high glucose exposure, autophagy can impair endothelial progenitor cells, lead to mitochondrial oxidative stress [115], and prevent angiogenesis [185].

6. Conclusion and Future Perspectives

Neurodegenerative disorders impact more than one billion individuals in the world and at least seven million individuals die each year from neurodegenerative disorders. In addition, metabolic disorders lead to neurodegenerative diseases and impact over nine hundred individuals throughput the globe when cone considers those with active disease and individuals presently at risk for developing metabolic disease. Nicotinamide plays a critical role for the treatment of both neurodegenerative diseases and metabolic disorders, such as DM. In neuronal and vascular systems, nicotinamide protects against oxidative stress, anoxia, excitotoxicity, ethanol-induced neuronal injury, Aß toxicity, ultraviolet light, age-related vascular disease, mitochondrial dysfunction, and vascular mimicry during cancer.

In regard to metabolic disorders, nicotinamide reduces insulin resistance, blocks skeletal muscle atrophy during DM, maintains normal fasting blood glucose, improves glucose utilization, blocks excess lactate production, and protects pancreatic β-cell function.

Nicotinamide intimately oversees pathways tied to oxidative stress, apoptosis, and autophagy (Fig. 1). Through nicotinamide, the maintenance of adequate NAD^+ stores has been linked to reduction in the aging process and increased resistance to oxidative stress. Nicotinamide can block apoptotic cell death during the early phase with membrane PS asymmetry and the later phase with genomic DNA degradation. Nicotinamide also relies upon pathways of autophagy such as to reduce metabolic dysfunction through the maintenance of mitochondrial function and to maintain metabolic homeostasis. Yet, nicotinamide has been shown to offer cellular protection in a specific concentration range with dosing outside of this range or prolonged administration leading to detrimental effects. The underlying pathways of nicotinamide that involve SIRT1, mTOR, FoxOs, and AMPK may offer insight into these observations for the efficacy and safety of nicotinamide. These pathways require a fine balance in control since each has the potential to foster cellular demise, mitochondrial oxidative stress, and loss of metabolic homeostasis. Nicotinamide presents significant promise for the development of innovative treatments for neurodegenerative disorders and metabolic disease, but the success of such programs rests on gaining further understanding of the complex relationship nicotinamide holds with the pathways of oxidative stress, apoptosis, autophagy, SIRT1, mTOR, FoxOs, and AMPK.

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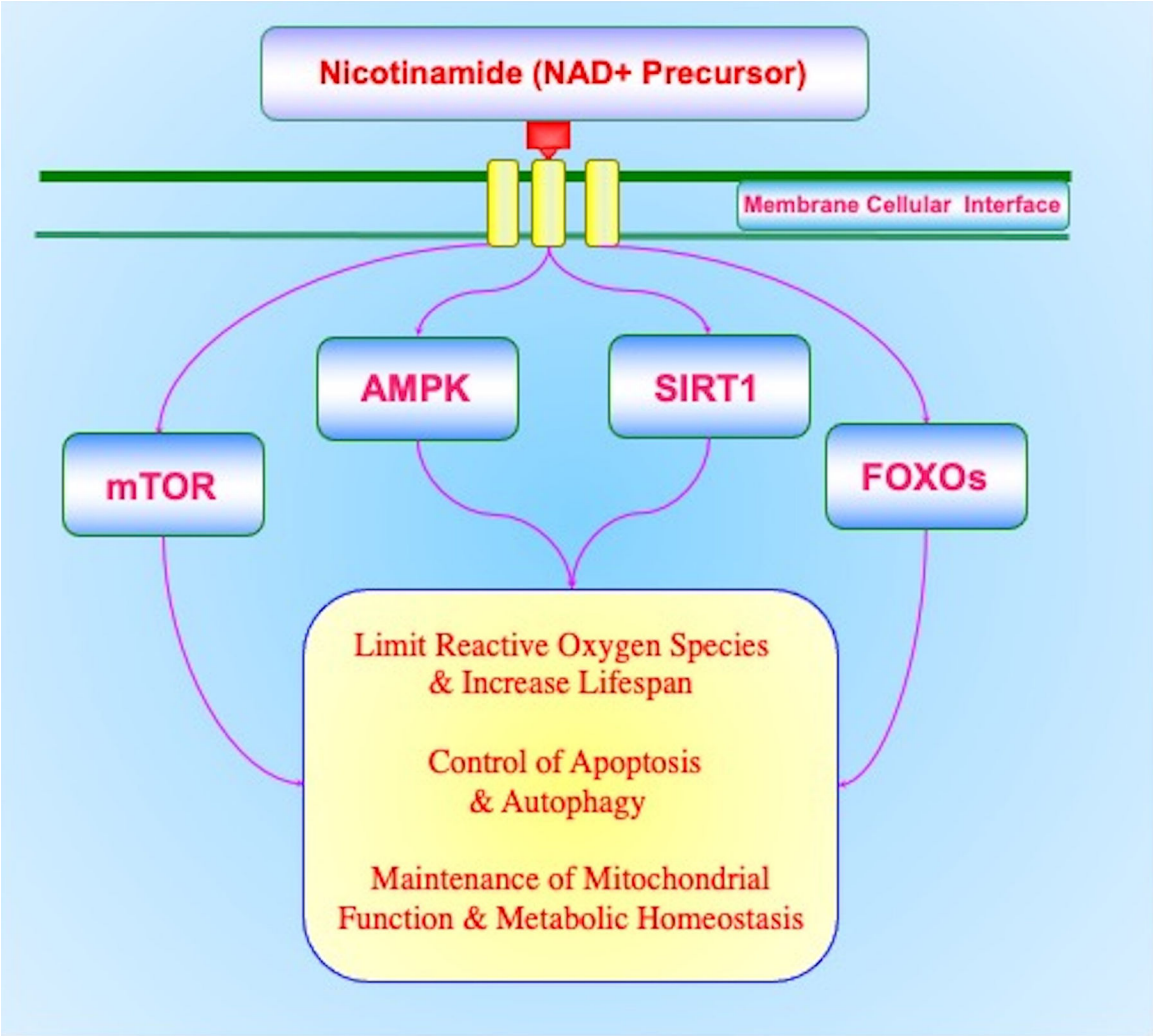

Figure 1: Nicotinamide Pathways for Neurodegenerative Disorders and Metabolic Disease.

Nicotinamide is vital for the development of treatment strategies for neurodegenerative diseases and metabolic disorders. Nicotinamide relies upon a complex relationship with the silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1), the mechanistic target of rapamycin (mTOR), AMP activated protein kinase (AMPK), mammalian forkead transcription factors (FoxOs), oxidative stress (reactive oxygen species), apoptosis, and autophagy. Each of these pathways for nicotinamide requires a fine balance in control to maximize clinical efficacy and limit unwanted effects such as cellular demise, mitochondrial oxidative stress, and loss of metabolic homeostasis.