

The Use of Nicotinamide as a Treatment for Experimental Traumatic Brain Injury and Stroke: A Review and Evaluation

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Abstract

Traumatic Brain Injury (TBI) and stroke are leading causes of neurological dysfunction and are major health concerns worldwide. Much research has been conducted on the processes at work in TBI and stroke; however, to date no pharmaceutical treatments have been shown to be effective in treating human clinical TBI and only one drug has been approved for human stroke treatment. Thus, many laboratories have begun to investigate organic compounds such as vitamins and other nutrients. Specifically, nicotinamide (vitamin B₃) has been studied in the laboratory to assess its effectiveness as a treatment following TBI or stroke. This review evaluates the experimental evidence for the use of nicotinamide to treat brain injury. Based on the evidence from animal models, there is considerable potential for the use of nicotinamide to treat TBI and stroke. However there are still some factors that need to be further investigated before considering clinical trials.

Keywords: TBI; Stroke; Therapy; Recovery of function; Neuroprotection; B-Vitamin

Introduction

Traumatic brain injury (TBI) and stroke are leading health issues for industrialized countries around the world. In the United States, over 1.7 million people suffer from a TBI each year. From these injuries, 52,000 people die and 275,000 become hospitalized [1]. Sadly, these statistics only reflect data on individuals that seek hospital treatment. They do not include TBIs suffered in military situations, estimated at 180,000 soldiers who survived injuries from 2000-2010 [2] or those receiving mild TBIs who do not seek medical treatment, estimated at more than 200,000 per year [3]. Worldwide estimates for TBI place the number of brain injuries at approximately 10 million annually [4]. In the United States, the incidence rate for stroke is approximately 795,000 annually resulting in nearly 140,000 deaths [5,6]. To date, there is no approved pharmaceutical therapy for the treatment of TBI in humans and only one available for the treatment of human stroke [7]. This has generated a growing need to identify compounds that can be effective in the treatment of brain injury. To this end, nicotinamide (NAM; niacinamide; vitamin B₃), has been extensively explored in animal models of TBI and stroke. NAM is an essential nutrient that participates in a number of cellular functions and has been identified as a cytoprotectant [8]. This review will examine the potential benefit of NAM therapy in the treatment of TBI and stroke by examining the evidence from models of experimental brain injury, identifying neuroprotective mechanisms and evaluating its therapeutic potential.

An ischemic stroke consists of two primary types of damage: damage due to ischemia and damage as a result of reperfusion of the tissue [9]. A TBI is induced as a result of mechanical impact, rotational forces, concussive diffuse blows or some combination of these [10]. While the risk factors for TBI and stroke are very different, they share many similarities with respect to the secondary cascade of injury that follows them. The secondary cascade is a complex multi-modal series of events which are strongly tied to the initial disruption in energy metabolism induced by either forces applied or a lack of blood flow to a given brain region. As a result of this, several pathological processes such as excitotoxicity, apoptosis, edema, increases in free radicals and immune responses occur [11]. Excitotoxicity occurs when a neuron is no longer able to maintain its resting potential as a result of impairment of the sodium-potassium pump in combination with

large-scale increases in extracellular excitatory neurotransmitters such as glutamate [12,13]. This results in the neuron firing repeatedly, thus accumulating fatal levels of sodium and calcium [14,15]. Several other neurotoxic processes occur both concurrently and as a result of excitotoxicity. Edema causes a swelling in cells as a result of imbalances in interstitial osmolarity and can contribute to intracranial pressure and apoptosis after injury [11,16,17]. Apoptosis, or programmed cell death, is primarily initiated by internal genetic cascades that occur as a result of several of the factors above and is characterized by an energy-intensive process in which the cell is broken down into constituent parts [18-21]. In addition to these processes, large-scale increases in free radical production occur, which have been shown to contribute to detrimental outcome and are major risk factors for other neurological disorders such as Alzheimer's disease, some cancers and recurrent strokes [22-24]. As a result of cell death and signals from dying cells, inflammatory responses are also initiated. While these may be beneficial initially, they have been shown to contribute to long-term detrimental outcomes following TBI and stroke [25-27].

Though there is a widely established literature on the physiological processes that occur in the secondary injury phase of TBI and stroke, there have been relatively few treatments approved for use in human populations. In the field of TBI, several promising drugs and therapies have been tested, but currently none have passed clinical trials [28-30]. The stroke field is fairly similar in that many therapies that have been tested in clinical populations have failed, with one major exception: tissue plasminogen activator (TPA). TPA is a protein involved in the

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breakdown of blood clots and has been approved for therapeutic use in stroke patients up to three hours after the incident [7]. Use of this drug has helped improve the outcome for many stroke patients and reduced the mortality rate. However, the limit of a three hour window can be troublesome for those that have strokes overnight or do not become immediately symptomatic. Thus, there is a strong need for the development of additional effective therapies to treat both stroke and TBI.

To address the need for treatments, researchers working in preclinical models of TBI and stroke have begun to examine the use of vitamins and other nutrients as pharmacotherapies for injury. These include essential nutrients like NAM, riboflavin, magnesium and vitamin-E. Vita-nutrients have been used as treatments in models of neural dysfunction, specifically in the treatment of stroke [31-33] and TBI [34-36]. In particular, NAM, an essential water-soluble nutrient, has shown considerable beneficial effects in models of stroke and TBI [31,35]. This review will focus on the effects that NAM administration has had on recovery of function in models of experimental stroke and TBI, the mechanisms by which these actions occur and an evaluation of the therapeutic potential of NAM as a treatment for brain injury.

Effects of Nicotinamide on Experimental Brain Injury

Nicotinamide (niacinamide; NAM; vitamin B₃) is the amide form of nicotinic acid (niacin) and is currently used in the treatment of pellagra, a vitamin deficiency [32]. It has been widely studied in cellular biology for its role as a precursor to nicotinamide adenine dinucleotide (NAD⁺). It has also been identified as a neuroprotective agent and its abilities have been extensively reviewed (see below for an overview) [8,37,38]. NAM administration has been shown to be

beneficial for a range of conditions and disorders. It has been shown to increase growth factors in a mouse model of Huntington's disease [39], reduce excitotoxicity *in vitro* [40,41], prevent cell death from oxidative damage both *in vitro* [42] and *in vivo* [43,44] and improve behavioral and histopathological outcomes following experimental TBI and stroke [31,35,45-53].

The potential for nicotinamide as a therapeutic agent for disorders such as stroke and TBI was first recognized when it was shown to be successful at reducing damage seen in models of oxidative stress [43,44,54] in addition to preventing damage associated with neurotoxic lesions [55]. These early studies established an effective dose of NAM at 500 mg/kg. Several other studies have evaluated the dosing parameters of NAM which are necessary to facilitate behavioral recovery in rodents following stroke and TBI. A study in 2002 showed the ED50 for NAM following MCAO in the rat to be 239 mg/kg, but suggested that optimal results would be observed at a dose of 500 mg/kg [53]. However, using the same model, some improvements in infarct size and increases in NAD⁺ levels were found at a dose as low as 125 mg/kg [56]. Whether the tissue sparing at this dose would translate into behavioral improvements in a stroke model remains to be seen. In a global ischemia stroke model, 500 mg/kg was suggested to be the optimal dose [52]. Early studies of NAM in TBI found the same 500 mg/kg dose of NAM identified in the stroke literature to be effective [35,45,46] and subsequent studies began to investigate whether a much lower dose would obtain similar results. The results from these studies indicated that a 50 mg/kg dose also resulted in strong behavioral and histological neuroprotective effects following TBI [47,49]. Other studies in TBI have made direct comparisons between the 50 and 500 mg/kg dose of NAM and found

Study	Injury Model	Dose	Type of Study	Beneficial Effects on	Null Effects on
Hoane et al. (2003) [35]	CCI Bilateral Frontal	500 mg/kg	Behavioral Histological	BTART, MWM, Lesion size, Astrocyte response	Forelimb reaching
Hoane et al. (2006) [46]	CCI Bilateral Frontal	500 mg/kg	Histological	Apoptosis, Edema	
Hoane et al. (2006) [45]	CCI Unilateral Sensorimotor	500 mg/kg	Histological	Lesion size, BBB compromise, Apoptosis	
Hoane et al. (2006) [48]	FPI Unilateral Hippocampal	50 mg/kg 500 mg/kg	Behavioral Histological Dose-response	BTART, Vibrissae reflex, Tapered beam (500>50 mg dose), MWM (500 mg dose), Serum NAM (500>50 mg dose), Lesion size, Astrocyte response (500 mg dose)	MWM (50 mg dose), Astrocyte response (50 mg dose)
Hoane et al. (2008) [47]	CCI Bilateral Frontal	50 mg/kg @15 min, 4 h or 8 h	Behavioral Treatment window	BTART, Vibrissae reflex, Serum NAM, MWM (15 min & 4 h), Lesion size (15 min & 4 h)	MWM (8 h), Lesion size (8 h)
Hoane et al. (2008) [49]	CCI Unilateral Sensorimotor	50 mg/kg @ 4 h, 8 h or 24 h	Behavioral Treatment window	BTART, Locomotor placing, Vibrissae reflex (4 h & 8 h), Forelimb asymmetry (4 h & 8 h), Lesion size (4 h & 8 h)	Vibrissae reflex (24 h), Forelimb placing (24 h)
Holland et al. (2008) [57]	FPI Unilateral Hippocampal	50 mg/kg 500 mg/kg	Histological Dose-response	Lesion size, Astrocyte response, Apoptosis	
Quigley et al. (2009) [63]	CCI Unilateral Sensorimotor	500 mg/kg	Behavioral Drug comparison	Tapered beam, Locomotor placing, MWM	Forelimb reaching, Lesion size
Goffus et al. (2010) [59]	CCI Unilateral Sensorimotor	~50 mg/kg	Behavioral Novel dose Novel route of administration	BTART, Locomotor placing, Forelimb asymmetry, Serum NAM, Lesion size	Serum NAD ⁺
Swan et al. (2011) [64]	CCI Unilateral Sensorimotor	50 mg/kg 500 mg/kg	Behavioral Histological Dose-response Aged model	Edema	Tapered beam, MWM, Lesion size, BBB compromise, Astrocyte response
Vonder Haar et al. (2011) [50]	CCI Bilateral Frontal	~150 mg/kg	Behavioral Novel dose	BTART, Locomotor placing, MWM, Serum NAM, Lesion size	
Peterson et al. (2012) [58]	CCI Unilateral Sensorimotor	~150 mg/kg	Behavioral Drug comparison	MWM, Lesion size, Serum NAM	

Table 1: This table provides a brief outline of the TBI studies reviewed in this article, highlighting where the beneficial effects were found from NAM administration.

Study	Injury Model	Dose	Type of Study	Beneficial Effects on	Null Effects on
Mokudai et al. (2000) [33]	Focal Ischemia MCAO	500 mg/kg	Behavioral	Sensory neurological score, Motor neurological score, Infarct volume, Weight	
Ayoub and Maynard (2001) [60]	Focal Ischemia MCAO	500 mg/kg	Behavioral Treatment window	Sensory neurological score, Motor neurological score, Infarct volume	
Yang et al. (2002) [53]	Focal Ischemia MCAO	31.25 to 1000 mg/kg	Behavioral Dose-response Treatment window	Sensory neurological score, Motor neurological score, Infarct volume, Apoptosis	
Yang et al. (2002) [62]	Focal Ischemia MCAO	500 mg/kg	Cellular metabolism Polytherapy	NAD ⁺ levels, ATP levels, PARP activity	
Chang et al. (2002) [51]	Focal Ischemia MCAO	500 mg/kg	Polytherapy	Lesion size (polytherapy), DNA fragmentation	Infarct size (NAM alone)
Sadanaga-Akiyoshi et al. (2003) [56]	Focal Ischemia MCAO	125 mg/kg 250 mg/kg	Dose-response Cellular metabolism	CBF (250 mg/kg), infarct size, NAD ⁺ levels (penumbra)	CBF (125 mg/kg), NAD ⁺ levels (ischemic core)
Klaidman et al. (2003) [31]	Global Ischemia Carotid Occlusion	500 mg/kg	Pretreatment Cellular metabolism NAM Mechanism	ATP levels, NAD ⁺ levels, Mitochondrial metabolism	
Feng et al. (2006) [52]	Global Ischemia Hypoxia	250 mg/kg 500 mg/kg	Behavioral Dose-response Molecular quantification	Locomotor coordination, Lipid peroxidation, Lesion size (500 mg/kg), Apoptosis	Lesion size (250 mg/kg)

Table 2: This table provides a brief outline of the stroke studies reviewed in this article, highlighting where the beneficial effects were found from NAM administration.

that both doses provide acute neuroprotection [57]; however while the low dose is sufficient for improvement on most behavior, cognitive improvements may require somewhat higher doses [48]. More recent work has used recent pharmacological data collected in our lab to attempt to reach a therapeutic steady-state of approximately 150 mg/kg/day of NAM via subcutaneous pumps [50,58]. These pumps deliver a continuous amount of NAM via osmotic pressure and have shown considerable success in both bilateral frontal and unilateral sensorimotor injury models of TBI [50,58,59]. Tables 1 and 2 for a summary and comparison.

Additionally, several studies have examined the time-table for NAM administration after injury. Studies in the stroke field have been able to see improvements on infarct volume and behavioral measures with NAM administered as late as six hours after reperfusion [53,60]. After a bilateral frontal TBI, NAM administered as late as four hours after injury showed behavioral and histological sparing [47], while a second study that same year showed that NAM could induce sparing when administered as late as eight hours following a unilateral TBI [49]. Tables 1 and 2 for a summary and comparison.

Based on the results from previous studies of oxidative damage, NAM was tested in stroke models of both global and focal ischemia. Global models of ischemia result in widespread damage and disruptions in cellular metabolism that cause large-scale behavioral impairments and death [61]. In models of global ischemia, NAM treatment was shown to increase ATP levels, NAD⁺ levels and mitochondrial metabolism as well as reduce markers for apoptosis, lipid peroxidation and locomotor impairments [31,52]. In focal models of ischemia, which result in regionalized disruptions in cell metabolism and targeted behavioral impairments [9], NAM has also been shown to be effective. In the middle cerebral artery occlusion (MCAO) model, NAM has been shown to increase levels of ATP and NAD⁺ as well as reduce PARP activation and DNA fragmentation [31,51,62]. It also improved performance on measures of both sensory and motor behaviors and can even contribute to weight gain and maintenance [33,53,60]. Even at a lower dose, it can help to increase cerebral blood flow (CBF) [56]. Table 2 for a summary and comparison.

Following experimental TBI, NAM treatment, in a range of doses, has been shown to be effective on behavioral and histological outcomes,

in both controlled cortical impact (CCI) and fluid percussion injury (FPI) models [46-48]. This effectiveness has been shown across multiple injury locations, helping to promote recovery from a variety of behavioral deficits. In frontal injuries, which result in severe cognitive deficits, motor planning issues and somatosensory neglect, NAM treatment has been shown to improve function on the locomotor placing task (motor planning/coordination), the bilateral tactile adhesive removal task (BTART; somatosensory/attention), Morris water maze (MWM; spatial learning) and vibrissae-forelimb placing test (somatosensory reflex) [35,47,50]. In unilateral sensorimotor injuries, which result in mild to moderate cognitive deficits, motor dysfunction and somatosensory impairment, NAM administration has been shown to improve function on the BTART, beam walk tasks (motor coordination), locomotor placing task, forelimb asymmetry test (limb reliance), vibrissae-forelimb placing test and MWM [47-49,58,59,63]. Despite these successes, not every single behavior has been spared due to NAM administration. No study has ever shown an effect on skilled reaching tasks (fine motor coordination) [35,63]. In examining the effect of NAM administration on special populations, the only study to examine aged rats not only showed no beneficial effects on behavior but identified trends towards detrimental effects at higher doses [64]. Additionally, several studies have also shown dose-dependent effects of NAM on behavior (discussed further below), particularly on the MWM and vibrissae-forelimb placing test [47-49]. Figure 1 and Table 1 for a summary and comparison.

Histopathological outcome measures have also shown many neuroprotective effects of NAM treatment on recovery from stroke and TBI. Multiple stroke studies have seen reductions in the size of the infarct/lesion [33,51-53,60]. Studies that examined outcomes in the chronic phase of TBI (greater than 20 days post-injury) have also found that NAM administration reduced lesion sizes and reduced numbers of reactive astrocytes [35,47-50,58,59]. Studies examining recovery markers in the acute phase of TBI (less than 7 days) have shown reductions in apoptosis and degenerating neurons, reduction of edema, lessened blood-brain barrier (BBB) compromise, changes in numbers of activated astrocytes and decreased lesion size [45,46,57]. However, in aged rats, these effects are not shown as strongly. Edema reduction was the only beneficial measure present in aged rats, while lesion size, BBB compromise and the astrocyte response were not

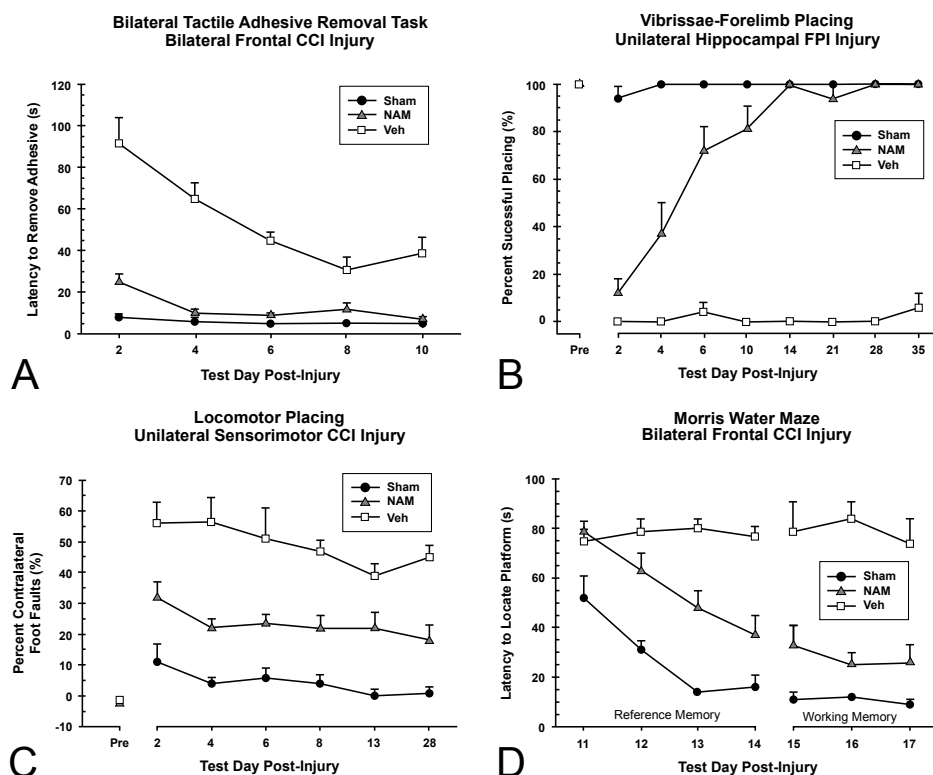


Figure 1: This figure provides examples from research studies that have shown the effects of NAM administration on behavior following brain injury. Details and dosing information from each study can be found in table 1. Panel A shows data from the bilateral tactile adhesive removal task. NAM administration significantly reduced latencies to remove the adhesive patch from the forepaws. Adapted from Hoane et al. (2003) [35]. Panel B shows data from the vibrissae-forelimb placing task. NAM administration significantly improved recovery of the placing reflex. Adapted from Hoane et al. (2006) [48]. Panel C shows data from the locomotor placing task. NAM administration significantly reduced the number of faults made on the injured side. Adapted from Goffus et al. [59]. Panel D shows the Morris water maze. NAM administration significantly reduced latencies to locate the platform in the reference and working memory paradigms. Adapted from Hoane et al. (2008) [47].

improved when compared to a vehicle group [64]. Figure 2, Tables 1 and 2 for a summary and comparison.

Mechanisms of Action of Nicotinamide

The role of NAM in basic cellular functioning is primarily as a precursor to NAD^+ and this is also where many of the therapeutic effects are centered. NAD^+ is an important component of the electron transport chain and assists in the production of ATP [8,65]. In the normally functioning brain, NAD^+ is also a source of free radical scavenging. It acts by donating excess electrons to free radicals in order to stabilize them [66].

Although direct mechanistic studies on NAM following TBI are lacking, much information can be drawn both from the findings from the stroke literature as well as what is known regarding the normal functions of NAM/ NAD^+ . The ability to supplement adenosine triphosphate (ATP) by increasing available levels of NAD^+ can be very beneficial following injury. When energy intake via normal means is impaired or halted, energy supplementation can help to prevent apoptotic and necrotic cell death [12,18]. In addition, increases in available NAD^+ increase the free radical scavenging abilities of the cell, which is also a promoter of cell survival after injury. This is accomplished through the associated compound nicotinamide-adenine dinucleotide phosphate ($NADP^+$) as it becomes reduced nicotinamide-adenine dinucleotide phosphate ($NADPH$) [38].

NAM also has another action independent of its role in forming the NAD^+ complex. It directly inhibits the formation of poly(ADP-ribose)polymerase-1 (PARP-1) [31,66]. In the normally-functioning brain, PARP-1 is a beneficial process. The PARP-1 enzyme works to repair DNA damage by utilizing NAD^+ [67]. However, after injury, PARP-1 is taxing on cellular ATP stores and increases in PARP-1 have been shown promote apoptosis [65], especially when considering the depletion of ATP after brain injury [12]. Activation of the PARP-1 pathway after injury has been demonstrated to be detrimental in experimental models of injury [68-70] and inhibitors of PARP-1 have found beneficial effects when administered to injured tissue [71,72].

Another mechanism by which NAM is potentially neuroprotective is through the inhibition of sirtuins [37]. The sirtuins are a family of proteins that are involved in regulation of cell homeostasis. Specifically, they are involved in inhibiting the repair of DNA damage by modulating PARP-mediated processes [73]. Sirtuins also utilize the NAD^+ complex as a source of energy and can contribute to NAD^+ depletion [66]. NAM is involved with the sirtuins by being a direct inhibitor at the sirtuin-1 receptor. Additionally, NAM is part of a negative feedback loop as it is produced when sirtuins deacetylate proteins [65]. Thus when sirtuins are active, additional NAM is produced which then begins to reduce the activity of sirtuins. Although activation of sirtuins generally promote cell survival, increased activation following injury has been shown to be detrimental [74]. Figure 3 for a summary of its mechanism.

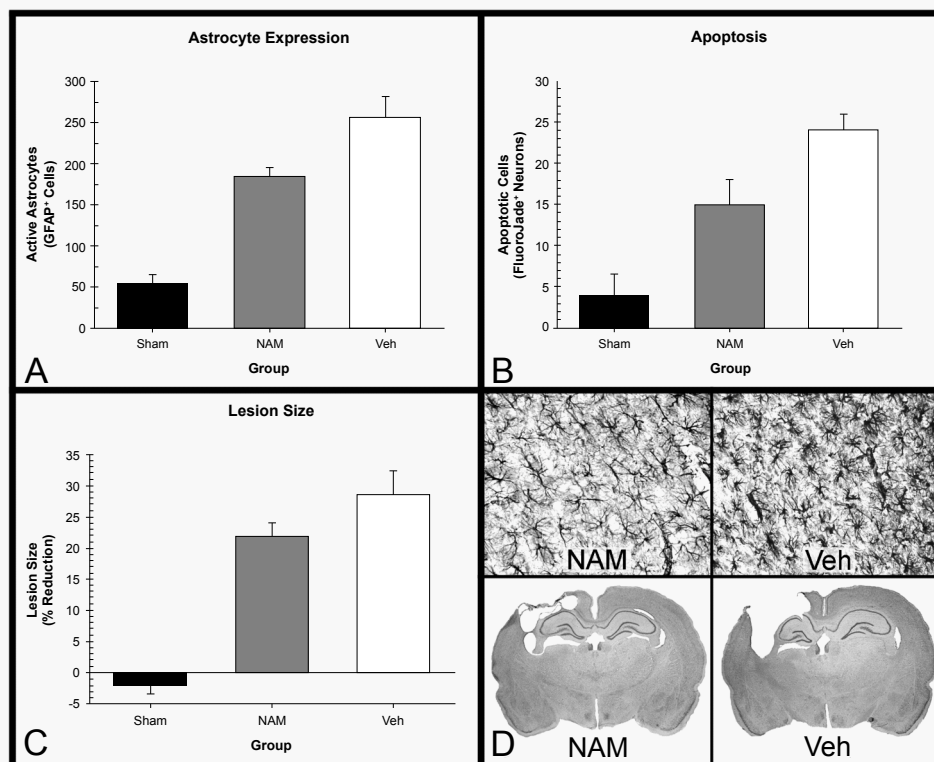


Figure 2: This figure provides examples from research studies that have shown the effects of NAM administration on histopathological markers. Details and dosing information from each study can be found in table 1. Panel A shows quantification of reactive astrocytes after injury. NAM administration significantly reduced the number of reactive astrocytes. Adapted from Hoane et al. (2003) [35]. Panel B shows a quantification of degenerating neurons following injury. NAM administration significantly reduced the number of degenerating neurons. Adapted from Hoane et al. (2006) [46]. Panel C shows the lesion size following injury. NAM administration significantly reduced lesion size. Adapted from Goffus et al. [59]. Panel D shows representative lesions and astrocyte expression following injury and NAM treatment.

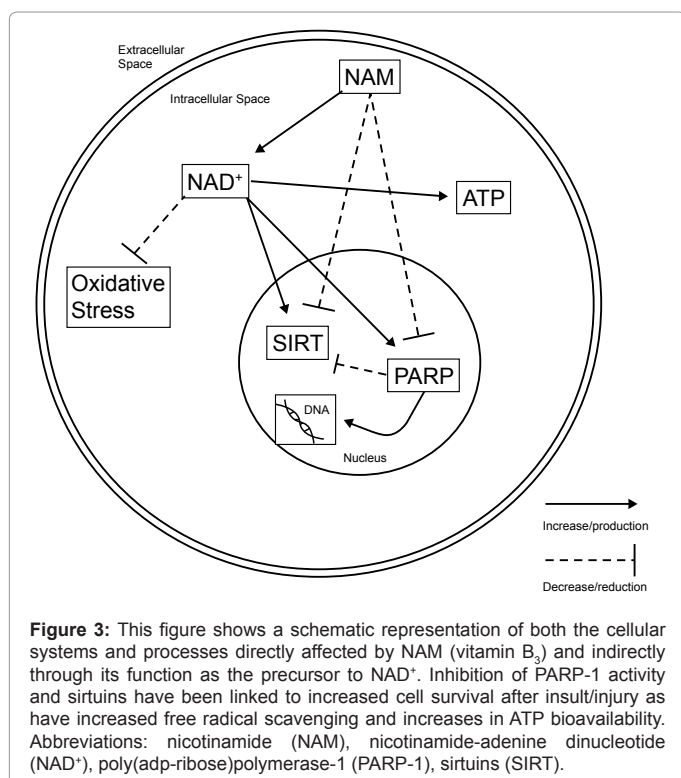


Figure 3: This figure shows a schematic representation of both the cellular systems and processes directly affected by NAM (vitamin B₃) and indirectly through its function as the precursor to NAD⁺. Inhibition of PARP-1 activity and sirtuins have been linked to increased cell survival after insult/injury as have increased free radical scavenging and increases in ATP bioavailability. Abbreviations: nicotinamide (NAM), nicotinamide-adenine dinucleotide (NAD⁺), poly(ADP-ribose)polymerase-1 (PARP-1), sirtuins (SIRT).

One concern regarding NAM is the changes that occur when looking at the aging process. Studies have shown that the metabolism of the NAD⁺ complex fundamentally changes during cellular aging such that higher levels of NAM may be associated with toxicity to cells [75,76]. Though the reason for this is not entirely clear, some have suggested that the metabolic changes may come from the actions at the sirtuin receptors [65,77], while others have suggested that the metabolic issues with NAM in aging come from fundamental changes in free radical scavenging of the NAD⁺ complex [37,65].

Therapeutic Directions and Evaluation

Evidence from animal models suggests that NAM treatment may be an interesting avenue to explore in clinical populations of TBI and stroke. It is naturally occurring and inexpensive. It has shown considerable improvements of deficits in rodent models on multiple types of injury. It even has a reasonable time-window for administration (up to 4-8 hours in the rodent). With regards to dosing in rodent models of TBI, it was shown that the 50 mg/kg dose showed considerable behavioral effects [47,49] and that to exhibit maximal recovery, a dose closer to 150 mg/kg per day may be necessary [50]. In rodent models of stroke, it was shown that doses as low as 125-250 mg/kg could have some effect [52,56], but that maximal recovery would be exhibited at 500 mg/kg [53]. However, it remains to be seen whether a dose of 150 mg/kg or more would be necessary to see improvement in humans and whether it would be tolerated with minimal side-effects. In humans, doses as high as 80 mg/kg have been shown to be tolerated

reasonably well [78,79] and one study showed no detrimental effects of long-term NAM dosing at 50 mg/kg [80]. Even considering potential toxicity issues, NAM may exert reasonable protective effects following human TBI. It may be a particularly interesting target to be used in combination therapies as it is a relatively easily administered drug and is likely to have very few negative interactions with other drugs. However, its use may be limited to younger populations due to the negative effects seen in aged populations.

Conclusion

The experimental literature that has evaluated the efficacy of NAM as a treatment for neural dysfunction following brain injury is robust and provides evidence from multiple different perspectives and disciplines. Following TBI and stroke, multiple studies have shown improvements in behavioral function [33,35,47-50,59,60,62,63], improvements in histopathological markers [31,35,45,46,48,51-53,57,62] and evidence of the mechanisms responsible for these changes [8,31,37,43,44,56,62]. Appropriate dosing and time windows for maximal recovery in rodents have also been identified [47,49,50,52,53,56]. Based on the evidence from preclinical animal work, NAM may be nearing readiness to be evaluated in clinical populations.

However, there are still some questions regarding NAM following brain injury that should be investigated prior to considering treatment in humans. One is the question of the upper limits for human toxicity of NAM. Very high doses are tolerated in rats, but can have undesirable side-effects in humans, with nausea being the primary complaint [79]. Many studies looking at disorders such as diabetes and skin conditions have had an upper limit of 3000 mg/day for humans, translating into roughly a 35-50 mg/kg dose (depending on weight) [81]. However, side-effects such as nausea may be tolerable when considering the damage associated with TBI, particularly if looking at a short-term treatment. Another question requiring investigation is the long-term efficacy of NAM. A large portion of the studies discussed above were conducted in the acute period (24 hours to 7 days) following the injury event and the ones that assessed function in the chronic period were rarely longer than 30 days. While strong effects were seen in the early post-injury period, it remains to be seen whether or not there are improvements in long-term functional recovery. However, even if NAM is found only to accelerate recovery, it still may be a good candidate for investigation in clinical trials. One final question requiring investigation is the efficacy of NAM in older populations. This is of particular interest since the risk for stroke increases with age and aged populations are one of the larger at-risk groups for TBI. The single study that evaluated aged populations in rats showed severely reduced effects of NAM treatment [64]. However, this finding needs to be further investigated to determine whether or not NAM is only effective in certain populations.

In addition to NAM, there are several related compounds that are pharmacologically active and may provide neuroprotection. In particular, nicotinamide mononucleotide (NMN) is a particularly interesting compound as it is a key intermediate step in the formation of NAD⁺ from NAM [82]. As such, it may increase energy production beyond what NAM is capable of. In the liver, NMN has been shown to rapidly increase NAD⁺ levels [83]. Another NAM-related compound that has neuroprotective potential is nicotinamide riboside (NR). Although known to be involved in NAD⁺ formation in non-animal species, NR has only recently come to attention for its role as an additional precursor to NAD⁺ in mammals [84,85]. Further investigation into these and other related compounds may

yield additional neuroprotective agents to be tested in alone or in conjunction with NAM administration.

It is unlikely that any single drug will be the 'silver bullet' that has been hoped for in TBI or stroke treatment. Many have expressed the opinion that poly-therapies will be the way brain injury is ultimately treated in clinical settings [29]. To this end, NAM may become an important arm of a poly-treatment regimen. Since NAM has already been seen to exert neuroprotective effects in experimental populations, supplementation of these within a poly-therapy regimen may help to improve functional outcome beyond what is possible with a single drug alone.

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