International Journal for Pharmaceutical Research Scholars (IJPRS)

V-4, I-3, 2015 ISSN No: 2277 - 7873

REVIEW ARTICLE

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

Afiya Ansari*, Osman Ahmed, Talath Fatima, Humeera Rafeeq

Deccan School of Pharmacy, Hyderabad-01, Telangana, India.

Manuscript No: IJPRS/V4/I3/00174, Received On: 15/09/2015, Accepted On: 19/09/2015

ABSTRACT

Traumatic Brain Injury (TBI) and Stroke are leading matter of concern worldwide mostly in United States more than one million people endure agony from Traumatic Brain Injury (TBI) every year due to which, 52,000 people died and 2,75,000 become hospitalized. When a brain is injured traumatically through eternal force, intracranial injury Traumatic Brain Injury (TBI) occurs. Nicotinamide (NAM; niacin amide; vitamin B3) is a vital nutrient which is also discerned as a cytoprotectant which is involved in various cellular functions has been broadly evaluated in animal models of Traumatic Brain Injury (TBI) and Stroke. TBI is caused by a blow or other traumatic injury to the head. The potential for Nicotinamide as a therapeutic agent for disorderliness of Traumatic Brain Injury (TBI) and Stroke first came into existence after the success of suppressing ability of the injury seen in models of oxidative stress. According to its results of oxidative injury to brain Nicotinamide was used in the treatment of stroke models of global and focal ischemia. Nicotinamide adenine dinucleotide phosphate (NAD^+) is a chief integral of electron transport chain and it also helps in producing ATP. Nicotinamide plays a primary role in basic cellular functioning as a precursor of Nicotinamide adenine dinucleotide phosphate **(**NAD^+) which is very beneficial therapeutically. Nicotinamide has also shown convincing results in the Middle Cerebral Artery Occlusion model with the increase of ATP and NAD+ with the decrease of DNA fragmentation and Poly (ADP-ribose) polymerase-1 activation (PARP) activation. The use of Nicotinamide (NAM) in Experimental Traumatic Brain Injury (TBI) or Disorder or dysfunction has been evaluated and was found to be beneficial.

KEYWORDS

Traumatic Brain Injury (TBI), Nicotinamide (NAM; niacin amide; vitamin B3), Nicotinamide Riboside (NR), Middle Cerebral Artery Occlusion (MCAO) Model, Poly (ADP-Ribose), Polymerase-1 (PARP-1), Controlled Cortical Impact (CCI) Model, Fluid Percussion Injury (FPI) model

INTRODUCTION

Traumatic Brain Injury and Stroke are leading matter of concern worldwide and mostly in the United States more than one million people endure agony from Traumatic Brain Injury every year due to which 52,000 people died and 2, 75,000 become hospitalized[1].

***Address for Correspondence:**
Ms. Afiya Ansari
Deccan School of Pharmacy, Hyderabad,
Telangana State, India.
E-Mail Id: afiya.ansari5416@gmail.com

But these are the statistics of patients who are hospitalized, rest is unnoticed regardlessly[2]. When a brain is injured traumatically through eternal force, intracranial injury or Traumatic Brain Injury (TBI) occurs. Basically it is a head injury which involves the severe damage of brain along with its structures like skull bones which is a huge cause of malady[3]. Till now there is no specific pharmaceutical treatment particularly designated for the treatment of Traumatic Brain

Injury in humans and a single treatment is introduced for human stroke[4]. This has provoked the desire to engender the compounds that are efficacious for the remedy of brain injury. Nicotinamide (NAM; niacin amide; vitamin B3) is a vital nutrient which is also discerned as a cytoprotectant which is involved in various cellular functions has been broadly evaluated in animal models of Traumatic Brain Injury and Stroke[5].

Basically the damage caused by ischemial stroke is composed of two types:

- Damage caused by ischemia
- Damage caused by reperfusion of tissue[6].

Traumatic Brain injury is caused by a blow or other traumatic injury to the head. Even though the risk factors of stroke and Traumatic Brain Injury is unique they possess little similitude in regard to the secondary cascade of injury that follows them.

The secondary cascade, which is a complex multi-model series is responsible for the phenomenon of initial disruption in energy metabolism impelled by lack of blood flow to brain regions or by other factors because of which excitotoxicity, apoptosis, increase in immune response and free radicals may take place and in addition to this it also adds up to detrimental outcome and which allows the initialization of various other neurological dysfunctional disorders like Alzheimer's disease, few types of cancer and repeated strokes[7,12-14].

When a neuron is disabled for the maintenance of its resting potential because of impairment of sodium-potassium pump in allowance with the contribution to the large-scale increases in intracellular excitatory neurotransmitters and this is how excitotoxicity occurs[8,9]. Thus causes repeated neuron firing which in turn causes accumulation of sodium and calcium at deadly levels[10,11]. The consequence of this will be death of the cells while signaling the responses of inflammation before cell death is initiated which further leads to long term detrimental outcomes along with Strokes and Traumatic Brain Disorder [15-17].

Therapeutic Approaches

Although many therapies and few relative treatments are being produced, but subsequently all of them fail in clinical trials and because of this there is no particular promising treatment for the secondary injury phase of Traumatic Brain Injury or Stroke[18-20]. However a protein called Tissue Plasminogen Activator (TPA) is used in the therapeutic treatment of Stroke in patients immediately after Stroke occurs for at least three hours which helps in breakdown of blood clots[4]. This therapeutic remedy was a bit helpful and the death cases or the rate of mortality was declined up to extend but the result is not up to the mark as it causes problems for the patients those who suffer from overnight stroke and in the patients whose symptomatic response is not immediate. Thus many efficacious therapeutic methods should be taken into consideration for the treatment of Traumatic Brain Injury (TBI) and stroke.

While the research work pertaining to the treatment of Traumatic Brain Injury or Stroke is still under progress, many nutrients and vitamins are used for pharmacotherapies for injuries which involves few nutrients comprising Nicotinamide (NAM), magnesium, riboflavin and vitamin-E and also Vita-nutrients has been used in the treatment of neural disorders and mainly for Stroke[21-23] and also in the treatment of Traumatic Brain Injury (TBI)[24-26].

Effects of Nicotinamide on Experimental Brain Injury

Nicotinamide (NAM; niacin amide; vitamin B3) is presently used in the treatment of Pellagra (a vitamin deficiency), is an amide which is derived from nicotinic acid (Niacin)[22].

The potential for nicotinamide as a therapeutic agent for disorderliness of Traumatic Brain Injury (TBI) and Stroke first came into existence after the success of suppressing ability of the injury seen in models of oxidative stress[27-29]. According to earlier studies based on this, the dose of Nicotinamide (NAM) was 500 mg/kg. While variations is in dosage of Nicotinamide is necessary to ease the bearing cure in rodents

following Stroke and Traumatic Brain Injury (TBI)[30]. The recent study shows the use of Nicotinamide along with the subcutaneous pumps to obtain firm state of therapeutic activity with use of approximately 150 mg/kg/day of Nicotinamide (NAM). The pump assists in providing continuous values of Nicotinamide (NAM) with osmotic pressure and this therapy finds a great way of success in bilateral frontal and unilateral sensorimotor injury models of Traumatic Brain Injury (TBI)[31-33].

According to its results of oxidative injury to brain Nicotinamide (NAM) was used in the treatment of stroke models of global and focal ischemia. Among these two, global models of ischemia play a major role in destruction in cellular metabolism that leads to large scale behavioral impairments and deaths[34]. By the use of Nicotinamide (NAM) in models of global ischemia results in high levels of ATP, NAD+ and mitochondrial metabolism[21] and by the use of Nicotinamide (NAM) in models of focal ischemia results in destructions in cell metabolism and targeted behavioral ruinations[6]. Even its low dose permits the increase of cerebral blood flow (CBF)[37]. Also in Fluid Percussion Injury (FPI) and Controlled Cortical Impact (CCI) models, Nicotinamide (NAM) in specific dosage range values in different variations has shown variable effective result in behavioral and histological results following Traumatic Brain Injury (TBI)[38-40]. Reduced size of infracts and lesions can be observed by the use of Nicotinamide (NAM) in multiple Stroke studies[23,35,29,41,42]. Its studies also shows that administering nicotinamide (NAM) in Chronic phase of Traumatic Brain Injury (TBI) (more than 20 days of post-injury) depreciate lesion size and number of active astrocytes.[25,31,42-45]

Mechanism of Action of Nicotinamide

NAD+ is a chief integral of electron transport chain and it also helps in producing ATP. Nicotinamide (NAM) plays a primary role in basic cellular functioning as a precursor of NAD+ which is very beneficial therapeutically[5,46]. In a brain which functions normally, NAD+ is a chief of free radical scavenging by giving a large number of electrons to free radicals in need of stabilizing them[47]. Apart from treating Traumatic Brain Injury (TBI) Nicotinamide (NAM) plays a crucial role in the formation ofNAD+ complex thereby inhibiting the synthesis of Poly (ADP-Ribose) Polymerase-1 (PARP-1)[21,47]. After injury PARP-1 enervates on cellular ATP stores which simultaneously gives rise to PARP-1 levels and which in turn support Apoptosis[46]. Another possible mechanism in which Nicotinamide is effectively neuroprotective by the suppression of sirtuins[48]. Sirtuins are considered as group of protiens which provoke the regulation of cell homeostasis involves particularly in suppression in repair of DNA impairment by mediating PARP-mediated processes[49].

Therapeutic Directions and Evaluations

Studies on animal models shows that the use of Nicotinamide (NAM) in treating Traumatic Brain Injury (TBI) and Stroke is an elevating matter of concern in the treatment of its widespread in clinical population as it is not artificially prepared because of its occurrence in nature and so it is also inexpensive. In multiple type injury it is highly effective when observed in rodent models. Nicotinamide (NAM) has also shown convincing results in the Middle Cerebral Artery Occlusion (MCAO) model with the increase of ATP and NAD+ with the decrease of DNA fragmentation and Poly (ADP-ribose) polymerase-1 activation (PARP) activation.[21,35,36]

CONCLUSION

The use of Nicotinamide (NAM) in Experimental Traumatic Brain Injury (TBI) or Disorder or dysfunction has been evaluated and was found to be beneficial. Nicotinamide (NAM) may be used with numerous specified drugs for more efficacious results. Basically the use of Nicotinamide (NAM) in the treatment of Traumatic Brain Injury (TBI) is to compile the treatment in a comfortable and cheapest way possible. Nicotinamide, along with other drugs which are tested and administered acts as Neuroprotective agents. Example of Nicotinamide (NAM) related compound is Nicotinamide Riboside (NR). According to the

studies, poly-therapies should be used in the treatment of Traumatic Brain Injury (TBI) and Stroke and we came to a conclusion that Nicotinamide (NAM) can play a crucial role in poly-therapies of Traumatic Brain Injuries (TBI's). With the help of poly-therapy system, the functional results can be made much better which can be achievable with a single drug.

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