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Review Article

## Literature Review on the Therapeutic Potential of NAMPT in Brain Diseases

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### Abstract

Nicotinamide Phosphoribosyl transferase (NAMPT) is an important enzyme in the biosynthesis NAD<sup>+</sup> and the byproduct nicotinamide mononucleotide (NMN) is also a vital intermediate in NAD<sup>+</sup> synthesis. More importantly, the enzyme has been found to have therapeutic potential in the management and treatment of brain diseases such as stroke, depression, and cerebral ischemic injury. In this review, we looked critically at studies that have sought to explore the activities of NAMPT in the brain, the relevant pathways, the byproducts, and precursors of NAMPT with the hope of utilizing the knowledge gotten from the studies to project the possibility of utilizing the enzyme as a better way to treat brain diseases. The enzyme is projected to have a double-edged influence on cell processes and aging. Likewise, it has neuroprotective advantages in neurons that express them. More scientific studies have shown that NAMPT is involved in the chain of activities involved in preventing depression. This review further elaborates on the therapeutic potentials of NAMPT, and also seeks to recommend further studies in this field to be carried out on a regular basis due to its promising potential.

Keywords: NAMPT; Brain; Therapeutic potential; Diseases; NAD; Cerebral ischemic injury, Stroke

## 1. Introduction

Nicotinamide phosphoribosyl transferase (NAMPT) is the rate-limiting enzyme in the nicotinamide adenine dinucleotide (NAD) pathway in mammals<sup>1</sup>. It can be expressed in a variety of tissues and organs, including the brain<sup>2</sup>, liver, and adipose tissue<sup>3</sup>, either intracellularly (iNAMPT) or extracellularly (eNAMPT)<sup>4</sup>.

Intracellular NAMPT participates in the salvage pathway of NAD synthesis, as it thereby plays a vital role in energy metabolism; serving as a cofactor of histone deacetylase sirtuins, and regulates cell death through Poly (ADP-ribose) polymerase 1 (PARP-1), thus linking to these important cellular processes<sup>5</sup>.

An important interaction catalyzed by NAMPT is the one involving Nicotinamide mononucleotide (NMN), an important intermediate in the biosynthesis of NAD, which is produced when nicotinamide reacts with 5-phosphoribosyl-1-pyrophosphate<sup>6</sup>. Interestingly, this NAD pool that is being catalyzed by NAMPT has received a lot of attention as a substrate and a regulator in cellular homeostasis and processes like metabolism, circadian rhythms, immunity, and cell death<sup>7,8</sup>.

## 2. Nicotinamide Phosphoribosyl transferase May Be Involved in Age-Related Brain Diseases

The author in<sup>9</sup> revealed that depending on its expression level and distribution, NAMPT has a double-edged influence on aging and cellular processes.

As neurons account for 70% of the oxidative metabolism in the cortical gray matter while the brain consumes 20% of the body's oxygen, iNAMPT is primarily expressed in neurons in the brain<sup>2</sup>. This helps to meet the high energy demand. In contrast to an increase in microglia activity with aging, neuronal energy metabolism diminishes<sup>10</sup>.

The study in<sup>9</sup> showed that the level of NAMPT in the microglia of the brain is higher than in the neuron, while reduced in the brain compared to the serum.

However, the level of NAMPT in serum has been implicated in the occurrence of age-related brain disorders, especially with a tendency that it can cross the blood-brain barrier<sup>11</sup>. The fact derived from these studies can contribute to combating brain illnesses that are traceable to aging.

## 3. NAMPT Critical Role in Cerebral Ischemic Injury

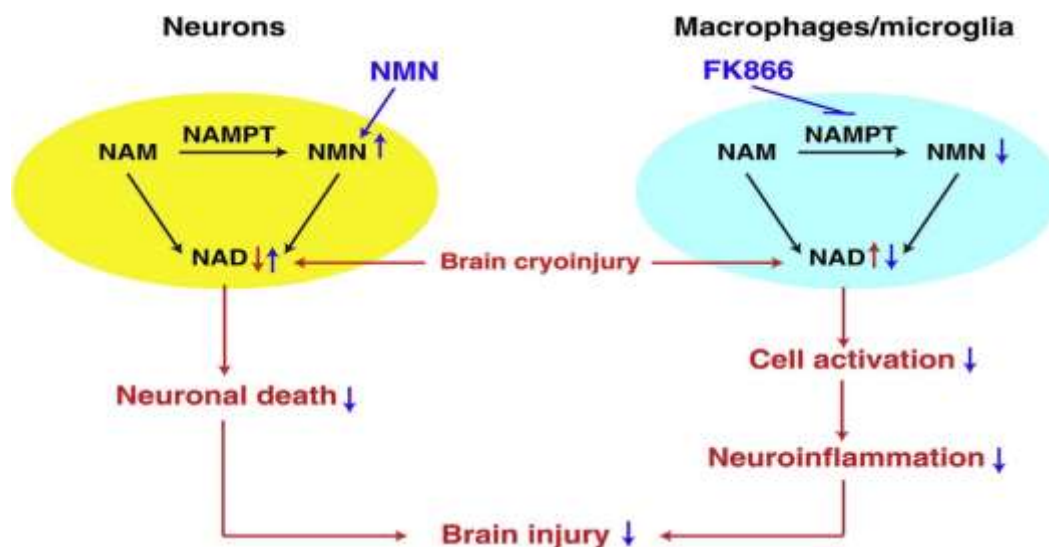
Neurons that express NAMPT have neuroprotective properties after ischemic brain injury<sup>12,13</sup> further demonstrates that FK866, a known NAMPT inhibitor indirectly shields neurons from ischemia damage by reducing neuroinflammation. This

has been further proven according to a work conducted by <sup>14</sup> whose results show that FK866 has both protective effects against injury to the brain and spinal cord of the mouse used for the study.

However, through studies in <sup>9</sup> and <sup>15</sup>, the lowest concentration of FK866 required to cause neuron damage is 10 nM, whereas 0.1–1 nM FK866 effectively inhibits microglia activation. This allows for the optimization of the dose of FK866 to a concentration that doesn't result in neuronal damage.

Also, according to the results of a recent investigation to ascertain that neuronal NAMPT is released after cerebral ischemia and protects against white matter injury, it was discovered that transgenic mice that overexpress NAMPT in a neuron-specific manner are extremely resistant to focal cerebral ischemia brain injury <sup>16,17</sup>.

On the other hand, NAMPT is also involved in the activation of inflammatory cells and is the cause of many inflammatory illnesses <sup>18,19</sup>. This signals the potential double-faced activity of NAMPT.



**Figure 1: NAMPT inhibitor and metabolite protect mouse brain from cryoinjury through distinct mechanisms**

**Source:** Zhang XQ, Lu JT, Jiang WX, Lu YB, Wu M, Wei EQ, Zhang WP, Tan C, NAMPT inhibitor and metabolite protect mouse brain from cryoinjury through distinct mechanisms, *J Neuroscience*, 2015; vol 291, pg 230-240.

#### 4. NAMPT as a Therapeutic Target against Depression

Nicotinamide Adenine Dinucleotide, NAD, is important for the control of emotion related behaviors, according to findings <sup>20</sup>. Further studies have shown that increasing the level of intracellular NAD concentrations in animals with lower levels of NAD showed positive outcomes against depression <sup>21</sup>. This is because NAD has the potential to reduce depression in the signal pathways by increasing the activities of SIRT1.

As NAMPT catalyzes the production of nicotinamide mononucleotides when 5-phosphoribosyl pyrophosphate combines with NAM, which then leads to the adenylation of NMN to produce NAD, it is a crucial component of the salvage pathway for NAD biosynthesis, therefore may have an important role to play in the therapeutics of depression <sup>22</sup>.

In a recent study in <sup>23</sup>, it is established that the inhibition of NAMPT pre-frontal cortex can worsen cognitive functions and behaviors associated with depression, and that improvement in the level of NAD leads to an increased depressive state in the mice used for the study.

#### 5. NAMPT potential in Stroke Treatment

NAMPT level changes in cases of brain diseases such as stroke in animal models while its level in the blood of stroke patients is increased significantly <sup>24</sup>. The neurogenetic regeneration potential of NAMPT has been however positively demonstrated in studies that have shown the autophagy stimulating function of intracellular NAMPT in brain disease conditions such as stroke especially at an early stage <sup>25</sup>.

The author in <sup>26</sup> was able to find out in their study that overexpressing NAMPT and not H247A-mutant dominating-negative NAMPT are able to show that the intracellular NAMPT–NAD+/--SIRT1 cascade advances vascular repair after ischemia in endothelial progenitors. Also, there is an increased flow of blood recovery, higher proliferated endothelial cells, and improved capillary density <sup>26</sup>.

More so, by investigating the ability of NAMPT to promote regenerative neurogenesis, The findings by the author in <sup>27</sup> contribute to the growing body of evidence supporting the idea that modulating the NAMPT-NAD axis, such as by supplementing NMN, may be a potential way out for treating stroke. Therefore, advancement in in vivo and in vitro NAMPT studies can be explored in the aspect of the elaboration of NAMPT; its enzymatic products, and their precursors in the treatment of stroke.

#### 6. Conclusion

NAMPT has vital roles to play in the body which further scientific studies must explore especially in its promising potential to be an important option in the treatment and management of brain diseases. For example, the NAMPT-NAD signaling indicates a viable defense system against energy deletion which is ischemia-induced, death of neuron cells, and death of brain tissues due to lack of blood supply. Exploring more potentials of the NAMPT-NAD signaling and the enzymatic products of NAMPT will no doubt be resourceful in the journey of combating brain diseases such as stroke effectively.

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## Authors Contribution

Each author of this review was actively involved in providing valuable resources and information needed to make the work up to the required standard.

## Disclosure of Conflict of Interest

The Authors declare no conflict of interest.

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