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## RESEARCH ARTICLE

# NMN “Nicotinamide Mononucleotide” Activates Intracellular Energy and Approaches the Prevention and Improvement of Aging

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## ABSTRACT

Aging was defined as one of the diseases by ICD-11. Preventing aging may avoid the risk of various diseases. However, it is difficult to simply prevent aging in daily life. The presence of nutrients is essential there. This time, we reviewed NMN “nicotinamide nucleotide”, which is attracting attention as an anti-aging component, and conducted additional experiments using AMPK “AMP-activated protein kinase” and NAD<sup>+</sup> as indicators to determine whether or not it actually prevents aging gone. As a result, a significant increase in AMPK and NAD<sup>+</sup> was confirmed, suggesting that NMN may help prevent aging in the future.

## INTRODUCTION

From ICD-11, aging has been treated as a disease [1]. Aging is said to be a physical and mental decline associated with aging [2,3]. Since aging is considered to be the cause of all diseases [4], countermeasures are urgently needed. In order to prevent aging, it is said that active intake of nutrients that are good for the body [5], good sleep [6], and moderate exercise [7], but if it is not done by one's own will, it is said. It is said to cause stress and generate active oxygen that causes aging [8]. It is said that active oxygen and aging are closely related [8]. Reactive oxygen species are generated by various external and internal factors [9], weaken normal mitochondrial function [10], and may be a risk of aging-related diseases such as cancer. There are four types of active oxygen in a nutshell [11], which can be divided into superoxide, hydroxyl radical, hydrogen peroxide, and singlet oxygen [12]. Normally, these active oxygens are produced by enzymes for removing active oxygen, such as SOD (superoxide dismutase) and catalase that exist in the living body [12,13]. In addition, active oxygen is also removed by antioxidants taken from the diet, such as vitamin C and vitamin E [14,15]. However, these reactive oxygen species are usually produced in small amounts in the body and are involved in functions such as maintenance of homeostasis, signal transduction, gene expression, and receptor activation in cells [16], so it is not possible to remove them altogether. It is

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considered undesirable. Therefore, appropriate antioxidants are required. In addition to antioxidants, activation of AMPK (AMP-activated protein kinase) is also required to approach aging [17]. AMPK (AMP-activated protein kinase) is an energy sensor in the body and is a serine / threonine kinase that works to maintain homeostasis of sugar and lipid metabolism [18]. It is thought that aging can be prevented by activating, promoting autophagy, and enhancing mitochondrial function [19,20]. Therefore, in this study, the activity of AMPK was measured from the concept of nutrition using NMN "nicotinamide mononucleotide" [21], which is currently attracting attention as an anti-aging substance, and the expression level of NAD +, which is said to decrease with aging, is also measured. It was measured. NAD + decreases with age, and it is said that when NAD + decreases, age-related diseases are caused. It is considered that the presence of NAD + as well as AMPK is necessary to prevent aging. Therefore, it is considered that activation of both leads to prevention of aging. If NMN can mention the possibility of preventing aging in this study, it will be useful not only for aging-related diseases but also for maintaining / promoting health or preventing diseases in the future.

AMPK (AMP-activated protein kinase) is an energy sensor in the body and is a serine / threonine kinase that works to maintain homeostasis of glucose and lipid metabolism [18]. It is said that activation of AMPK regulates energy metabolism and maintains energy homeostasis, and is attracting attention as a potential therapeutic effect for metabolic diseases including type 2 diabetes and cancer [22]. The existence of energy is indispensable for human beings to live, and the energy source is ATP (adenosine triphosphate), and when ATP is hydrolyzed and converted to ADP (adenosine diphosphate). Occurs [23]. By regulating this ATP level, AMPK is expected to maintain homeostasis and be effective against metabolic diseases such as cancer, type II diabetes, and obesity [24-26].

In other words, it is expected that the increase in AMPK activity can be expected to prevent lifestyle-related diseases including cancer. It is also considered that AMPK regulates metabolism by inhibiting the ATP consumption pathway [27,28]. From that, the following effects can be expected. AMPK is known to have the following effects.

#### 1. Adjust the balance of inflammation [29].

By suppressing chronic inflammation with AMPK, it approaches cancer and heart disease and contributes to the maintenance of health in the living body [30,31].

#### 2. Improvement of insulin sensitivity and glucose tolerance [32].

It has been reported that activation of AMPK can suppress insulin resistance and high insulin status, which cause metabolic diseases [33]. In addition, by shifting to a state of fat burning, it induces a decrease in body fat mass

and suppresses the secretion of inflammatory cytokines from excess body fat [33].

#### 3. Promote autophagy [34].

AMPK activates cell autophagy.

#### 4. Enhances mitochondrial function [35].

Restoring intracellular energy (ATP) levels is one of the main objectives of AMPK activation. AMPK may increase intracellular ATP levels by activating mitochondrial biosynthesis [36,37].

#### 5. Immune system regulation [38].

When AMPK is activated, the immune monitoring function is strengthened, and the host's defense against pathogens is enhanced, which may enhance the immune function [38]. Autophagy is indispensable for innate immunity, which is the forefront of the immune system, and this autophagy is also activated by AMPK [34].

#### 6. It acts on the sirtuin gene and may lead to longevity [39].

AMPK activates the production of longevity genes sirtuins and FOXO proteins associated with healthy longevity [40].

## MATERIALS AND METHODS

### NMN

NMN purchased from Wellness-One Co., Ltd. (Iwate, Japan) is adjusted to a final concentration of 1 mg/ml.

### AMPK activity measurement

In this experiment, the CycLex® AMPK kinase assay kit (Institute of Medical Biology, Tokyo, Japan) was used to confirm the activity of AMPK using MCF-7 cells as usual. The group was divided into a PBS-added group and an NMN-added group (final concentration 1 mg/ml), each was compared, and the PBS group was used as a control for evaluation. With this kit, AMPK activity was measured 1 hour, 12 hours, and 24 hours after addition. The evaluation was performed by statistical processing software (IBM SPSS Statistics Ver.26). Statistical evaluation was performed by the Mann-Whitney U test).

### NAD + measurement

In this experiment, NAD/NADH (DOJINDO LABORATORIES (Kumamoto Prefecture, Japan) was purchased and measured using MCF-7 cells according to the operation of the kit. Compared with the control group (PBS group), NMN Addition group (final concentration 1 mg/ml). The amount of NADH and total NAD +/NADH were measured at a wavelength of 450 nm using an absorber, and the amount of NAD + expressed was measured by subtracting the amount

of NADH from the total amount of NAD/NAD. The evaluation was performed by statistical processing software (IBM SPSS Statistics Ver.26). Statistical evaluation was performed by the Mann-Whitney U test).

## RESULTS

### AMPK activity measurement

In this experiment, the CycLex® AMPK Kinase Assay Kit (MEDICAL & BIOLOGICAL LABORATORIES CO., LTD. Tokyo, Japan) was used as per the standard method, and the PBS-added group was used for the AMPK activity in the NMN-added group (final concentration 1 mg/ml). It was compared and evaluated as a control. In this kit, in order to measure the current amount of AMPK activity, the activity of AMPK was confirmed 1 hour, 12 hours, and 24 hours after the addition. In addition, the evaluation was performed statistically by the Mann-Whitney U test using statistical processing software (IBM SPSS Statistics Ver.26) (Table 1, figure 1).

### NAD + measurement

In this experiment, NAD/NADH (DOJINDO LABORATORIES (Kumamoto, Japan) was purchased and measured according to the operation contents of the kit.

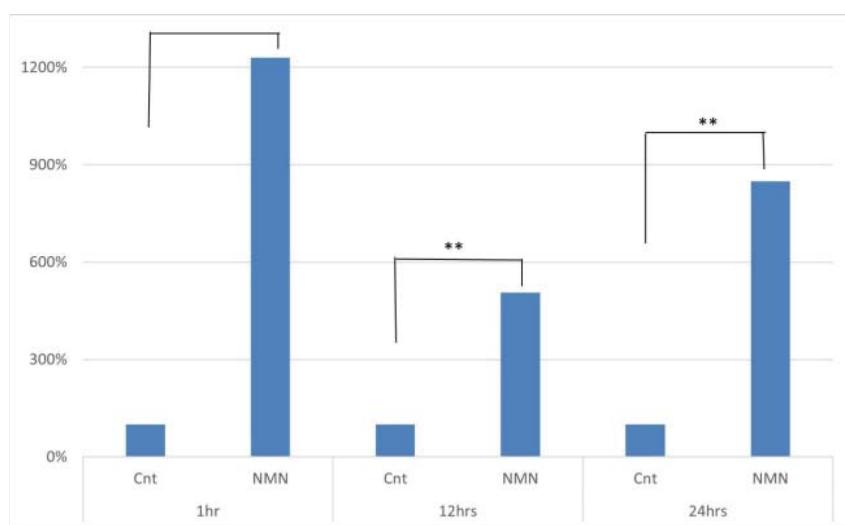
Compared with the control group (PBS group), the NMN-added group (final concentration 1 mg/ml) NADH amount and total NAD +/NADH were measured at a wavelength of 450 nm with an absorptiometer, and the expression level of NAD + was measured by subtracting the NADH amount from the total NAD/NAD amount. The evaluation was performed by statistical processing software (IBM SPSS Statistics). Statistical evaluation was performed by Mann-Whitney U test using Ver.26) (Table 2, figure 2).

## DISCUSSION

This time, we examined the mechanism at the in vitro level using the nutritional component "NMN (nicotinamide mononucleotide)" that is currently attracting attention. NMN is a substance contained in nicotinic acid (niacin), a coenzyme present in the cells of all living organisms, and is produced in the body [41]. In this study, we measured whether NMN increased the activity of AMPK. As a result, in the NMN-added group, when the control group was set to 100%, the activity increased by 1230.5% 1 hour after the addition, 506.5% after 12 hours, and 849.2% after 24 hours. In other words, the activity of AMPK was significantly observed even after 24 hours, suggesting that NMN is involved in the activity of AMPK. In addition, the activity

**Table 1:** Absorbance of an hourly control group and NMN-added group.

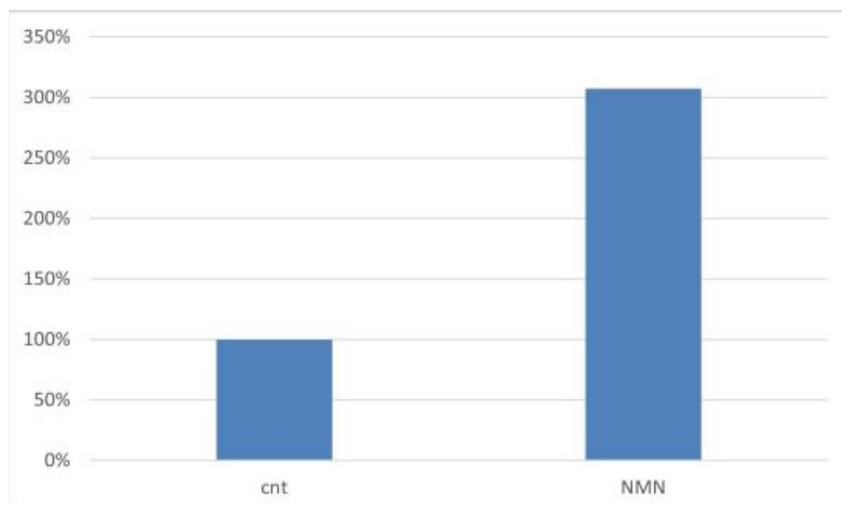
1. Absorbance					
1hr		12hrs		24hrs	
Cnt	NMN	Cnt	NMN	Cnt	NMN
0.285 ± 0.013	3.507 ± 0.136	0.352 ± 0.019	1.783 ± 0.311	0.264 ± 0.034	2.242 ± 0.182
2. AMPK activity increase rate when Cnt is 100%					
1hr		12hrs		24hrs	
Cnt	NMN	Cnt	NMN	Cnt	NMN
100%	1230.50%	100%	506.50%	100%	849.20%



**Figure 1** Rate of increase in AMPK activity in the control group and NMN-added group at each time (Mann-Whitney U test  $p < 0.01$ ).

**Table 2:** Absorbance of NAD<sup>+</sup> in the control group and the NMN-added group.

Both of n = 3	Average of OD value
Control	0.177 ± 0.005 (100%)
Addition group of NMN(1 mg/ml)	0.544 ± 0.008 (307.3%)

**Figure 2** When the Mann-Whitney U test was performed, the expression level of NAD<sup>+</sup> in the NMN-added group increased significantly at  $p < 0.01$ .

was increased compared to the control group even after 24 hours had passed, so a sustained action was expected. By activating AMPK, the various effects mentioned above can be expected. Among them, autophagy and mitochondrial activation were observed [34,35], suggesting prevention and improvement of aging. In this study, we focused on the activity of mitochondria and measured NAD<sup>+</sup>, which is one of the indicators [35]. In the NMN-added group, a significant increase was observed compared to the control group. It was also suggested that the function would be improved. NMN is synthesized from vitamin B3 and is known as a precursor of NAD [41]. It is considered that administration of NMN efficiently promotes NAD<sup>+</sup> synthesis and further activates sirtuins [42]. Since it has been found that NAD<sup>+</sup> is reduced in many aged organs [43,44], it is considered important to maintain organ function by supplying NAD<sup>+</sup> [45]. NAD<sup>+</sup> is an important coenzyme involved in the redox reaction of major metabolic pathways in cells [46]. NAD exists in cells as oxidized NAD<sup>+</sup> and reduced NADH, and the balance between these two is essential for maintaining cell function [47]. In recent years, a causal relationship between a decrease in the amount of NAD<sup>+</sup> and diseases associated with aging has also been pointed out [48]. In this study, not only the activation of AMPK but also the amount of NAD<sup>+</sup> was confirmed to increase, suggesting that it can approach aging. In addition, at this stage, no report on the antioxidant activity, which is one of the causes of aging, can be seen in NMN. However, there are reports that it improves mitochondrial function and increases metabolism [49]. In addition, NMN is said to be deeply involved in the maintenance and promotion of health by acting on the sirtuin gene [50]. From the above, it

was suggested that NMN may prevent aging in the future, leading to an extension of healthy life expectancy and ultimately an extension of life expectancy.

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## Conflicts of Interest

The authors declare no conflict of interest.

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