Adipocyte

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/kadi20

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To cite this article: So Young Kwon & Yoon Jung Park (2024) Function of NAD metabolism in white adipose tissue: lessons from mouse models, Adipocyte, 13:1, 2313297, DOI: 10.1080/21623945.2024.2313297

To link to this article: https://doi.org/10.1080/21623945.2024.2313297

Published online: 15 Feb 2024.

ADIPOCYTE
2024, VOL. 13, NO. 1, 2313297
https://doi.org/10.1080/21623945.2024.2313297

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REVIEW

Function of NAD metabolism in white adipose tissue: lessons from mouse models

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ABSTRACT

Nicotinamide Adenine Dinucleotide (NAD) is an endogenous substance in redox reactions and regulates various functions in metabolism. NAD and its precursors are known for their anti-ageing and anti-obesity properties and are mainly active in the liver and muscle. Boosting NAD+ through supplementation with the precursors, such as nicotinamide mononucleotide (NMN) or nicotinamide riboside (NR), enhances insulin sensitivity and circadian rhythm in the liver, and improves mitochondrial function in the muscle. Recent evidence has revealed that the adipose tissue could be another direct target of NAD supplementation by attenuating inflammation and fat accumulation. Moreover, murine studies with genetically modified models demonstrated that nicotinamide phosphoribosyltransferase (NAMPT), a NAD regulatory enzyme that synthesizes NMN, played a critical role in lipogenesis and lipolysis in an adipocyte-specific manner. The tissue-specific effects of NAD+ metabolic pathways indicate a potential of the NAD precursors to control metabolic stress particularly via focusing on adipose tissue. Therefore, this narrative review raises an importance of NAD metabolism in white adipose tissue (WAT) through a variety of studies using different mouse models.

ARTICLE HISTORY
Received 14 December 2023
Revised 16 January 2024
Accepted 22 January 2024

KEYWORDS
NAD metabolism; white adipose tissue; nicotinamide phosphoribosyltransferase; NAD supplementation; Nicotinamide Adenine Dinucleotide

1. Introduction

NAD+, the oxidized form of nicotinamide adenine dinucleotide (NAD), is a well-known coenzyme that possesses anti-ageing properties [1]. Decreasing NAD + levels induces ageing-like effects, including cell senescence, DNA damage, defective mitochondrial function, and abnormal epigenetic pattern [1]. Cluster of differentiation 38 (CD38), an enzyme that breaks down NAD +, is a key regulator of NAD+ metabolism [2] and has been known to increase with ageing [3]. Additionally, other enzymes that use NAD as a substrate have also been reported to possess anti-ageing properties. Particularly, sirtuin 1 (SIRT1) is a NAD+-dependent deacetylase that produces nicotinamide (NAM) and acetyl group, altering activity of several transcription factors to regulate biological functions [4]. It protects against DNA damage during ageing [5], and SIRT1 overexpression has been shown to prevent age-induced transcriptional changes [6]. Moreover, previous studies have demonstrated that calorie restriction (CR) NAD+-dependent regulates life span through SIRTs/Sir2 [7,8], which supports the hypothesis that boosting NAD+ levels would induce anti-ageing effects.

NAD+ plays a crucial role as a cofactor and therefore early studies reported the existence of a 'conferment' agent that was critical for the alcoholic fermentation of sugar [9]. Later studies revealed that NAD+ is metabolically reactive, thus establishing a crucial basis for future research on NAD metabolism [10]. This was followed by the discovery of nicotinic acid (NA), a NAD precursor that prevents pellagra, a disease caused by vitamin B_3 (*i.e.*, niacin) deficiency [11]. Since these early findings, NAD+ has been reported to be not only a vital redox cofactor but also an important signalling molecule that regulates inflammation, mitochondrial function, and circadian rhythm [12]. For example, NAD+ compartmentalized in adipocytes regulates adipocyte differentiation and gene expression, in addition to controlling glucose metabolism [13].

Recent studies have demonstrated that boosting NAD+ and its precursors such as nicotinamide mononucleotide (NMN), NAM, or nicotinamide riboside (NR) prevented age-induced metabolic stress [14–17]. Aging impairs the NAD^+ salvage pathway in the liver, which is associated with liver dysfunction [18]. In fat tissue, visfatin/NAMPT (nicotinamide phosphoribosyltransferase), an adipocytokine involved in the first

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limiting step in the NAD+ salvage pathway, was reported to induce similar effects to those of insulin [19], thus preventing metabolic disorders such as insulin resistance and inflammation in adipocytes [20–23]. However, NAD metabolism in adipose tissue has remained relatively less explored and several conflicting results have been reported. Therefore, this narrative review discusses the adipocyte-specific functions of NAD+ precursors and NAMPT, as well as the discrepancies among their reported functions.

2. Main pathways of NAD+ biosynthesis in mammals

There are several NAD+ synthesis pathways, and two of the most representative biosynthesis and consumption pathways are illustrated in Figure 1. One of the NAD+ synthesis pathways is the *de novo* biosynthesis from tryptophan. When tryptophan from food enters the body, it is converted to α-amino-β-carboxymuconate-ε-semialdehyde (ACMS), which is then converted to NAM in the liver and transported to other tissues [24]. This tryptophan catabolism process is also commonly referred to as the kynurenine pathway. In the absence of niacin supplementation, dietary tryptophan can thus be converted to NA [25] and alterations in this tryptophan-nicotinamide pathway can lead to adverse physiological changes (*i.e.*, diseases) [24], suggesting that NAD+ *de novo* biosynthesis supplies a portion of NAD+ to compensate for ageing-related NAD+ decline.

The other pathway is the NAD+ salvage pathway, which consists of the recycling of NAM through enzymes that consume NAD+, such as SIRTs, poly (ADP-ribose) polymerase (PARP), and CD38. In this pathway, NAMPT catalyzes NAM into NMN. When

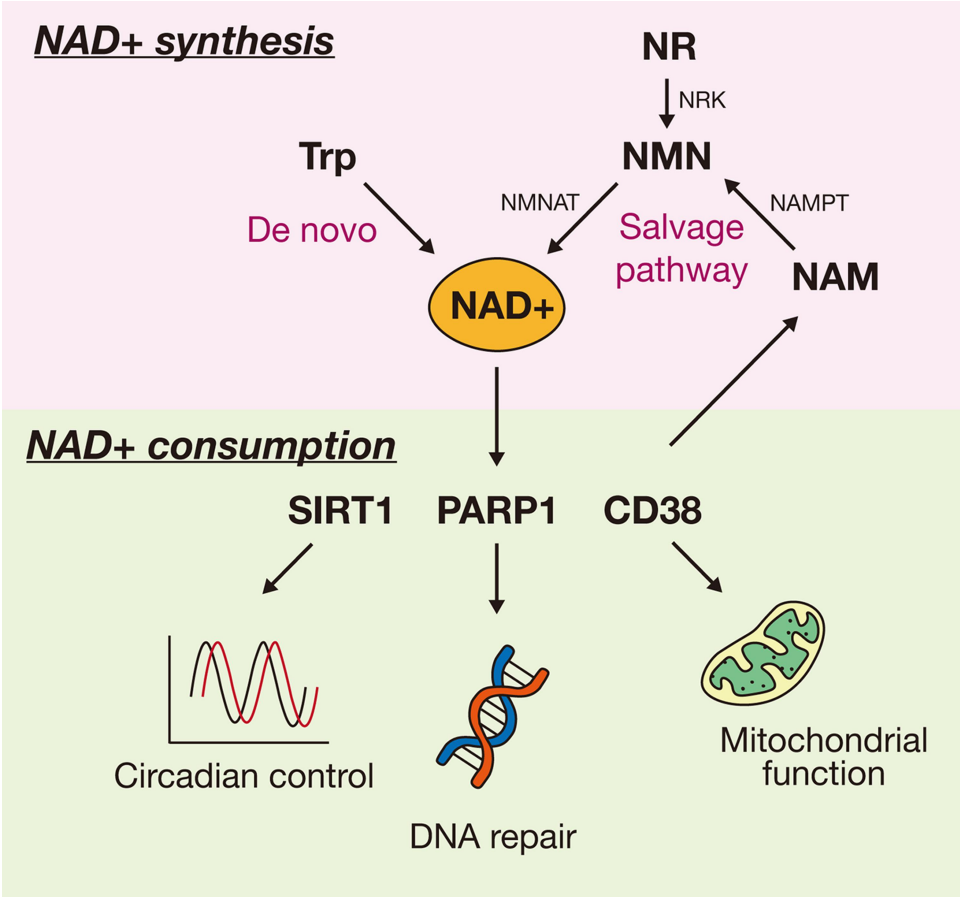

Figure 1. Main pathways of NAD+ synthesis and consumption in mammals. NAD+ is either synthesized from tryptophan (*de novo* biosynthesis) or from NMN by NMNAT. NMN can be provided by NR and NAM. The synthesized NAD+ is broken down by NAD+-dependent enzymes such as SIRT1, PARP1, and CD38, and therefore the recycled NAM can be re-synthesized to NAD+ via the NAD+ salvage pathway. NAD±consuming enzymes have several functions. For example, SIRT1 controls circadian rhythm, whereas PARP1 and CD38 regulate DNA repair and mitochondrial function, respectively. Trp, tryptophan; NAD+, a reduced form of nicotinamide adenine dinucleotide; NMNAT, nicotinamide mononucleotide adenylyltransferase; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; NRK, nicotinamide riboside kinase; NAMPT, nicotinamide phosphoribosyltransferase; NAM, nicotinamide; SIRT1, sirtuin 1; PARP1, poly (ADP-ribose) polymerase 1; CD38, cluster of differentiation 38.

NAD+ precursors such as NR or NMN enter the cell, NR is converted to NMN with ATP, after which NAD+ is synthesized from NMN through the activity of nicotinamide mononucleotide adenylyltransferase (NMNAT). NAD+-dependent enzymes including SIRT1 and PARP1 have been known to possess health-promoting effects. For example, SIRT1 regulates circadian rhythm by recruiting the circadian complex [26] and improves life span by stimulating cell survival in mammalian cells [27]. Additionally, SIRT1 reportedly prevents obesity and age-induced physiological disorders such as cellular senescence and inflammation [4]. Other NAD+-dependents enzymes have different functions. For instance, PARP1 mediates DNA repair and chromatin remodelling in response to DNA damage [28], whereas CD38 is involved in the degradation of NAD precursors generated due to age-related mitochondrial dysfunction via SIRT3 [3]. Several enzymes that use NAD+ as a substrate and are known to prevent metabolic decline have also been associated with cell survival. Therefore, the evidence suggests that the NAD + salvage pathway is essential to sustain cellular activity. When both NAD+ synthesis pathways function properly, most NAD+ is exclusively generated via the salvage pathway rather than the *de novo* synthesis pathway [29], and many studies on the importance of NAMPT have been recently conducted.

3. Metabolic effects of boosting NAD+ levels in liver and muscle tissues

The liver is an organ that controls the balance of uptake and storage of glucose by gluconeogenesis and glycogenesis to maintain blood glucose level in the body and plays a crucial role in detoxifying toxins. In mammalian models of high-fat diet (HFD)-induced diabetes, decreased NAD+ levels and expression of NAMPT in the liver can be reversed via NMN supplementation [14]. Figure 2 illustrates the effects of boosting NAD+ levels through the salvage pathway in the liver, skeletal muscle, and white adipose tissue (WAT). NAD+ in the liver restores hepatic gene expression changes caused by ageing through 6-month NMN supplementation [15] and improves metabolic dysfunction such as hepatic insulin resistance in obesity models even after 1-week administration [14]. 4-month supplementation of NR also enhances the remodelling of the hepatic circadian transcriptome via the binding of chromatin to basic helix-loop-helix ARNT like 1 (BMAL1) [30], which is one of the main transcription factors that regulate circadian rhythm. Additionally, enhancing NAD+ level recovers abnormal rhythmic transcriptome patterns in the liver in a SIRT1-dependent manner, thus regulating the acetylation of period circadian regulator 2 (PER2) [30], which is associated with circadian rhythm negative feedback. These observations highlight the importance of the NAMPT/NAD/SIRT1 axis as a therapeutic target for chronic diseases caused by obesity and ageing [31]. Alcohol-induced hepatic steatosis, which is caused by an excessive intake of alcohol and also contributes to obesity, can be treated by decreasing triglyceride accumulation in a SIRT1-dependent manner [32]. Additionally, previous studies have demonstrated that the anti-obesity and anti-ageing effects of NAD+ in the maternal liver are transgenerational and can thus be passed down to the offspring through epigenetic mechanisms [33,34].

Skeletal muscle makes up most of the total muscle mass in the body and accounts for approximately 40% of the total body mass [35]. Moreover, muscle excitation and contraction are responsible for all body movements. One of the most common ageing-related muscle disorders is sarcopenia, a condition characterized by a decline in muscle volume, strength, and function [35]. Ageing causes the NAD+ levels in the muscles to decrease, thus affecting other metabolic functions. Similarly, obesity diminishes muscle mass and power, thus impairing exercise capacity and lipid oxidation [36]. In humans, supplementation with NAD+ precursors enhances NAD+ metabolism in the muscle [17] and improves muscular insulin signalling [16], albeit without significant changes in muscle metabolism [17]. However, another study demonstrated that the physiological alterations caused by ageing and HFD-induced metabolic stress could be alleviated via NAD+ supplementation in a mouse model [15,37]. Additionally, muscle-specific *Nampt* knockout mice exhibited mitochondrial dysfunction and muscle weakness that is reversible with NR supplementation [38]. Therefore, the differences in the effects of NAD+ in muscle and liver tissues suggest that the mechanisms of NAD+ metabolism vary in a tissue-specific manner.

In addition to the liver and muscle, other tissues have also been reported to benefit from NAD+ supplementation. In the brain, NMN treatment improves neurological function and protects against brain damage including forebrain ischaemia and hippocampus injury [39]. In the heart, boosting NAD+ prevents NAD+ depletion during ischaemia and protects against reperfusion injury through SIRT1-mediated forkhead box protein O1 (FOXO1) deacetylation [40]. Moreover, enhancing NAD+ levels can promote reproductive health in a sex-dependent manner. In females, both NMN and NR treatment restores ovary quality [41,42] thus improving fertility indicators such as litter size, live birth, and ovulation rate. In contrast, increased NAD+ levels in the testis have been linked to reductions in sperm count and vitality and increased sperm oxidative DNA damage [43]. However, given that these results varied

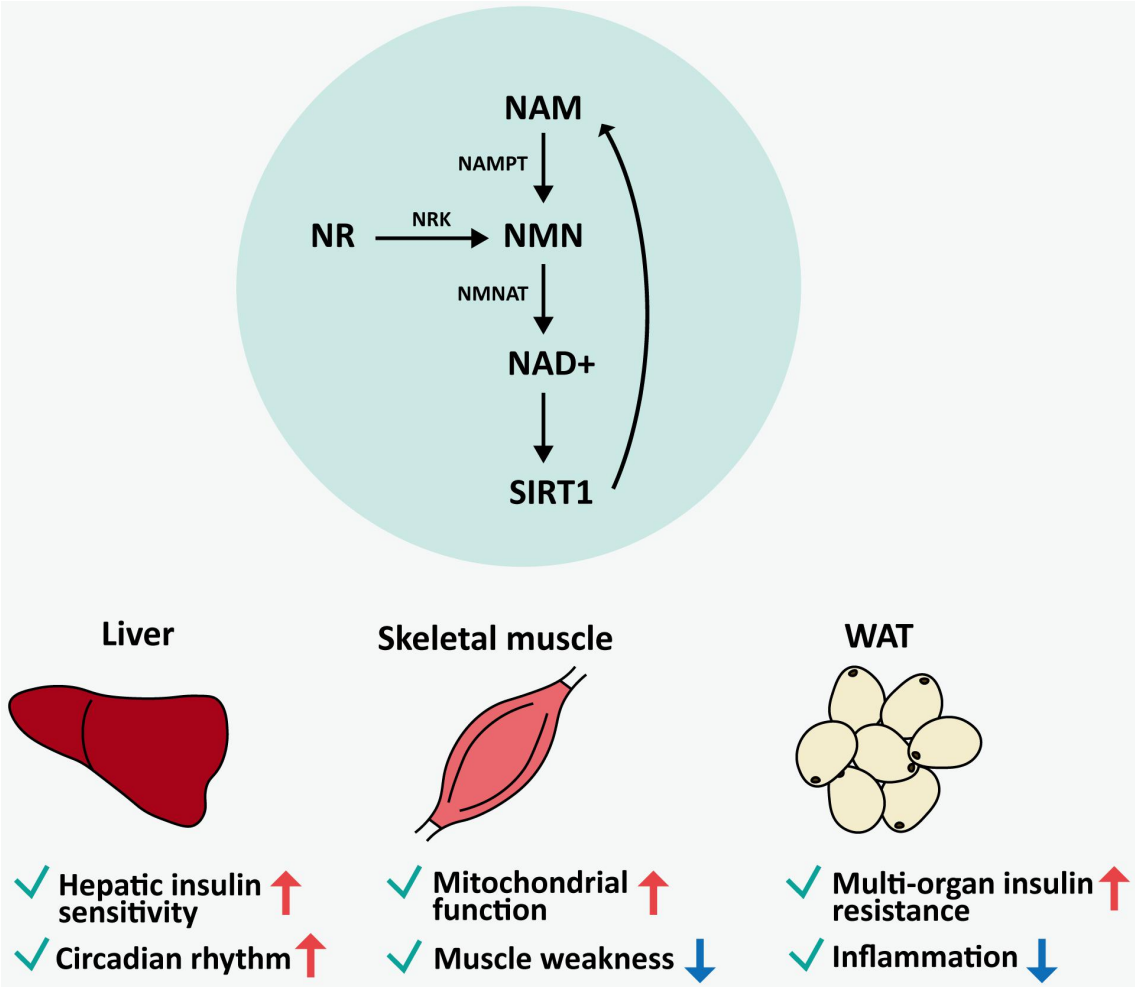

Figure 2. Effects of boosting NAD+ through the NAD+ salvage pathway by SIRT1 in the liver, skeletal muscle, and white adipose tissue. NMN is synthesized from NAM and NR by NAMPT and NRK, respectively. The synthesized NAD+ from NMN is used as a SIRT1 substrate, which leads to the recycling of NAD+ via the salvage pathway. In this process, NAD+ can exert different effects depending on the tissue. NAMPT, nicotinamide phosphoribosyltransferase; NAM, nicotinamide; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; NRK, nicotinamide riboside kinase; NMNAT, nicotinamide mononucleotide adenylyltransferase; NAD+, reduced form of nicotinamide adenine dinucleotide; SIRT1, sirtuin 1.

depending on the method of NAD+ supplementation [43], no clear relationship has been identified between male fertility and NAD+. Moreover, NAD+ boosters also possess renoprotective effects, anti-inflammatory effects in lymphoid tissue, and increase insulin sensitivity in the pancreas [12]. Most studies in WAT have focused on genetic models rather than investigating systemic effects of NAD+, and therefore these effects and current research discrepancies will be discussed in the next section.

4. Metabolic effects of boosting NAD+ in white adipose tissue

Adipose tissue stores fat to produce energy but is also an endocrine organ that receives signals and secretes endocrine factors to regulate many important metabolic functions [44]. Adipose tissue mainly consists of brown and white adipose tissue (BAT and WAT), which have different functions and structures. BAT consists of multilocular fat cells that contain a large number of mitochondria. Additionally, uncoupling protein 1 (UCP1) is mostly expressed in BAT and is involved in the release of energy as a heat [45]. In contrast, WAT cells contain a single lipid droplet and few mitochondria [45] and mainly function as a fuel storage [46]. WAT also regulates immune response, inflammation, and glucose metabolism via the endocrine system. Particularly, WAT controls leptin, which in turn modulates many other functions including appetite and energy expenditure [46]. Among the many proteins secreted by WAT, visfatin is an adipocytokine that is known to improve insulin resistance and activates insulin

receptors, thereby exerting anti-diabetic effects [19]. Interestingly, visfatin is in fact extracellular NAMPT originating from WAT, suggesting that the NAD regulator in WAT is a promising therapeutic target for the treatment of metabolic disorders.

Studies on NAD+ precursor supplementation have mainly focussed on its effects in the liver [14,15,30,33,34,47] and the muscle [15–17,37], whereas very few studies have explored its role in WAT. However, recent studies have provided novel and promising insights into the effects of boosting NAD+ on WAT (Table 1), as well as the adipose-specific effects of NAMPT (Table 2). NMN and NR supplementation has been shown to reduce body weight and enhance insulin sensitivity in aged chow-fed wild-type mice and die-induced obese mice, respectively [15,47]. NAM supplementation reduced fat accumulation in diet-induced obese mice [48]. Additionally, both NMN and NR supplementation prevented inflammation even with different treatment durations [15,47]. NAM administration increased mitochondrial biogenesis and glutathione synthesis in WAT [48]. Similarly, another study reported that NMN treatment in HFD-induced type 2 diabetes mouse model promoted the recovery of glutathione S-transferase alpha 2 (*Gsta2*) gene expression in the liver [14]. Given that various effects were observed depending on the types of tissue, additional research is needed to elucidate the molecular mechanisms underlying the health-promoting effects of NAD+, as well as their tissue-specific variations.

Tissue-specific functions of NAMPT using genetically modified mouse models have been investigated (Table 2). Due to the importance of NAMPT in the NAD+ salvage pathway, several studies have investigated the functions of NAMPT in a variety of tissues such as the liver, muscle, and fat [20–23,38,49–52] using genetically modified mouse models with ubiquitous and tissue-specific deletion. Dall and colleagues reported that the liver-specific *Nampt* knockout model exhibited only minor metabolic changes despite a 50% decrease in liver NAD+ levels [50]. In contrast, *Nampt* muscle-specific knockout mice had increased body weight with reduced muscle mass and impaired muscle function such as myonecrosis [38]. Ubiquitous homozygous knockout was lethal in mice [49], suggesting that NAMPT plays a vital role in systemic functions and may even participate in early development. Another mouse model with ubiquitous deletion generated by mating *Nampt* exon 2-floxed mice and inducible ubiquitin C-Cre mice resulted in death within 5–10 days upon tamoxifen treatment. Before dying, the mice exhibited rapid weight loss, which was accompanied by high serum triglyceride levels and attenuation of metabolic processes including glucose and fatty acid metabolism in the liver [49]. Moreover, visceral fat was dramatically depleted [49], indicating a potential role of NAMPT in adipose tissue homoeostasis.

Similarly, adipocyte-specific *Nampt* knockout mice, generated by mating exon 3-floxed mice and adiponectin-Cre mice, exhibited reduced fat mass [23]. The results were consistent with the results from *in vitro* experiments with 3T3-L1 cell lines investigating the function and mechanism of NAMPT in adipocytes [13,20,53–55]. In the process of adipocyte differentiation, genes associated with NAD+ synthesis via the salvage pathway were significantly up-regulated [54]. Treatment of the NAMPT inhibitor FK866 significantly blocked adipocyte differentiation [54] and lipid synthesis [53] *in vitro*, confirming the crucial role of NAMPT in these processes. In terms of circadian rhythm, adipocyte-specific *Nampt* deletion targeting exon 3 showed disrupted circadian transcriptome

Table 1. Effects of NAD+ precursors in white adipose tissue[1].

Supplementation	Sex	Age	Systemic results	Results in WAT	Ref
12 months NMN (300 mg/kg) fed normal diet	♂	5-month-old	• Suppressed age-associated weight gain • Maintained food and water consumption level • Improved insulin sensitivity	• Decreased tendency of fat mass • Down-regulated biological pathways associated with immune function and inflammation in WAT	[15]
3 weeks NAM (37.5 mg/g) fed high fat diet (60 kcal% fat)		4-week-old	• Reduced body weight	• Reduced fat accumulation • Enhanced mitochondrial biogenesis and functions in WAT • Increased glucose-derived glutathione biosynthesis	[48]
20 weeks NR (400 mg/kg) Fed high fat/sucrose/ cholesterol diet (34 kcal% fat)	♀	8 or 16-week-old	*8-week-old (young mice)* • Unaltered body weight • Unaltered insulin sensitivity *16-week-old (old mice)* • Reduced body weight • Increased metabolic rate, energy expenditure, and physical activity	*8-week-old (young mice)* No result *16-week-old (old mice)* • Reduced fat mass • Improved insulin sensitivity and glucose tolerance • Reduced fibrosis and inflammation in WAT	[47]

[1]C57BL/6N wild type mice were used as models in all references.

Table 2. Evidence of NAMPT function based on NAMPT genetically modified mouse models.

Model	Target tissue	Target location	Sex	Age (months)	Systemic results	Results in tissues	Ref
Nampt floxed & Ubc-Cre mice	Ubiquitous	Exon 2	-	-	• Reduced body weight (20% loss) • Abnormal serum lipid profile • Delayed metabolic and biosynthetic processes in the liver	• Depleted fat tissue	[49]
			♀	2–6	• Unchanged body weight • Decreased plasma eNAMPT levels in both fed and fasted condition • Decreased NAD+ levels in the hypothalamus • Decreased physical activity during dark periods	• Unchanged fat mass	[51]
Nampt^{tm1Oleo}/ImaiJ & Adiponectin-Cre mice	Fat	Exon 5–6		2–9	• Unchanged body weight • Multiple organ insulin resistance	• Unchanged fat mass • Increased inflammation and dysfunction in WAT but not systemic inflammation • Decreased expression of obesity-linked target genes in WAT	[20]
			-	-	• Decreased rectal temperature during cold exposure • Decreased oxygen consumption	• Impaired adrenergic-mediated lipolytic activity in WAT	[21]
			-	3~	• Insulin resistance • Unaltered energy expenditure and food intake • Impaired whole-body metabolic flexibility such as RQ value and glucose/fat oxidation	• Upregulation of genes associated with inflammation and oxidative stress in WAT • Downregulation of genes associated with lipolysis and mitochondrial oxidative metabolism in WAT	[22]
Nampt^{tm1Oleo}/ImaiJ & Myosin light-chain 1f (*Mlc1f*)-Cre mice	Muscle		♂/♀	3–7	• Increased body weight	• Decreased muscle mass • Myonecrosis and progressive loss of muscle function • Stimulation of pathways related to muscle injury, inflammation, and immune response	[38]
Nampt^{tm1Jtree} & Adiponectin-Cre mice	Fat	Exon 3	♂	5–9	• Resistant to HFD-induced obesity • Decreased food intake • Improved glucose tolerance	• Reduced fat mass • Decreased adipocyte marker gene expression in WAT • Massive fibrosis in WAT	[23]
			♂	-	• Unchanged food intake • Unchanged physical activity	• Disrupted circadian transcriptome in WAT and BAT • Abolished biorhythms of energy metabolism in BAT • Increased cold tolerance without rhythmicity changes in BAT	[52]
Nampt floxed & Albumin-Cre mice	Liver		♀	2–6	• Unchanged body weight • Unchanged insulin sensitivity and glucose tolerance	• Unchanged liver weight • Unaltered mitochondrial respiratory function in liver	[50]

in WAT and BAT [52]. Especially in BAT, disrupted rhythm of metabolites in energy metabolism occurred [52], indicating that fat tissue controls peripheral clock leading to regulate metabolic biorhythms in NAMPT-dependent manner. However, despite under the same mouse model, food intake was differently reported [23,52] which might be due to other factors such as age of mice.

Another adipocyte-specific *Nampt* knockout model obtained by mating exon 5–6-floxed mice and adiponectin-Cre mice showed inconsistent results [20–22,51]. The mouse model did not show changes in fat mass compared to the wild-type [20,51], although systemic insulin resistance was detected [20,22]. Despite a lack of significant effects on fat mass, the model exhibited impaired lipolysis and elevated inflammation levels in WAT [20,22], which was consistent with previous reports showing the anti-inflammatory effects of NMN supplementation in wild-type mice [15,47]. The inconsistent results regarding the effects of NAMPT on fat mass might be attributed to differences in the sex and age of the experimental organisms and/or the knockout strategy employed to obtain the models. Sex-dependent metabolic differences have previously been explored in mouse studies [56] and the results have demonstrated that males became leaner in response to food restriction, whereas females exhibited more fat accumulation to protect themselves from energy imbalances. The increased energy storage capacity of females is a consequence of menstrual periods, which was linked to differences in sex hormones [57]. These differences might contribute to sex-specific differences in transgenerational inheritance of metabolic stress, as reported in previous studies [58,59].

Additionally, the effects of NMN on adipogenic differentiation remain unclear [53–55]. NMN

supplementation significantly recovered adipogenesis, which was hindered by NAMPT inhibition via FK866 treatment [53,54]. However, NMN did not seem to affect adipogenesis when NAMPT was not inhibited [55]. These results suggest that the effects of NMN treatment vary depending on the availability of NAMPT in adipocytes. Therefore, additional studies are needed to understand the roles of NAD+ precursors and NAMPT in the regulation of adipocyte development and metabolism.

5. Conclusion

NAD metabolism is a central pathway involved in energy and redox homoeostasis, which in turn determines the risk of chronic disease and ageing. Moreover, current studies have suggested that the roles and effects of NAD are tissue-specific. Enhancing NAD+ improves hepatic insulin sensitivity and circadian rhythm in the liver, while also promoting mitochondrial function in the muscle. Although few studies have assessed the effects of NAD+ metabolism on WAT, current evidence suggests that supplementation with NAD+ precursors reduce fat accumulation and inflammation in fat tissue. Nevertheless, research on the direct effects of NAD+ metabolism on adipocytes using the adipocyte-specific *Nampt* deletion mouse model or *in vitro* cell models has rendered inconclusive results, which might be attributed to sex or age differences, and/or basal levels of cellular NAD+ availability, respectively. Further studies are thus needed to fully understand the effects of NAD+ supplementation and the distinct functions of NAMPT in adipocytes.

Disclosure statement

There are no relevant financial or non-financial competing interests to report.

Funding

This work was funded by the National Research Foundation (funded by the Korea government 2021R1A2C2012578).

Abbreviations

ACMS	α-amino-β-carboxymuconate-ε-semialdehyde;
BAT	brown adipose tissue;
BMAL1	basic helix-loop-helix ARNT like 1;
CD38	cluster of differentiation 38;
CR	calorie restriction;
FOXO1	forkhead box protein O1;
GSTA2	glutathione S-transferase alpha 2;
HFD	high-fat diet; NA, nicotinic acid;
NAD	nicotinamide adenine dinucleotide;
NAM	nicotinamide;
NAMPT	nicotinamide phosphoribosyltransferase;
NMN	nicotinamide mononucleotide;
NMNAT	nicotinamide mononucleotide adenylyltransferase;
NR	nicotinamide riboside;
PARP	poly (ADP-ribose) polymerase;
PER2	period circadian regulator 2;
SIRT	sirtuin;
UCP1	uncoupling protein 1;
WAT	white adipose tissue.

Author contributions

Park YJ has made contributed to the conceptualization, study design, and funding acquisition. Under Park JY's supervision, Kwon SY performed data collection and prepared a manuscript. The final manuscript underwent review and editing by all authors.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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