

## Spotlight

NR Supplementation  
During Lactation:  
Benefiting Mother and  
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**Abnormal nicotinamide adenine dinucleotide (NAD<sup>+</sup>) metabolism causes a wide spectrum of diseases. A recent study (*Cell Rep.* 2019;26:969–983) shows that postpartum NAD<sup>+</sup> homeostasis is depressed. By restoring NAD<sup>+</sup> homeostasis, maternal nicotinamide riboside (NR) supplementation during lactation enhances postpartum weight loss, as well as juvenile development and adult neurogenesis in the offspring.**

NAD<sup>+</sup> acts as a classical cofactor for many redox reactions, such as glycolysis and oxidative phosphorylation. It also functions as a cosubstrate for NAD<sup>+</sup>-consuming enzymes, including the sirtuin deacetylases (SIRTs), poly-ADP-ribose polymerases (PARPs), and the cyclic ADP-ribose (cADPR) synthases, such as CD38 and CD157 [1]. Dysregulated NAD<sup>+</sup> metabolism is frequently implicated in ageing and metabolic disorders characterized by mitochondrial dysfunction [1,2]. Conversely, raising and maintaining NAD<sup>+</sup> levels by supplementation with NAD<sup>+</sup> precursors or intermediates has been shown to be of great therapeutic potential in preclinical animal models [3,4].

Lactation during the postpartum period represents a highly energy- and nutrient-demanding physiological process that is crucial for the normal development of newborn mammals. However, little is known about the role of NAD<sup>+</sup> metabolism in this

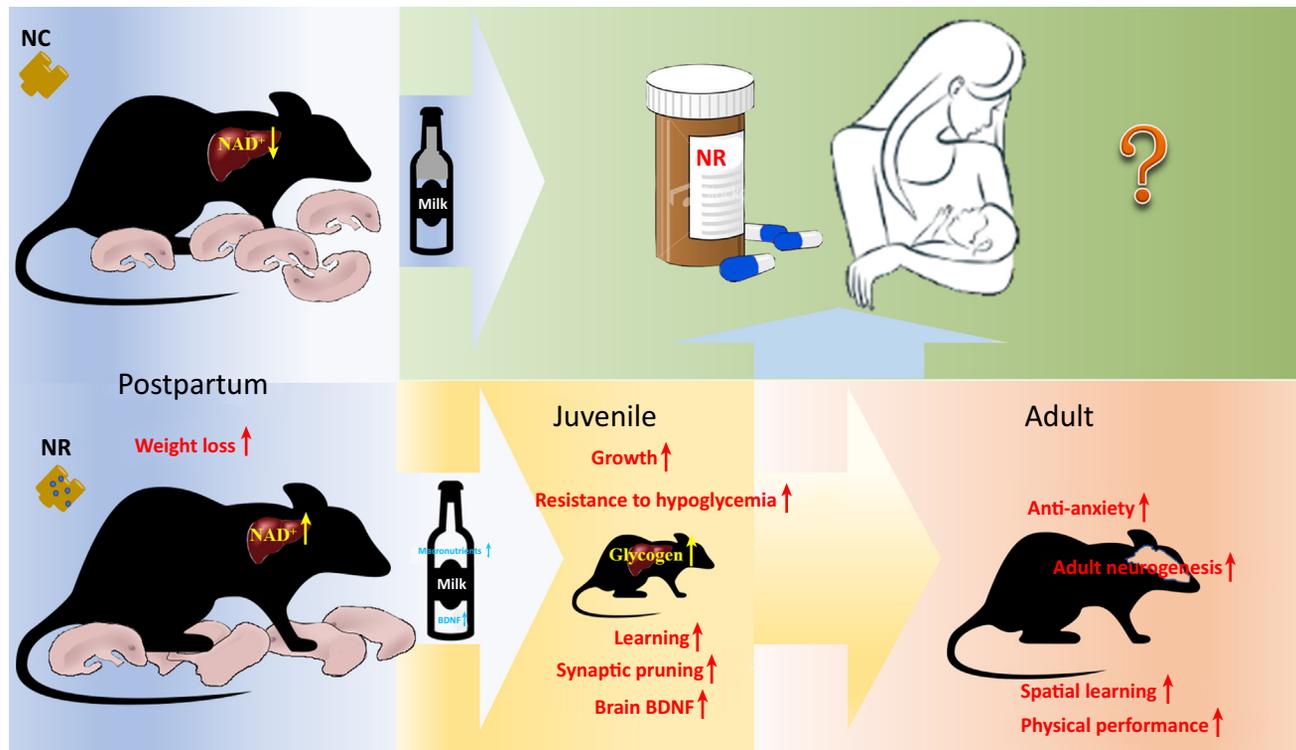
energetically and nutritionally unfavorable process. A recent study published in *Cell Reports* by Ear *et al.* [5] has systematically investigated NAD<sup>+</sup> metabolism at the maternal-offspring interface during lactation in rodent models. Based on the approach of quantitative targeted NAD metabolomics, the authors have found that NAD<sup>+</sup> in the liver is dramatically reduced in postpartum mothers (Figure 1), while NAD metabolites in the circulation are increased to enable a >20-fold higher level of NAD metabolites in the lactating mammary glands. The NAD<sup>+</sup> reallocation from liver to the mammary glands suggests that NAD<sup>+</sup> may be a limiting resource during lactation. Similar to the roles of organ remodeling during lactation, one may speculate that these adaptive changes in NAD<sup>+</sup> metabolism in postpartum mothers are also critical for the functions of milk production. An important question is whether raising NAD<sup>+</sup> by supplementing the mothers with NAD<sup>+</sup> precursors can ameliorate the metabolic stress induced by the NAD<sup>+</sup> reallocation during lactation and therefore improve both maternal health and offspring development.

To answer this question, the authors have asked specifically whether the depressed liver NAD<sup>+</sup> during postpartum can be restored by oral supplementation of NR, which is an NAD<sup>+</sup> precursor in eukaryotes and also a natural nutrient found in milk [6]. It has been established that NR can be converted to NAD<sup>+</sup> by nicotinamide mononucleotide adenylyltransferases (NMNATs) after phosphorylation to nicotinamide mononucleotide (NMN) by nicotinamide riboside kinase, Nrk1/2 [7,8]. Importantly, NR is orally available and has been tested in many preclinical animal and human studies for elevation of NAD<sup>+</sup> level [4,9]. The result shows that maternal NR supplementation during lactation not only restores liver NAD<sup>+</sup> to a level even greater than that in nonlactating females (Figure 1) but also super-induces both

circulating and mammary NAD metabolome. Interestingly, by relieving the metabolic stress in the postpartum liver, NR supplementation confers a number of benefits on both the mothers and their offspring (Figure 1).

One benefit for mothers is that NR supplementation is sufficient to promote postpartum weight loss, which is a common challenge faced by many mothers. Another benefit is that NR supplementation enhances lactation, reflected mainly by increased milk production and nursing behavior, which is supported by an accelerated mammary remodeling and a higher level of prolactin in both the pituitary and circulation. Thus, the increased postpartum weight loss may be a direct result of the increased lactation output. Mobilized maternal metabolism by NR supplementation is the key to promote the transmission of macronutrients (fat, carbohydrate, and protein) to milk. Consistently, mammary biosynthetic programs for these macronutrients are also elevated by maternal NR supplementation, as evidenced by increased mammalian target of rapamycin (mTOR) pathway for protein biosynthesis and increased expression of genes involved in lactose and lipid biosynthesis.

Directly benefiting from the increased provision of milk and nursing care, juvenile offspring from NR-supplemented mothers grow faster than those from nonsupplemented mothers and are more resistant to fasting-induced hypoglycemia due to the higher glycogen storage in liver. These juvenile offspring have better neurodevelopment, as indicated by advanced synaptic pruning and enhanced learning ability. Benefits for offspring from mothers with NR supplementation persist into adulthood, with lower body fat and substantial advantages in physical performance, anti-anxiety, spatial memory, and delayed onset of behavioral immobility. Importantly, brain



## Trends in Endocrinology &amp; Metabolism

**Figure 1. Maternal NR Supplementation Confers Multiple Benefits on Mother and Offspring.** Liver NAD<sup>+</sup> is depressed in postpartum mothers. Maternal NR supplementation during lactation restores liver NAD<sup>+</sup> level, enhances postpartum weight loss, and promotes milk production with increased transmission of macronutrients and BDNF to the nursing neonates. Juvenile offspring from NR-supplemented mothers grow faster than those from nonsupplemented mothers and are more resistant to fasting-induced hypoglycemia due to the higher glycogen storage in liver. They also show enhanced learning ability, advanced synaptic pruning, and increased brain BDNF. Adult offspring from mothers with NR supplementation exhibit substantial advantages in physical performance, anti-anxiety, spatial learning, and hippocampal neurogenesis. Translation of these findings to humans will be of great significance. BDNF, Brain-derived neurotrophic factor; NAD<sup>+</sup>, nicotinamide adenine dinucleotide; NC, normal chow; NR, nicotinamide riboside.

weight and hippocampal neurogenesis in adult offspring are increased by maternal NR supplementation, which may be responsible for the improved neurobehavioral traits. By transmitting a greater volume of milk, NR-supplemented mothers also deliver more micronutrients in addition to macronutrients. Brain-derived neurotrophic factor (BDNF) is a strong candidate for the key micronutrients that drive the heightened adult neurogenesis, as higher levels of BDNF are found in the brain of juvenile offspring from mothers supplemented with NR, as well as in the mammary glands and milk of NR-supplemented mothers. Possibly, other unknown beneficial bioactive factors may also be involved and are worth

future analysis. For example, the authors have found that transmission of NAD metabolites to milk is also enhanced by maternal NR supplementation, although it is unclear whether they play a direct role in these beneficial effects on the offspring.

In conclusion, maternal NR supplementation during lactation, at least in rodents, is protective for their offspring during juvenile and adult stages in physical and neurobehavioral development, through improved NAD<sup>+</sup> metabolism. This study indicates that a new mother's dietary supplement choices may have an immediate impact on maternal and neonatal health, and long-lasting effects on the future

health of their offspring. These discoveries by Ear *et al.* [5] are important and intriguing. Nonetheless, the molecular mechanisms underlying these observations are not yet fully understood and warrant further study. For example, the impact of maternal NAD<sup>+</sup> supplementation on offspring epigenetic modifications in early life may be responsible for their improved health during the adult stage. Considering the timing of neurodevelopment, the lactation period in rodents may be more comparable with the third trimester of pregnancy in humans. So perhaps one of the most important questions is: do these reported phenomena also occur in humans (Figure 1)? Translating these

findings to humans is potentially of great clinical significance for both maternal health and childhood development. NR has been shown to be well tolerated and is generally considered safe as a dietary supplement in humans [9,10]. However, future clinical trials are needed to determine the potentially exciting benefits of NR at the maternal–offspring interface.

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### References

- Imai, S.-i. and Guarente, L. (2014) NAD<sup>+</sup> and sirtuins in aging and disease. *Trends Cell Biol.* 24, 464–471
- Belenky, P. et al. (2007) NAD<sup>+</sup> metabolism in health and disease. *Trends Biochem. Sci.* 32, 12–19
- Katsyuba, E. and Auwerx, J. (2017) Modulating NAD<sup>+</sup> metabolism, from bench to bedside. *EMBO J.* 36, 2670–2683
- Rajman, L. et al. (2018) Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. *Cell Metab.* 27, 529–547
- Ear, P.H. et al. (2019) Maternal nicotinamide riboside enhances postpartum weight loss, juvenile offspring development, and neurogenesis of adult offspring. *Cell Rep.* 26, 969–983
- Bieganowski, P. and Brenner, C. (2004) Discoveries of nicotinamide riboside as a nutrient and conserved NRK genes establish a Preiss-Handler independent route to NAD<sup>+</sup> in fungi and humans. *Cell* 117, 495–502
- Belenky, P. et al. (2007) Nicotinamide riboside promotes Sir2 silencing and extends lifespan via Nrk and Urh1/Pnp1/Meu1 pathways to NAD<sup>+</sup>. *Cell* 129, 473–484
- Ratajczak, J. et al. (2016) NRK1 controls nicotinamide mononucleotide and nicotinamide riboside metabolism in mammalian cells. *Nat. Commun.* 7, 13103
- Trammell, S.A.J. et al. (2016) Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. *Nat. Commun.* 7, 12948
- Martens, C.R. et al. (2018) Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD<sup>+</sup> in healthy middle-aged and older adults. *Nat. Commun.* 9, 1286

## Spotlight

### Anticatabolic Effects of Ketone Bodies in Skeletal Muscle

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**The ketone bodies acetoacetate (AcAc) and β-hydroxybutyrate (βHB) are the subject of renewed interest given recently established pleiotropic effects regulating inflammation, oxidative stress, and gene expression. Anticatabolic effects of β-hydroxybutyrate have recently been demonstrated in human skeletal muscle under inflammatory insult, thereby expanding upon the wide-ranging therapeutic applications of nutritional ketosis.**

AcAc, βHB, and acetone are lipid-derived ketone bodies whose production is amplified through ketogenesis during fasting, starvation, and carbohydrate restriction [1]. Metabolic effects of AcAc and βHB in many organs are well established, including anticatabolic processes such as attenuation of glycolysis, hepatic glucose output, and adipose tissue lipolysis [1]. Among more recent discoveries are the pleiotropic effects of βHB as a signaling metabolite regulating oxidative stress, inflammation, and gene expression [2]. Renewed scientific interest into the

therapeutic and performance potential of ketone bodies has emerged with the development of ingestible exogenous ketone supplements [3]. These compounds rapidly induce nutritional and/or therapeutic ketosis without dietary restriction.

A growing area of interest is the anabolic and anticatabolic potential of ketone bodies in skeletal muscle provided by therapeutic ketosis. Thomsen and colleagues [4] have recently made a significant contribution to this paradigm by examining both the anticatabolic and anabolic potential of βHB in human skeletal muscle under an acute inflammatory insult provided by lipopolysaccharide (LPS) endotoxin. This is salient because with aging, cancer, HIV/AIDS, chronic heart and renal failure, chronic obstructive pulmonary disease, and rheumatoid and osteoarthritis, dramatic losses in muscle mass and function are often observed. Additionally, a pathological decline in skeletal muscle health is not only a strong predictor of mortality, but also predicts a reduced ability to receive, tolerate, and respond to disease burden and/or standard of care therapies [5]. However, with minimal to no anticatabolic therapeutic options, novel mitigation strategies are critical for altering disease course and improving patient outcomes.

Therapeutic strategies for skeletal muscle health primarily address muscle protein turnover; the continuous process of synthesis and degradation of skeletal muscle proteins. The balance between the rates of muscle protein synthesis (MPS) and degradation (muscle protein breakdown; MPB) determines changes in skeletal muscle mass in both acute and long-term scenarios. Inflammation is a primary factor and/or underlying characteristic of many atrophy-related conditions, including those impacting on skeletal muscle, likely through augmenting MPB, and/or attenuating MPS (Figure 1).