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Abstract

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Full Text

Effects of Nicotinic Acid on Energy Metabolism in Transition Dairy Cows and Its Regulatory Mechanism

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Abstract: The transition period represents a critical phase in the lactation cycle of dairy cows. During this time, cows undergo dramatic physiological changes characterized by enhanced metabolism, oxidative stress, and altered immune function, leading to negative energy balance (NEB) and increased incidence of energy metabolism disorders. Nicotinic acid plays a vital regulatory role in glucose and lipid metabolism in transition dairy cows. This review synthesizes recent research on the effects of nicotinic acid on energy metabolism and its underlying regulatory mechanisms, aiming to provide a reference for further investigation and rational application of nicotinic acid during this crucial period.

Key words: nicotinic acid; transition dairy cow; energy metabolism; regulation; mechanism

The transition period, comprising the prepartum (21 days before calving) and postpartum (21 days after calving) phases, represents a unique physiological

stage in the lactation cycle of dairy cows, also known as the transition phase. During this period, cows are highly susceptible to stress and negative energy balance (NEB), making it a disease-prone interval. Approximately 75% of dairy cow diseases occur within one month postpartum [?], severely constraining the development of the dairy industry. Implementing rational and effective nutritional strategies to regulate energy metabolism is therefore of paramount importance.

Nicotinic acid (NA), also known as niacin, is a water-soluble B-vitamin that converts to biologically active nicotinamide (NAM) in animals. As a component of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), NA participates in both anabolic and catabolic metabolism, exerting important influences on carbohydrate, lipid, and protein metabolism. Research on NA supplementation in transition dairy cows has gradually increased, though its regulatory mechanisms in energy metabolism remain incompletely understood. This review summarizes recent applications of NA in transition dairy cows and its effects on glucose and lipid metabolism, providing foundational information for further research and rational application.

1. Research Status of NA in Dairy Cows

Under normal conditions, dairy cows obtain NA through three pathways: dietary intake, conversion from tryptophan and quinolinic acid, and rumen microbial synthesis, which generally meets their requirements. However, during the transition period, dry matter intake (DMI) declines sharply, reducing NA intake from feed. Simultaneously, to meet nutritional demands, cows undergo dietary transitions with varying nutrient compositions, altering rumen microbial flora and affecting ruminal NA synthesis. Niehoff et al. [?] found that different forage-to-concentrate ratios significantly affected NAM concentrations in blood and milk, speculating that high-concentrate diets facilitate greater NA passage to the duodenum, where NA is rapidly converted to NAM. Studies have shown that NA supplementation improves production performance in transition dairy cows [?], further indicating that endogenous NA is insufficient to meet metabolic and production demands during this critical period.

According to NRC (2001), dairy cows require only small amounts of NA for physiological needs. However, when fed the recommended dosage, most NA is degraded or utilized by rumen microorganisms, resulting in a bioavailability of only 5% [?]. Moreover, Schwab et al. [?] conducted a meta-analysis showing that feeding recommended levels of NA had no significant effect on production performance. Consequently, recent studies have recommended using rumen-protected technology (Table 1 [?, ?]) or abomasal infusion of NA [?, ?] to increase rumen bypass rate and reduce ruminal losses, thereby effectively exerting NA's biological functions [?, ?]. Additionally, when high doses of NA are fed, even small amounts reaching the small intestine can exert biological effects [?, ?]. The authors compiled recent studies on NA supplementation in transition dairy cows, with results summarized in Table 2 [?, ?, ?].

Table 1: Existing Rumen-Protected Niacin Products

Effective content/%	Manufacturers	Reference
	USA Balchem	Yuan et al. [3]; Morey et al. [7]; Zimbelman et al. [8]
	USA Quali	Wrinkle et al. [9]

Table 2: Effects of Niacin on Blood Parameters and Performance of Transition Dairy Cows

Supplemental level	Start time/d	Trial period/d	Blood glucose	Blood NEFA	Performance	Reference
Holstein cow	0, 24 g/d	P				Morey et al. [7]
Holstein cow	0, 12 g/d	P				Yuan et al. [3]
Holstein cow	0, 48 g/d	N				Aragona et al. [4]
Holstein cow	0, 24 g/d	N				Tienken et al. [11]
Egyptian buffalo	0, 6, 12 g/d	N				El-Barody et al. [12]
Holstein cow	0, 24 g/d	N				Kinoshita et al. [13]
Holstein cow	0, 34, 68 g/d	N				Chamberlain et al. [14]

Note: +: increase; -: decrease; 0: no effect; ND: not determined. N: non-rumen-protected niacin; P: rumen-protected niacin. Start time was set as 0 d on parturition day.

2. Regulatory Effects and Mechanism of NA on Negative Energy Balance in Dairy Cows

During the transition period, dairy cows undergo physiological changes from pregnancy through parturition to lactation, requiring substantial nutrients (carbohydrates, lipids, proteins, etc.) [?]. However, due to sharply decreased DMI during calving and the influence of hormones such as leptin, nutrient intake falls far below consumption, resulting in NEB that primarily occurs during the postpartum period [?], along with negative protein balance [?]. Research indicates that postpartum energy intake accounts for only 80% of requirements, with protein negative balance being even more severe than NEB during early lactation [?].

2.1 Lipid Metabolism

Normally, transition dairy cows alleviate NEB through body fat mobilization, with adipose tissue releasing large amounts of non-esterified fatty acids (NEFA) for hepatic metabolism. However, the liver's capacity to metabolize NEFA is limited, and excessive fat mobilization can lead to ketosis and fatty liver, compromising liver health and immune function.

NA is widely recognized as a feed additive with anti-lipolytic effects, and its primary mechanism is relatively well understood. Upon entering the body, NA immediately binds to the G-protein-coupled receptor 109A (GPR109A) in adipose tissue. Studies have shown that NA binds to GPR109A within 5 minutes of intravenous injection [?]. This binding inhibits adenylate cyclase activity in adipocytes, thereby reducing cyclic adenosine monophosphate (cAMP) levels and suppressing lipolysis. Recent research indicates that GPR109A is expressed not only in adipose and immune tissues but also in bovine brain and liver [?]. Additionally, Ganji et al. [?] demonstrated in vitro using mouse hepatocytes that NA non-competitively inhibits diacylglycerol acyltransferase 2 (DGAT2), a key rate-limiting enzyme in triglyceride (TG) synthesis, reducing TG synthesis and lipoprotein secretion and thereby preventing metabolic diseases such as fatty liver. Some studies still report no reduction in blood NEFA concentration with NA supplementation, possibly related to supplementation method, dosage, timing, and sampling time.

Interestingly, Martinez et al. [?] found that NA supplementation in lactating cows actually increased blood NEFA concentration, similar to some findings in human medicine [?]. Researchers speculated this might result from NA increasing lipoprotein lipase activity, promoting TG breakdown and consequently elevating NEFA levels. Furthermore, when NA supplementation ceases, blood NEFA concentration rebounds rapidly [?], possibly related to supplementation level and duration, further demonstrating NA's inhibitory effect on fat mobilization [?, ?, ?]. Some researchers propose that NA regulates phosphodiesterase gene expression in adipose tissue; phosphodiesterase reduces cAMP bioactivity, so decreased expression leads to rapid increases in lipolysis. When NA sup-

plementation is abruptly stopped, its suppressive effect on phosphodiesterase expression disappears, exacerbating lipolysis and causing a sudden NEFA rebound [?].

After supplementation, NA is rapidly converted to NAM, which is the transport form of NA in animals and exists at much higher concentrations than NA [?, ?]. However, compared to NA, NAM has low sensitivity for GPR109A and is generally considered to lack anti-lipolytic effects [?], with limited research in dairy cows. Recent studies in rodents and pigs have found that NAM enhances adipogenesis and reduces lipolysis in adipocytes or tissues [?]. Li et al. [?] suggested that NAM can promote lipid synthesis in bovine adipocytes, primarily by inhibiting silent information regulator 2-related enzyme 1 (SIRT1) deacetylase activity. SIRT1 is an NAD-dependent histone deacetylase belonging to the Sirtuins family, closely associated with cell proliferation, differentiation, aging, apoptosis, and metabolism. When SIRT1 is overexpressed in adipocytes, it inhibits adipogenesis and promotes lipolysis through interactions with peroxisome proliferator-activated receptor γ (PPAR γ), PPAR γ coactivator 1 α (PGC1 α), and forkhead box protein O3 (FOXO1) [?].

However, since dairy cows experience NEB during early lactation, mobilizing body fat for energy is a self-regulatory mechanism to meet energy demands and provides important precursors for milk fat synthesis. Simply suppressing lipolysis and reducing NEFA concentration is not the optimal approach to alleviate NEB during this period and may instead compromise production performance [?].

2.2 Glucose Metabolism

Glucose serves as the primary energy source in ruminants, participating in energy and protein metabolism and serving as a crucial precursor for lactose synthesis in the mammary gland. Its metabolic rate and pattern significantly impact energy supply in transition dairy cows. Studies have shown that directly increasing exogenous glucose supply through abomasal infusion or intravenous injection elevates blood glucose concentration, improves lactation performance, reduces β -hydroxybutyric acid (BHBA) concentration, and alleviates NEB [?].

As shown in Table 2, the effects of NA on blood glucose concentration in transition dairy cows are inconsistent across studies. Currently, three potential mechanisms are proposed for NA's glucose-increasing effect: (1) participating in hepatic gluconeogenesis as a component of energy metabolism coenzymes; (2) promoting vasodilation and increasing blood flow; and (3) regulating hormone sensitivity such as insulin. Pires et al. [?] abomasally infused NA in feed-restricted cows and found that blood glucose decreased significantly after glucose injection compared to controls, related to NA's reduction of blood NEFA concentration and alleviation of insulin resistance. However, in a subsequent trial, the same authors found that abomasal NA infusion followed by glucose injection slowed the decline in blood glucose compared to controls, completely opposite to

their previous results [?]. NA' s effects on blood glucose involve not only direct impacts on glucose metabolism but also participation in multiple insulin-related metabolic reactions. Choi et al. [?] found that NA regulates protein kinase B (Akt) and FOXO1 phosphorylation levels, but in directions opposite to insulin. Specifically, NA reduces FOXO1 phosphorylation, increasing its transcriptional activity in liver tissue, enhancing phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) activities, and promoting hepatic gluconeogenesis. However, Kinoshita et al. [?] found that although NA supplementation increased blood glucose concentration in transition dairy cows, it significantly reduced glucose transporter 2 (GLUT2) gene and protein expression in liver tissue without affecting adipose tissue. Researchers speculated this might relate to NA' s kinetic effects, allowing small residues to function in the liver, though the underlying mechanism remains unclear.

Evidently, NA can influence glucose metabolism both indirectly through lipid metabolism and directly by affecting expression of multiple genes and indirectly through hormones and blood metabolites [?]. However, blood glucose is a comprehensive indicator of glucose absorption, production, and utilization, and judging NA' s effects on glucose metabolism solely by blood glucose elevation is insufficient; deeper parameters are needed to understand its mechanisms. Currently, the regulatory mechanisms of NA on glucose metabolism in transition dairy cows remain unclear, necessitating further research on NA' s effects on hepatic gluconeogenic capacity and glucose output.

2.3 Insulin

Insulin plays a crucial role in carbohydrate, lipid, and protein metabolism. During the transition period, particularly at parturition and early lactation, insulin resistance commonly occurs, which is believed to help reduce glucose utilization by peripheral tissues and ensure energy supply for the dam and fetus. At parturition, the sharp increase in NEFA concentration due to body fat mobilization is the primary cause of systemic insulin resistance [?]. Zachut et al. [?] conducted glucose tolerance tests during the prepartum and postpartum periods and found tissue-specific insulin resistance in transition dairy cows through comparative analysis of live tissue samples. No insulin resistance was observed in liver tissue, while adipose tissue insulin resistance only occurred in cows with severe body weight loss, primarily due to reduced Akt phosphorylation levels, which decreased phosphorylation of tyrosine residues on insulin receptors and inhibited insulin function [?]. Severe body weight loss may result from excessive prepartum body condition, leading to stronger postpartum fat mobilization [?] and increased NEFA concentration.

Research on NA' s effects on insulin in dairy cows has yielded inconsistent results. Some studies show that 11-hour continuous abomasal infusion of NA improves insulin responsiveness [?], while 74-hour infusion trials show no such effect [?], and NA has no significant effect on insulin signaling pathway proteins in adipose tissue [?]. However, due to the rebound phenomenon of NEFA concentration

after NA supplementation, increased fatty acid circulation may instead induce insulin resistance [?].

Additionally, NA treatment can increase concentrations of growth hormone, epinephrine, adiponectin, and corticosterone in blood, participating in gene expression regulation and cell signaling pathways across multiple tissues [?].

2.4 Stress and Immunity

The transition period is the most critical physiological stage for dairy cows, during which they are prone to energy metabolism disorders. Heat stress further increases the difficulty of navigating this period [?]. Current research shows that NA supplementation can reduce respiration rate, panting score, and rectal temperature, alleviating heat stress in dairy cows [?, ?], possibly by increasing cutaneous blood flow. Since heat-stressed cows primarily dissipate heat through sweating, increased skin blood flow enhances heat loss through the skin. Meanwhile, heat stress conditions increase gene expression of intracellular heat shock proteins 27 and 70, which helps cows resist heat stress damage.

Researchers widely believe that due to high metabolic demands, transition dairy cows universally experience oxidative stress and immunosuppression. The rapidly increasing NEFA and BHBA concentrations during calving can induce oxidative stress in liver tissue, reducing antioxidant capacity [?] and activating the nuclear factor κ B (NF- κ B) signaling pathway, promoting synthesis and release of pro-inflammatory cytokines tumor necrosis factor α (TNF α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β), and triggering inflammatory responses in hepatocytes [?]. Studies show that NA can reduce reduced nicotinamide adenine dinucleotide phosphate oxidase activity, reactive oxygen species production, and pro-inflammatory cytokine interleukin-8 (IL-8) levels in hepatocytes [?], helping maintain liver health and function. Aragona et al. [?] recently found that prepartum NA supplementation increased immunoglobulin G (IgG) concentration in colostrum, improving colostrum quality, which is inseparable from NA's important role in the transition period.

The transition period is a crucial stage in the lactation cycle of dairy cows, and nutrition and management during this phase are extremely important. Regulating metabolism through nutritional strategies to alleviate NEB can prevent and reduce energy metabolism disorders and improve milk production performance. NA can participate in regulating glucose and lipid metabolism, alleviate heat stress, and enhance production performance in transition dairy cows.

However, due to NA's involvement in multiple metabolic pathways, its supplementation level, method, and timing have varying effects on cow metabolism, and the underlying mechanisms remain unclear, requiring further investigation.

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