Induction of Oxidative Stress in Dairy Cows by Non-esterified Fatty Acids and Its Mechanisms: Postprint

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Abstract

Periparturient dairy cows experience lipid mobilization due to negative energy balance, resulting in the release of large amounts of non-esterified fatty acids (NEFA) into the liver and blood. At elevated NEFA concentrations, the balance between the antioxidant system and oxidative system in the body can be altered, and the nuclear factor B signaling pathway and mitogen-activated protein kinase signaling pathway can be activated, while the activation of the nuclear factor E2-related factor 2 signaling pathway is inhibited, inducing inflammatory damage in the body and ultimately leading to oxidative stress in dairy cows, thereby directly affecting the economic efficiency of the dairy industry. This review primarily summarizes research progress on the induction of oxidative stress by NEFA in periparturient dairy cows and its underlying mechanisms, aiming to provide a theoretical basis for alleviating oxidative stress, improving immune function, and promoting productive performance in dairy production.

Full Text

Mechanism of Oxidative Stress Induced by Non-Esterified Fatty Acids in Dairy Cows

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Abstract

Transition dairy cows experience lipid mobilization due to negative energy balance, leading to the release of large amounts of non-esterified fatty acids (NEFA)

into the liver and bloodstream. At high concentrations, NEFA disrupt the balance between antioxidant defense and oxidative systems, activate the nuclear factor kappa-B (NF- B) and mitogen-activated protein kinase (MAPK) signaling pathways, and simultaneously inhibit the nuclear factor-E2-related factor 2 (Nrf2) signaling pathway. This triggers inflammatory injury and ultimately induces oxidative stress in dairy cows, directly impacting the economic efficiency of the dairy industry. This review summarizes research progress on the induction of oxidative stress by NEFA in transition dairy cows and its underlying mechanisms, aiming to provide a theoretical basis for alleviating oxidative stress, enhancing immune function, and improving production performance in dairy cattle.

Keywords: transition dairy cows; lipid mobilization; non-esterified fatty acids; oxidative stress; mechanism

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1. Lipid Mobilization and NEFA in Transition Dairy Cows

After calving, dairy cows experience reduced appetite and significantly decreased dry matter intake, with peak feed intake lagging behind peak lactation. Simultaneously, energy demand increases due to milk production, placing cows in a negative energy balance (NEB) state. Consequently, transition cows must compensatorily mobilize substantial body fat reserves to meet energy requirements. Lipid mobilization is a physiological adaptive response in mammals to reduced available energy, representing an imbalance between lipogenesis and lipolysis in adipose tissue and serving as a hallmark characteristic of the NEB phase [5]. Lipid mobilization is also the most extensively studied biomarker for transition cow health monitoring to date, as concentrations of β-hydroxybutyric acid (BHBA), ketone bodies, and NEFA in blood can predict the risk of herd diseases or oxidative stress-induced tissue damage—a notion supported by numerous studies [6].

NEFA produced through lipid mobilization are metabolized through three primary pathways: (1) transport to the liver for complete oxidation via the tricarboxylic acid cycle to produce carbon dioxide and energy; (2) incomplete oxidation to generate ketone bodies; and (3) re-esterification to form triacylglycerol (TAG) stored in the liver. Some TAG combines with apolipoproteins to form very low-density lipoproteins that are exported from the liver into circulation or stored in hepatocytes [7]. When NEFA concentrations are limited to levels that can be processed by the liver, cows successfully adapt to NEB [8]. However, excessive body fat mobilization produces NEFA concentrations exceeding hepatic capacity, leading to massive TAG accumulation in the liver, impaired liver function, fatty liver development, and elevated ketone body production such as BHBA. During late lactation and the dry period, plasma NEFA concentrations remain below 0.20 mmol/L, but begin rising two weeks before calving and peak

within 10 days postpartum, reaching up to 0.75 mmol/L depending on the degree of fat mobilization. Plasma NEFA concentrations exceeding 1.00 mmol/L can develop into ketosis [9], while cows in severe NEB may reach 1.50 mmol/L [10-11].

2. Induction of Oxidative Stress by NEFA in Dairy Cows

Free radicals are atoms or molecules with unpaired electrons produced during metabolic processes. Under normal physiological conditions, their generation and elimination are maintained in dynamic equilibrium by the antioxidant enzyme system. Normal metabolism and disease defense processes produce reactive oxygen species (ROS) and reactive nitrogen species (RNS), such as superoxide anions (O_2^-), hydroxyl radicals, hydrogen peroxide (H_2O_2), and nitric oxide. When the balance between oxidative and antioxidant systems is disrupted, free radicals cannot be cleared promptly and accumulate extensively. Due to their strong oxidizing properties, these radicals damage tissues and cells, placing the organism in a state of oxidative stress.

Oxidative stress represents an important early pathophysiological phenomenon in disease development [12]. In fact, lipid mobilization is typically accompanied by oxidative stress, inflammatory responses, and immune function changes. Mitochondria are the primary sites of ROS generation, and numerous studies have shown that NEFA concentrations affect ROS production. Lipid mobilization elevates blood NEFA concentrations, which regulate mitochondrial ROS generation, particularly H_2O_2 and O_2^- [13]. The initiation of lactation, high milk yield, and lipid mobilization in transition cows are all intense oxygen-consuming activities, with greater oxygen consumption generating more free radicals [14]. Elevated NEFA concentrations from lipid mobilization constitute a physiological factor inducing oxidative stress in dairy cows, not only triggering oxidative stress but also disrupting redox system balance [13,15]. When NEFA serve as energy substrates for peripheral tissues, they promote ROS production during β-oxidation. Additionally, NEFA exhibit lipotoxicity that can damage mitochondrial structure and function, causing normal respiratory processes to generate more free radicals [16]. Oxidative stress can trigger additional lipolysis, further increasing NEFA concentrations in transition cows [8]. Excessive β-oxidation of NEFA in hepatocyte mitochondria generates adenosine triphosphate (ATP) but also produces substantial ROS and RNS [13]. The dramatic metabolic and physiological adaptations from late pregnancy to lactation further exacerbate oxidative stress, creating a vicious cycle of lipid mobilization and ROS production [17].

Wei [18] found that high NEFA concentrations increased intracellular ROS and malondialdehyde (MDA) content in dairy cow abomasal smooth muscle cells, demonstrating that NEFA can induce oxidative stress in these cells. Antioxidant supplementation inhibited this pro-oxidant effect, further confirming NEFA as a primary oxidative stress inducer. Moreover, lipid peroxidation of NEFA under specific conditions generates various products such as 4-hydroxynonenal and

MDA, which cause oxidative damage to intracellular macromolecules [19].

3.1 By Inhibiting Antioxidant Enzyme Activity

NEFA-induced oxidative stress is associated with suppressed antioxidant enzyme activity. Liu [20] reported that in transition dairy cows, elevated blood NEFA concentrations showed significant positive correlations with oxidative markers (H_2O_2, MDA, ROS, and RNS) but significant negative correlations with multiple antioxidant enzymes (such as superoxide dismutase and catalase). This indicates that high NEFA concentrations inhibit antioxidant enzyme activity, alter mitochondrial ROS generation, and promote oxidative stress [21]. NEFA can also inhibit the conversion of oxidized glutathione to its reduced form, thereby decreasing glutathione peroxidase activity and promoting oxidative stress.

3.2 By Affecting Electron Transport in the Respiratory Chain

NEFA interactions with respiratory chain components can inhibit electron transfer. Inhibition of forward electron transport increases O_2^- generation. As protonophores, NEFA can cross the mitochondrial inner membrane and reduce O_2^- production from reverse electron transport through protonation-deprotonation cycles. Due to their amphiphilic nature, NEFA can fuse with the mitochondrial inner membrane, alter its fluidity, and increase electron leakage, leading to enhanced O_2^- production. NEFA acyl-CoA can also increase O_2^- generation associated with respiratory chain complex I by strengthening reverse electron transport [13].

3.3 By Activating the Nuclear Factor Kappa-B (NF- B) Signaling Pathway

NF- B is ubiquitously expressed in mammalian cells and represents a crucial signaling pathway regulating immune function. The immune system recognizes antigens and transmits signals through NF- B to regulate cell survival, differentiation, proliferation, and apoptosis. In quiescent cells, NF- B remains inactive in the cytoplasm bound to its inhibitor protein (I Bα), whose phosphorylation depends on I B kinase (IKK) β activation. Upon stimulation by bacteria, ROS, lipopolysaccharide, or other factors, the p65 subunit of NF- B dissociates from I B proteins, translocates to the nucleus, and binds to corresponding sites on target genes.

In the nucleus, activated NF- B regulates transcription of certain cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) [22]. NF- B also upregulates expression of numerous cytokines, chemokines, and their receptors, enhancing inflammatory responses. Studies show that saturated NEFA (including palmitic and stearic acids and their acyl-CoA derivatives) can directly activate the NF- B signaling pathway [17]. High NEFA concentrations increase IKKβ activity, induce I Bα phosphorylation, promote p65 nuclear translocation, activate the NF- B pathway, and elevate release

of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α, ultimately causing oxidative damage [23]. Palmitic and stearic acids can also directly induce Toll-like receptor 4 (TLR-4) and mediate IKKβ activation. NEFA serve as TLR4 ligands that are recognized by the cell, with signals transmitted through adaptor molecules to activate the NF- B pathway. Zhang [24] confirmed this in neutrophils cultured in vitro, showing NEFA activated the TLR4-NF- B pathway and increased pro-inflammatory cytokine release. Oxidative stress can significantly inhibit insulin signaling, playing a notable role in high-fat diet-induced insulin resistance. IKKβ exerts broad pro-inflammatory effects by reducing nitric oxide production, activating NF- B, and phosphorylating insulin receptors to weaken insulin signaling [25]. Reports indicate that multiple kinases (including IKKα, c-Jun N-terminal kinase (JNK), and protein kinase C- (PKC-)) are involved in inflammatory responses. JNK, IKKα, and PKC- knockout mice are protected from NEFA-induced insulin resistance [26], which is associated with activation of inflammatory pathways such as TLR-4.

However, omega-3 unsaturated fatty acids can inhibit NF- B pathway activation [27]. Lee et al. [28] reported that unsaturated fatty acids may suppress NF- B activation, possibly due to differences in cell origin, NEFA concentration, and composition, suggesting that saturated fatty acids are the primary inflammatory stimuli activating the NF- B pathway.

3.4 By Activating the Mitogen-Activated Protein Kinase (MAPK) Signaling Pathway

NEFA can induce oxidative stress and mediate cell damage by activating the MAPK signaling pathway. The MAPK family includes p38MAPK, JNK, and extracellular signal-regulated kinase (ERK). p38 is the primary member of this pathway and acts downstream of ROS; once phosphorylated and activated, it mediates apoptosis. Song et al. [29] demonstrated that NEFA induced oxidative stress in cultured dairy cow hepatocytes, with generated ROS further activating the p38MAPK pathway, promoting expression and nuclear localization of its downstream transcription factor p53 while enhancing its transcriptional activity. Concurrently, NEFA inhibited expression and nuclear localization of nuclear factor-E2-related factor 2 (Nrf2) and weakened its transcriptional activity, leading to upregulated pro-apoptotic gene expression and suppressed anti-apoptotic gene expression, ultimately inducing hepatocyte apoptosis. This indicates NEFA can activate the ROS-p38-p53/Nrf2 pathway to induce apoptosis. Studies also show that palmitic acid activates the p38 pathway in human aortic endothelial cells, inducing apoptosis [30]. p38 regulates apoptosis through multiple mechanisms, including promoting p53 phosphorylation, participating in Fas/FasL-mediated apoptosis, enhancing c-myc expression, and increasing TNF-α expression to induce apoptosis [31]. Therefore, high NEFA concentrations not only induce oxidative stress but can also cause cell apoptosis and necrosis.

Furthermore, research indicates NEFA promote pro-apoptotic protein expres-

sion and inhibit anti-apoptotic proteins (B-cell lymphoma-2 (Bcl-2), Bcl-w, and Bcl-xL) by activating JNK and suppressing ERK expression, mediating hepatocyte apoptosis through the mitochondrial pathway [32]. The anti-apoptotic protein Bcl-xL is an important downstream target of the MAPK pathway and a member of the mitochondrial Bcl-2 protein family. NEFA and their acyl-CoA derivatives can induce apoptosis by downregulating Bcl-2 expression. Cytochrome c release is regulated by Bcl-2 proteins; when Bcl-2 activity decreases, cytochrome c is released into the cytoplasm, marking the irreversible stage of apoptosis [33].

3.5 By Inhibiting the Nrf2 Signaling Pathway

The Nrf2 transcription factor is redox-sensitive and controls transcription of genes encoding numerous antioxidant and cytoprotective proteins [34], thereby protecting cells from oxidative stress damage. Under normal physiological conditions, Nrf2 binds to its cytoplasmic partner protein Kelch-like ECH-associated protein-1 (Keap1), anchoring it in the cytoplasm in a relatively inhibited state that prevents cellular hypersensitivity to stressors. Upon exogenous stimulation, Nrf2 dissociates from Keap1, becomes activated, and translocates to the nucleus [35], where it forms heterodimers with Maf proteins, recognizes antioxidant response elements (ARE), binds to them, and initiates transcription of downstream antioxidant genes and phase II detoxification enzymes, exerting powerful antioxidant effects [36].

ROS can activate Nrf2 [37], thereby blocking pro-inflammatory signaling pathways [38]. Due to increased ROS production, transition dairy cows are typically in an inflammatory state [39], particularly in the liver—the central organ for fat metabolism. During the transition period, the unfolded protein response is activated in the bovine liver [40], and Nrf2 is activated through the protein kinase R-like endoplasmic reticulum kinase (PERK) pathway [41], promoting antioxidant enzyme expression and enhancing antioxidant capacity.

Studies report that p38MAPK can activate the Nrf2 transcription factor through phosphorylation, causing Nrf2 to dissociate from the Nrf2/Keap1 complex. Free Nrf2 then translocates to the nucleus and regulates transcription and translation of antioxidant genes such as Bcl-2 [42]. High NEFA concentrations reduce Nrf2 expression, decrease nuclear translocation, and weaken transcriptional activity, ultimately leading to apoptosis [36]. Ren et al. [43] recently found that the primary Nrf2 antioxidant function was significantly impaired in mice fed high-fat diets. Ni [44] reported similar results, showing that high-fat feeding induced insulin resistance in mouse livers, possibly through mechanisms involving diet-induced oxidative stress and inflammatory responses. Nrf2 gene knockout exacerbated oxidative stress and inflammation while worsening hepatic insulin resistance, potentially due to activation of the IKK/NF- B pathway.

Currently, research on NEFA-induced oxidative stress damage, related signaling mechanisms, and pathway interactions primarily focuses on humans and

rodents, with limited studies on ruminants, particularly transition dairy cows—representing an important direction for future research.

In summary, high NEFA concentrations affect ROS generation and induce oxidative stress in dairy cows through mechanisms that modulate multiple cellular signaling pathways including NF- B, MAPK, and Nrf2, while inhibiting antioxidant enzyme activity. Since current research on NEFA' s oxidative stress mechanisms predominantly involves humans and rodents, in-depth investigation of NEFA' s induction of oxidative stress and its mechanisms in transition dairy cows holds profound theoretical and practical significance for effectively alleviating oxidative stress, improving health status, and enhancing production performance.

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Note: Figure translations are in progress. See original paper for figures.