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DOES THE SYNERGY OF BIOTECHNOLOGICAL AND MEDICAL APPROACHES SOLVE THE CHALLENGE OF HEAT STRESS IN DAIRY COWS? AN EXAMPLE OF INSULIN RESISTANCE AND METABOLIC-HORMONAL IMBALANCE

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Abstract: Heat stress (HS) significantly impacts dairy cow productivity and welfare, primarily by inducing metabolic and hormonal imbalances, particularly insulin resistance. By examining the underlying mechanisms of HS-induced insulin resistance and its downstream consequences, we evaluate the efficacy of biotechnological strategies like genetic selection and rumen microbiome manipulation, alongside medical approaches such as nutritional supplementation and hormonal therapies in addressing this complex challenge. This review highlights the importance of a holistic approach, combining advanced biotechnologies with targeted veterinary interventions to develop effective strategies for improving dairy cow resilience to HS and ensuring sustainable milk production in a changing climate.

Keywords: heat stress, cow, metabolite, insulin resistance, welfare,

Introduction

Global climate change is exacerbating the frequency and intensity of extreme weather events, placing significant pressure on agricultural systems, particularly dairy farming (Cincović et al., 2023; Čukić et al., 2023). Dairy cows, with their high metabolic rate and increased body temperature associated with metabolic adaptation and milk production, are exceptionally vulnerable to heat stress (HS) (Blond et a.l, 2024). HS occurs when environmental temperatures exceed the thermoneutral zone of the animal, leading to elevated body temperature, increased respiration rate, and decreased feed intake. This cascade of physiological responses negatively impacts milk yield, reproductive

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efficiency, and overall animal welfare, resulting in substantial economic losses for the dairy industry (Bernabucci et al., 2010).

A primary consequence of HS in dairy cows is the disruption of metabolic and hormonal homeostasis, leading to insulin resistance (IR) (Baumgard et al., 2012). IR compromises glucose utilization by peripheral tissues, forcing the body to rely on alternative energy sources such as fat, leading to negative energy balance (NEB). The hormonal milieu is further disrupted by altered secretion of insulin-like growth factor-1 (IGF-1), cortisol, and other stress hormones. These metabolic and hormonal disturbances collectively contribute to reduced milk synthesis, impaired reproductive performance, and increased susceptibility to diseases.

Tackling the complex challenge of HS in dairy cows requires an integrated approach that combines the strengths of both biotechnological and medical strategies. This paper explores the synergistic potential of these combined strategies in addressing HS-induced IR and metabolic-hormonal imbalance, ultimately contributing to improved dairy cow health, productivity, and welfare under challenging environmental conditions.

The Insidious Influence of Heat Stress on Forage Utilization in Livestock: A Multi-faceted Impact on Quality, Intake and Digestibility

Elevated temperatures and altered precipitation patterns associated with HS events significantly impact forage quality. High temperatures accelerate plant maturation, leading to increased stem-to-leaf ratio, reduced leaf area, and increased fiber content (Van Soest, 1994). Specifically, HS promotes lignification, increasing the proportion of indigestible fiber factions like neutral detergent fiber (NDF) and acid detergent fiber (ADF) (Allen et al., 2005). This, in turn, reduces the concentration of readily digestible carbohydrates and protein, ultimately diminishing the overall nutritional value of the forage base. In addition, HS can interfere with nitrogen assimilation in plants, resulting in lower crude protein content in forages (Taub, 2010). This decline in nutritional value, particularly protein, can lead to reduced rumen microbial activity and poorer overall nutrient availability for the animal (Russell et al., 1992). Certain studies have also demonstrated that HS can induce the accumulation of anti-nutritional factors in forages, further reducing palatability and digestibility (Mangan, 1988). Changes in species composition within a pasture are also likely. Some plant species are more resilient to HS meaning that more palatable and digestible species may be replaced (Morales-de la Cruz et al., 2022).

A primary physiological response to HS is a reduction in DMI. This is a well-documented phenomenon across various livestock species, including cattle, sheep, and goats (Gaughran et al., 2020). The reduction in DMI is a complex process mediated by hormonal changes, altered hypothalamic function, and increased circulating concentrations of inflammatory cytokines (West, 2003). Elevated body temperature triggers a cascade of events leading to decreased appetite and reduced feed consumption. Specifically, elevated ambient temperatures influence the activity of anorexigenic (appetite-suppressing) peptides in the brain (Aggarwal and Morrow, 2019). The reduction in DMI is further compounded by reduced palatability of forages directly impacted by HS, as discussed earlier. Animals may preferentially select lower fiber, more palatable forages, but the overall intake is generally reduced. Reduced DMI has significant implications for nutrient supply, potentially leading to energy and protein deficiencies, which negatively impact growth, milk production, and reproductive performance (Bernabucci et al., 2010a).

HS can significantly compromise forage digestibility. This is a multi-faceted issue involving alterations in both rumen function and gut motility. Elevated body temperature can directly impact the activity of rumen microorganisms, disrupting the delicate balance of the microbial ecosystem (Hall, 2005). Changes in rumen pH, volatile fatty acid (VFA) production, and microbial species composition have been observed during HS (Dado and Allen, 1993). These alterations can reduce the efficiency of fiber digestion and overall nutrient extraction from forages. Reduced gut motility during HS can also increase the passage rate of digesta through the gastrointestinal tract, shortening the time available for microbial fermentation and enzymatic digestion (Deng et al., 2021). This leads to a reduction in nutrient absorption and increased fecal excretion of undigested feed particles. Furthermore, HS-induced oxidative stress can damage the gut lining, further impairing nutrient absorption (Pearce et al., 2013). The combination of rumen dysfunction, altered gut motility, and compromised gut integrity significantly reduces forage digestibility during HS.

Insulin Response and Heat Stress

Insulin, a crucial hormone regulating glucose metabolism and nutrient partitioning, is also affected by HS. Studies have shown that HS can disrupt insulin signaling pathways in livestock (Rhoads et al., 2010; Baumgard et al., 2012). This can lead to insulin resistance, where cells become less responsive to insulin's effects, leading to elevated blood glucose levels and altered nutrient

utilization. The proposed mechanisms include increased levels of glucocorticoids (stress hormones) and inflammatory cytokines, which are known to interfere with insulin signaling (Aguilar-Valles et al., 2015). In dairy cattle, for example, HS-induced insulin resistance can reduce glucose uptake by the mammary gland, negatively impacting milk production (Baumgard and Rhoads, 2013). The altered insulin response during HS can also affect protein synthesis and muscle growth, further contributing to reduced overall productivity. The physiological response to HS involves a complex interplay of hormonal and metabolic adjustments aimed at maintaining body temperature and ensuring survival. However, these adaptive mechanisms often come at the expense of productive functions. HS triggers a cascade of events culminating in IR, characterized by a reduced sensitivity of peripheral tissues (e.g., muscle, adipose tissue, liver) to the effects of insulin (Rhoads et al., 2016). Several factors contribute to HS-induced IR in dairy cows. Firstly, reduced feed intake during HS leads to a decreased glucose supply, forcing the body to mobilize fat reserves to meet energy demands. Increased lipolysis leads to elevated circulating non-esterified fatty acids (NEFA), which interfere with insulin signaling pathways in peripheral tissues, ultimately promoting IR (Derbré et al., 2012). Secondly, HS activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased cortisol secretion. Cortisol, a potent stress hormone, promotes gluconeogenesis in the liver and antagonizes insulin action in peripheral tissues, further exacerbating IR (Wheelock et al., 2010). Thirdly, HS-induced inflammation, characterized by elevated levels of inflammatory cytokines like TNF-α and IL-6, also contributes to IR by disrupting insulin signaling pathways (Ozgul et al., 2018). The consequences of IR extend beyond impaired glucose utilization. Reduced glucose uptake by the mammary gland limits lactose synthesis, leading to decreased milk yield.

Research has consistently shown that HS leads to an increase in circulating insulin concentrations in dairy cows. This phenomenon, termed "hyperinsulinemia," is a seemingly paradoxical response, as insulin sensitivity is often reduced in other tissues during HS. The exact mechanisms responsible for HS-induced hyperinsulinemia are still under investigation, but several contributing factors have been proposed. HS may directly stimulate pancreatic beta-cells to secrete more insulin. This could be driven by increased sympathetic nervous system activity or changes in gut microbiome composition. HS may impair the liver and kidney's ability to clear insulin from the circulation, leading to an accumulation of the hormone. While insulin levels rise, certain tissues become less responsive to its effects, leading to a build-up in

the bloodstream. This insulin resistance in peripheral tissues, particularly skeletal muscle, could be a protective mechanism to spare glucose for essential functions, but it also reduces overall glucose utilization, leading to a complex metabolic landscape.

The mammary gland, responsible for synthesizing milk, relies heavily on glucose as a primary precursor for lactose production (Guo et al., 2021). Lactose is a key determinant of milk volume, making glucose availability critical for milk yield. However, during HS, the increased circulating insulin levels do not translate into increased glucose uptake by the mammary gland. Paradoxically, studies suggest that HS may decrease glucose input into the mammary gland, despite hyperinsulinemia. This reduction in mammary glucose uptake can be attributed to several factors: a) Downregulation of Glucose Transporters: Insulin typically stimulates glucose uptake by increasing the translocation of glucose transporters, such as GLUT1, to the cell membrane. However, HS could impair this process in the mammary gland; b) Competition for Glucose: With decreased insulin sensitivity in other tissues, more glucose might remain circulating, but its availability to the mammary gland is still limited due to reduced uptake capacity; c) Altered Mammary Gland Metabolism: HS could alter the mammary gland's metabolic pathways, reducing its reliance on glucose and increasing the utilization of other substrates. The reduced glucose availability ultimately limits lactose synthesis, contributing to the observed decrease in milk production during HS.

Management strategies for mitigation

Tivity Biotechnological tools offer promising long-term solutions for mitigating the impact of HS on dairy cows by improving their inherent resilience.

Genetic Selection: Genetic selection for heat tolerance traits is a powerful strategy for improving the adaptive capacity of dairy cows to HS. Traits related to thermoregulation, such as coat type, sweating rate, and body temperature, are heritable and can be incorporated into breeding programs (Collier et al., 2008). Genomic selection, leveraging genome-wide association studies (GWAS) and single nucleotide polymorphism (SNP) markers, allows for more accurate identification of heat-tolerant individuals at a young age, accelerating genetic progress. Furthermore, focusing on selecting for improved feed efficiency and metabolic stability can indirectly improve resilience to HS by reducing metabolic heat production.

Rumen Microbiome Manipulation: The rumen microbiome plays a crucial role in feed digestion and nutrient utilization. HS can significantly alter rumen microbial communities, leading to reduced fiber digestion and increased production of heat-generating fermentation products (Guan et al., 2017). Manipulating the rumen microbiome through dietary interventions, supplementation with prebiotics or probiotics, or even fecal microbial transplantation (FMT) can modulate rumen fermentation, improve feed efficiency, and reduce metabolic heat production (Mao et al., 2015). Specifically, promoting the growth of fibrolytic bacteria and reducing the abundance of methane-producing archaea can enhance energy capture and reduce heat production.

Epigenetic Modifications: Emerging evidence suggests that HS can induce epigenetic modifications in dairy cows, altering gene expression patterns and potentially impacting future generations (Monteiro et al., 2016). Understanding these epigenetic changes could lead to novel strategies for improving HS resilience. For example, dietary supplementation with methyl donors, such as choline or betaine, could influence DNA methylation patterns and potentially enhance the expression of genes involved in thermoregulation or metabolic homeostasis.

Nutritional Supplementation and Management: Strategic nutritional supplementation can mitigate HS-induced metabolic imbalances and enhance cow performance. Supplementing with antioxidants, such as vitamins E and C, can reduce oxidative stress and inflammation associated with HS (Sivakumar et al., 2010). Providing rumen-protected fat can increase energy density without increasing metabolic heat production from fermentation. Supplementation with chromium picolinate or other insulin sensitizers can improve glucose utilization and reduce IR (Hayirli, 2006). Furthermore, adjusting the dietary cation-anion difference (DCAD) can improve acid-base balance and reduce the negative impact of HS on mineral metabolism. Adjust feed rations to maintain energy intake and minimize metabolic heat production. Increasing the dietary fiber content can help buffer against rumen acidosis associated with panting (West, 2003). Supplementation with electrolytes and antioxidants can help mitigate physiological stress. Ensure access to clean and cool water at all times. Water sources should be easily accessible and regularly cleaned to prevent contamination.

Hormonal Therapies: Hormonal therapies can be used to directly address specific hormonal imbalances associated with HS. For example, administration of recombinant bovine somatotropin (rBST) can improve milk yield and

metabolic efficiency, although its use remains controversial due to concerns about animal welfare and human health. Exogenous administration of IGF-1 or growth hormone secretagogues could potentially improve insulin sensitivity and promote glucose uptake by peripheral tissues. However, more research is needed to evaluate the efficacy and safety of these hormonal therapies in HS-stressed dairy cows.

Cooling Strategies: Cooling strategies are crucial for mitigating the acute effects of HS. Providing shade, access to fans, and sprinkler systems can significantly reduce body temperature and alleviate physiological stress (Berman, 2006). Improving air flow in barns and providing access to cool drinking water are also essential for maintaining cow comfort and mitigating the negative impacts of HS. Provide shade, fans, and sprinklers to reduce ambient temperature and humidity. Optimizing ventilation in housing structures is crucial for heat dissipation. Evaporative cooling systems and misters are also effective in reducing heat load.

Protocols: Implement rigorous cleaning and disinfection protocols to minimize bacterial load. Bedding should be frequently changed and kept dry. Regular hoof trimming and footbath treatments are essential for preventing lameness (Cook et al., 2004). Monitoring and early detection: Regularly monitor cows for signs of heat stress. Early detection and treatment are crucial for minimizing the impact on welfare and productivity. Use of automated sensors and monitoring systems can help detect subtle changes in behavior and physiology (Halachmi et al., 2019). Understanding and managing space allowance and social dynamics can reduce competition for resources and minimize stress. Providing sufficient lying space and shade can reduce aggression during periods of heat stress (Sreekumar and Seijan, 2024).

Conclusion

Heat stress poses a significant threat to dairy cow productivity and welfare, primarily by inducing insulin resistance and disrupting metabolic-hormonal balance. Addressing this challenge requires a multifaceted approach that integrates the strengths of both biotechnological and medical interventions. Biotechnological strategies, such as genetic selection and rumen microbiome manipulation, offer long-term solutions by enhancing the inherent resilience of cows to HS. Medical approaches, including nutritional supplementation and cooling strategies, provide immediate relief by mitigating the acute metabolic and physiological consequences of HS. A synergistic combination of these

approaches is essential for developing sustainable and effective strategies for improving dairy cow health, productivity, and welfare in a changing climate. Further research is needed to refine these strategies and optimize their application in diverse dairy farming systems. This holistic approach will ensure the long-term sustainability of the dairy industry and contribute to food security in a world facing increasing environmental challenges.

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