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Abstract

Cattle are susceptible to various stresses in current agricultural systems, including environmental challenges and management-related factors. Understanding the mechanisms underlying stress responses is critical to ensure animal welfare and improve their overall productivity and well-being. Ongoing scientific research focuses on the complex regulatory pathways associated with stress responses in cattle. Despite the extensive research in this field, comprehensive reviews integrating current knowledge with recent advances are lacking. In this comprehensive review, we explore the intricate regulatory systems underlying stress responses in cattle and provide a comprehensive overview of these regulatory mechanisms and physiological responses of cattle under stress conditions. The physiological responses to stress stimuli can differ and involve both positive and negative feedback mechanisms regulating stress reactions in cattle, leading to hormonal responses and altered immune function. This review highlights the effects of stress on cattle well-being, which includes physiological and hormonal regulation, health, and immune function. Moreover, the effects of environmental conditions, stocking density, and management of stress responses in the cattle have been discussed. Furthermore, this review thoroughly examines the stress response-associated molecular pathways and signaling processes, including the activation of the hypothalamic-pituitary-adrenal axis, cortisol production, and cellular inflammatory responses. This review provides crucial insights into potential interventions and propose effective management strategies to mitigate the impact of stress on cattle health and productivity by elucidating the regulatory mechanisms underlying stress responses. An in-depth knowledge of stress regulation in cattle can improve the animal management practices and promote cattle health.

Keywords: Cattle, stress responses, animal welfare, management practices, hypothalamic-pituitary-adrenal axis, environmental factors.

Introduction

Cattle farming, associated with the supply of meat, milk, and other essential products for human consumption, plays a vital role in the global agricultural economy [1]. However, cattle welfare is often overlooked, resulting in elevated stress levels that compromise cattle health, behavior, and overall well-being in modern systems. Understanding and managing stress responses in cattle are crucial for ensuring their well-being and optimizing the quality and efficiency of production [2]. Elucidating the complex regulatory processes underlying stress responses in cattle is critical for improving animal welfare and productivity [2, 3]. Despite the extensive research in this field, a comprehensive review integrating current knowledge with recent advances is needed to elucidate the complexities of stress regulation in cattle.

Hence, we aimed to review the regulatory mechanisms involved in stress responses in cattle to provide insights into the complex nature of stress. Furthermore, we examined the molecular mechanisms underlying the stress responses in cattle, including activation of the hypothalamus-pituitary-adrenal (HPA) axis [4–6], inflammatory responses [7], and cortisol production [8–10], to elucidate the physiological adaptations to stressors and offer insights into potential therapeutic approaches and management strategies for mitigating the adverse effects of stress on cattle welfare and production.

Stress perception and HPA axis activation

Stress responses in cattle begin when environmental or internal challenges are recognized by the central nervous system. Factors such as heat exposure, transportation, handling, social instability, or nutritional imbalance are processed through neural pathways that ultimately activate endocrine stress signaling systems. Among these, the hypothalamic–pituitary–adrenal (HPA) axis functions as one of the primary regulatory pathways coordinating physiological adaptation to stress.

Within the hypothalamus, the paraventricular nucleus (PVN) responds rapidly to stress-related stimuli by releasing corticotropin-releasing hormone (CRH) together with arginine vasopressin (AVP)

[6,11,12]. Although CRH is considered the principal initiator of HPA axis activation, AVP enhances pituitary sensitivity to CRH and amplifies downstream hormonal responses. These hypothalamic signals stimulate corticotroph cells in the anterior pituitary, resulting in secretion of adrenocorticotropic hormone (ACTH) into the circulation [13]. ACTH subsequently targets the adrenal cortex, particularly the zona fasciculata, where glucocorticoid synthesis is induced and cortisol is released as the major stress-associated glucocorticoid in cattle [10,14].

This hypothalamic–pituitary–adrenal (HPA) axis represents the central endocrine pathway regulating stress responses and plays a critical role in maintaining physiological stability during exposure to stressors.

Elevated cortisol concentrations trigger broad physiological adjustments aimed at maintaining metabolic stability during stress exposure. One of its major functions is the redistribution of energy resources. Cortisol stimulates hepatic gluconeogenesis, promotes lipolysis, and accelerates protein catabolism, thereby increasing the availability of glucose and other metabolic substrates required to cope with increased physiological demand [15]. At the same time, cortisol strongly influences immune regulation. Increased glucocorticoid activity suppresses the production of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, and TNF while also reducing the activity and proliferation of immune cells including lymphocytes, macrophages, neutrophils, and mast cells [16–18]. Many of these immunosuppressive effects occur through glucocorticoid receptor-mediated inhibition of transcriptional regulators such as nuclear factor kappa B (NF-κB), leading to reduced expression of inflammatory genes [18,19].

Stress perception also activates the sympathetic–adrenomedullary (SAM) system, which acts more rapidly than the HPA axis. Activation of sympathetic pathways stimulates the release of epinephrine and norepinephrine from the adrenal medulla [20]. These catecholamines increase heart rate, alter blood flow distribution, and rapidly mobilize glucose, supporting immediate physiological responses during acute stress situations. In general, the SAM system is associated with rapid short-term adaptation, whereas the HPA axis contributes more strongly to prolonged endocrine regulation.

To avoid excessive hormonal activation, the HPA axis is regulated through negative feedback mechanisms. Circulating cortisol binds to glucocorticoid receptors located in the hypothalamus, pituitary gland, and hippocampus, suppressing additional CRH and ACTH secretion [19,21]. Other neuroregulatory pathways, including γ-aminobutyric acid (GABA)-mediated signaling, opioid peptides, and benzodiazepine-associated pathways, also participate in modulation of HPA axis activity [22].

Under chronic or repeated stress conditions, however, these regulatory systems may become disrupted. Sustained cortisol exposure has been associated with altered metabolism, impaired immune responsiveness, and increased disease susceptibility, ultimately reducing both animal welfare and production efficiency [23]. For this reason, understanding the mechanisms underlying stress perception and HPA axis activation remains important for developing effective management strategies aimed at improving stress resilience in cattle.

Neuroendocrine-immune crosstalk

Although the HPA axis is primarily recognized as an endocrine stress-response pathway, its activity is also closely connected to immune regulation. Stress-related hormonal changes influence immune cell function, inflammatory signaling, and disease susceptibility, indicating that neuroendocrine and immune systems operate through continuous bidirectional communication rather than as independent pathways. A schematic overview of HPA axis activation and its interaction with immune responses in cattle is presented in Figure 1.

Stress exposure activates the HPA axis and increases circulating glucocorticoid concentrations, particularly cortisol, which plays a major role in immune modulation [24,25]. Cortisol acts through intracellular glucocorticoid receptors that are widely expressed in immune cells, including lymphocytes, macrophages, neutrophils, and mast cells. After receptor binding, the cortisol–glucocorticoid receptor complex translocates to the nucleus and alters transcriptional activity associated with inflammatory responses. One important mechanism involves suppression of nuclear factor kappa B (NF-κB) signaling, which subsequently reduces the expression of pro-inflammatory cytokines such as IL-1, IL-2, IL-3, IL-6,

TNF, and interferon gamma [16–18]. Prolonged glucocorticoid exposure also suppresses lymphocyte proliferation, antigen presentation, and immune cell activation, leading to reduced immune responsiveness during chronic stress conditions [26–28].

Changes in cytokine balance further contribute to stress-associated immune dysregulation. Under normal conditions, pro-inflammatory and anti-inflammatory pathways remain relatively balanced; however, persistent stress can disturb this equilibrium and shift immune function toward either excessive suppression or chronic low-grade inflammation [24,29]. Long-term activation of inflammatory pathways has been associated with tissue damage, impaired recovery capacity, and increased susceptibility to infectious disease [30–32].

Communication between the immune and neuroendocrine systems is not unidirectional. Cytokines released during inflammation can also influence endocrine stress signaling. For example, IL-1 and TNF-α can stimulate the hypothalamus and enhance corticotropin-releasing hormone (CRH) secretion, thereby activating the HPA axis [24]. This reciprocal signaling network allows immune activity to directly affect neuroendocrine responses during physiological stress or infection.

At the cellular level, stress affects both innate and adaptive immunity. Innate immune responses involve rapid, non-specific defense mechanisms mediated largely by neutrophils and macrophages, whereas adaptive immunity depends on antigen-specific responses involving T and B lymphocytes [26–28]. Chronic stress has been associated with reduced lymphocyte proliferation, altered antibody production, and impaired natural killer (NK) cell activity. Stress hormones can additionally influence immune cell trafficking, apoptosis, and bone marrow proliferation, collectively altering immune competence over time.

These interactions are closely linked to the concept of allostasis, which refers to physiological adaptation aimed at maintaining stability during environmental or biological challenges. Acute stress responses may temporarily enhance immune surveillance and support short-term adaptation. In contrast, prolonged activation of neuroendocrine pathways contributes to allostatic load, a condition characterized by cumulative physiological strain, dysregulated inflammation, and increased disease risk [29].

Overall, neuroendocrine–immune crosstalk represents an important regulatory network involved in maintaining physiological balance in cattle. Disruption of this system under chronic stress conditions can negatively affect immune function, animal health, and production performance. Therefore, a better understanding of these interactions may help improve stress management strategies and support the development of more resilient cattle production systems.

Acute vs. chronic stress

Because neuroendocrine and immune systems are closely interconnected, the physiological consequences of stress depend not only on the type of stressor but also on how long and how frequently the animal is exposed to it. In cattle, stress responses are generally categorized as either acute or chronic, and these two conditions differ substantially in their biological significance and long-term outcomes [28,30].

Acute stress is typically considered a short-term adaptive response that helps animals cope with immediate challenges such as handling, transportation, restraint, or sudden environmental changes. During acute stress exposure, rapid activation of both the HPA axis and the sympathetic–adrenomedullary (SAM) system leads to transient increases in cortisol and catecholamine concentrations [34–36]. These endocrine responses promote rapid physiological adjustments, including increased glucose mobilization, elevated cardiovascular activity, and heightened behavioral alertness. In most situations, once the stressor is removed, negative feedback mechanisms within the HPA axis restore hormonal balance and physiological homeostasis relatively quickly [37].

In contrast, chronic stress develops when animals experience prolonged or repeated exposure to stressors without sufficient recovery time [38]. Under these conditions, persistent activation of neuroendocrine pathways can disrupt normal regulatory processes and lead to sustained elevation of cortisol concentrations. Chronic hypercortisolemia has been associated with widespread physiological disturbances involving metabolism, endocrine function, and immune regulation [8].

Long-term glucocorticoid exposure can negatively affect immune competence through multiple mechanisms. Sustained cortisol signaling suppresses lymphocyte proliferation, impairs natural killer (NK)

cell activity, and alters cytokine production pattern [26–28]. As a result, chronically stressed cattle may become more susceptible to infectious disease and exhibit reduced overall disease resistance. In addition to immunosuppression, chronic stress is frequently linked to persistent low-grade inflammation caused by dysregulated cytokine activity, which may contribute to tissue damage and metabolic imbalance over time [30–32].

Behavioral and productive performance are also affected during chronic stress conditions. Cattle exposed to prolonged stress often show reduced feed intake, altered feeding behavior, lower growth performance, and impaired reproductive efficiency [8]. These effects are particularly important in livestock production systems because they directly influence both animal welfare and economic productivity.

Differences between acute and chronic stress can also be evaluated using physiological biomarkers. Acute stress is commonly associated with temporary increases in circulating cortisol concentrations, whereas chronic stress is more effectively assessed using long-term indicators such as hair cortisol accumulation and heat shock protein (HSP) expression in hair follicles [6,39,40]. These biomarkers are increasingly used to estimate cumulative stress exposure and long-term physiological adaptation in cattle.

From a biological perspective, acute stress responses are generally adaptive and support short-term survival, whereas chronic stress represents a maladaptive state associated with allostatic overload. Whether stress responses remain adaptive or progress toward physiological dysfunction depends largely on stress duration, intensity, and the animal's ability to recover. Therefore, distinguishing acute from chronic stress is important for understanding stress-associated pathology and for developing management strategies aimed at improving resilience and welfare in cattle production systems.

Factors influencing stress responses in cattle

Stress responses in cattle are not determined by a single factor but instead result from complex interactions among environmental conditions, genetic background, and management practices. These

188 factors influence not only the severity of stress exposure but also the animal's capacity to adapt and
189 recover. Consequently, variability in stress responsiveness among cattle is often shaped by both intrinsic
190 and extrinsic conditions.

191 Environmental conditions are among the most important contributors to stress in cattle production
192 systems. Temperature, humidity, ventilation, noise, and access to feed and water all directly influence
193 physiological stability and animal comfort [8,31]. Among environmental stressors, heat stress remains
194 one of the most critical challenges, particularly in regions characterized by high ambient temperature and
195 humidity. Excessive thermal load disrupts thermoregulatory balance and alters endocrine and metabolic
196 activity, frequently leading to reduced feed intake and impaired immune function. Heat stress can also
197 decrease production efficiency by limiting nutrient utilization and increasing maintenance energy
198 requirements.

199 Housing conditions additionally influence stress severity. Poor ventilation, inadequate hygiene,
200 and overcrowding may worsen stress by increasing pathogen exposure and limiting the animal's ability to
201 maintain normal behavioral patterns. High stocking density often increases social competition for feed,
202 water, and resting space, resulting in behavioral disturbances and elevated physiological stress indicators
203 [26,30]. In many cases, environmental stressors occur simultaneously, further amplifying their
204 physiological impact.

205 Genetic background also contributes substantially to differences in stress tolerance among cattle.
206 Breed, genotype, and individual temperament can influence how animals perceive and physiologically
207 respond to stressors [41,42]. Some cattle populations exhibit greater thermotolerance and maintain more
208 stable physiological function during environmental stress exposure. Particular attention has been given to
209 HSPs, especially HSP70, because of their role in protecting cellular integrity during thermal stress
210 [39,40]. These molecular chaperones help prevent protein denaturation and assist in protein refolding
211 under adverse conditions. Variability in HSP expression and stress-related genetic polymorphisms has
212 been associated with differences in heat tolerance, immune stability, and productive performance [43,44].
213 Such findings suggest that genetic selection for stress resilience could become increasingly important in
214 future breeding strategies.

Management practices further influence how cattle experience and respond to stress. Daily handling, feeding schedules, housing systems, and stocking density all contribute to overall stress load [45]. Consistent feeding routines and low-stress handling techniques can reduce unnecessary activation of stress pathways, whereas abrupt environmental changes, rough handling, or irregular feeding patterns may intensify physiological stress responses. Intensive production systems with limited space and high animal density have also been associated with altered behavior, increased aggression, and compromised immune function [46,47].

Importantly, these factors rarely operate independently. Environmental challenges such as heat stress may have greater physiological consequences in animals with lower genetic tolerance or under poor management conditions. Similarly, appropriate housing and nutritional management may partially alleviate the impact of environmental stressors even in susceptible animals. Therefore, improving stress resilience in cattle requires an integrated approach that combines environmental management, genetic selection, and welfare-oriented production practices.

Implications for productivity

These influencing factors ultimately determine how stress manifests at both physiological and production levels. Understanding their combined effects is therefore important when evaluating the impact of stress on cattle productivity. Stress can substantially affect productivity through changes in metabolism, immune function, feed intake, and overall physiological performance. The integrated pathways linking stress-induced neuroendocrine, immune, and metabolic alterations to reduced productivity in cattle are summarized in Figure 2.

Prolonged or severe stress exposure disrupts physiological homeostasis and has been associated with lower growth performance, impaired reproductive efficiency, and decreased production outcomes [3,48,49]. One of the most common consequences of stress is reduced dry matter intake (DMI), which directly decreases nutrient availability for maintenance, growth, and production. This response is

particularly evident during heat stress, when cattle often exhibit altered feeding behavior and decreased appetite, resulting in negative energy balance and reduced productivity [50].

At the metabolic level, activation of the HPA axis and increased cortisol secretion influence nutrient partitioning and energy metabolism. Elevated cortisol promotes gluconeogenesis and protein catabolism while also modifying lipid metabolism, ultimately affecting nutrient utilization efficiency. Stress-related endocrine alterations may additionally increase insulin secretion during heat stress conditions, producing anti-lipolytic effects that restrict mobilization of stored fat as an energy source [51]. Consequently, cattle may become increasingly dependent on dietary energy intake despite reductions in feed consumption.

Nutritional management therefore becomes an important component of stress mitigation. Under heat stress conditions, increasing dietary nutrient density may help compensate for reduced DMI and support adequate intake of energy and protein. Protein supply is especially important because it supports tissue maintenance, growth, and metabolic activity. However, when feed intake declines substantially, insufficient protein intake can contribute to negative nitrogen balance and reduced productive performance [52]. Increasing crude protein (CP) concentrations has been reported to partially offset reductions in DMI and improve growth and milk production, although excessive supplementation may reduce nitrogen utilization efficiency and increase nitrogen excretion [53].

The balance between rumen degradable protein (RDP) and rumen undegradable protein (RUP) also influences productivity under stress conditions. Changes in the RDP-to-RUP ratio can alter rumen microbial activity, nutrient digestion, and overall production performance. For instance, reduced RDP availability has been associated with lower DMI and decreased milk yield, emphasizing the importance of optimizing protein fractions in stress-related nutritional management [54]. In addition, soluble protein proportions can affect nitrogen utilization efficiency and productive outcomes, indicating that both protein quantity and protein quality should be considered during diet formulation.

Energy supplementation strategies are also commonly used to support productivity during stress exposure. Dietary fat supplementation can increase energy density without substantially increasing heat production, making it potentially beneficial during heat stress conditions. However, responses to

supplemental energy may differ between dairy and beef cattle because of differences in metabolic demand and nutrient utilization pathways [55–58]. Furthermore, endocrine alterations associated with stress, including elevated insulin concentrations, may limit adipose tissue mobilization, further increasing dependence on dietary energy supply [59].

In addition to metabolic and nutritional effects, stress-induced immunosuppression can negatively influence productivity by increasing susceptibility to disease and infection. Reduced immune competence may increase morbidity and decrease growth efficiency, ultimately contributing to production losses. Behavioral changes associated with stress, including reduced feeding activity and altered social interactions, may further aggravate these negative effects.

Overall, stress influences cattle productivity through complex interactions among endocrine regulation, metabolism, immunity, and nutrition. Therefore, effective mitigation strategies should integrate nutritional management, environmental modification, and improved husbandry practices to maintain both productivity and animal welfare under stressful conditions.

Future directions

Given the substantial effects of stress on productivity and animal welfare, there is increasing interest in developing more effective approaches for monitoring, predicting, and mitigating stress responses in cattle. This has highlighted the importance of future research directions and continued technological advancement in this field. Improving current understanding of stress physiology in cattle will likely require integration of emerging technologies, interdisciplinary research approaches, and more standardized evaluation systems.

Recent technological developments have made it possible to monitor stress-associated physiological and behavioral changes with greater precision and in real time. Wearable sensors, biometric monitoring devices, and remote sensing systems can continuously measure parameters such as body temperature, heart rate variability, activity patterns, and feeding behavior [60,61]. When combined with advanced analytical approaches, including machine learning algorithms, these data streams may help

identify stress triggers, predict stress responses, and support early intervention strategies within precision livestock farming systems.

Advances in molecular biology and omics technologies are also contributing to improved understanding of stress resilience at the genetic and cellular levels. Genomic and transcriptomic analyses have facilitated identification of genetic markers associated with thermotolerance and adaptation to stress, supporting breeding strategies aimed at improving resilience in cattle populations [42,62]. In particular, studies involving heat shock proteins and genes related to HPA axis regulation have provided valuable insight into the biological mechanisms underlying variation in stress responsiveness among individuals.

Despite these advances, important knowledge gaps remain in cattle stress research. The long-term consequences of chronic stress on animal health, productivity, and welfare are still not fully understood, especially under varying environmental and management conditions. In addition, differences in methodology and the lack of standardized biomarkers limit comparisons among studies and reduce the practical application of current findings. Although biomarkers such as cortisol concentrations in hair, blood, or saliva and heat shock protein expression are widely used, additional validation is needed to improve their reliability and sensitivity under different production conditions [6,39,40].

Another important area for future research involves integrating environmental, physiological, and behavioral information into comprehensive models of stress responses. Multidisciplinary approaches that combine animal physiology, immunology, genetics, and data science may help clarify the complex regulatory interactions underlying stress adaptation. Such approaches could also contribute to the development of predictive models capable of supporting management decisions and improving animal welfare outcomes.

From a practical standpoint, translating scientific findings into effective management strategies and policy frameworks remains challenging. Greater collaboration among researchers, veterinarians, industry stakeholders, and policymakers will be necessary to improve communication between research and field application. Development of evidence-based guidelines tailored to specific production systems and environmental conditions may further improve implementation of stress mitigation practices in cattle farming. In addition, investment in infrastructure, training of livestock handlers, and adoption of low-

stress management practices are likely to play important roles in improving both welfare and production efficiency.

Overall, future cattle stress research should continue integrating technological innovation with biological understanding while addressing existing knowledge gaps and improving practical application of research findings. Such efforts will be important for supporting sustainable livestock production systems that prioritize both animal welfare and long-term productivity under increasingly challenging environmental conditions.

Conclusion

Stress responses in cattle involve complex interactions among neuroendocrine, immune, and metabolic systems. Among these pathways, activation of the hypothalamic–pituitary–adrenal (HPA) axis plays a major role in coordinating physiological adaptation to stressful conditions, while associated changes in immune and metabolic function largely determine the consequences for animal health and productive performance.

When stress exposure becomes prolonged or poorly managed, negative physiological effects become increasingly evident. Chronic stress has been associated with impaired immune responsiveness, metabolic imbalance, reduced feed intake, and declines in growth and reproductive performance. Collectively, these alterations can compromise both animal welfare and the efficiency of cattle production systems. Consequently, effective stress management is important not only from a welfare perspective but also for maintaining long-term productivity and sustainability.

Reducing the adverse effects of stress requires an integrated approach that considers environmental conditions, genetic background, and management practices simultaneously. Improvements in housing conditions, handling procedures, nutritional management, and selection for stress-resilient traits may collectively improve the ability of cattle to adapt to challenging conditions. In addition, emerging technologies such as precision monitoring systems and data-driven management tools may provide new opportunities for earlier stress detection and more effective intervention strategies.

Although substantial progress has been made in understanding stress physiology in cattle, several important knowledge gaps still remain. In particular, additional research is needed to better understand the long-term biological consequences of chronic stress and to establish reliable, standardized biomarkers that can be applied across different production systems. Addressing these limitations will require continued collaboration among researchers, veterinarians, and industry stakeholders together with the development of evidence-based management guidelines.

Overall, improving stress management in cattle will depend on combining mechanistic understanding with practical application. Continued progress in this field will be important for supporting resilient and sustainable cattle production systems while improving both animal welfare and production efficiency under increasingly challenging environmental conditions.

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References

1. Rhoads ML, Rhoads RP, VanBaale MJ, Collier RJ, Sanders SR, Weber WJ, et al. Effects of heat stress and plane of nutrition on lactating holstein cows: I. Production, metabolism, and aspects of circulating somatotropin. J Dairy Sci. 2009;92:1986–97. https://doi.org/10.3168/jds.2008-1641
2. Tilbrook AJ, Ralph CR. Hormones, stress and the welfare of animals. Anim Prod Sci. 2018;58:408–15. https://doi.org/10.1071/AN16808
3. Ryan KK. Stress and metabolic disease. In: Sociality, hierarchy, health: Comparative biodemography: A collection of papers. National Academies Press; 2014
4. Mormède P, Andanson S, Aupérin B, Beerda B, Guémené D, Malmkvist J, et al. Exploration of the hypothalamic–pituitary–adrenal function as a tool to evaluate animal welfare. Physiol Behav. 2007;92:317–39. https://doi.org/10.1016/j.physbeh.2006.12.003
5. Meyer JS, Novak MA. Minireview: Hair cortisol: A novel biomarker of hypothalamic-pituitary-adrenocortical activity. Endocrinology. 2012;153:4120–7. https://doi.org/10.1210/en.2012-1226
6. Ghassemi Nejad J, Kim BW, Lee BH, Sung KI. Coat and hair color: Hair cortisol and serotonin levels in lactating holstein cows under heat stress conditions. Anim Sci J. 2017;88:190–4. https://doi.org/10.1111/asj.12662
7. Antoni MH, Dhabhar FS. The impact of psychosocial stress and stress management on immune responses in patients with cancer. Cancer. 2019;125:1417–31. https://doi.org/10.1002/cncr.31943
8. Ataallahi M, Nejad JG, Takahashi J, Song Y-H, Sung K-I, Yun J-I, et al. Effects of environmental changes during different seasons on hair cortisol concentration as a biomarker of chronic stress in Korean native cattle. Int J Agric Biol. 2019;21:1166–72
9. Ghassemi Nejad J, Park K-H, Forghani F, Lee H-G, Lee J-S, Sung K-I. Measuring hair and blood cortisol in sheep and dairy cattle using ria and elisa assay: A comparison. Biol Rhythm Res. 2020;51:887–97. https://doi.org/10.1080/09291016.2019.1611335

10. Ghassemi Nejad JG, Lee BH, Kim JY, Chemere B, Sung KI, Lee HG. Effect of alpine grazing on plasma and hair cortisol, serotonin, and dhea in dairy cows and its welfare impact. Domest Anim Endocrinol. 2021;75:106581. https://doi.org/10.1016/j.domaniend.2020.106581
11. Ghassemi Nejad JG, Lohakare JD, Son JK, Kwon EG, West JW, Sung KI. Wool cortisol is a better indicator of stress than blood cortisol in ewes exposed to heat stress and water restriction. Animal. 2014;8:128–32. https://doi.org/10.1017/S1751731113001870
12. Ghassemi Nejad J, Ghaffari MH, Ataallahi M, Jo J-H, Lee H-G. Stress concepts and applications in various matrices with a focus on hair cortisol and analytical methods. Animals (Basel). 2022;12:3096. https://doi.org/10.3390/ani12223096
13. Morrow CJ, Kolver ES, Verkerk GA, Matthews LR. Fecal glucocorticoid metabolites as a measure of adrenal activity in dairy cattle. Gen Comp Endocrinol. 2002;126:229–41. https://doi.org/10.1006/gcen.2002.7797
14. Ataallahi M, Nejad JG, Song J-I, Kim J-S, Park K-H. Effects of feather processing methods on quantity of extracted corticosterone in broiler chickens. J Anim Sci Technol. 2020;62:884–92. https://doi.org/10.5187/jast.2020.62.6.884
15. Patel MS, Owen OE, Goldman LI, Hanson RW. Fatty acid synthesis by human adipose tissue. Metabolism. 1975;24:161–73. https://doi.org/10.1016/0026-0495(75)90017-7
16. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000;21:55–89. https://doi.org/10.1210/edrv.21.1.0389
17. Jefferies WM. Cortisol and immunity. Med Hypotheses. 1991;34:198–208. https://doi.org/10.1016/0306-9877(91)90212-h
18. Elenkov IJ, Chrousos GP. Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. Ann N Y Acad Sci. 2002;966:290–303. https://doi.org/10.1111/j.1749-6632.2002.tb04229.x

19. De Bosscher K, Vanden Berghe W, Haegeman G. The interplay between the glucocorticoid receptor and nuclear factor-κB or activator protein-1: Molecular mechanisms for gene repression. Endocr Rev. 2003;24:488–522. https://doi.org/10.1210/er.2002-0006
20. González-de-la-Vara G-d-l-V, Valdez RA, Lemus-Ramirez V, Vázquez-Chagoyán JC, Villa-Godoy A, Romano MC. Effects of adrenocorticotropic hormone challenge and age on hair cortisol concentrations in dairy cattle. Can J Vet Res. 2011;75:216–21
21. Gjerstad JK, Lightman SL, Spiga F. Role of glucocorticoid negative feedback in the regulation of hpa axis pulsatility. Stress. 2018;21:403–16. https://doi.org/10.1080/10253890.2018.1470238
22. Giordano R, Pellegrino M, Picu A, Bonelli L, Balbo M, Berardelli R, et al. Neuroregulation of the hypothalamus-pituitary-adrenal (hpa) axis in humans: Effects of gaba-, mineralocorticoid-, and gh-secretagogue-receptor modulation. Scientific World Journal. 2006;6:1–11. https://doi.org/10.1100/tsw.2006.09
23. Kersey DC, Dehnhard M. The use of noninvasive and minimally invasive methods in endocrinology for threatened mammalian species conservation. Gen Comp Endocrinol. 2014;203:296–306. https://doi.org/10.1016/j.ygcen.2014.04.022
24. Mountjoy KG. Elisa versus Luminex assay for measuring mouse metabolic hormones and cytokines: Sharing the lessons I have learned. J Immunoassay Immunochem. 2021;42:154–73. https://doi.org/10.1080/15321819.2020.1838924
25. Arck PC, Slominski A, Theoharides TC, Peters EMJ, Paus R. Neuroimmunology of stress: Skin takes center stage. J Invest Dermatol. 2006;126:1697–704. https://doi.org/10.1038/sj.jid.5700104
26. Takahashi A, Flanigan ME, McEwen BS, Russo SJ. Aggression, social stress, and the immune system in humans and animal models. Front Behav Neurosci. 2018;12:56. https://doi.org/10.3389/fnbeh.2018.00056
27. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: Implications for immunoprotection and immunopathology. Neuroimmunomodulation. 2009;16:300–17. https://doi.org/10.1159/000216188

28. Hughes HD, Carroll JA, Burdick Sanchez NCB, Richeson JT. Natural variations in the stress and acute phase responses of cattle. Innate Immun. 2014;20:888–96. https://doi.org/10.1177/1753425913508993
29. Pruett SB. Stress and the immune system. Pathophysiology. 2003;9:133–53. https://doi.org/10.1016/s0928-4680(03)00003-8
30. Mendoza SP, Capitanio JP, Mason WA. Chronic social stress: Studies in non-human primates. In: Moberg GP, Mench JA, editors. The biology of animal stress: Basic principles and implications for animal welfare. Wallingford, UK: CABI Publishing; 2000, p. 227–47. https://doi.org/10.1079/9780851993591.0227
31. Contreras ET, Vanderstichel R, Hovenga C, Lappin MR. Evaluation of hair and nail cortisol concentrations and associations with behavioral, physical, and environmental indicators of chronic stress in cats. J Vet Intern Med. 2021;35:2662–72. https://doi.org/10.1111/jvim.16283
32. Mack Z, Fokidis HB. A novel method for assessing chronic cortisol concentrations in dogs using the nail as a source. Domest Anim Endocrinol. 2017;59:53–7. https://doi.org/10.1016/j.domaniend.2016.11.003
33. Bomfim GF, Merighe GKF, de Oliveira SA, Negrao JA. Acute and chronic effects of cortisol on milk yield, the expression of key receptors, and apoptosis of mammary epithelial cells in Saanen goats. J Dairy Sci. 2022;105:818–30. https://doi.org/10.3168/jds.2021-20364
34. Trevisi E, Bertoni G. Some physiological and biochemical methods for acute and chronic stress evaluationin dairy cows. Ital J Anim Sci. 2009;8 sup1:265–86. https://doi.org/10.4081/ijas.2009.s1.265
35. Comin A, Peric T, Corazzin M, Veronesi MC, Meloni T, Zufferli V, et al. Hair cortisol as a marker of hypothalamic-pituitary-adrenal axis activation in Friesian dairy cows clinically or physiologically compromised. Livest Sci. 2013;152:36–41. https://doi.org/10.1016/j.livsci.2012.11.021

36. Burnard C, Ralph C, Hynd P, Hocking Edwards JH, Tilbrook A. Hair cortisol and its potential value as a physiological measure of stress response in human and non-human animals. Anim Prod Sci. 2017;57:401–14. https://doi.org/10.1071/AN15622
37. Ewert A, Chang Y. Levels of nature and stress response. Behav Sci (Basel). 2018;8:49. https://doi.org/10.3390/bs8050049
38. Newman AEM, Pradhan DS, Soma KK. Dehydroepiandrosterone and corticosterone are regulated by season and acute stress in a wild songbird: Jugular versus brachial plasma. Endocrinology. 2008;149:2537–45. https://doi.org/10.1210/en.2007-1363
39. Kim W-S, Ghassemi Nejad J, Roh S-G, Lee H-G. Heat-shock proteins gene expression in peripheral blood mononuclear cells as an indicator of heat stress in beef calves. Animals (Basel). 2020;10:895. https://doi.org/10.3390/ani10050895
40. Kim WS, Ghassemi Nejad JG, Peng DQ, Jung US, Kim MJ, Jo YH, et al. Identification of heat shock protein gene expression in hair follicles as a novel indicator of heat stress in beef calves. Animal. 2020;14:1502–9. https://doi.org/10.1017/S1751731120000075
41. Trut LN. Early canid domestication: The farm-fox experiment: Foxes bred for tamability in a 40-year experiment exhibit remarkable transformations that suggest an interplay between behavioral genetics and development. Am Sci. 1999;87:160–9. https://doi.org/10.1511/1999.20.160
42. Lockwood SA, Kattesh HG, Rhinehart JD, Strickland LG, Krawczel PD, Wilkerson JB, et al. Relationships among temperament, acute and chronic cortisol and testosterone concentrations, and breeding soundness during performance testing of Angus bulls. Theriogenology. 2017;89:140–5. https://doi.org/10.1016/j.theriogenology.2016.10.019
43. Hariyono DNH, Prihandini PW. Association of selected gene polymorphisms with thermotolerance traits in cattle—A review. Anim Biosci. 2022;35:1635–48. https://doi.org/10.5713/ab.22.0055
44. Kim WS, Jo YH, Nejad JG, Lee HG. Effects of heat shock protein 70 gene polymorphism on heat resistance in beef and dairy calves based on proliferation and heat shock protein 70 gene

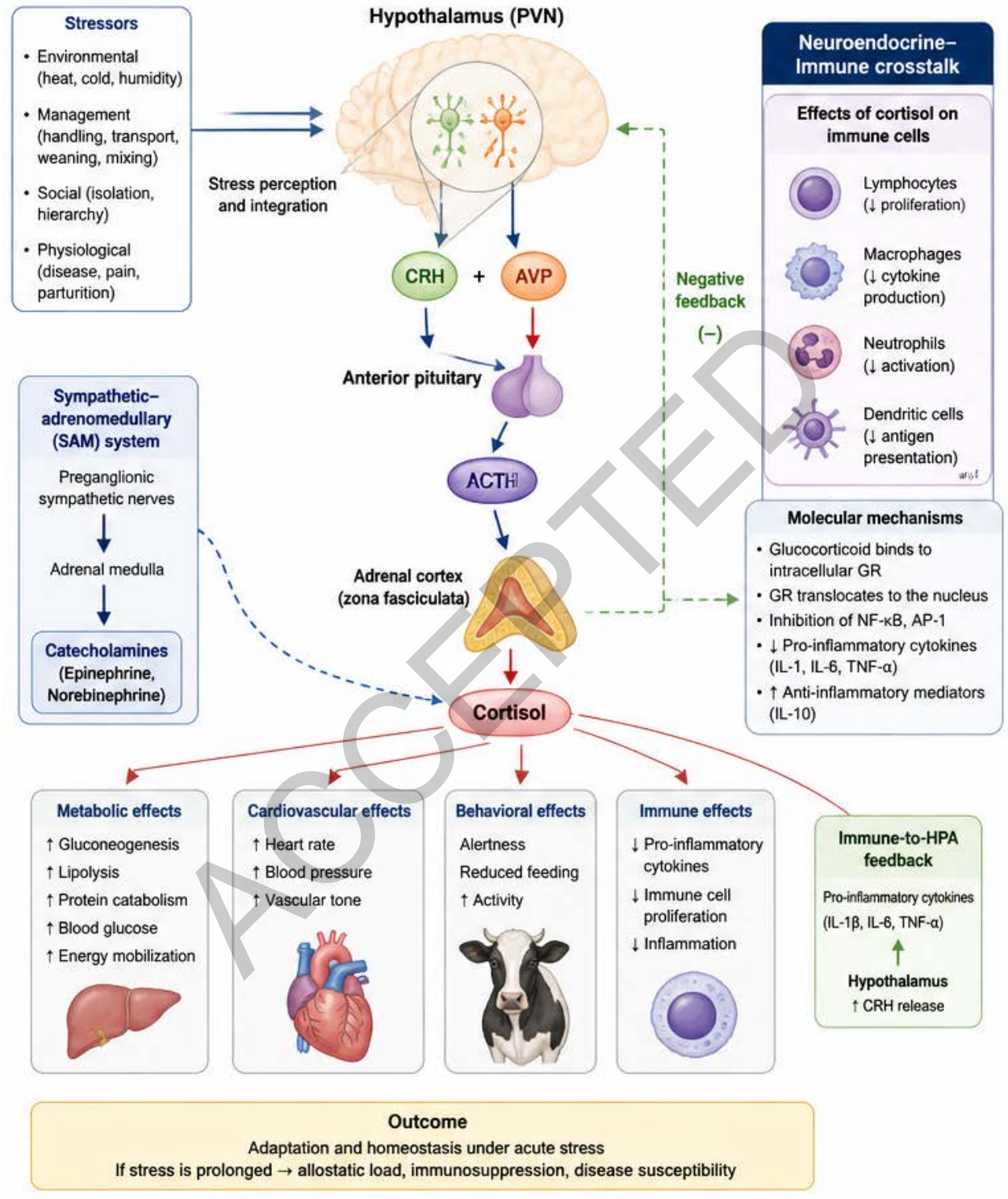
expression in peripheral blood mononuclear cells and hair follicles. Animals (Basel). 2025;15:475. https://doi.org/10.3390/ani15040475

45. von Borell EH. The biology of stress and its application to livestock housing and transportation assessment. J Anim Sci. 2001;79:E260–E7. https://doi.org/10.2527/jas2001.79E-SupplE260x
46. Marti S, Wilde RE, Moya D, Heuston CEM, Brown F, Schwartzkopf-Genswein KS. Effect of rest stop duration during long-distance transport on welfare indicators in recently weaned beef calves1. J Anim Sci. 2017;95:636–44. https://doi.org/10.2527/jas.2016.0739
47. Huzzey JM, Devries TJ, Valois P, Von Keyserlingk MAG. Stocking density and feed barrier design affect the feeding and social behavior of dairy cattle. J Dairy Sci. 2006;89:126–133. http://doi.org/10.3168/jds.S0022-0302(06)72075-6
48. Almoosavi SMMS, Ghoorchi T, Naserian AA, Ramezanpor SS, Ghaffari MH. Long-term impacts of late-gestation maternal heat stress on growth performance, blood hormones and metabolites of newborn calves independent of maternal reduced feed intake. Domest Anim Endocrinol. 2020;72:106433. https://doi.org/10.1016/j.domaniend.2019.106433
49. Smith RF, Dobson H. Hormonal interactions within the hypothalamus and pituitary with respect to stress and reproduction in sheep. Domest Anim Endocrinol. 2002;23:75–85. https://doi.org/10.1016/s0739-7240(02)00147-9
50. Johnson JS. Heat stress: Impact on livestock well-being and productivity and mitigation strategies to alleviate the negative effects. Anim Prod Sci. 2018;58:1404–13. https://doi.org/10.1071/AN17725
51. O'Brien MD, Rhoads RP, Sanders SR, Duff GC, Baumgard LH. Metabolic adaptations to heat stress in growing cattle. Domest Anim Endocrinol. 2010;38:86–94. https://doi.org/10.1016/j.domaniend.2009.08.005
52. Hassan A, Roussel JD. Effect of protein concentration in the diet on blood composition and productivity of lactating holstein cows under thermal stress. J Agric Sci. 1975;85:409–15. https://doi.org/10.1017/S0021859600062286
53. National Academies of Sciences E, Medicine. Nutrient requirements of beef cattle; 2016

54. Jennings JS, Meyer BE, Guiroy PJ, Cole NA. Energy costs of feeding excess protein from corn-based by-products to finishing cattle. J Anim Sci. 2018;96:653–69. https://doi.org/10.1093/jas/sky021
55. Moallem U, Altmark G, Lehrer H, Arieli A. Performance of high-yielding dairy cows supplemented with fat or concentrate under hot and humid climates. J Dairy Sci. 2010;93:3192–202. https://doi.org/10.3168/jds.2009-2979
56. Kang HJ, Piao MY, Lee IK, Kim HJ, Gu MJ, Yun C-H, et al. Effects of ambient temperature and dietary glycerol addition on growth performance, blood parameters and immune cell populations of Korean cattle steers. Asian-Australas J Anim Sci. 2017;30:505–13. https://doi.org/10.5713/ajas.16.0474
57. Drackley JK, Cicela TM, LaCount DW. Responses of primiparous and multiparous holstein cows to additional energy from fat or concentrate during summer. J Dairy Sci. 2003;86:1306–14. https://doi.org/10.3168/jds.S0022-0302(03)73714-X
58. Kang HJ, Piao MY, Park SJ, Na SW, Kim HJ, Baik M. Effects of heat stress and rumen-protected fat supplementation on growth performance, rumen characteristics, and blood parameters in growing Korean cattle steers. Asian-Australas J Anim Sci. 2019;32:826–33. https://doi.org/10.5713/ajas.18.0725
59. Wheelock JB, Rhoads RP, VanBaale MJ, Sanders SR, Baumgard LH. Effects of heat stress on energetic metabolism in lactating Holstein cows. J Dairy Sci. 2010;93:644–55. https://doi.org/10.3168/jds.2009-2295
60. Sejian V, Shashank CG, Silpa MV, Madhusoodan AP, Devaraj C, Koenig S. Non-invasive methods of quantifying heat stress response in farm animals with special reference to dairy cattle. Atmosphere. 2022;13:1642. https://doi.org/10.3390/atmos13101642
61. Rebez EB, Sejian V, Silpa MV, Kalaignazhal G, Thirunavukkarasu D, Devaraj C, et al. Applications of artificial intelligence for heat stress management in ruminant livestock. Sensors (Basel). 2024;24:5890. https://doi.org/10.3390/s24185890

62. Dhama K, Latheef SK, Dadar M, Samad HA, Munjal A, Khandia R, et al. Biomarkers in stress related diseases/disorders: Diagnostic, prognostic, and therapeutic values. Front Mol Biosci. 2019;6:91. https://doi.org/10.3389/fmolb.2019.00091

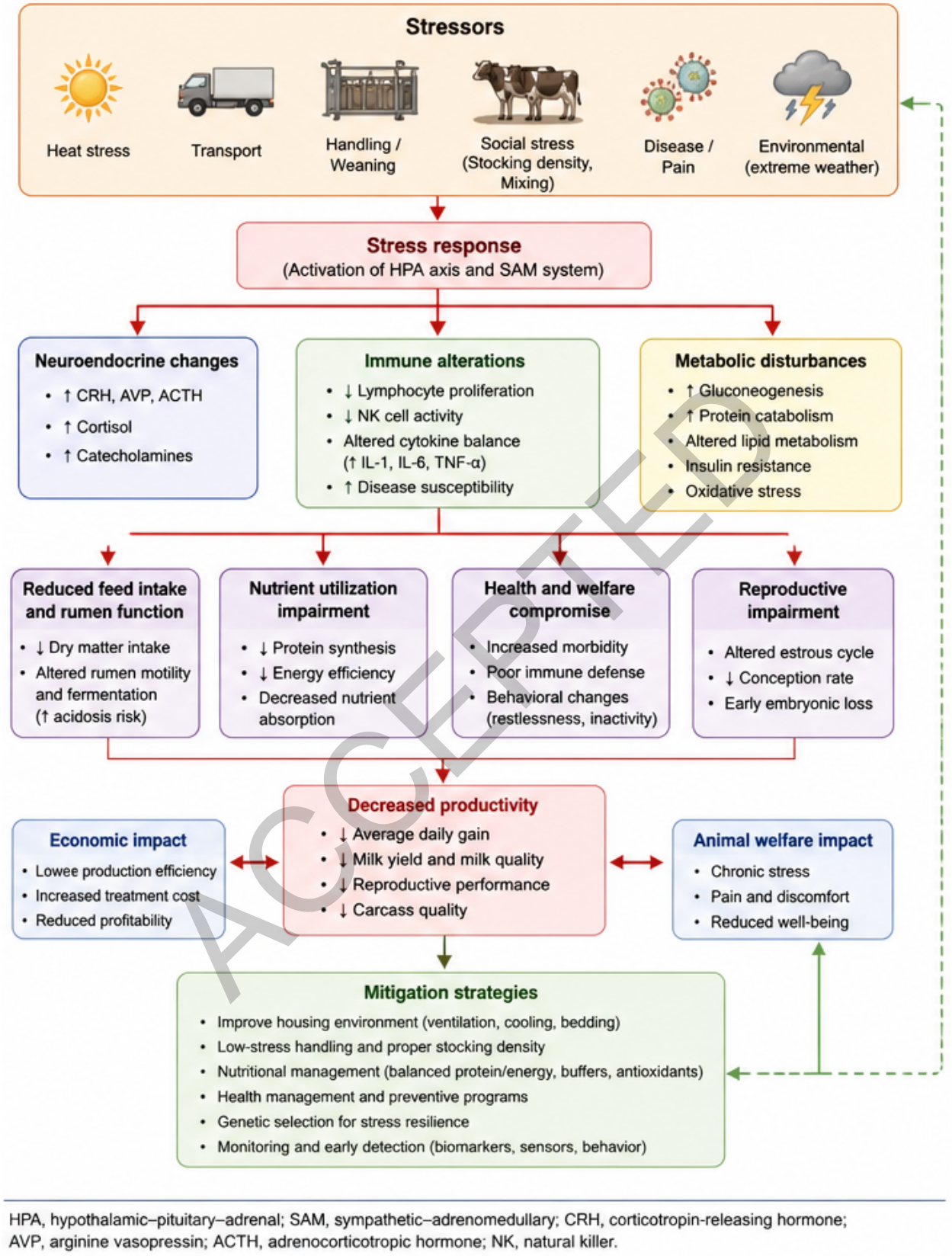
Figure legend



CRH, corticotropin-releasing hormone; AVP, arginine vasopressin; ACTH, adrenocorticotropic hormone; GR, glucocorticoid receptor; NF-κB, nuclear factor-κB; AP-1, activator protein-1.

Figure 1. Schematic representation of stress-induced HPA axis activation and neuroendocrine immune crosstalk in cattle.

Schematic representation of stress-induced activation of the hypothalamic–pituitary–adrenal (HPA) axis and its interaction with the immune system in cattle. Exposure to stressors activates the hypothalamus, leading to the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which stimulate the anterior pituitary to secrete adrenocorticotropic hormone (ACTH). ACTH subsequently induces cortisol secretion from the adrenal cortex. Cortisol modulates metabolic processes and exerts immunoregulatory effects through glucocorticoid receptor-mediated pathways, including suppression of pro-inflammatory cytokine production (e.g., IL-1, IL-6, TNF-α) and inhibition of immune cell activity. In parallel, activation of the sympathetic–adrenomedullary (SAM) system results in catecholamine release, contributing to rapid stress responses. Bidirectional communication between the immune and neuroendocrine systems is illustrated by cytokine-mediated stimulation of the HPA axis. Chronic activation of these pathways may lead to immune dysregulation and increased disease susceptibility.



HPA, hypothalamic–pituitary–adrenal; SAM, sympathetic–adrenomedullary; CRH, corticotropin-releasing hormone; AVP, arginine vasopressin; ACTH, adrenocorticotropic hormone; NK, natural killer.

Figure 2. Pathways linking stress to reduced productivity in cattle.

Integrated pathways linking stress responses to reduced productivity in cattle. Exposure to environmental, physiological, or management-related stressors activates neuroendocrine responses, primarily through the HPA axis and associated cortisol secretion. Elevated cortisol levels alter nutrient partitioning by promoting gluconeogenesis and protein catabolism, while stress-induced hormonal changes, including increased insulin levels, can limit lipid mobilization. These metabolic alterations, combined with reduced dry matter intake (DMI) and impaired immune function, contribute to decreased growth performance, reduced milk production, and compromised reproductive efficiency. Nutritional and management interventions, including optimization of dietary energy and protein supply, can mitigate these effects; however, prolonged stress exposure ultimately results in decreased productivity and animal welfare.