PROJECT SUMMARY: IMPROVING IMMUNITY, HEALTH, AND WELL-BEING OF BEEF CATTLE IN PRODUCTION ENVIRONMENTS

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INTRODUCTION

Livestock are exposed to a multitude of varying stressful stimuli throughout their production cycle; for example weaning, the transportation process, castration and other less appreciated stressors such as extreme fluctuations in temperature, poor nutrition, and mixing of unfamiliar animals. While chronic stress negatively impacts immunity, literature has demonstrated that acute stress can potentially prime the immune system (Dhabhar, 2009). Animals that possess an adequate level of immunological protection exhibit greater reproductive capabilities, enhanced growth, and increased feed efficiency (Galyean et al., 1999).

Our research efforts have primarily focused on identifying natural variations and nutritionally-induced variations in the stress and innate immune response of cattle exposed to a provocative immune challenge. While the generic innate immune response is a highly conserved and essential immunological response necessary for life in livestock, both natural and nutritionally-induced variations exist that can have a significant impact on the animal’s overall health and productivity. Within our laboratory, we have developed reliable endotoxemia models utilizing an *E. coli*-derived lipopolysaccharide (LPS) that can be effectively utilized to discern these individual variations in cattle. Utilizing this model, we characterized variations in the stress and innate immune responses following exposure to LPS in different breeds of *Bos taurus* cattle that are considered to be either heat-tolerant or heat-sensitive. Our group has also demonstrated natural variations in
the stress and innate immune responses of *Bos indicus* cattle following administration of LPS. These studies revealed sexually dimorphic variations following exposure to LPS, as well as variations directly linked to the disposition of the animal. Elucidating these naturally occurring and nutritionally-induced variations in the stress and innate immune responses is essential to developing new management strategies that will improve the overall health, productivity, and well-being of livestock.

**STRESS REGULATION**

The stress response is a complex and coordinated series of events initiated when stress sensors in the brain stimulate the release of two neurohormones, corticotropin-releasing hormone (CRH) and vasopressin (VP) in response to a stimulus. CRH and VP can independently and synergistically stimulate the production of adrenocorticotropic hormone (ACTH) from the anterior pituitary (Aguilera, 1998; Carrasco and Van de Kar, 2003). Subsequently, ACTH stimulates the production of glucocorticoids (i.e., primarily cortisol in mammals) from the cortex of the adrenal gland (Markara et al., 1981; Carrasco and Van de Kar, 2003). This systematic cascade is often referred to as the hypothalamic-pituitary-adrenal (HPA) axis (Figure 1).

When released into the blood stream, cortisol elicits a plethora of biological effects on the body including changes in metabolism of carbohydrates and protein, alterations in the growth and reproductive axes, regulation of the stress response, and influencing overall immune function. During the “fight or flight” response, cortisol plays an important role in gluconeogenesis, the generation of glucose from other organic molecules like pyruvate, lactate, glycerol, and amino acids. Cortisol increases blood glucose by stimulating the liver to convert fat and protein to these intermediate metabolites that are ultimately converted to glucose for energy (Long et al., 1940; McGuinness et al., 2005). Cortisol
also supports the primary defense response by enhancing the synthesis and secretion of catecholamines, which control essential physiological processes such as heart rate, pupil dilation, vasoconstriction in the skin and gut, vasodilation in leg muscles, and increased glucose production by the liver (Charmandari et al., 2005).

THE INNATE IMMUNE SYSTEM

The immune system is not a single entity, but rather a complex, integrated system regulated by a multitude of specialized cells and chemical messengers. In general, the immune system can be separated into three broad components; natural immunity, innate immunity, and acquired immunity, all of which must be fully developed and functioning properly to provide adequate immunological protection. Natural and innate immunity are typically grouped together under the category of innate immunity. Therefore, when discussing innate immunity, it is typically assumed that one is including natural immunity as well.

Innate immunity is considered to be the first line of defense against pathogens; whether bacterial, viral, protozoal or fungal. It includes physical barriers such as the skin, mucosal secretions, tears, urine, and stomach acid, as well as complement and antigen-nonspecific cellular components and is designed to elicit an immediate or acute response (0 to 4 h) following exposure to an antigenic agent (Männel, 2007; Barton, 2008). While it is often assumed that this aspect of the immune system becomes a constant entity once developed by the animal, this is certainly not the case. The innate immune system, while always present to some degree, can be modulated in either a beneficial or detrimental manner by a number of factors including wounds, dehydration, nutritional status, genetics, stress, and various peptide hormones.
STRESS EFFECTS ON IMMUNE FUNCTION

Scientists have known for decades that “stress” can have detrimental effects on the immune system. However, what had not been distinguished until recently are the divergent effects of “acute” stress compared to long-term or “chronic” stress. As scientists expanded their scope of exploration beyond traditionally defined pathways of neuroendocrinology, endocrinology, and immunology, multidisciplinary efforts emerged that have elucidated cross-communication among these systems and lead to a better understanding of homeostatic regulation within the animal. No longer is the stress response considered an “all or none” biological activity strictly associated with the “fight or flight” behavior, nor is stress considered strictly immunosuppressive. Indeed, stress may elicit “bi-directional” effects on immune function such that acute stress may be immunoenhancing, while chronic stress may be immunosuppressive.

The immune system can be regulated by several different endocrine secretions, with the most prominent being those secreted in response to stress. There has been an increased effort to elucidate the interactions between stress responsiveness and immunological parameters in cattle that may be either predisposed to or resistant to the detrimental effects of stress due to genetic programming and/or nutritional manipulation. Interestingly, there are cattle that demonstrate differential stress and immunological responses due to previous exposure to various managerial, environmental, nutritional, or pathogenic stressors or due to varying temperaments within a genetically similar group of animals.

As researchers have continued to explore the complex interactions between stress and production parameters such as growth, reproduction, and health, our knowledge has extended beyond the "all or none" biological activity strictly associated with
the "fight or flight" response. Researchers have demonstrated that the combined immunological effects of cortisol and catecholamines result in a well-orchestrated biological event designed to prevent over-stimulation of innate immunity and the production of pro-inflammatory cytokines while simultaneously priming the humoral immune response in an effort to provide adequate immunological protection (Sorrells and Salpolsky, 2007).

ANIMAL TEMPERAMENT AND IMMUNE FUNCTION

In addition to the complex relationship between “stress” and the immune system, our research team has explored the existence of natural variations with the innate immune system of cattle. A major research effort of our team during the past decade has been to elucidate the relationship between an animal’s temperament classification and the stress hormone and innate immune responses of cattle following a provocative LPS challenge. Specifically, we have demonstrated that temperamental cattle maintain a greater basal rectal temperature prior to, and produced a lesser rectal temperature response following an endotoxin challenge (Burdick et al., 2010). Additionally, we have reported that temperamental bulls exhibited lower sickness behavior scores when compared with calm cattle and maintained greater epinephrine concentrations throughout the study. More recently, we have demonstrated that these natural variations within temperamental cattle may be linked to metabolic differences between temperamental and calm cattle. Collectively, these data suggest that level of flightiness or arousal can modulate the physiological, behavioral, and endocrine responses of cattle to a provocative immune challenge that targets activation of the innate immune system. Developing a more precise understanding of the relationship among stress hormones, the immune system, and animal temperament to early inflammation may lead to methods of early intervention to
CONCLUSION

Given that the innate immune system provides the first line of defense, understanding the effects of stress hormones on innate immunity holds a great deal of potential with regard to improving livestock health, and ultimately productivity. Continued research efforts into these complex interactions may allow the implementation of alternative management practices, improved selection programs, and/or implementation of various nutritional and management strategies to prevent or overcome significant production losses and animal health care costs for livestock producers.

REFERENCES


Figure 1. The hypothalamic-pituitary-adrenal (HPA) axis or more commonly known as the “stress axis” controls the release of cortisol into the bloodstream. Cortisol elicits a plethora of biological effects on the body including changes in metabolism of carbohydrates and protein, alterations in the growth and reproductive axes, regulation of the stress response, and influencing overall immune function.