

The Connection Between Animal Stress and Meat Production: Uncoupling of the Growth Hormone/Insulin-Like Growth Factor 1 Axis^{1,2,3}

J. A. Carroll,* E. P. Berg,† R. C. Vann,‡ R. D. Randel,§ and T. H. Welsh Jr.¶

*Livestock Issues Research Unit, ARS-USDA, 1604 East FM 1294, Lubbock, TX 79403;

†Animal and Range Sciences, North Dakota State University, Fargo, ND 58105-5727;

‡MAFES, Mississippi State University, Raymond, MS 39154;

§Texas AgriLife Research, Texas A&M System, Overton, TX 75684-0200; and

¶Departments of Animal Science and Veterinary Integrative Biosciences, Texas AgriLife Research, Texas A&M System, College Station, TX 77843-2471

Introduction

What is Stress?

Although numerous factors can be identified that contribute to the growth and overall performance of domestic livestock, in general, genetics, nutrition, environment, medication, and stress are 5 categories that represent some of the more commonly recognized and manageable inputs that continue to be of significant interest to scientists and producers. The economic importance of the detrimental impacts that stress can have on animal growth and performance continues to be downplayed/overlooked due to a lack of understanding regarding the regulation of stress in animals and the connection to animal productivity.

Cannon (1935) provided one of the earliest characterizations of stress, the fight-or-flight response, when he wrote that environmental stimuli that disrupt a biological

organism's homeostasis are dealt with in a coordinated and automatic response. Specifically, an automatic series of biological events are triggered in response to an emergency or life-threatening event. As summarized in his 1973 review, noted stress physiologist Hans Selye followed Cannon's concept of acute, automatic responses when he suggested that the physiological actions associated with external stress may be more complex than survival of the fittest (Selye, 1973). Selye (1973, 1973) suggested a general adaptations syndrome in which a similar physiological response is triggered by a broad array of physical stressors that could be a function of eustress (positive) or distress (negative). Indeed, the automatic instinct for survival in any given animal is so strong that a perceived stress can trigger a physiological or behavioral, or both, response similar to an actual physical threat (McEwen, 2000). In fact, Mason (1975) suggested that psychological and experiential factors were perhaps the most powerful stressors, stating that anticipation of punishment, rather than the physical administration of punishment, triggered a more pronounced activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). Today, scientists recognize and appreciate the fact that the neuroendocrine and physiological responses within an animal can be as specific as the stressor itself. Although there are virtually an infinite number of possible stressors that an animal could encounter, the most commonly recognized types of stress in animal production systems include social (mixing of unfamiliar animals or isolation), psychological (barking dog, unfamiliar surroundings, strange smell), nutritional (inadequate diet, dehydration), physical (injury, strenuous exercise), immunological (pathogens), or any combination of these above stressors.

Throughout the literature, one can find several definitions of stress as it relates to animals. However, due to the

J. A. Carroll
Livestock Issues Research Unit, ARS-USDA, 1604 East FM 1294,
Lubbock, TX 79403

Proceedings of the 61st American Meat Science Association
Reciprocal Meat Conference (pp. 1–6)
June 22–25, 2008, Gainesville, Florida
www.meatscience.org

¹We thank J. Sartin and T. Elsasser for providing access to their data and L. Hulbert for technical assistance with anatomical figures.

²Mention of trade names or proprietary products does not constitute a guarantee or warranty of the product by the USDA and does not imply its approval to the exclusion of other products that may also be suitable.

³Some data presented within tables and figures of this manuscript have been recreated with permission from the primary authors.

Corresponding author: Jeff.Carroll@ars.usda.gov

complexity associated with elucidating all of the potential pathways involved in the regulation of the HPA axis and SNS, there has been no universally accepted definition of stress within the scientific community, nor has there been a universally accepted method for quantifying stress in animals. That said, the following 2 definitions are offered, because they are simple, complete, speak to the point of homeostasis, and are appropriate to the theme of this proceedings paper. Stress is...

- 1) Coordinated physiological responses within the body in an attempt to reestablish homeostasis primarily through activation of the HPA axis and activation of the SNS (Elenkov et al., 2000).
- 2) The sum of all biological reactions to physical, emotional, or mental stimuli that disturb an individual's homeostasis (Pacák and Palkovits, 2001).

Although the debate among animal scientists concerning the definition and quantification of stress as it relates to animal productivity and well-being is ongoing, there is little doubt that an increased appreciation and understanding of the effects of stress on livestock production has emerged throughout the scientific community and with livestock producers. In recent years, livestock producers have become more knowledgeable with regard to understanding the influence of stress on animal production and have been proactive in implementing changes to reduce various types of stress to increase productivity and overall well-being in their animals.

Endocrine Regulation of Stress Hormones and the Somatotropic Axis

Anatomy of the Stress/Growth Response

Stress hormones are vital for maintenance of systemic homeostasis and although they provide essential protection over the short-term to the animal via their roles in the negative feedback system, they can elicit strong negative consequences when overproduced or not downregulated after the system returns to homeostasis. When an animal perceives a stress (whether it is a true threat or not), neurotransmitters cause the release of corticotrophin-releasing hormone (CRH) and vasopressin from the hypothalamus and posterior pituitary gland, respectively (Figure 1a). It has been found that CRH and vasopressin can both stimulate independently or in concert the release of adrenocorticotrophic hormone from the anterior pituitary gland. Adrenocorticotrophic hormone travels through the blood stream and stimulates the release of cortisol from the adrenal cortex. Although adrenocorticotrophic hormone is considered as the primary physiological regulator of cortisol production, it's noteworthy to mention that researchers continue to investigate the relative roles and physiological relevance of other adrenal steroid regulators such as angiotensin II, cytokines, and various growth factors. Ultimately, the release of cortisol into the bloodstream elicits

various actions upon numerous target tissues within the body including adipose tissue (stimulatory and inhibitory based upon length of exposure), muscle (catabolic), and bone (catabolic) tissue.

As stated above, prolonged activation of the HPA/stress axis can have negative consequences, which can interfere with the somatotropic axis, leading to a restriction of an animal's overall growth potential. Growth hormone secretion is primarily controlled via the release of growth hormone-releasing hormone (GHRH) and somatostatin (SS) from the hypothalamus (Figure 1b). Although growth hormone (GH) stimulates insulin-like growth factor (IGF) 1 release from the liver, it also stimulates the production of IGF-1 in target tissues throughout the body such as muscle and bone (Gosteli-Peter et al., 1994; Ohlsson et al., 1998; Velloso, 2008). Aside from GHRH, numerous other compounds have been identified as potential stimulators of GH secretion: pituitary adenylate cyclase-activating peptide, interleukin (IL)-1, IL-6, vasoactive intestinal peptide, gastric inhibitory protein, neurotensin, bombesin, cholecystokinin, peptide histidine isoleucine, peptide histidine methionine, arginine, and ghrelin. Inhibitors of GH secretion include SS, IGF-1, IGF-2, IL-2, insulin, secretin, CRH, and cortisol.

For several years now, scientific interest has been in identifying the relationships among the various proinflammatory cytokines and the regulation of GH secretion. Although some proinflammatory cytokines have been reported to stimulate GH release (IL-1 and IL-6), others such as IL-2 have been reported to inhibit GH release. Glucocorticoids have been reported to both stimulate and inhibit GH release based upon the duration of exposure. In rodents, the primary glucocorticoid is corticosterone, but in humans and most mammals, cortisol is the primary glucocorticoid. Cortisol inhibits GH release in short-term culture and is stimulatory in long-term cultures of rat and human pituitary cells. Activation of the stress axis and the subsequent release of cortisol can shut down the positive effects of GH on target tissues (Figure 1c). During times of stress, the animal's nutrient priorities shift from growth and reproduction to physiological processes that are critical for survival.

Somatotropic Axis

Some of the known biological actions of GH include activation of hyperplasia, enhancement of amino acid uptake and nitrogen retention, increases mRNA for protein synthesis, decreases lipogenesis while increasing fatty acid oxidation and fatty acid release, increases plasma glucose, triggers insulin secretion, and enhances bone mineralization. It is plain that GH has both direct (i.e., amino acid uptake and nitrogen retention, increased mRNA for protein synthesis, glucose sparing) and indirect actions (through IGF-1 or cell proliferation, or both) favoring development of skeletal muscle.

As stated above, GH stimulates IGF-1 release from the liver as well as from target tissues such as muscle and

bone. Insulin-like growth factor 1 has a paracrine and endocrine release with the major target tissues being muscle, cartilage, bone, liver, kidney, nerves, skin, and lungs.

Insulin-like growth factor 1 promotes the growth of muscle and bone and tissue regeneration of the other more biologically active target organs in part through regulation of cell growth by moving cells from a resting phase (G0) to an active phase of the cell cycle and by increasing a cell's ability to complete DNA synthesis.

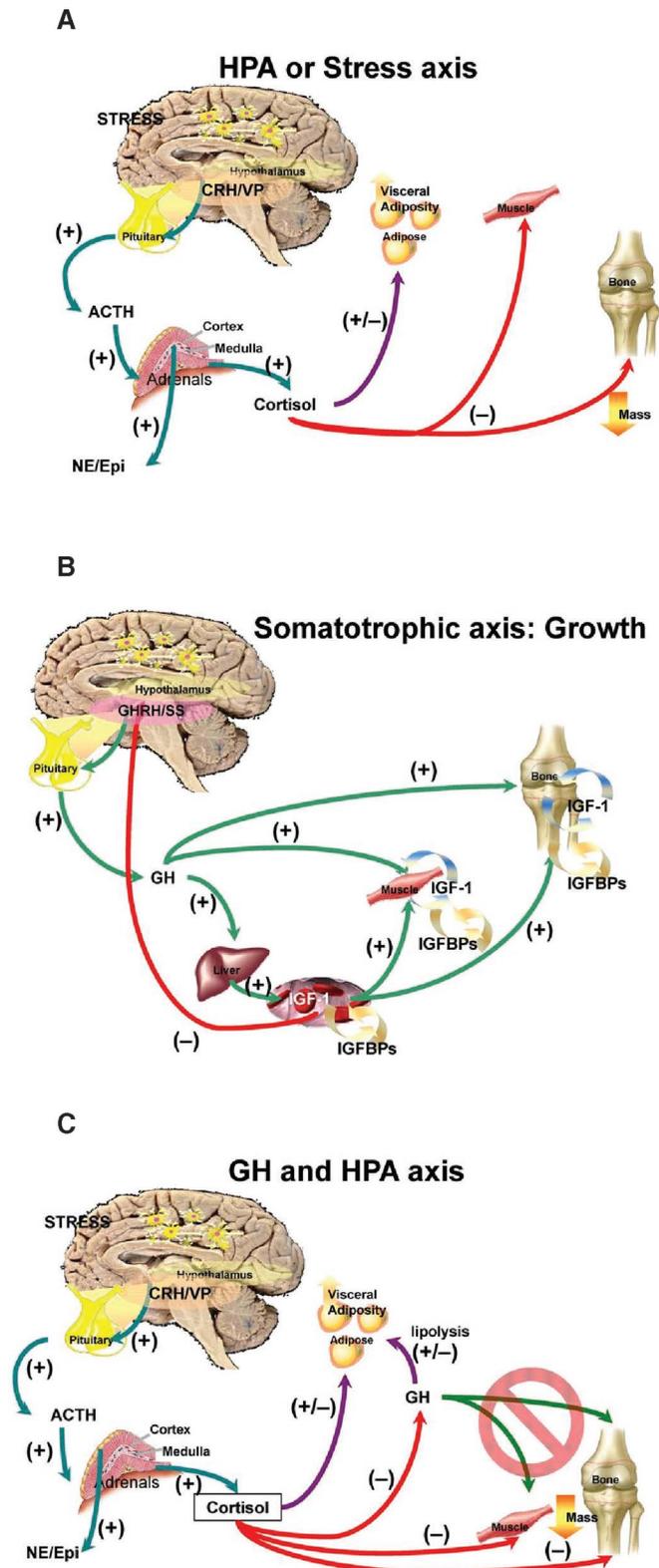


Figure 1. Anatomical presentation of the (a) hypothalamic-pituitary-adrenal (HPA) axis, (b) somatotrophic axis: growth, and (c) growth hormone (GH) and HPA axis.

The dual effector theory (Green et al., 1985) is based on the observation that IGF-1 stimulates amino acid uptake into the muscle in vitro but does not necessarily promote growth if given in vivo. Thus, GH is thought to control circulating as well as local tissue production of IGF-1. The theory proposes that GH not only controls IGF-1 production but also controls differentiation of cells so that they can respond to the mitogenic effect of IGF-1. The dual effector theory really comes into play during periods when there is uncoupling of the GH/IGF-1 axis. Having high concentrations of GH and low concentrations of IGF-1, such as during the acute phase immune response, suggests that GH plays a different role under these circumstances. However, it is important to note that changes in circulating concentrations of GH have been reported to be species-specific (Daniel et al., 2002). In humans, sheep, and pigs, GH concentrations increase following activation of the innate immune system, whereas in rats, cattle, and birds, GH concentrations decrease.

Immunological stress is often overlooked as being a stressor. However, even subclinical immunological stress brought about by pathogenic challenges can have a significant impact on animal production. Evidence continues to mount supporting the existence of bidirectional communication pathways between the animal's growth axis and immune system. For more than 3 decades, researchers have sought, and identified, linkages between the somatotrophic axis and health in domestic livestock. For further information regarding growth and immunity, see Carroll (2007).

Immunological Stress and the Somatotrophic Axis

Background

For decades, researchers have demonstrated 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 associated with subclinical immunological burdens on the animal versus long-term or chronic stress associated with disease and severe pathogenic challenges. Livestock experience numerous environmental, managerial, and nutritional stressors throughout the production cycle that could potentially inhibit overall productivity and well-being due to stress-induced immunosuppression.

Typically, sick animals experience a period of anorexia, thus requiring nutrient repartitioning and nutrient sparing to liberate nutrients for the production of proteins such as the proinflammatory cytokines and acute-phase proteins that are critical for reestablishing homeostasis. Acti-

vating and maintaining an immune response is essential for survival; however, there is an associated energy cost to the animal during a time when incoming nutrients are limited due to the animal's anorexic behavior. Creating and maintaining a febrile response alone is very energy-intensive. It has been estimated that there is approximately a 10 to 13% increase in metabolism for every degree of body temperature increase associated with an immune response (Kluger and Rothenburg, 1979). Although the energy-liberating effects of GH are well-recognized, the significance of elevated GH during times of sickness-induced anorexia may be more profound due to its stimulatory actions on immune cells. In addition to GH, IGF-1 and its associated binding proteins have also generated significant interest with regard to their interactions with various proinflammatory cytokines and the overall effect on muscle growth and repair. In contrast to the catabolic actions of IL-1 β and IL-6 on muscle tissue, IL-15 (a cytokine produced in various tissues including placenta, skeletal muscle, kidney, lung, heart, and macrophages) has been reported to act in an additive fashion with IGF-1 on muscle fiber growth (Quinn et al., 1995). It is tempting to speculate that IL-15 may play a role for cytokines in the repair of muscle tissue following a potential immunological insult (wound) to muscle tissue. The remainder of this proceedings paper will address the linkages between immunological stress and the somatotrophic axis relative to meat-producing livestock.

Sheep

Elucidating the potential communication pathways between immunological stress and the somatotrophic axis has been explored more extensively in sheep than in any other livestock species. More than a decade ago, Coleman et al. (1993) demonstrated that intravenous administration of endotoxin (lipopolysaccharide; LPS) increased both circulating concentrations of TNF- α and GH secretion in sheep. Subsequent studies from this group (Daniel et al., 2005) revealed that intravenous injections of both TNF- α and IL-1 β also induced a rapid increase in circulating concentrations of GH, which occurred in a biphasic manner that lasted for more than 2 h. Collectively, the results from this research suggested that endotoxin may mediate GH release via a direct action on the hypothalamus, possibly through the regulation of SS or GHRH. Briard et al. (1998) had also suggested a potential hypothalamic pathway by which LPS increased GH secretion in sheep. However, Daniel et al. (2005) reported that neither TNF- α nor IL-1 β increased circulating concentrations of GH and that intracerebroventricular administration of human IL-1 receptor antagonist and human soluble TNF-receptor 1 failed to blunt the increase in circulating GH following intracerebroventricular injections of LPS. Through these series of elegant experiments, these authors were able to confirm several pathways by which LPS and proinflammatory cytokines could stimulate the release of GH from the pituitary gland (Figure 2).

In addition to the effects of LPS and proinflammatory cytokines on GH secretion, Briard and colleagues also demonstrated that in sheep, endotoxin caused a decrease in IGF-1 and increased IGF binding protein 1 in the presence of a sustained biphasic increase in GH secretion (Briard et al., 1998, 2000). These authors suggested that the LPS-induced changes observed with regard to IGF-1 and its associated binding proteins could be associated with the LPS-induced increase in SS that they previously reported in sheep (Briard et al., 1998). Collectively, the aforementioned studies clearly demonstrate that the release of proinflammatory cytokines associated with immunological stress induced by administration of endotoxin to sheep can have significant effects on the regulation of both GH and IGF-1.

Cattle

Associations between the proinflammatory response to infection and the lasting impacts on the somatotrophic axis in cattle were described and characterized in a series of studies performed by Elsasser and colleagues during the mid 1980s and early 1990s (Elsasser et al., 1986, 1988; Fayer and Elsasser 1991). Several aspects of the communication network that we now know to exist between the immune system and the somatotrophic axis in cattle were elucidated through the traditional LPS challenge model, as well as the proinflammatory response to systemic parasite challenges (Elsasser et al., 1990). The authors demonstrat-

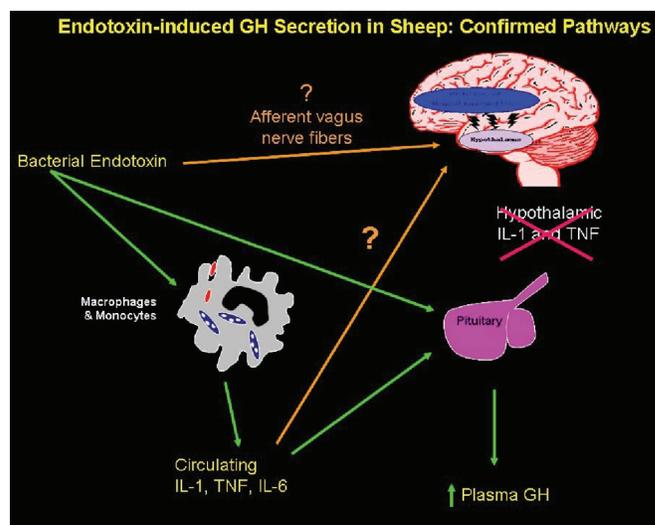


Figure 2. Potential pathways by which bacterial endotoxin and the proinflammatory cytokines, tumor necrosis factor (TNF)- α , interleukin (IL) 1 β , and IL-6 stimulate growth hormone (GH) in sheep. Potential pathways include systemic release of proinflammatory cytokines from macrophages and monocytes, acting at the level of the hypothalamus or pituitary gland, or both, and mediated via afferent limbs of the vagus nerve. The green arrows represent confirmed pathways, whereas the orange arrows represent pathways that remain unresolved.

Table 1. Circulating concentrations of insulin-like growth factor I (IGF-I) in calves infected with *Sarcocystis cruzi* or on a restricted plane of nutrition as compared with noninfected, nonrestricted control calves¹

Time (d) relative to infection ²	IGF-I concentration, nmol/L		
	Control	Infected	Pair-fed ³
Preinfection	9.7	11.3	11.6
+27 ⁴	10.1	3.1*	5.3*
+35	10.3	1.9*	6.4*
+42	10.1	2.7*	8.7
+58	10.2	3.3*	9.1

¹Recreated from Elsasser et al. (1988).

²Days postinfection with the parasite *S. cruzi* (oral dose of 250,000 oocysts per calf).

³Calves were pair-fed to match the intake of *S. cruzi*-infected calves.

⁴Day at which an intense proinflammatory response occurred.

*Denotes IGF-1 concentrations that are lower ($P < 0.05$) as compared with control.

ed that the onset of an intense proinflammatory response, similar to the physiological responses as observed in LPS-challenged calves, occurred around 27 to 28 d following infection with a coccidia-like parasite (e.g., *Sarcocystis cruzi*; Elsasser et al., 1988). The results from their research demonstrated that reduced IGF-I concentrations following a proinflammatory response could not be attributed solely to the anorexic behavior and associated decrease in feed intake normally observed in sick animals (Table 1). We have recently provided supporting data associated with the tight linkage between the immune system and growth axis in cattle by demonstrating that LPS administration to steers caused a rapid increase in circulating concentrations of proinflammatory cytokines that is associated with an abrupt decrease in circulating concentrations of IGF-1

that persists for more than 8 h (Figure 3; our unpublished data).

Recent research has provided even more evidence of this bidirectional communication pathway by demonstrating the ability of GH treatment to modulate changes in inducible nitric oxide and signal transduction pathway elements in the liver following an LPS challenge (Li et al., 2007). Specifically, the authors of this research reported that daily injections of exogenous GH not only augmented LPS-induced production of inducible nitric oxide within the liver but also differentially altered the signal transduction pathway elements within the liver following LPS activation. As exploratory research into the complex and intricate communication network between the immune system and growth axis advances, evidence continues to mount supporting this economically important linkage associated with the overall productivity and well-being of cattle.

Swine

Explaining the bidirectional communication network between the immune system and the growth axis has not been as extensive in swine as in sheep and cattle. With that said, there is sufficient data within the literature and studies from our laboratory that do indeed support the existence of this intricate linkage between the immune system and somatotrophic axis in swine. Earlier studies primarily revealed that exogenous GH treatment could alter various aspects of the activated immune system. In 1995, researchers (Parrott et al., 1995) demonstrated acute increases in circulating concentrations of GH in pigs during the first 20 min following an LPS challenge. A subsequent study by Hevener and colleagues (Hevener et al., 1997) in finishing pigs also demonstrated an acute increase in GH 40 min after an intraperitoneal challenge with LPS that was short-lived, followed by a subsequent uncoupling of the GH/IGF-I axis that persisted for 96 h after LPS exposure. In weanling pigs, we have demonstrated that subsequent to an intravenous challenge with LPS, serum concentrations of GH are dramatically reduced during the first 30 min post-LPS challenge, an event that is associated with a significant increase in circulating concentrations of IGF-1. Subsequent to this initial acute response, GH concentrations spike at 3 h post-LPS challenge, whereas IGF-1 concentrations continue to decline (our unpublished data). These data highlight the importance of intensive serial blood sampling when attempting to profile the dynamic aspect associated with the uncoupling of the GH/IGF-1 axis. Additionally, these data suggest not only a time-dependent but also age-dependent aspect associated with the uncoupling of the GH/IGF-1 axis in swine.

As with the cattle research conducted by Elsasser et al. (1988), the research by Hevener et al. (1997) suggested that the persistent uncoupling of the GH/IGF-I axis could be attributed to factors beyond nutritional influences, because feed consumption did not differ between control and LPS-challenged pigs. This hypothesis is supported by

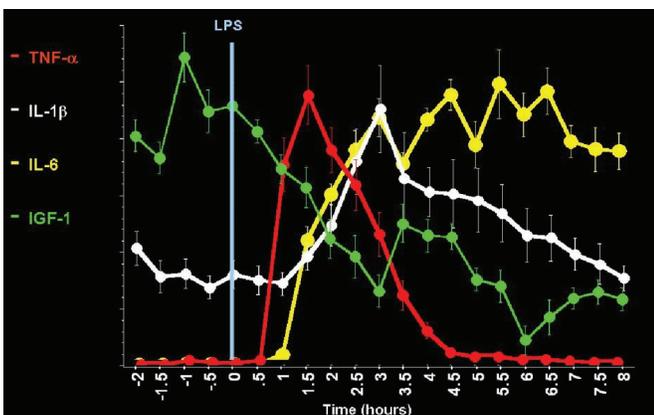


Figure 3. Lipopolysaccharide (LPS)-induced changes in circulating concentrations of tumor necrosis factor α (TNF- α), interleukin (IL) 1 β , IL-6, and insulin-like growth factor 1 (IGF-1) in steers.

a subsequent study by Wright et al. (2000), in which the authors reported that pigs challenged with LPS exhibited a decrease in feed intake that was associated with a rapid reduction in IGF-I, an increase GH, and that IGF-I concentrations remained low even after the pigs resumed normal feed consumption.

Conclusion

The currently available literature supports the possibility that the uncoupling of the GH/IGF-1 axis during periods of immunological stress in domestic livestock extends beyond a simple nutritional influence and warrants continued investigation to further elucidate this complex bidirectional communication pathway. Further understanding of the bidirectional communication within the body will undoubtedly continue to be unveiled as new research tools become available and as researchers develop multidisciplinary teams to pursue the complexities associated with the regulation of animal growth, performance, and meat quality.

References

- Briard, N., F. Dadoun, G. Pommier, N. Sauze, Y. Lebouc, C. Oliver, and A. Dutour. 2000. IGF-1/IGFBPs system response to endotoxin challenge in sheep. *Endocrinology* 164:361–369.
- Briard, N., V. Guillaume, C. Frachebois, M. Rico-Gomez, N. Sauze, C. Oliver, and A. Dutour. 1998. Endotoxin injection increases growth hormone and somatostatin secretion in sheep. *Endocrinology* 139:2662–2669.
- Cannon, W. B. 1935. Stress and the environment. *Am. J. Med. Sci.* 189:1–4.
- Carroll, J. A. 2007. Bidirectional communication: Growth and immunity in domestic livestock. *J. Anim. Sci.* 86:E126–E137.
- Coleman, E. S., T. H. Elsasser, R. J. Kempainen, D. A. Coleman, and J. L. Sartin. 1993. Effect of endotoxin on pituitary hormone secretion in sheep. *Neuroendocrinology* 58:111–122.
- Daniel, J. A., T. H. Elsasser, A. Martinez, B. Steele, B. K. Whitlock, and J. L. Sartin. 2005. Interleukin-1 β and tumor necrosis factor- α mediation of endotoxin action on growth hormone. *Am. J. Physiol. Endocrinol. Metab.* 289:E650–E657.
- Daniel, J. A., B. K. Whitlock, C. G. Wagner, and J. L. Sartin. 2002. Regulation of the growth hormone and luteinizing hormone response to endotoxin in sheep. *Domest. Anim. Endocrinol.* 23:361–370.
- Elenkov, I. J., R. L. Wilder, G. P. Chrousos, and E. S. Vizi. 2000. The sympathetic nerve – An integrated interface between two supersystems: The brain and the immune system. *Pharmacol. Rev.* 52:595–638.
- Elsasser, T. H., R. Fayer, T. S. Rumsey, and A. C. Hammond. 1990. Plasma and tissue concentrations and molecular forms of somatostatin in calves infected with *Sarcocystis cruzi*. *Domest. Anim. Endocrinol.* 7:537–550.
- Elsasser, T. H., T. S. Rumsey, A. C. Hammond, and R. Fayer. 1986. Perturbed metabolism and hormonal profiles in calves infected with *Sarcocystis cruzi*. *Domest. Anim. Endocrinol.* 3:277–287.
- Elsasser, T. H., T. S. Rumsey, A. C. Hammond, and R. Fayer. 1988. Influence of parasitism on plasma concentrations of growth hormone, somatomedin-C and somatomedin-binding proteins in calves. *J. Endocrinol.* 116:191–200.
- Fayer, R., and T. H. Elsasser. 1991. Bovine sarcocystosis: How parasites negatively affect growth. *Parasitol. Today* 7:250–255.
- Gosteli-Peter, M., K. H. Winterhalter, C. Schmid, E. R. Froesch, and J. Zapf. 1994. Expression and regulation of insulin like growth factor I (IGF-I) and IGF binding protein messenger ribonucleic acid levels in tissues of hypophysectomized rats infused with IGF-I and growth hormone. *Endocrinology* 135:2558–2567.
- Green, H., M. Morikawa, and T. Mxon. 1985. A dual effector theory of growth-hormone action. *Differentiation* 29:195–198.
- Hevener, W., G. W. Almond, J. D. Armstrong, and R. G. Richards. 1997. Effects of acute endotoxemia on serum somatotropin and insulin-like growth factor I concentrations in prepubertal gilts. *Am. J. Vet. Res.* 58:1010–1013.
- Kluger, M. J., and B. A. Rothenburg. 1979. Fever and reduced iron: Their interaction as a host defense response to bacterial infection. *Science* 4378:374–376.
- Li, C. J., S. Kahl, D. Carbaugh, and T. H. Elsasser. 2007. Temporal response of liver signal transduction elements during in vivo endotoxin challenge in cattle: Effects of growth hormone treatment. *Domest. Anim. Endocrinol.* 32:79–92.
- Mason, J. W. 1975. A historical view of the stress field. *J. Human Stress* 1:6–12.
- McEwen, B. S. 2000. The neurobiology of stress: From serendipity to clinical relevance. *Brain Res.* 886:172–189.
- Ohlsson, C., B. A. Bengtsson, O. G. Isaksson, T. T. Andreassen, and M. C. Słotweg. 1998. Growth hormone and bone. *Endocr. Rev.* 19:55–79.
- Pacák, K., and M. Palkovits. 2001. Stress and neuroendocrine responses. *Endocr. Rev.* 22:502–548.
- Parrott, R. F., S. V. Vellucci, J. A. Goode, D. M. Lloyd, and M. L. Forsling. 1995. Cyclo-oxygenase mediation of endotoxin-induced fever, anterior and posterior pituitary hormone release, and hypothalamic c-Fos expression in the prepubertal pig. *Exp. Physiol.* 80:663–674.
- Quinn, L. S., K. L. Haughk, and K. H. Grabstein. 1995. Interleukin-15: A novel anabolic cytokine for skeletal muscle. *Endocrinology* 136:3669–3672.
- Selye, H. 1973. The evolution of the stress concept. *Am. Sci.* 61:692–699.
- Velloso, C. P. 2008. Regulation of muscle mass by growth hormone and IGF-1. *Br. J. Pharmacol.* 154:557–568.
- Wright, K. J., R. Balaji, C. M. Hill, S. S. Dritz, E. L. Knoppel, and J. E. Minton. 2000. Integrated adrenal, somatotropic, and immune responses of growing pigs to treatment with lipopolysaccharide. *J. Anim. Sci.* 78:1892–1899.