Review Article

RELATIONSHIPS BETWEEN THE IMMUNE SYSTEM AND STRESS REACTIVITY IN PIG: VISUALIZING THE IMMUNO-NEUROENDOCRINE FRAMEWORK IN ACTION

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Abstract

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Activation of the immune system is regulated through several mechanisms, within the system itself and by other body systems, in order to maintain disease resistance, and prevent immune-mediated disorders within the host. It is well accepted that the immunological, physiological, behavioral, and psychological state of an animal are closely linked and the factors affecting one feature of the network can influence the rest of the system. In recent years, our understanding of the interactions between the neuroendocrine network (i.e. the hypothalamic-pituitary-adrenal axis, HPA) and immune-mediated inflammatory reactions has expanded enormously. This article outlines the nature of the immuno-neuroendocrine network and the implications of these interactions on swine health management strategies. In addition, various factors including stress, nutrition, genetics, the cost of immune activation and disease resistance will be explored under the context of the immune-neuroendocrine network.

Keywords : immune system, pig, stress reactivity, neuroendocrine network.

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บทคัดย่อ

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ความสัมพันธ์ระหว่างระบบภูมิคุ้มกันและความเครียดในสุกร

เป็นที่ยอมรับกันโดยทั่วไปว่าระบบภูมิคุ้มกัน มีจุดประสงค์หลักในการทำงานเพื่อการป้องกันการติดเชื้อจากภายนอกอย่างมีประสิทธิภาพ และในขณะเดียวกันจะต้องมีกลไกที่สามารถป้องกันหรือควบคุมความเสียหายของเนื้อเยื่อของร่างกายจากการทำงานของระบบภูมิคุ้มกันโดยไม่จำเป็น กลไกดังกล่าวนี้อาจมาจากการทำงานของเซลล์ภายในระบบภูมิคุ้มกันเองหรืออาจเป็นกลไกการควบคุมจากเซลล์ในระบบอื่นของร่างกายก็ได้ ในปัจจุบันเป็นที่ยอมรับว่าสภาวะทางด้านภูมิคุ้มกัน สรีรวิทยา พฤติกรรม รวมไปถึงสภาวะทางจิตใจของสัตว์ ล้วนมีความเกี่ยวข้องสัมพันธ์กันอย่างใกล้ชิด และการปรับเปลี่ยนสถานะของระบบใดระบบหนึ่งย่อมจะส่งผลกระทบถึงการทำงานระบบอื่นๆ ในร่างกายของสัตว์ด้วย ในช่วงเวลาที่ผ่านมามีองค์ความรู้ใหม่ที่ช่วยอธิบายถึงกลไกการทำงาน และความสัมพันธ์ของระบบภูมิคุ้มกัน ระบบต่อมไร้ท่อ และระบบประสาทเพิ่มขึ้นเป็นอันมาก บทความนี้จะกล่าวถึงความรู้ที่เกี่ยวข้องกับความสัมพันธ์ในการทำงานของระบบต่างๆ ในร่างกาย โดยจะเน้นถึงความสัมพันธ์ของระบบภูมิคุ้มกัน กับระบบต่อมไร้ท่อและระบบประสาท (immuno-neuroendocrine network) เป็นสำคัญ และจะชี้ให้เห็นถึงแนวคิดที่อาจสามารถนำไปประยุกต์ใช้ได้ในวงจรการผลิตสุกรได้ นอกจากนี้บทความนี้จะอภิปรายถึงปัจจัยที่อาจมีผลกระทบถึงการทำงานของระบบเครือข่ายเหล่านี้ อาทิเช่น ความเครียด อาหาร สายพันธุ์ รวมถึงวิเคราะห์ถึงปัจจัยทางกายภาพของสัตว์ในองค์รวมที่จะต้องเสียไปเพื่อแลกกับการทำงานของระบบภูมิคุ้มกันในการต่อต้านการเกิดโรค

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Introduction

"It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most adaptable to change"

Charles Darwin (1809-1882)

For millions of years, animal creatures have evolved to survive when subjected to numerous selective pressures. The successful creatures had to achieve effective "stress reactivity" strategies that coordinated the functions of their body systems in order to cope with the "stress" (i.e. threats and challenges) that they had encountered. The ultimate goal of these activities was to maintain homeostasis within the organisms that would eventually increase their chances of survival. One of the major systems that has evolved during the selective pressure is the immune system. The system comprises networks of numerous cells, cytokines, and proteins working in an orchestrated manner to protect the organism from both external and internal challenges using several elaborate defense mechanisms. Apart from sophisticated ways of cellular communication, the immune system is not just working by itself. To maximize the chance of survival, animals have developed an intricated network that connects the various body systems, including the immune system, the central nervous system, and the endocrine system. It is now well accepted that the immunological, physiological, behavioral, and psychological state of the animal are closely linked and factors affecting one feature of the network can influence the rest of the system. In recent years, our understanding of the interactions between the neuroendocrine network

(i.e. the hypothalamic-pituitary-adrenal axis, HPA) and immune-mediated inflammatory reactions has expanded enormously. This article will outline the nature of the immuno-neuroendocrine system and the implications of these interactions on pig health management strategies.

The immune system

The immune system maintains the integrity of the host by sensing the presence of foreign molecular structures, through pathogen recognition receptors (PRRs) of the host's innate cells, or abnormal tissue damage that leads to activation of the defense mechanism to remove the threat. The first strategy of the immune system involves production of a wide range of molecules such as antibacterial peptides, acute phase proteins, proteins involved in an alternative complement pathway, and pro-inflammatory cytokines (e.g. interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α etc.) by various cells at the infected and/or affected sites, in order to activate the early defense mechanisms and phagocytic cells (i.e. dendritic cells, macrophages, neutrophils) in nearby tissue. This so-called innate immunity can be initiated immediately after sensing the danger, i.e. pathogen invasion, and typically leads to 1) an inflammatory reaction at the infected site by the activity of pro-inflammatory cytokines, and 2) departure of mature antigen-presenting cells (APCs), carrying the antigen and co-stimulatory signals required for the activation of antigen-specific lymphocytes, to the draining lymphoid tissues. At this stage, APCs provide both the antigen and co-stimulatory signals (generated from ligation of PRRs) to the specific lymphocyte and direct the development of protective specific-immunity, according the information obtained from the APCs. This fine-tuning of the subsequent specific immunity partly relies on the co-evolution of the host and pathogen via the APCs activities.

The second strategy employed by the immune system relies on the generation of a diversity of antibodies and T lymphocyte receptors (TCRs) within the host and the activation of specific lymphocytes in secondary lymphoid tissues, in an antigen-dependent manner, i.e. acquired or adaptive immunity. In the lymphoid tissues, antigen-specific lymphocytes are selected to expand and differentiate to either effector lymphocyte populations, that initiate humoral and cell-mediated immunity during the activation phase, or memory populations that facilitate more rapid recruitment of the immunological defense mechanisms in case of subsequent exposure to a specific antigen. Once the induction of humoral and cell-mediated immune responses and the elimination of the pathogens or threats is achieved, the effector cells are deleted or suppressed by several mechanisms, including the induction of apoptosis and the production of immuno-suppressive cytokines such as IL-10 and/or transforming growth factor (TGF)-β. Subsequently, the immunological activities decline and the body resumes its homeostasis, leaving just the reserved memory population. Generally, activation of the immune system is tightly regulated through several mechanisms in order to maintain disease resistance and prevent immune-mediated disorder within the host.

The immuno-neuroendocrine interface

Most selection pressures, that shape evolution, are stressors which are physical (wound, infection), psychological (fear, aggression), or physiological (food and water deprivation). Thus, one of the primary functions of the brain is to perceive stressors, warn of the danger, and enable an organism to deal with the consequences. For example, activation of the stress system heightens arousal, accelerates motor reflexes, improves attention and cognitive function, increases the tolerance of pain, decreases appetite and sexual arousal and inhibits immune-mediated inflammation. This series of stress reactivities are accomplished through the release of stress-responsive neurotransmitters and hormones (Dhabhar, 2002). It is now well accepted that the immune system, central nervous system and the various endocrine organs are linked in a dynamic manner through networks of mutual interactions.

It is believed that the main function of the hypothalamus-pituitary-adrenal (HPA) and autonomic nervous system (ANS) is to maintain basal and stress-related homeostasis. The function of the immune system is, therefore, linked to the neuroendocrine network, via the HPA axis, and ANS. These systems provide both the checks and balances for maximizing immunological defense properties and at the same time, minimizing the potential destructive properties of immune activation, i.e. immuno-pathology. The HPA axis consists of 3 components: the hypothalamus, in particular the paraventricular nucleus (PVN), the anterior pituitary and the adrenal cortex. The stress signals, including pro-inflammatory cytokine productions in the host's tissues, stimulate the release of corticotrophin-releasing hormone (CRH) from the hypothalamus. CRH is an obligatory and primary stimulus for adrenocorticotropin hormone (ACTH) production and secretion by the pituitary gland. Subsequently, ACTH stimulates glucocorticoid (cortisol in humans, corticoster-one in animals) synthesis from the cells of adrenal cortex. Glucocorticoid is the final activation product in the HPA axis and the primary effector molecule of this neuroen-docrine circuit (Fig. 1). It should be noted that glucocorticoid receptors are also found in both the PVN and the anterior pituitary. The negative feedback effects of glucocorticoids on CRH and ACTH synthesis and secretion are well documented. Thus, the HPA axis is a closed-loop circuit (McEwen et al., 1997). Although, it was previously believed that glucocorticoid imposes a strong negative effect on the immune system, recent evidence suggests that it is not always the case. In fact, glucocorticoid is important for immune regulation and the prevention of immunopathology by maintaining host homeostasis (see below).

Apart from the endocrine system, the autonomic nervous system plays a crucial role in the immuno-neuroendocrine network that can influence the function of the immune system. Recent evidence has demonstrated significant influence of the ANS in the development, maturation, and function of lymphocytes. Virtually, every organ in the immune system is "hardwired" through nerve fibers and the control of immune regulation by the nervous system *in vivo* is achieved through a hierarchy of neural and endocrine contacts. Free nerve endings in the skin and mucous membrane respond to noxious stimuli, neuropeptides and/or pro-inflammatory cytokines, released from the damage tissues, by sending afferent signals to the central nervous system via the afferent (sensory) nerve fibers, leading to activation of HPA activity. In return, CRH drives both pituitary (HPA) and autonomic efferent (motor) outputs, in an independent manner. The involvement of ANS on local monitoring, coordination, and modulation of the host defense mechanisms has been reviewed extensively elsewhere (Downing and Miyan, 2000). In addition, local cytokine production in the brain in response to various stressors (e.g. life events, depression, anxiety, stress, local brain injury), without systemic inflammation, can also initiate brain-mediated immunosuppression via HPA activity and sympathetic activation. Apart from activating the release of corticosteroids, local cytokine production in the brain can activate the synthesis and release of catecholamine, which stimulates the production and secretion of the potent immunosuppressive cytokine, IL-10 by monocytes. It has been shown that monocytes and macrophages express both glucocorticoid receptors and β-adrenoceptors, suggesting that they are important targets in the neuroimmune interaction (Woiciechowsky et al., 1999). A simplified diagram of the immuno-neuroendocrine network is summarized in Fig. 2.

The roles of corticosteroids on the immune system

Corticosteroids have been regarded as the "bad guys" for immune functions for many years, due to evidence derived from effects of synthetic glucocorticoids (e.g. dexamethasone, prednisolone etc.) on the immune system. However, recent evidence suggests that endogenous corticosteroids produced by the host can

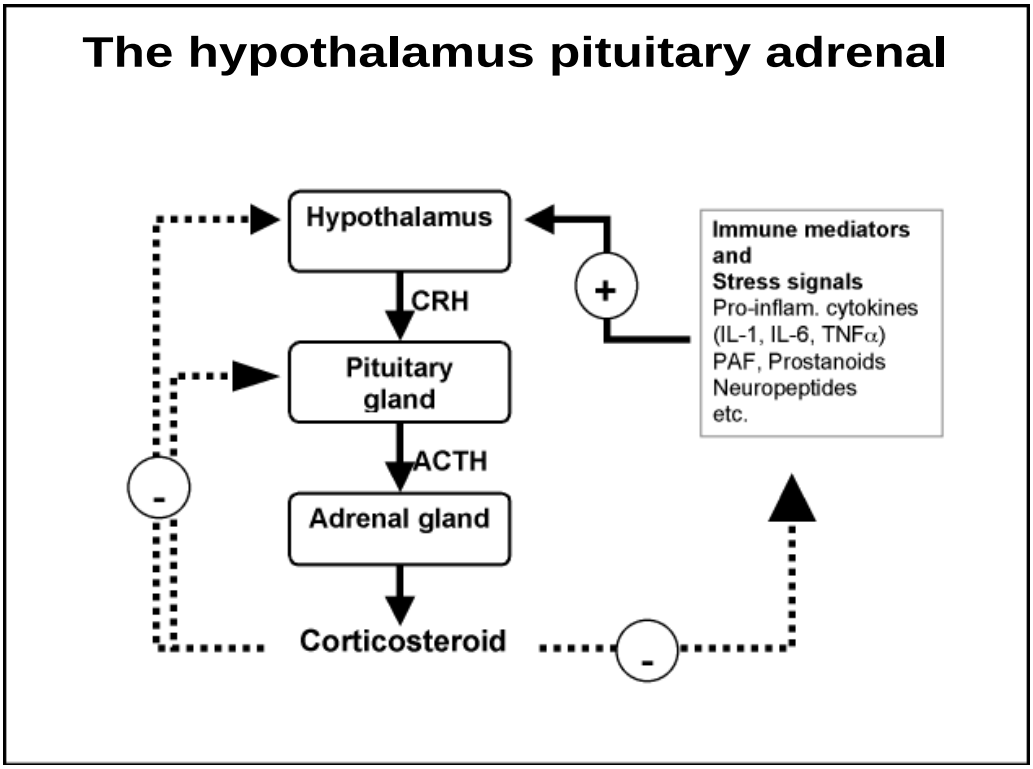


Figure 1 The hypothalamus pituitary adrenal axis (HPA) and its regulatory role on immune activation.

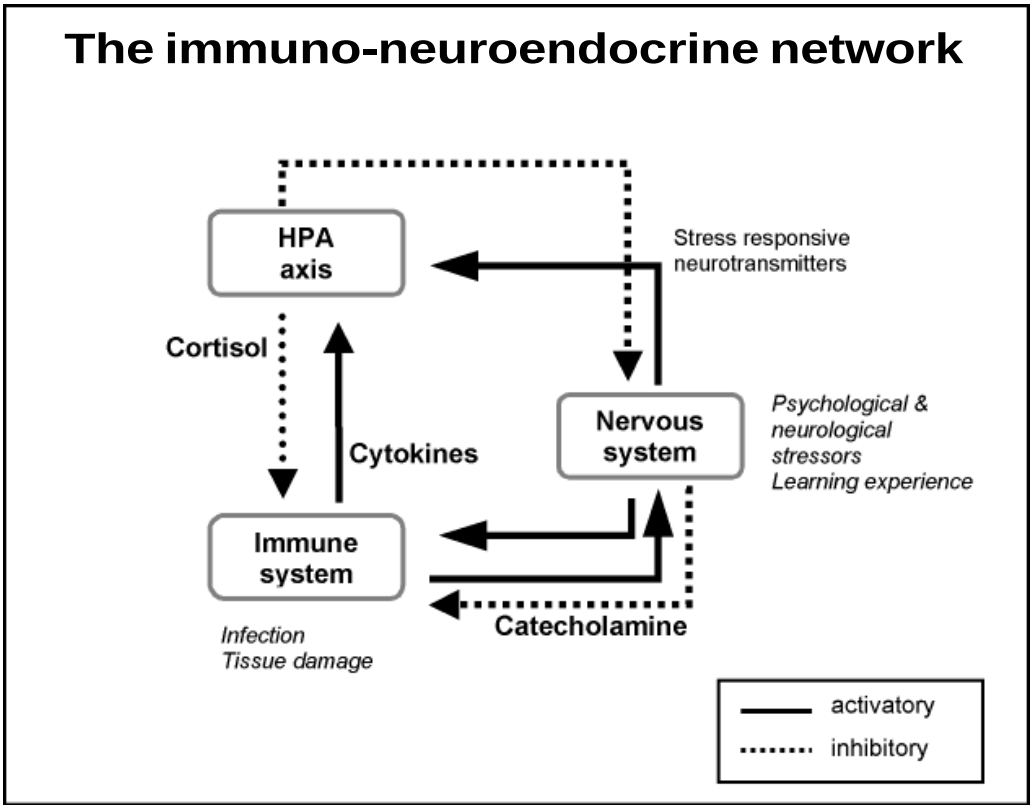


Figure 2 Schematic diagram of interactions within the immuno-neuroendocrine network.

have either a positive or a negative effect on immune functions, depending on the stage of stress. The biological effects of endogenous corticosteroids reflect "stress reactivity" when homeostasis of the host is jeopardized. As an acute stress response prepares the cardiovascular and musculoskeletal systems of the host for fight or flight, it also prepares the immune system for any challenge which may be imposed by the stressors. During the early hours of acute stress, endogenous corticosteroids produced by activation of the HPA axis, transiently redirect leukocyte trafficking and stimulate cytokine gene expression at the site of antigen entry. Granulocyte production is increased, making them available in large numbers in the bloodstream for recruitment and activation at the sites of antigen entry (e.g. skin, mucosal linings, lung and lymph nodes, etc.). At the same time, lymphocytes and monocytes are directed to secondary lymphoid tissues where antigen-specific cells are activated, resulting in a drastic reduction of their numbers in the circulation (Dhabhar, 2002). Endocrine mediators released during acute stress, in this context, would ensure that appropriate leukocyte subsets are present in the right place at the right time, thus enhancing immunological vigilance to the potential or ongoing immunological challenge.

As stress induced corticosteroids help prepare the immune system for any possible challenges during the early stages of stress, it should be noted that any excessive immune activation may lead to immunopathology or immune-mediated disorders. Several mechanisms have been developed to prevent or inhibit any excessive immune activation that may lead to immune-mediated disorders. These can be initiated by the immune system, for example; induction of apoptosis of the activated effector cells, immune deviation (skewing towards Th2 development), stimulation of immunosuppressive cytokine production (e.g. IL-10, TGF-β) or induction of regulatory (or suppressor) T cells. Interestingly, it has been demonstrated that corticosteroids have potent inhibitory effects on both innate and acquired immunity, particularly during chronic stress. Adrenal steroids inhibit a wide range of immunological functions including antigen presentation by APCs, cytokine production and/or the expression of cytokine receptors by the immune cells and the effector functions of immune cells. Furthermore, corticosteroids have been shown to modulate Th development (by suppressing Th1 and enhancing Th2 development), to enhance the production of IL-10, and be involved in the induction of regulatory cells (McEwen et al., 1997; Woiciechowsky et al., 1999). In this context, glucocorticoids would serve as regulators, preventing any potentially harmful immune-mediated activities. Theoretically, this would benefit the resumption of host homeostasis following the removal of any temporary stress or acute infection. However, in chronic infections or chronic stress situations, the immunomodulatory effects of corticosteroids can eventually lead to long term immunosuppression or inappropriate immune responses following the new antigen exposure.

The cost of immune activation on behavior and nutritional status

The meaning of stress nowadays is substantially different from that which our ancestors perceived. Stress in the present day can refer to "the physiological, behavioral, and psychological state of the animal when confronted with, from the animal's point of view, a potentially threatening situation" (Terlouw, 2005). The concept of clonal selection and expansion during the activation of the immune response and accumulating information on neuro-immunoendocrinology, indicates that there is a "cost" for immune activation. Outputs from the immune system also affect pathways that regulate metabolism, nutrient partitioning, behavior, thermoregulation and HPA activity. Pro-inflammatory cytokines produced during the acute phase response, modify metabolic activity in the liver, resulting in the production of several acute phase proteins, including haptoglobin, C-reactive protein, complement proteins, and clotting

factors (Colditz, 2002). IL-1β and TNF-α reduce protein accretion in muscle and redirect amino acids to energy production, leading to an increase in O_2 consumption and the metabolic rate (Klasing, 1988). During the peak of an immune response, oxygen consumption and glucose utilization per cell increases approximately 2 fold. In addition, the requirement for glutamine (an energy source and a substrate for nucleotide synthesis) and other amino acids also increases 2-3 fold, during antigen induced cellular proliferation (Wilmore and Shabert, 1998; Pond and Newsholme, 1999). Interestingly, glucocorticoids stimulate the production and release of glutamine from muscle cells (Wilmore and Shabert, 1998) and favour nutrient partitioning of fat over lean (Annison and Bryden, 1999). Thus, the indirect effect of immune responses through the production of cytokines and acute phase responses, can have remarkable effect on nutrient partitioning and a significant affect on animal production. The negative effects of pathogen load on growth performance has been previously demonstrated (Fossum, 1998).

The effects of pro-inflammatory cytokines expand further to alter the behavioral characteristics of the animals. IL-1β and IL-6 activate the hypothalamus, inducing fever and sickness behavior (Colditz, 2002; Dantzer, 2004). It is believed that higher temperature, attained during the activation of innate immunity, is unfavorable for the growth of many pathogens. However, it should be noted that the energy required to increase the body temperature during the febrile process is quite high. In humans, it requires a 13% increase in the basal metabolic rate to increase the body temperature by 1°C. Because of the high metabolic cost of fever, there is little room for other activities, except for those favoring heat production (e.g. shivering) and minimizing thermal losses (e.g. rest, curl up position, piloerection). Thus, sickness behavior is an expression of physiological adaptation rather than a consequence of weakness. In addition, behavioral responses induced by pro-inflammatory cytokines may lessen the availability of nutrients, through depression of appetite, as cytokines provide inputs to the CNS (Dantzer, 2004). Chronic gastrointestinal diseases, where lesions are associated with the impairment of protein absorption and/or protein losses through damaged intestinal walls, may exacerbate the nutrient deprivation of the host. Thus, proinflammatory cytokines can significantly affect both the behavior and the performance of domestic animals. It should be emphasized that, apart from pathogen exposures, any physical and psychological stressors can also activate the acute phase responses that affect HPA activities. Environments where the sum of environmental and immunological stressors are high, redirect nutrients away from muscle growth and animal production to liver anabolism and the host's defense mechanisms. On the other hand, minimizing unnecessary immune activation (i.e. the amount of pathogen load in the rearing system) and stress reactivity would allow maximum feed utilization and performance. By creating a "healthy" rearing system through improvements in pig management and husbandry, the animal's potential can be realized. As it has been suggested that apparently healthy animals commonly have subclinical infections that affect their well-being and growth (Fossum, 1998). Assessments of acute phase protein production (e.g. IL-1, IL-6, haptoglobin, etc.) may be used as direct indicators for the evaluation of immunological status and potential metabolic losses within a pig production system. In addition, information regarding the nutrient economy during stress reactivity and immune activation opens the area of immunonutrition, in which certain nutritional supplement strategies can be implemented to improve the overall health outcome during "stressful" moments in a swine production system.

Stress and intestinal barrier function

The intestinal mucosa is continuously exposed to tremendous antigenic challenges. The common mucosal immune system has a unique strategy of immune

regulation. Disease resistance is achieved through the preferential induction of non-inflammatory mechanisms, allowing the system to maintain its normal physiological function in the face of immunological challenge. The intestinal barriers, consists of physical diffusion barriers, regulated physiological and enzymatic barriers and immunological barriers, are under the neurohormonal control of the HPA axis, and can be influenced by stress signals. Recently the influence of psychological stress, on the clinical course of chronic intestinal disease, has been increasingly recognized in humans (Bennett et al., 1998). Stress has also been shown to reactivate animal colitis. Experiments using animal models demonstrate that various types of psychological and physical stress induce dysfunction of the intestinal barrier, resulting in enhanced uptake of noxious material from the gut lumen (Söderholm and Perdue, 2001). The endogenous glucocorticoid production induced by stress from transportation and handling, impairs the intestinal barrier and increases intestinal permeability (Meddings and Swain, 2000). Several studies suggest that there are signaling pathways between the central nervous system, via enteric neurons, and mucosal mast cells. Mast cells are often found close to neurons and can be activated through stress-induced CRH and/or acetylcholine production, from mucosal nerves. It should be emphasized that the stress signals can be derived from both local (cytokines induced from local infection) and through the HPA activity, in response to stressors. In an acute phase, mast cells regulate mucin release from globlet cells in the mucosal tissue, thus increasing the barrier property and providing a degree of protection against invasion. However, over a longer period of time, globlet cell depletion would be detrimental to the ability of the mucosal tissue to respond to ongoing or new threats. In addition, mediators released from activated mast cells (and possibly neurons) exacerbate tissue inflammation and enhance epithelial permeability by both transcellular and paracellular pathways. Subsequently, this barrier defect leads to enhanced movement of noxious molecules into the mucosa (Söderholm and Perdue, 2001).

The metabolic cost of disease resistance: a perspective on genetics and stress reactivity

Sacrificing metabolic cost in exchange for improving disease resistance is well accepted in evolutionary biology (Owen and Wilson, 2000). In animals, behavioral, physiological and metabolic responses to challenge depends on the genetic background and previous learning experiences (Terlouw, 2005). This leads to the idea that selection of animal traits that can cope well with challenges, with a minimal burden on production, i.e. resilience, may be possible through breeding strategies. Selection for production traits on immune competence and disease susceptibility have been under investigation for many years. However, an attempt to generate "super pigs" that do well for both disease resistance and performance can be problematic as the two parameters seem to be inversely correlated. In a multiple regression analysis on the association between productivity and a range of immune traits in Large White pigs, a decrease in the performance trait was associated with a significant increase in immune cell numbers, in particular mononuclear cell subsets. As the proportions of specific cell types increase, performance, in terms of live weight gain and feed intake, significantly decreases (Clapperton et al., 2005). Selection over several generations for immune responses in pigs has resulted in improved growth rates and disease resistance, but, this selection pressure has also resulted in over active immunopathology (Magnusson et al., 1999). Therefore, measuring a combination of variables for both disease resistance and production traits will be required for swine genetic improvements to be made.

Interestingly, certain high, lean gain, swine genotypes have higher sensitivity to pathogen and non-pathogen stressors, as shown by reduced productivity and increased mortality, during disease stress or in

sub-optimal production environments. There are significant differences among swine populations in their metabolic, acute phase protein and leptin (a regulator, induced by TNF-α and corticosteroid, that is involved in the mechanisms of feed intake) production in response to immunologic challenge. This may, in part, explain increase sensitivity to disease stress in certain swine genotypes (Leininger et al., 2000). In some reports, a 30% lower ADG has been observed under a poor management conditions (Holck et al., 1998). Thus, additional factors including environmental, psychological, and physiological stress burdens and ongoing disease patterns in the farm will be needed to be included in the genetic selection process. These findings also imply that in order to achieve the maximal potential for the selected high yield traits in a commercial rearing system, improvements in animal management and husbandry, i.e. the reduction of any possible stressors, will be essential.

Summary

This article explores the relationships between the various parameters that can influence the well-being of pigs in a commercial production system. Information regarding the mechanisms of stress reactivity and its effect on pig performance has been discussed. Advanced knowledge and technology can now be applied and integrated into almost every step of the pig production system. However, information concerning the interactions of several body functions has only recently begun to be understood. Improved knowledge of the interactions between genetic, nutrition, immune function and disease resistance will contribute greatly to the perfection of strategies for improving the welfare and performance of pigs in the future.

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References

Annison, E. F. and Bryden, W. L. 1999. Perspectives of ruminant nutrition and metabolism. II. Metabolism in ruminant tissues. Nutr. Res. Rev. 12: 147-177.

Bennett, E. J., C.C., T., Piesse, C., Badcock, C. A. and Kellow, J. E. 1998. Level of chronic life stress predicts clinical outcome in irritable bowel syndrome. Gut. 43: 256-261.

Clapperton, M., Bishop, S. C., Cameron, N. D. and Glass, E. J. 2005. Associations of weight gain and food intake with leukocyte sub-sets in Large White pigs. Livest. Prod. Sci. 96: 249-260.

Colditz, I. G. 2002. Effects of the immune system on metabolism: implications for production and disease resistance in livestock. Livest. Prod. Sci. 75: 257-268.

Dantzer, R. 2004. Cytokine-induced sickness behavior: a neuroimmune response to activation of innate immunity. Eu. J. Pharmacol. 500: 399-411.

Dhabhar, F. S. 2002. Stress-induced augmentation of immune function-the role of stress hormones, leukocyte trafficking, and cytokine. Brain Behav. Imm. 16: 785-798.

Downing, J. E. G. and Miyan, J. A. 2000. Neural immunoregulation: emerging roles for nerves in immune homeostasis and disease. Immunol. Today. 21: 281-289.

Fossum, C. 1998. Cytokines as markers for infections and their effect on growth performance and well-being in the pig. Domes. Anim. Endocrinol. 15: 439-444.

Holck, J. T., Schinckel, A. P., Coleman, J. L., Wilt, V. M., Senn, M. K., Thacker, B. J., Thacker, E. L. and Grant, A. L. 1998. The influence of environment on the growth of commercial finisher pigs. Sw. Health Prod. 6: 141-149.

Klasing, K. C. 1988. Nutritional aspects of leukocytic cytokines. J. Nutr. 118: 1436-1446.

Leininger, M. T., Portocarrero, C. P., Schinckel, A. P., Spurlock, M. E., Bidwell, C. A., Nielsen, J. N. and Houseknecht, K. L. 2000. Physiological response to acute endotoxemia in swine: effect of genotype on energy metabolites and leptin. Domes. Anim. Endocrinol. 18: 71-82.

Magnusson, U., Wilkie, B., Artursson, K. and Mallard, B. 1999. Interferon alpha and haptoglobin in pigs selectively bred for high and low immune response and infected with Mycoplasma hyorhinis. Vet. Immunol. Immunopathol. 68: 131-137.

McEwen, B. S., Biron, C. A., Brunson, K. W., Bulloch, K., Chambers, W. H., Dhabhar, F. S., Goldfarb, R. H., Kitson, R. P., Miller, A. H., Spencer, R. L. and Weiss, J. M. 1997. The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine, and immune interactions. Brain. Res. Rev. 23: 79-133.

Meddings, J. B. and Swain, M. G. 2000. Environmental stress induces a generalized increase in gastrointestinal permeability mediated by endogenous glucocorticoids in the rats. Gastroenterology. 119: 1019-1028.

Owen, I. P. F. and Wilson, K. 2000. Immunocompetence: a neglected life history trait or a conspicuous red herring. Trends Evo. Ecol. 14: 170-171.

Pond, C. M. and Newsholme, E. A. 1999. Coping with metabolic stress in wild and domestic animals. Brit. Soc. Anim. Sci. Publ. Series. 24: 9-20.

Söderholm, J. D. and Perdue, M. H. 2001. Stress and gastrointestinal tract, II. Stress and intestinal barrier function. Am. J. Physiol-Gastr. L. 280: G1-G13.

Terlouw, C. 2005. Stress reactions at slaughter and meat quality in pigs: genetic background and prior experience: A brief review of recent findings. Livest. Prod. Sci. 94: 125-135.

Wilmore, D. W. and Shabert, J. K. 1998. Role of glutamine in immunologic responses. Nutrition. 14: 618-626.

Woiciechowsky, C., Schoning, B., Lanksch, W. R., Volk, H.-D. and D_cke, W.-D. 1999. Mechanisms of brain-mediated systemic anti-inflammatory syndrome causing immunosuppression. J. Mol. Med. 77: 769-780.