HOW MUCH DOES IMMUNE STATUS INFLUENCE NUTRIENT REQUIREMENTS? THE NUTRITIONAL REGULATION OF CYTOKINES

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INTRODUCTION

In today's high-density production systems, pigs are exposed to multiple stressors, including pathogenic and non-pathogenic immunogens. The detrimental effect of disease and immunological stress poses an enormous economic burden for pork producers, and similar scenarios also encompass other production animal species. Perpetual immune stimulation in the rearing environment results in the production of potent proinflammatory cytokines such as tumour necrosis factor-α (TNFα), interleukin-1 (IL1) and 6 (IL6) and interferon-γ (INFγ). These cytokines antagonize anabolic growth factors, and thus suppress growth and development (Johnson, 1997; Spurlock, 1997; Broussard et al., 2003), partly to insure adequate energy and nutrients are available for high priority immunological and homeostatic pathways.

There are considerable economic and welfare incentives to understand the regulation of the immune system and proinflammatory cytokine production, and equally as important, the anti-inflammatory factors which counter them. In relation to pork production, it is exciting that the adipocyte and the myofiber are emerging as regulatory cells that produce cytokines and other molecules which influence energy metabolism, locally, and in peripheral tissues (Sethi and Hotamisligil, 1999; Chaldakov et al., 2003; Ajuwon et al., 2004; Ajuwon and Spurlock, 2005). Both these cell types possess toll-like receptors that are critical sentinels in the recognition of pathogens (Iwasaki and Medzhitov, 2004). In addition, muscle (Frost et al., 2002) and adipose (Lin et al., 2000) express toll-like receptor 2 (TLR2) which recognises bacterial and mycoplasma lipoproteins and glycolipids, and toll-like receptor 4 (TLR4), which recognise a lipid component of the cell wall of gram negative bacteria such as E. coli (Akira et al., 2001). Many researchers use lipopolysaccharide (LPS) to activate these two receptors and induce early to late immune response cytokines.

Many important interactions which are directly or indirectly governed by cytokines exist between nutrition and the physiological processes involved in immune system function and animal growth. Assessment of how nutrients may interact with the immune response and function is a complex undertaking, and to date little is known about whether animals with varying degrees of immunological stress (activation), require different nutritional requirements. Currently the majority of swine nutrition is based of the National Research Council (NRC) guidelines, which were obtained in research settings with minimal stressor exposure. Although specific nutrient requirements have not yet been determined for optimal immune function, it is a plausible option for pigs reared in environments that have different levels of pathogen exposure to have tailored nutrition to have more or less of a given nutrient.

Both macro and micro-nutrients derived from the diet directly and indirectly affect immune system function (Chandra, 1996). The immune system can be impaired as a consequence of under nutrition or nutrient imbalance. This compromises the immune response and limits protection against pathogen challenge. This review will focus on the role the immune system plays in pork production and potential nutritional strategies to modulate the immune response and enhance muscle growth.

THE BASICS OF PORCINE IMMUNOLOGY

The first order of the pig's immune system is to recognise that the invading micro-organism is not part of itself and then mount an effective defence against it. To combat this foreign substance, the pig's immune system can use either the innate or adaptive/acquired response. The innate immune response is an early non-adaptive response, to mute the pathogen until the adaptive immune response can be initiated. It is non-specific, comprised of physical barriers like the skin, mucous membranes, and fine hairs (nostril hairs etc…), and the capacity of the response does not change or adapt from one infection to the next. Should these primary barriers be breached, chemical and microbial barriers within the mucous, limit pathogen proliferation and spread within the host. When the pathogen penetrates the epithelial barriers, the cells of the innate immune system are called into play. These phagocytic cells include macrophages, monocytes, natural killer cells and neutrophilic leukocytes which recognise pathogens via surface molecules recognised by pattern recognition receptors. Antigen recognition results in the engagement of mechanisms directed to eliminate the pathogen through cytokine secretion and leukocyte activation. Neutrophils engulf and kill extracellular pathogens, natural killer cells are involved more in viral and intracellular pathogen recognition, while macrophages ingest and degrade pathogenic organisms and present antigens to lymphocytes. Activated macrophages additionally secrete numerous inflammatory cytokines which activate B and T lymphocytes to promote the adaptive immune response. Cytokines also enable the immune system to communicate with unrelated physiological and metabolic systems. Additionally, local inflammation and the phagocytosis of foreign substance may also be initiated by the activation of complement proteins on the pathogen surface that are then recognised by macrophages and by acute phase proteins.

The adaptive immune response is extremely powerful, regulated and flexible all at the same time. This highly specific response to a specific pathogen takes over from the innate immune if the infection can not be cleared in a short time and takes about 7 to 14 days to become fully effective. The majority of the cells involved in the adaptive response are antigen-specific T or B lymphocytes which respond to antigen and develop an immunological "memory". Adaptive responses are generally by clonal selection of lymphocytes which bear surface receptors with a single antigenic specificity. B lymphocytes are responsible for antibody production and antigen presentation. T lymphocytes destroy infected cells and combat intracellular pathogens by activating macrophages or extracellular pathogens by stimulating B cells to produce antibodies.

IMPACT OF IMMUNE ACTIVITY OF METABOLISM, GROWTH PERFORMANCE AND NUTRIENT PARTITIONING

Immune system activation is beneficial for pigs under pathogenic stress, but it can come at a considerable bioenergetic cost and cause an overall change in the metabolism and behaviour of the pig. Immunological stress in pigs reduces growth rate and feed efficiency 10 to 25% compared with pigs reared in highly sanitized facilities (Coffey and Cromwell, 1995; Williams et al., 1997c, 1997b). Existing evidence for the energetic costs (direct or indirect) of immune activity in pigs is currently equivocal. However, it has been estimated in profoundly challenged pigs that have mounted a series of immune responses to generate the required immune function will divert up to 6% of net energy intake (Koutsos and Klasing, 2001; Varley, 2004). Work in immune-challenged laboratory mice and birds have shown elevated resting metabolic rate of 27% (Demas et al., 1997) and by 29% (Martin II et al., 2002), respectively, due to direct and indirect immune system function.

Consequential to a pathogenic challenge, the immune system must compete with growth and reproductive processes for nutrients and energy. The nutrient demands are increased as a result of substrate utilization by clonal proliferation of stimulated lymphocytes, antibody production and the secretion of acute phase proteins and cytokines. Accordingly, the indirect effects of the immune response via the production of cytokines can cause negative nitrogen balance and loss of muscle mass as a hallmark of chronic immune activation (Rennie, 1985; Chang and Bistrian, 1998). Therefore, muscle catabolism is a characteristic metabolic response to sepsis, injury or infection, and reflects a net total amino acid release from muscle.

Klasing and Calvert (1999) estimated that LPS-induced immune responses in the chicken increased lysine utilization by the immune system by about 5% of daily intake during the immune response. Therefore, 60% of the decrease in growth during this period could be attributed to activities of the immune response, although 40% was due to indirect responses such as inappetence. Interestingly, researchers are still divided as to whether manipulation of dietary amino acids during the immune challenge is a valid way to combat the growth declines due to inflammatory processes. It has been demonstrated in pigs, that minimizing immune system activation increases the capacity of pigs to deposit lean tissue and in turn increases the animals' dietary lysine needs (Williams et al., 1997c, 1997a, 1997b). Furthermore, the authors stated that the dietary lysine needs were increased to a greater degree than dietary energy needs in the low challenged pigs as a result of the differential effects of this activation on tissue growth and the differential nutrients requirements for the various tissues. Therefore, the pig's total needs during an immune challenge are similar to that of a healthy pig, but the amino acid partitioning is altered. One could also argue that the quantity of amino acids to support maximal growth is less in immunological stressed pigs than their healthy counterparts due to reductions in growth rates and feed intake.

SKELETAL MUSCLE AND CYTOKINES

Protein loss during an immune challenge is greater than that caused by reduced feed intake (Tracey et al., 1988). Skeletal muscle protein accretion in the growing pig is a reflection of the balance between synthesis and degradation. Proinflammatory cytokines and glucocorticords are

important mediators of muscle breakdown. It is therefore important to control the cytokines responsible for the detrimental effect on muscle metabolism. Enhanced gene expression of IL6, IL1, TNFα and nitric oxide synthase 2 (NOS2) have been seen in skeletal muscle under stress conditions (Frost et al., 2002; Frost and Lang, 2005). An inflammatory insult caused by TNFα decreased the rate of protein synthesis in the gastrocnemius, soleus, and heart between 20 and 40% in rats, due to decreases in both myofibrillar and sarcoplasmic protein synthesis via a reduction in translational efficiency (Lang et al., 2002). Similar results were seen by the direct infusion of IL6 into muscle in which myofibrillar protein fraction was reduced by 17% (Haddad et al., 2005). Total and myofibril protein breakdown rates were also significantly increased by the administration of IL1, although this was completely abolished by an IL1 antagonist (Zamir et al., 1994). Together, these studies provided clear evidence that cytokines directly influence skeletal muscle metabolism.

The impact of clinical and sub-clinical immune challenge on growth can be seen in skeletal muscle which becomes resistant to anabolic signals such as growth hormone, insulin and IGF-1. Evidence is mounting that the signalling potential of certain cytokines is intensified in skeletal muscle during the immune response in that expression of their receptors is markedly up-regulated (Zhang et al., 2000). Consequently, muscle and liver production of IGF-1 is reduced and circulating IGF-1 concentrations fall. The loss in anabolic stimuli, coupled with the mobilization and repartitioning of energy and amino acids away from skeletal muscle, results in a diminution of growth in favour of higher priority immunological functions. Additionally, proinflammatory cytokines decrease protein synthesis and increase muscle proteolysis through the induction of muscle specific ubiquitin ligases, by glucocorticoids and inhibit anabolic pathways controlled by IGF-1, Akt and mammalian target of rapamycin (mTOR) (Frost and Lang, 2005).

Furthermore, experiments performed with cultured C2C12 myoblasts (Frost et al., 2003) or fused myotubes (Frost et al., 2002) indicate that skeletal muscle respond to bacterial LPS through TLR by producing TNFα and IL6, classical proinflammatory cytokines. Coupling of the TLR to LPS or an endotoxin invokes the activation, nuclear translocation, and transcriptional activity of the nuclear factor kappa B (NFκB) transcription factor, which Frost et al. (2002) have shown to be pivotal to the innate immune response within skeletal muscle. This transcription factor is also a major mediator of TNFα and IL6 production in classical immune cells. Mechanistically, nutrition can be used to counter these cytokine induced reduction in skeletal muscle and therefore pork. One such approach would be nutritional targeting of the TLRs by using nutrient ligands for these receptors.

THE EFFECT OF n3-PUFA AND ANTIOXIDANT NUTRITION ON CYTOKINES AND INFLAMMATION

In both human and animal studies, polyunsaturated fatty acids (PUFA) have been linked to anti-inflammatory responses (Belluzzi et al., 2000), improved immune status (Fritsche et al., 1993b; Calder and Grimble, 2002), insulin sensitivity and diabetes prevention (Nettleton and Katz, 2005). Three important n3-PUFA are α-linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acids (DHA). The latter two fatty acids are largely of marine based origin and found in high quantities in fish based products. Additionally, the ratio of n6-PUFA (arachidonic

or linoleic acids etc.) to n3-PUFA can greatly influence the disease state (Simopoulos, 2004). Increasing this ratio causes a shift in the production of arachidonic acid derived proinflammatory eicosanoids. This is due to n3 and n6-PUFA substrates competing for cyclo-oxygenase and lipoxygenase enzymes.

The idea that n3-PUFAs improve growth in swine was strengthened by the fact that some n3-PUFA inhibit the activation of NFκB by lipopolysaccarides in a murine monolytic cell line (Lee et al., 2003a). Thus, this inhibition would disrupt an inflammation cascade and attenuate production of proinflammatory cytokines. This anti-inflammatory effect may be an effect of the dietary fatty acids directly or indirectly regulating peroxisome proliferator-activated receptors (PPAR) (Clarke and Jump, 1997; Nguyen et al., 1999), which in turn have been linked to the regulation of NFκB through a physical interaction that blocks its transcriptional activity (Simonin et al., 2002; Vanden Berghe et al., 2003). Alternatively, dietary fatty acids have been shown to differentially modulate immune responses through Toll-like receptor 4 (TLR4) (Weatherill et al., 2005), the primary cell surface receptor that detects endotoxin and initiates the immune response. Lee et al. (2003a; 2003b) suggested that PUFA mediate their anti-inflammatory responses in part through the inhibition of TLR-induced signaling pathways and target genes. However, preliminary work conducted in our laboratory, suggest that the fatty acids themselves may bind and partially block the TLR by acting as competitive ligands to the endotoxin (Unpublished data).

Another line of thought is that the mechanisms of by which proinflammatory cytokines exert there negative effects may be related to oxidative stress, as proinflammatory cytokines have been shown to increase reactive oxygen species and impair anabolic pathways (Lang et al., 2001; Patel et al., 2002; Broussard et al., 2003; Lang et al., 2005; O'Loghlen et al., 2006). This in turn may also explain the growth hormone resistance in animal production due to disease (Hull and Harvey, 1999; Takano et al., 2001). Although n3-PUFA have been shown to prevent defects in insulin receptor signaling in muscle (Taouis et al., 2002) and to increase muscle proteasome activity (Vigouroux et al., 2003), direct control of the anabolic pathways by these fatty acids has not yet been shown.

The antioxidant and anti-inflammatory properties of n3-PUFA such as EPA, DHA and α-linolenic acid are widely known (Calder and Grimble, 2002). Pig immune cell membranes that are enriched with n3-PUFA at the expense of arachidonic acid, an n-6 PUFA, will produce less proinflammatory prostaglandins and leukotrienes during an inflammatory response (Fritsche et al., 1993a). The immune system and inflammatory response is essentially an oxidative state, since a key defensive mechanism by immune cells is to cause oxidative stress by the generation of reactive oxygen species. Therefore, important nutrient antioxidants include vitamin E, A and C, carotenoids and selenium antioxidants, can modulate the immune response by inhibiting the magnitude of the response and the activation of proinflammatory transcripts and intermediates (Thurnham and Northrop-Clewes, 2004). Vitamin A supplementation attenuates the response due to several endotoxaemia in pigs (Eriksson et al., 1997). While, Webel et al, (1998) showed that prior exposure of pigs to the vitamin E analogue *d*-α-tocopherol, reduced the production of proinflammatory cytokines in LPS induce innate immune response. However, feeding dietary concentration of vitamin E nearly 50 times that recommended by the NRC to nursery pigs, could not overcome the increased cytokine level and the decreased feed intake and growth rate caused

by porcine reproductive and respiratory syndrome virus infection (Toepfer-Berg et al., 2004). Although, the authors of this study suggested that if the study had continued beyond the 12 days, the recovery rates of the high vitamin E pigs could have been faster. Therefore, as infection can depress the plasma concentrations of antioxidants such as vitamins A and C, and minerals, such as iron and zinc irrespective of nutritional status (Thurnham and Northrop-Clewes, 2004), prior enrichment of tissues with antioxidants appears to be more effect in providing protection from inflammation.

CONCLUSION & TAKE-HOME MESSAGE

Activation of the immune system and the concomitant repartitioning of nutrients away from growth and development to support immunocyte needs is a complex system. The proinflammatory cytokines are important and integral players in this process. Additionally, antioxidant and n3-PUFA status is important in determining the innate immune response of tissues to stress. In order for pigs reared in the commercial environment to reach their genetic potential for growth performance and muscle accretion, the impact of cytokines on catabolic and anabolic pathways in skeletal muscle need to be addressed. An exciting area of research which needs further development is the potential modulation of the TLR by n-3 fatty acids and antioxidants. Through a better understanding of the mechanisms by which cytokines and nutrients can modulate the immune system and muscle metabolism during pathogenic challenge, nutritionists will be able to customise feeding programs to improve or maintain animal growth performance and well being, and ultimately improve producer profitability. Finally, antioxidant and n3-PUFA feeding should be approached with caution as pigs housed in cleaner facilities may require a different level versus those housed in facilities with higher pathogen burdens.

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