256 Somatotropic function: the somatomedin theory revisited. T. D. Etherton*, *Penn State University*.

Impressive progress has been made during the past 20 years in our understanding of the biology of somatotropin (ST) in domestic animals. Collectively, studies have established that administration of porcine ST (pST) to growing pigs markedly stimulates muscle growth and decreases fat deposition. In addition to these "efficacy" studies, a substantial number of investigations examined the mechanisms by which ST regulates growth of domestic animals. A central concept proposed initially to explain the effects of ST was the "somatomedin hypothesis", i.e., that the effects of ST, secreted by the pituitary, are mediated by circulating IGF-I (initially characterized as sulfation factor and then somatomedin) produced exclusively in the liver. Much subsequent research has established that the somatomedin theory needs to be revised (and has been). Work conducted in our lab has shown that the effects of ST on lipid metabolism and insulin sensitivity in adipose tissue are not mediated by IGF-I and are direct effects of ST. While circulating IGF-I is important for postnatal growth, studies have demonstrated that mice lacking the liver IGF-I gene have an 80% reduction in total IGF-I (and IGF binding proteins), however, postnatal growth is normal. In these mice, free IGF-I levels (not bound to IGF binding proteins) are normal. Thus, the original somatomedin hypothesis has undergone considerable remodeling to a contemporary version that better explains the complexities of GH effects on adipose tissue metabolism and growth. The latter appear to reflect a situation where liver-derived IGF-I, at least in mice, is not essential for growth. Further studies will be necessary to unravel the importance of endocrine versus autocrine/paracrine IGF-I.

257 A new plasmid-mediated approach to enhance somatotropin function in pigs. R. Draghia*, *ADViSYS Inc*.

Tremendous progress is being made in identifying and understanding the stimulatory molecules that regulate growth and the potential application of these molecules in animals. A parallel and significant effort is focused on the discovery and development of economically feasible gene delivery technologies. Plasmid-mediated growth hormone releasing hormone (GHRH) therapy has emerged as an excellent candidate. GHRH, a hypothalamic hormone, stimulates normal growth hormone (GH) production and release. We have shown that pigs directly injected with 0.1mg myogenic plasmid expressing porcine GHRH had significantly greater weight gain than controls. With plasmid treatment, body composition studies have shown a 22% decrease in fat deposition and a 10% increase in bone mineral density. In a different study, gilts were injected intramuscularly at day 85 of gestation with 0, 0.1, 0.5, 1, or 5 mg of a synthetic GHRH-expressing plasmid (HV-GHRH). Piglets from gilts treated with 1 or 5 mg of HV-GHRH were larger at birth and weaning compared to controls. These two groups reached 100 kg 9 days earlier than the other groups. GHRH levels were higher at birth, and IGF-I levels were significantly increased in the 5 mg group beginning at 21 days of age when compared with controls. Pituitaries from the 5 mg group contained a significantly increased number of somatotrophs and lactotrophs from birth to 100 kg. Because of the central role of the GHRH-GH-IGF-I axis in the regulation and coordination of the anabolic processes of growth and reproduction, the benefits of plasmid-mediated GHRH supplementation to pregnant animals are far-reaching. During pregnancy, maternal changes impact intrauterine and postnatal development. Direct GHRH action induces changes in pituitary cell lineage of the offspring which can then directly enhance growth and welfare once the postnatal growth comes under the control of GH and IGF-I. Administration of GHRH to the gilt has an additional advantage over the direct administration of growth-promoting agents to the adult individual animal. By improving fetal growth, GHRH treatment of the gilts diminishes the incidence of neonatal deaths, which has always represented a major economic loss for the swine industry.

Key Words: GHRH, GH, Plasmid

258 Somatotropin regulation of skeletal muscle protein deposition in pigs. T. A. Davis, J. A. Bush, R. C. Vann, A. Suryawan, and D. G. Burrin, *USDA-ARS Children's Nutrition Research Center*.

A primary goal of exogenous somatotropin (ST) treatment is to increase lean body mass. This is accomplished, in part, by increasing the efficiency with which dietary amino acids are used for protein deposition. ST administration also improves protein balance by minimizing the loss of protein during fasting and maximizing the protein gained during meal absorption. Amino acid catabolism is reduced by ST treatment as indicated by reductions in blood urea nitrogen concentrations, urea synthesis, liver urea cycle enzyme activity, and amino acid oxidation. Stable isotope tracer/mass transorgan balance studies have recently demonstrated that ST treatment increases protein anabolism in young, growing swine by increasing protein synthesis in the hindlimb and portal-drained viscera in the fully-fed state, with no effect of ST on protein degradation. More detailed study to examine the tissue-specific response to ST treatment indicates that GH treatment increases protein synthesis in skeletal muscle by increasing the efficiency of the translational process, but only in the fed state. The ST-induced stimulation of skeletal muscle protein synthesis in the postprandial state involves mechanisms that enhance the binding of both mRNA and initiator methionyl-tRNA to the 40S ribosomal subunit. ST increases protein synthesis in the intestine and liver in both the fasted and fed state by increasing ribosome number, with no change in translation initiation. Thus, the protein synthetic response to ST treatment is tissue specific and dependent upon nutritional state.

259 Alteration of somatotropic function by proinflammatory cytokines. R. A. Frost* and C. H. Lang, *Penn State University College of Medicine*.

Unsanitary living and rearing conditions contribute to infection and weight loss in animals and humans. Infectious insults direct amino acids away from growth and skeletal muscle accretion towards the synthesis of acute phase proteins. The loss of skeletal muscle protein stores results in both a decrease in muscle function and increased mortality. In general, muscle protein synthesis is decreased in rat models of sepsis including after the injection of components of the bacterial cell wall such as lipopolysaccharide (LPS). Although the over-expression of proinflammatory cytokines is known to hasten the loss of skeletal muscle protein it is not known whether this is a direct effect of cytokines or if it is secondary to changes in the IGF-system. The drop in muscle protein synthesis is preceded by changes in the expression of IGF-system components. Plasma levels of IGF-I are dramatically lowered by infection in rats, mice, pigs and steers. The drop in IGF-I occurs despite an increase in the plasma concentration of somatropin (GH). Animals are therefore GH resistant. IGF bioactivity is determined not only by its plasma concentration but also by IGF binding proteins (IGFBPs). IGFBP-3 the most abundant IGFBP is degraded during some catabolic states. Administration of IGF-I as a complex with IGFBP-3 restores both plasma IGF-I levels and muscle protein synthesis in septic rats. In contrast to IGFBP-3, the plasma concentration of inhibitory IGFBPs such as IGFBP-1 are increased during infection. IGFBP-1 accumulates in skeletal muscle where it can inhibit IGF dependent protein synthesis. IGF-I and IGFBP-1 are regulated at the level of gene transcription by proinflammatory cytokines. Prophylactic administration of an IL-1 receptor antagonist or a TNF binding protein can prevent the changes in IGF-I, IGFBP-1, and muscle protein synthesis. Recent studies demonstrate that bacterial components that activate immune cells also activate the innate immune response in skeletal muscle. LPS increases proinflammatory cytokine mRNA expression in muscle from control mice but not mice with a mutation in the LPS receptor (TLR4). LPS also increases cytokine expression in human and mouse myoblasts. Local expression of cytokines in skeletal muscle may negatively regulate the autocrine synthesis of IGF-I. Current work is focused on deciphering the mechanism by which muscle becomes GH resistant and the development of therapies to maintain muscle protein stores during infection.