Growth and Development: IGF and IGF Binding Proteins

286 Insulin-like growth factor-I, a link between nutrient intake and growth. D. Clemmons*, *University of North Carolina*, *Chapel Hill*.

Insulin-like growth factor-I (IGF-I) is a small poly peptide hormone that is synthesized in multiple tissues. IGF synthesis is controlled principally by nutrient intake and by pituitary GH secretion. In periods of adequate intake, GH is the predominant stimulant of IGF-I synthesis however in periods of caloric or protein restriction organisms become refractory to GH and the effect of nutritional deficiency predominates. This change in IGF-I synthesis functions to regulate protein metabolism in tissues. IGF-I is a predominant stimulant of both skeletal muscle, growth and differentiation and it inhibits apoptosis. In multiple tissues IGF functions to maintain tissue hypertrophy in response to either exercise induced stress or changes in nutrient intake. In adult organisms IGF-I stimulates hyperplasia only in cell types that are susceptible to stimulation but it stimulates hypertrophy in almost all cell types. IGF-I stimulated growth is a mixture of the two processes. Under normal conditions certain cell types such as vascular smooth muscle respond to IGF-I with increases in cell size and protein content however during some periods of stress these cell types such as smooth muscle cells, endothelial cells, osteoblasts, chondrocytes are capable of partially dedifferentiating and responding to IGF-I with a hyperplastic response. In contrast skeletal muscle always responds with a hypertrophic response except for myoblasts that proliferate in response to IGF-I. IGF-I is a potent antiapoptotic factor for both skeletal muscle and neural tissue. The IGF-I synthesis and blood concentrations decline in all aging organisms but the significance of this decline for changes in tissue mass and protein synthesis that occur with aging has not been definitively determined. IGF-I is an important systemic growth factor that is responsible for the growth of multiple tissues. In adult organisms this growth occurs as a result of hypertrophy although certain specialized cell types can undergo a hypoplastic response. IGF-I protein balance, and tissue responsiveness, will continue to be an important goal of future studies.

Key Words: Muscle hypertrophy, Somatic growth, Protein metabolism

287 Effects of short day photoperiod on mammary growth of dry cows: Altered prolactin and IGF signaling. G. E. Dahl*[1], E. H. Wall[2], and T. B. McFadden[2], [1]*University of Illinois*, *Urbana*, [2]*University of Vermont*, *Burlington*.

Manipulation of photoperiod has dramatic physiological and production effects on mature dairy cows. During lactation, exposure to long day photoperiod (LDPP) increases milk yield and circulating IGF-I and prolactin (PRL). In contrast, dry cows housed under a short day photoperiod (SDPP) produce more milk in the subsequent lactation than cows exposed to LDPP or natural photoperiod. Relative to LDPP, exposure to SDPP depresses PRL secretion but expression of PRL-receptor (PRL-R) mRNA increases in mammary and hepatic tissue and in lymphocytes. Under SDPP, PRL signaling emerges as a possible mechanism to drive more extensive mammary cell differentiation and growth relative to LDPP. Using sequential mammary biopsies, we determined temporal changes in mammary cell proliferation and in expression of genes of the IGF and PRL signaling pathways during the dry period and transition into lactation. For both SDPP and LDPP, cell proliferation rate increased significantly as the dry period advanced, then decreased significantly in early lactation. However, timing of the proliferative response differed between treatments, increasing earlier in SDPP cows than in LDPP cows during the dry period. Overall, expression of IGF-II was significantly greater, whereas that of IGFBP-5 was lower, in SDPP versus LDPP cows. IGFBP-5 mRNA increased significantly during lactation in both groups. Expression of IGF-I did not differ over time or between treatments however, the lower IGFBP-5 expression in SDPP cows coupled with increased IGF-II expression may enhance mammary cell growth and survival. Key among the potential modulators of PRL signaling is the suppressors of cytokine signaling (SOCS) family, the best characterized of which are SOCS-1, -2, -3, and cytokine-inducible SH2-containing protein (CIS). Mammary expression of SOCS-1, -2, -3, and CIS were low during the dry period, but increased in lactation. During the dry period, SOCS expression of cows on SDPP was generally reduced, which may enhance PRL induced proliferation and subsequent milk production.

Key Words: Dry cow, Mammary growth, Prolactin signaling

Nonruminant Nutrition: New Frontiers in Amino Acid Research in Nonruminant Nutrition

288 Branched chain amino acid metabolism and nutrition in monogastric animals. S. M. Hutson*[1], P. She[2], T. M. Reid[1], M. Janket[1], S. K. Bronson[2], A. Sweatt[1], and C. J. Lynch[2], [1]*Wake Forest University School of Medicine*, *Winston-Salem, NC*, [2]*Penn State College of Medicine*, *Hershey*.

Studies in our laboratory have shown that several features of indispensable branched chain amino acid (BCAA) metabolism in animals sets them apart from other indispensable amino acids. The initial 2 steps of BCAA catabolism are common to all 3 BCAAs; reversible transamination followed by irreversible oxidative decarboxylation of the branched chain α-keto acid transamination products. Due to the shared steps, dietary intake of individual BCAAs impacts the catabolism of all three. Rather than being restricted to liver, BCAA catabolic enzymes are distributed widely in body tissues. With the exception of the nervous system, all reactions occur in the mitochondria. The tissue specific expression and intracellular compartmentalization of the branched chain aminotransferase isozymes (BCATm and BCATc) impact intra- and inter-organ exchange of BCAA metabolites, nitrogen cycling, and net nitrogen transfer. Transamination of the BCAAs makes them important nitrogen donors for synthesis of alanine and glutamine, as well as giving them a key role in the transfer of nitrogen between skeletal muscle and liver. In brain, BCAAs are important in neurotransmitter glutamate synthesis, and the localization of the BCAT isozymes separately in neurons and glia promotes intercellular shuttling of nitrogen. Dysregulation of the BCAA catabolic pathways that leads to excess BCAAs and their metabolites has been shown to result in severe neural dysfunction. Finally, leucine serves as a nutrient signal that regulates protein synthesis and cell growth pathways affected by mTOR and insulin secretion. Indeed the BCATm knockout mouse (blocked body BCAA catabolism) exhibits increased energy

expenditure, lower fat deposition, lower plasma glucose, and increased insulin sensitivity. The results indicate that BCAAs play an important role in macronutrient partitioning and suggest that leucine (and/or BCAAs) is the signal(s) that allows protein to communicate with other macronutrients. Together these features make the regulation of BCAA intake important in maintaining metabolic homeostasis, while avoiding the toxic effects of BCAA excess. (NIH NS038641, DK34738, DK053843 and DK062880)

Key Words: Leucine, Alanine, Nutrient signal

289 Nutrition of the arginine-family amino acids in nonruminant animals. G. Wu*[1,3], S. W. Kim[2,1], D. A. Knabe[1], and Y. L. Yin[3], [1]*Texas A&M University*, *College Station*, [2]*Texas Tech University*, *Lubbock*, [3]*The Chinese Academy of Sciences*, *Changsha, Hunan, P.R. China*.

The arginine-family amino acids include glutamine, glutamate, aspartate, proline, ornithine, citrulline, and arginine. They can be inter-converted in mammals through inter-organ metabolism and cell-specific pathways, although the rates of their conversion vary greatly with precursors, species, developmental stages, and disease. Growing interests in these amino acids in nonruminant nutrition mainly arise from the emerging knowledge about: 1) their high concentrations in fetal and postnatal animals; 2) remarkable species-differences in their tissue-specific catabolism and synthesis; 3) their roles in regulating the metabolic processes essential for animal growth and development (e.g., fat metabolism, protein turnover, glucose homeostasis, nucleotide synthesis, and immune response) via the production of unique metabolites and signaling pathways; 4) their dietary supplementation as a practical, effective means to maintain tissue integrity, improve pregnancy outcomes, enhance animal growth, and optimize health; and 5) their role in reducing dietary protein content to minimize nitrogen excretion and environmental pollution. Recent examples for the beneficial application of the arginine-family amino acids to swine nutrition are: 1) preventing intestinal atrophy and improving growth performance in weanling pigs through dietary supplementation with glutamine; and 2) increasing growth performance in milk-fed piglets and finishing pigs as well as enhancing fetal survival and growth in gestating sows through dietary supplementation with arginine. Future holds great promise for the use of the arginine-family amino acids in increasing the efficiency of animal agriculture. Supported by grants from USDA/NRI, TAES, Texas Tech University, The Chinese Academy of Sciences, and China NSF.

Key Words: Arginine, Nutrition, Nonruminants

290 Biological roles of tryptophan and its metabolism in pigs. N Le Floc'h* and B Sève, *UMR INRA-Agrocampus SENAH*, *Saint Gilles, France*.

Tryptophan (TRP) is an essential amino acid which content does not exceed 1.1% of whole-body protein. Apart from its incorporation into body proteins, TRP is known to play important biological roles, most of them being associated to metabolic pathways involved in its catabolism. Tryptophan deficiency was shown to depress the appetite parallel to slower gastric emptying and reduced insulin secretion in young pigs. However, independent of the latter effects, tolerance to glucose was reduced. This role of TRP in sensitivity to insulin appeared to depend on vitamin B6 supply. Otherwise, tryptophan transport and availability in the brain is one of the limiting steps for synthesis of serotonin which is involved in the appetite for protein. Serotonin is also involved in sleep, mood and stress response. It was recently shown that pigs receiving a large excess of TRP exhibit lower cortisol and catecholamine response to social stress. However, from a quantitative point of view, the proportion of tryptophan used for the production of serotonin is very low: less than 10% of tryptophan that is degraded would be into serotonin. Most of TRP degradation occurs through the kynurenine pathway. Two enzymes are involved in the first step of this pathway: TDO located in the liver degrades excess TRP; we focus our talk on the second enzyme, IDO expressed by immune cells and tissues targets by inflammation. Increased TRP catabolism through the IDO pathway occurs during inflammatory states and immune stress leading to reduced TRP availability when this amino acid is not provided at a sufficient amount by the diet. We showed that pigs fed with a low TRP diet were more sensitive to an inflammatory stress. We will discuss what can be the roles of TRP catabolism through IDO pathway in the regulation of T cells proliferation and the production of antioxidant molecules.

Key Words: Tryptophan, Serotonin, Inflammation

291 Methionine: Nutrition and metabolism. J. T. Brosnan*, *Memorial University of Newfoundland*, *St. John's, NF, Canada*.

Methionine, a dietary indispensable amino acid, is one of two sulfur-containing amino acids commonly found in proteins. A hydrophobic amino acid, it plays a critical role in protein structure. Oxidative damage to methionine residues in proteins may play a role in aging. The first step in methionine's metabolism gives rise to S-Adenosylmethionine (SAM) which plays a number of diverse metabolic roles, including methylation and polyamine synthesis. About 70 methyltransferases have been identified; bioinformatic analysis of a number of genomes suggest that as many as 1% of all genes may code for methyltransferases. Quantitatively major methylation reactions include the synthesis of creatine and phosphatidylcholine. Other critical reactions involve methylation of DNA, RNA and proteins. This transmethylation pathway produces homocysteine which may be oxidized, via conversion to cysteine, by the transsulfuration pathway, or may be reconverted to methionine (thus, conserving this indispensable amino acid) by the process of remethylation. Homocysteine removal by these reactions is impaired by folic acid, pyridoxal or Vitamin B12 deficiency as well as by some common genetic polymorphisms. Increased plasma homocysteine is associated with an increased incidence of cardiovascular disease, Alzheimer's disease and fractures.

Key Words: Methyltransferase, Homocysteine, S-adenosylmethionine

292 Effects of L-arginine supplementation on lactation performance of first parity sows. R. D. Mateo*[1], G. Wu[1,2], J. A. Carroll[3], I. Shinzato[4], H. K. Moon[5], and S. W. Kim[1,2], [1]*Texas Tech University*, *Lubbock*, [2]*Texas A&M University*, *College Station*, [3]*USDA-ARS-LIRU*, *Lubbock, TX*, [4]*Ajinomoto*, *Tokyo, Japan*, [5]*RDA*, *Suwon, Korea*.

This study was conducted to determine the effects of L-arginine (ARG) supplementation (1.0%) on lactation performance using 27 first parity sows with litter size greater than 9. An isonitrogenous diet (1.7% L-alanine, ALA) served as the control. Sows were allotted to four dietary treatments which consisted of gestation and lactation diets: ALA-ALA, ALA-ARG, ARG-ALA, and ARG-ARG (gestation-lactation). All gestation diets contained 3.1 Mcal/kg and 12.1% CP and all lactation diets contained 3.2 Mcal/kg and 18.6 % CP. Litter size was equalized by cross fostering within the treatment groups before 24 h postpartum.

Experimental diets were fed 2 kg/d during gestation and ad libitum during lactation. Individual feed intake of sows was recorded daily during lactation. Body weight and backfat thickness of sows as well as body weights of individual piglets were measured weekly until weaning at 21-d of lactation. The number of days return-to-estrus was recorded. Backfat thickness of sows measured at the P2 position did not differ (P=0.679) nor did average daily feed intake (P=0.524) among the treatments during the 21-d lactation period. All treatment groups had similar days return-to-estrus (P=0.778). Initial body weight of piglets did not differ among treatments after cross fostering (P=0.541). Piglets of sows fed 1 % L-arginine from gestation to lactation (ARG-ARG) were heavier (2.35 vs. 2.68 kg, P=0.026) at 7 d of lactation and had a greater weight gain (0.971 vs. 1.253 kg, P=0.037) from d 0 to d 7 of lactation compared to piglets of sows fed the isonitrogenous diet from gestation to lactation (ALA-ALA). However, there were no differences in weight gains from d 7 to 21 among the treatments. Arginine supplementation in sow diets may improve the growth of neonate during early lactation period.

Key Words: Arginine, Sows, Lactation

293 Skeletal muscle protein synthesis in neonatal pigs is stimulated by A-ketoisocaproic acid, but not by norleucine. J. Escobar*, J. W. Frank, A. Suryawan, H. V. Nguyen, and T. A. Davis, *Baylor College of Medicine*, *Houston, TX*.

In neonatal pigs, skeletal muscle protein synthesis is stimulated when plasma leucine is increased within the physiological postprandial range. We previously have shown that valine and isoleucine were not able to stimulate protein synthesis when their plasma concentrations were elevated within the physiological postprandial range. The objective of the present study was to determine the effect of an elevation in plasma levels of α-ketoisocaproic acid (KIC, the α-keto acid of leucine) and norleucine (an aliphatic leucine analogue that does not charge leucyl tRNA) on skeletal muscle protein synthesis and the activation of translation initiation factors. Piglets (5 d of age) were food-deprived overnight and infused intra-arterially with saline or 400 μmol•kg^{-1}•h^{-1} of leucine, KIC or norleucine for 60 min. At the end of the infusion period, protein synthesis and the activation of translation initiation factors were determined in longissimus dorsi muscle and liver. Plasma concentration of leucine was reduced ($P < 0.02$) by norleucine and increased ($P < 0.01$) by KIC compared to saline controls. Infusion of leucine and KIC increased the phosphorylation of eukaryotic initiation factor (eIF) 4E binding protein-1 (4E-BP1, $P < 0.01$), decreased ($P < 0.04$) the inactive 4E BP1•eIF4E complex, and numerically increased the active eIF4G•eIF4E complex in muscle. Both leucine and KIC increased ($P < 0.03$) muscle protein synthesis. Norleucine had no effect on muscle translation initiation factor activation or protein synthesis. In the liver, the activation of translation initiation factors and protein synthesis were not affected by any treatment. Our results indicate that the ability of leucine to act as a nutrient signal to stimulate skeletal muscle protein synthesis is likely specific for leucine or its metabolites. (NIH AR 44474 and USDA 58-6250-6-001)

Key Words: Leucine, Norleucine, α-Ketoisocaproic acid

294 A flooding dose of valine can be used to measure protein synthesis in growing pigs. A. J. Libao-Mercado*[1,3], M. Rademacher[2], and C. F. M. de Lange[1], [1]*University of Guelph*, *Guelph, Ontario, Canada*, [2]*Degussa AG*, *Hanau, Germany*, [3]*Cargill Animal Nutrition Phils.*, *Bulacan, Philippines*.

A key concern with flooding dose technique for measuring protein synthesis (PS) is that a large dose of amino acid (AA) can change the animals′ hormonal and nutritional status, which can influence PS. Among stable isotope tracers, 1-13C-valine is the preferred amino acid for measuring PS in gut tissue and mucins. A study was conducted to determine the impact of a flooding dose of valine on the metabolic status of pigs. Six barrows (12 kg BW) were randomly assigned, following a two-treatment cross-over design, to 12-minute intravenous infusions of either 150 mM valine (1.5 mmol/kg BW) or saline (control). Blood samples were taken at 10 min prior to infusion, at the end of infusion, at 10 min intervals for 1 hr, and at 90 and 120 min post infusion. Plasma concentration of insulin, glucose, AA, urea nitrogen and packed cell volume (PCV) were measured. Data were analyzed as repeated measures using Proc Mixed Procedure of SAS. Infusion of valine increased plasma valine levels (4178 vs. 532 μmol/L; $P<0.0001$) but had no influence on PCV (26.4 vs. 27.2%), glucose (5.8 vs. 5.9 mmol/L), urea nitrogen (8.5 vs. 7.8 mg/dL) and insulin (8.2 vs. 8.4 μU/mL; $P>0.10$). It also had no impact on plasma levels of most AA, particularly leucine (240 vs. 231 μmol/L) and isoleucine (308 vs. 332 μmol/L; $P> 0.10$). There was however a slight increase in threonine (225 vs. 263 μmol/L; $P<0.05$) and a tendency towards reduced glycine (1387 vs. 1312 μmol/L; $P<0.10$). There were also numerical increases in alanine (1186 vs. 1310 μmol/L) and glutamine (788 vs. 846 μmol/L) levels ($P>0.10$). The results indicate that a flooding dose of valine does not cause a substantial change in the metabolic status of growing pigs, and is therefore suitable for measuring PS rates in tissues with high protein turnover rates.

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295 Comparison of swine manure composition using multiple manure sampling methods. D. M. Sholly*, R. B. Hinson, K. L. Saddoris, M. C. Walsh, D. T. Kelly, B. T. Richert, A. L. Sutton, and J. S. Radcliffe, *Purdue University*, *West Lafayette*.

Sixteen manure pits (30 pigs/pit) were sampled monthly during a wean-finish trial (22 wks) to compare the effects of sampling method on estimates of manure DM and ash. Eight pits were emptied monthly in a pull plug/recharge (PP) system, and 8 were kept as a deep pit (DP) system. Manure pits were sampled using: 1) mechanical core sampler (Coswala); 2) vacuum core sampler (vacuum); 3) cup sampler; and 4) agitated slurrystore sample (control, CTL). For core sampling, manure was obtained from 12 locations/pit and pooled. Cup samples were taken from 6 locations/pit and pooled. All data were analyzed using the GLM procedure of SAS. Within the PP system (40 obs/method), manure DM was 14.8% higher ($P<0.05$) for vacuum samples compared