Functional Amino Acids and Fatty Acids for Enhancing Production
Performance of Sows and Piglets*

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ABSTRACT : The growth and health of the fetus and neonate are directly influenced by the nutritional and physiological status of sows. Sows are often under catabolic conditions due to restricted feeding program during pregnancy and low voluntary feed intake during lactation. The current restricted feeding program, which aims at controlling energy intake during gestation, results in an inadequate supply of dietary protein for fetal and mammary gland growth. Low voluntary feed intake during lactation also causes massive maternal tissue mobilization. Provision of amino acids and fatty acids with specific functions may enhance the performance of pregnant and lactating sows by modulating key metabolic pathways. These nutrients include arginine, branched-chain amino acids, glutamine, tryptophan, proline, conjugated linoleic acids, docosahexaenoic acid, and eicosapentaenoic acid, which can enhance conception rates, embryogenesis, blood flow, antioxidant synthesis capability, translation initiation for protein synthesis, immune cell proliferation, and gut development. The outcome is to improve sow reproductive performance as well as fetal and neonatal growth and health. Dietary supplementation with functional amino acids and fatty acids holds great promise in optimizing nutrition, health, and production performance of sows and piglets. (Supported by funds from Texas Tech, USDA, NLMR-RDA-Korea, and China NSF). (Key Words: Amino Acids, Fatty Acids, Growth, Health, Neonate, Piglets, Reproduction, Sows)

INTRODUCTION

Nutritional and physiological status of pregnant and lactating sows directly affects fetal and neonatal growth and health. Genetically improved modern sows are highly prolific and their progeny possess great potential for rapid growth. However, the current restricted feeding program for pregnant sows limits nutrient availability for fetal growth especially during mid- to late-pregnancy (Ji et al. 2005; Kim et al. 2005). Additionally, low voluntary feed intake during lactation resulted in reduced provision of nutrients for milk production (Zijlstra et al. 1996; Bressner et al., 2000; Kim et al. 2004), thereby causing massive maternal tissue mobilization (Dournad et al. 1994; Kim and Easter 2003). The maternal catabolic conditions may impair the growth of the fetus and the neonate as well as increase their morbidity and mortality (Wu et al. 2006). The underlying mechanisms are not fully understood but may involve a decrease in the availability of functional amino acids and fatty acids. These nutrients are essential not only for normal growth and maintenance of animals but also for the syntheses of many bioactive compounds (Uauy and Castillo 2003; Wu and Self 2005). Amino acids and fatty acids with special functions include arginine, branched-chain amino acids, glutamate, glutamine, tryptophan, glycine, taurine, conjugated linoleic acid (CLA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). They can benefit pregnant and lactating sows under catabolic conditions with outcomes of improving fetal growth, neonatal health, and lactation performance. The objective of this article is to review recent advances in dietary uses of functional amino acids and fatty acids to enhance reproductive performance and health of sows as well as the growth and immune status of their fetuses and neonates.

FUNCTIONAL AMINO ACIDS

The biochemical properties and functions of amino acids differ remarkably because of variations in their side chains. Their concentrations also vary greatly in fetal fluids during pregnancy (Kwon et al. 2003), plasma of neonates...
Over 300 amino acids occur in nature, but only 20 serve as building blocks of proteins in animal cells (Table 1). Recent evidence shows that some amino acids can regulate intracellular protein synthesis and degradation. In addition, amino acids are substrates for the synthesis of many biologically active substances (including NO, polyamines, glutathione, nucleic acids, hormones, and neurotransmitters) that are essential to the life and productivity of animals (Table 2). Their abnormal metabolism negatively alters feed intake, disturbs whole body homeostasis, impairs animal growth and development, and may even cause death (Wu and Self, 2005). In the following sections, we review the recent literature about the functional amino acids.

### Intracellular protein turnover

**Leucine**: The continuous synthesis and degradation of protein in the cell are collectively termed intracellular protein turnover, which determines protein balance in and the net release of amino acids from cells or tissues. Over 20 years ago, leucine was discovered to stimulate protein synthesis and inhibit protein degradation in incubated skeletal muscle under catabolic states (Tischler et al., 1982). Intensive in vivo studies have since extended these in vitro seminal findings to in vivo experiments and identified that elevated plasma levels of leucine through oral administration or dietary supplementation also increased muscle protein synthesis in young rats and neonatal pigs under physiological conditions (Escobar et al., 2005, 2006). Extensive research using molecular technologies has revealed that leucine enhances muscle protein synthesis via activating the signaling pathway of the mammalian target of rapamycin (mTOR, a serine/threonine protein kinase). The phosphorylation of mTOR in response to an elevated level of leucine results in the phosphorylation of p70 S6 kinase (S6K) and eukaryotic initiation factor (eIF) 4E-binding protein-1 (4E-BP1), which promotes the formation of the active initiation complex for poly-peptide synthesis (Meijer and Dubbeldtuis, 2004). The mechanisms responsible for an inhibition of muscle protein degradation by leucine may involve the transamination of leucine to yield α-ketoglutarate (Tischler et al., 1982). In addition to the skeletal muscle, leucine has been shown to decrease protein degradation in the perfused liver, probably via the mTOR-mediated inhibition of autophagy, a major mechanism for the entry of proteins into the lysosome for their hydrolysis (Meijer and Dubbeldtuis, 2004). Finally, leucine can also activate the mTOR signaling pathway in intestinal epithelial cells (Ban et al., 2004), but its functional significance remains unknown.

**Glutamine**: Intramuscular levels of glutamine exhibit a marked decline under various catabolic conditions (e.g., injury, sepsis, and lactation) associated with negative protein balance in skeletal muscle (Curthoys and Warford.

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**Table 1.** Nutritionally essential and nonessential amino acids in animals

<table>
<thead>
<tr>
<th>Monogastric mammals</th>
<th>Poultry</th>
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<tbody>
<tr>
<td><strong>EAA</strong></td>
<td><strong>NEAA</strong></td>
</tr>
<tr>
<td>Arginine</td>
<td>Alanine</td>
</tr>
<tr>
<td>Histidine</td>
<td>Asparagine</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Aspartate</td>
</tr>
<tr>
<td>Leucine</td>
<td>Cysteine</td>
</tr>
<tr>
<td>Lyseine</td>
<td>Glutamine</td>
</tr>
<tr>
<td>Methionine</td>
<td>Glutamine</td>
</tr>
<tr>
<td>Phenyplainine</td>
<td>Glycine</td>
</tr>
<tr>
<td>Threonine</td>
<td>Proline</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Serine</td>
</tr>
<tr>
<td>Valine</td>
<td>Tyrosine</td>
</tr>
</tbody>
</table>

1. Arginine may not be required in the diet to maintain nitrogen balance in most of adult mammals but its deficiency in the diet may result in metabolic, neurological or reproductive disorders.
2. Proline is an essential amino acid for young pigs.

during the first weeks of life (Flynn et al., 2000), and plasma of all animals under catabolic conditions (Melchior et al., 2003). Notably, glutamine is particularly abundant in sow's milk (3.5 mM at Day 28 of lactation) (Wu and Knabe, 1994), plasma (0.5 to 1 mM) (Flynn and Wu, 1996), skeletal muscle (5 to 20 mM) (Wu and Thompson, 1990; Flynn et al., 1996), as well as anamotic allantoic fluid (2-3 mM) and allantoic fluid (3 to 25 mM) during early pregnancy (Wu et al., 1996a; Kwon et al., 2003). Strikingly, arginine and citrulline (the precursor of arginine) are unusually rich in porcine allantoic fluid (4-6 mM) and ovine allantoic fluid (5-10 mM), respectively, during early gestation (Wu et al., 1996a; Kwon et al., 2003).

Traditionally, much attention has been directed justifiably to the role of essential amino acids in animal nutrition (Baker, 1997). They are defined as either those amino acids whose carbon skeletons cannot be synthesized by animals or those that are inadequate synthesized in animals relative to needs and which must be provided from the diet to meet requirements for maintenance, growth, and reproduction (Wu and Self, 2005). Recently, there has been growing interest in nonessential and conditionally essential amino acids because of their unique, versatile functions in metabolic regulation and physiology. Conditionally essential amino acids are those that normally can be synthesized in adequate amounts by animals, but which must be provided from the diet under conditions where rates of utilization are increased relative to rates of synthesis (Wu and Self, 2005). Nonessential amino acids are the amino acids whose carbon skeletons can be synthesized in adequate amounts by animals to meet requirements (Wu and Self, 2005). One can argue that animals have conserved the ability to synthesize amino acids during the thousands of years of evolution because these nutrients are indispensable for survival and reproduction.
Table 2. Important nitrogenous products of amino acid metabolism in animals

<table>
<thead>
<tr>
<th>Precursors</th>
<th>Products</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginine</td>
<td>NO</td>
<td>Vasodilation, neurotransmitter, signaling molecule; angiogenesis, cell metabolism, apoptosis (programmed cell death); immune response</td>
</tr>
<tr>
<td>Cysteine</td>
<td>Taurine</td>
<td>Neutrophil; muscle contraction; bile acid conjugates; retinal function</td>
</tr>
<tr>
<td>Glutamate</td>
<td>γ-Aminobutyrate</td>
<td>Neurotransmitter; inhibitor of glumastigic serotonin and NEPN activities</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Glucosamine</td>
<td>Glycogen; and ganglioside formation; inhibitor of NO synthesis</td>
</tr>
<tr>
<td>Serum</td>
<td>Heme</td>
<td>Heme proteins (e.g., hemoglobin, myoglobin, catalase, and cytochrome C); reduction of carbon monoxide (CO, a signaling molecule)</td>
</tr>
<tr>
<td>Histidine</td>
<td>Histamine</td>
<td>Allergic reaction; vasodilation; gastric acid and central acetylcholine secretion</td>
</tr>
<tr>
<td>Methionine</td>
<td>Betaine</td>
<td>Oxidant; inhibitor of NO synthesis; risk factor for cardiovascular disease</td>
</tr>
<tr>
<td>Phenylenamine</td>
<td>H2O</td>
<td>Killing pathogens; intestinal integrity; a signaling molecule; immunity</td>
</tr>
<tr>
<td>Proline</td>
<td>PSC</td>
<td>Cellular redox state; DNA synthesis; cell proliferation; neurotransmitter formation; bridging the urea cycle with Krebs cycle; gene expression; tumor growth</td>
</tr>
<tr>
<td>Serine</td>
<td>Serotonin</td>
<td>Neutrotransmitter; smooth muscle contraction; hormonal immunity</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>N-acetylserotonin</td>
<td>Inhibitor of serotonin reductase and thus tetrahydrobiopterin synthesis</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>Dopamine</td>
<td>Circadian and circulational rhythms; free radical scavenger; antioxidant</td>
</tr>
<tr>
<td>Arg and Met</td>
<td>Polyamines</td>
<td>Gene expression; DNA and protein synthesis; ion channel function; apoptosis; signal transduction; antioxidants; cell function; proliferation &amp; differentiation; spermatogenesis; viability of sperm cells</td>
</tr>
<tr>
<td>Gin, Asp and Gly</td>
<td>Nucleic acids</td>
<td>Coding for genetic information; gene expression; cell cycle and function; protein and uric acid synthesis</td>
</tr>
<tr>
<td>Gin and Thr</td>
<td>NAD(P)</td>
<td>Coenzyme for oxidoreductases; substrate of poly(ADP-ribose) polymerase</td>
</tr>
<tr>
<td>Gin, Pro or Glu</td>
<td>Ornithine</td>
<td>Glutamate, glutamine, and polyamine synthesis; mitochondrial integrity</td>
</tr>
<tr>
<td>Gin, Met and Gly</td>
<td>Cystine</td>
<td>Energy metabolism in muscle and nerve; antioxidant; antioxidant; antioxidant</td>
</tr>
<tr>
<td>Gin, Glu and Gly</td>
<td>Glutathione</td>
<td>Free radical scavenger; antioxidant; formation of leukotrienes, peroxidation, glutathione peroxidase, glutathione-N0 adduct and glutathione proteins; signal transduction; gene expression; apoptosis; spermatogenesis; sperm maturation; cellular redox state; immunity</td>
</tr>
<tr>
<td>Gin, Glu and Pro</td>
<td>Citrulline</td>
<td>Free radical scavenger; arginine synthesis; urea cycle</td>
</tr>
<tr>
<td>Gin, Met and Ser</td>
<td>Carnitine</td>
<td>Transport of long-chain fatty acids into mitochondria for oxidation; storage of energy as acetyl-CoA</td>
</tr>
</tbody>
</table>

DCSAM - Decarboxylated S-adenosylmethionine; EPN - Epinephrine; NEPN - Norepinephrine; PSC - Pyrroline-5-carboxylate; T3 - Triiodothyronine; T4 - Thyroxine.

1995), suggesting a possible link between this amino acid and protein turnover. In support of this possibility, Rennie and co-workers demonstrated that infusion of glutamate to the rat skeletal muscle increased protein synthesis (MacLennan et al. 1987) and inhibited protein breakdown (MacLennan et al. 1988). Subsequently, Wu and Thompson (1990) found that elevating extracellular concentrations of glutamate from 1 mM (physiological level in chick plasma) to 15 mM dose-dependently increased protein synthesis and decreased protein degradation in incubated skeletal muscle isolated from young chicks. These in vitro findings provide evidence for a beneficial role of glutamine to regulate muscle protein turnover. Results of a recent in vivo study have firmly established that there is a positive relationship between intramuscular glutamine concentrations and muscle protein synthesis in chickens (Watford and Wu, 2005). Besides skeletal muscle, glutamine also stimulates protein synthesis and inhibits proteolysis in the small-intestinal mucosa (Coeffler et al., 2003). The underlying mechanisms are unknown, but may involve the mTOR signaling events, as reported for cardiac myocytes (Xia et al., 2003) and Jurkat cells (Fumirola et al., 2005). Activation of the mTOR signaling pathway may be partly responsible for the beneficial effect of dietary L-glutamine supplementation on preventing intestinal atrophy in early-weaned pigs (Wu et al., 1996c). Because leucine, isoleucine and valine are substrates for glutamine synthesis in animal tissues (particularly skeletal muscle) (Wu and Self, 2005).
Table 3. Effects of dietary supplementation with omega-3 fatty acids on production performance of sows

<table>
<thead>
<tr>
<th>Reference</th>
<th>Source</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbsuckle and Junis (1993)</td>
<td>Fish oil</td>
<td>Increase in EPA and DHA concentrations in milk but ArA content was not affected. Increase in DHA contents of plasma, liver, RBC phospholipids, and brain and synaptic plasma membrane of 15-d old piglets.</td>
</tr>
<tr>
<td>Bazinet et al. (2003)</td>
<td>Flax seed oil</td>
<td>Increase in ALA and DHA contents in sow milk and piglet tissue. Decreased ArA in plasma and liver tissues. No effect on milk ArA content.</td>
</tr>
<tr>
<td>Fritsche et al. (1993a)</td>
<td>Fish oil</td>
<td>Increase in O3FA concentrations in sow serum and milk. Increase in O3FA concentrations in piglet serum.</td>
</tr>
<tr>
<td>Fritsche et al. (1993b)</td>
<td>Fish oil</td>
<td>Increase in O3FA in immune cells of nursing piglets and reduction in in vitro eicosanoid release by alveolar macrophages.</td>
</tr>
<tr>
<td>Brazle et al. (2005)</td>
<td>PFA</td>
<td>Increase in DHA in conceptus. No effect on ALA and ArA during early gestation.</td>
</tr>
<tr>
<td>Brazle et al. (2006)</td>
<td>PFA</td>
<td>Increase in O3FA both conceptus and endometrium during early gestation.</td>
</tr>
<tr>
<td>Rooke et al. (1998)</td>
<td>Fish oil</td>
<td>Increase in O3FA and reduced O6FA in colostrums and milk. Both EPA and DHA levels were maintained after wk 2 of lactation. Increase in piglet tissue O3FA content at birth.</td>
</tr>
<tr>
<td>Rooke et al. (2000a)</td>
<td>Fish oil</td>
<td>Decrease in piglet birth weight and pre-weaning mortality.</td>
</tr>
<tr>
<td>Spencer et al. (2004)</td>
<td>PFA</td>
<td>Increase in litter size when sows were supplemented from 30 d prior breeding up to farrowing. Decrease in piglet birth weight.</td>
</tr>
<tr>
<td>Taugbol et al. (1993)</td>
<td>Fish oil</td>
<td>Increase in EPA, DHA and EPA concentrations in milk at parturition. Both EPA and DHA levels were maintained after wk 2 of lactation.</td>
</tr>
<tr>
<td>Weibel et al. (2003; 2004)</td>
<td>PFA</td>
<td>Increase in subsequent litter size and early embryo survival.</td>
</tr>
</tbody>
</table>

O3FA = Omega-3 fatty acid; O6FA = Omega-6 fatty acid; RBC = Red blood cells; DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; ArA = Arachidonic acid; ALA = a-Linolenic acid; PFA = Protected marine source of omega-3-fatty acid (EPA and DHA).

Glutamine may partly mediate the anabolic effect of the branched-chain amino acids (BCAA) in animals. Such an effect is likely important for the lactating mammary gland, which produces more glutamine than its uptake from the blood circulation (Troutier et al., 1997), and for placenta, which synthesizes and releases a large amount of glutamine into the fetal circulation (Self et al., 2004).

Arginine: There is emerging evidence showing that arginine increases protein synthesis in the pig small intestine under catabolic conditions, including viral infection and malnutrition (Corti et al., 2005). However, addition of arginine to incubation medium has no effect on mTOR phosphorylation in mamalian hepatocytes (Meijer and Dubbelhuis, 2004). This finding can be explained by the fact the hepatocytes have an exceedingly low concentration of arginine (<50 μM) due to a very high activity of arginase for its rapid hydrolysis (Wu and Morris, 1998). However, arginase activity or arginine catabolism is virtually absent from enterocytes of neonatal pigs (Wu et al., 1996b). Thus, an increase in extracellular arginine concentration (e.g., intestinal luminal arginine) is highly effective in raising its intracellular levels (Wu et al., 1996b). Notably, recent studies have indicated that arginine activates the mTOR and other kinase-mediated signaling pathways in intestinal epithelial cells (Ban et al., 2004; Rhoads et al., 2004), thereby stimulating protein synthesis, enhancing cell migration, and facilitating the repair of the damaged intestinal epithelium. This may provide a mechanism for the beneficial effect of arginine in preventing intestinal integrity and function in neonates (Wu et al., 2004b). Excitingly, we recently found that elevating plasma levels of arginine in milk-fed piglets through either dietary arginine supplementation (Kim et al., 2004b) or metabolic activation of endogenous arginine synthesis (Wu et al., 2004b) increased protein accretion in skeletal muscle and the whole body. This anabolic effect was associated with an increase in muscle protein synthesis (Frank et al., 2006). The fact that muscle protein mass accrued to a greater extent than the increase in protein synthesis (Frank et al., 2006) suggests a possible role for arginine in regulating muscle protein degradation in neonatal pigs.

Fetal growth: There may be an important role for leucine, glutamine, and arginine in embryonic placental, and fetal development during pregnancy (Martin et al., 2003; Wu et al., 2004a). Remarkably, the concentrations of glutamine and arginine in porcine and ovine amniotic and allantoic fluids increase by 25 to 80 fold during the first trimester of pregnancy, the period that is critical for placental growth and development (Wu et al., 1996; Kwon et al., 2003). In addition, the concentrations of these two amino acids and leucine increased by 10 to 50 fold in ovine uterine fluids between Days 11 and 15 of gestation (Gao et al., 2006). The unusual abundance of these amino acids at sites critical for embryonic and fetal development has mixed
an important question of whether these nutrients play a crucial role in embryogenesis, angiogenesis, implantation, placental growth and development, blood flow, and fetal growth via modulation of intracellular protein turnover and cell proliferation (Wu et al., 2004a). In support of such a role, we recently found that dietary supplementation with 10% L-arginine-HCl to gilts between Day 30 of gestation and parturition increased the number of live-born piglets by 23% and the total litter weight by 28% (Mateo et al., 2006). This finding is exciting as it is the first report of an increase in live-born piglets by >2 per litter through nutritional intervention.

**Secretion of hormones and regulation of intermediary metabolism**

*Hormone secretion*: Many polypeptide and low-molecular-weight hormones are synthesized from specific amino acids (Table 2). For example, tyrosine (or phenylalanine) is the precursor for the synthesis of epinephrine, norepinephrine, and thyroid hormones. Amino acids are also potent regulators of secretion of hormones from endocrine cells (Newsholme et al., 2005). Arginine stimulates the secretion of insulin, growth hormone, prolactin, glucagon, and placental lactogen (Flynn et al., 2002). Glutamine and leucine also increase insulin release from the pancreatic β-cells (Newsholme et al., 2005). Interestingly, dietary supplementation with glutamine reduces the production of glucocorticoids in weaning pigs via yet an unknown mechanism (Zhou et al., 2006). These amino acids may partly mediate the effect of dietary protein on the metabolism of protein, lipids and glucose, fertility, growth and production performance, and health of animals.

*Regulation of intermediary metabolism*: Besides their effects on plasma levels of hormone, amino acids directly participate in the regulation of intermediary metabolism and thus the efficiency of utilization of dietary nutrients. For example, arginine is an allosteric activator of N-acetylglutamate synthase, a mitochondrial enzyme that uses glutamate and acetyl-CoA as substrates (Wu and Morris, 1998). Thus, arginine and glutamate maintain the urea cycle in an active state. Second, alanine inhibits pyruvate kinase, thereby regulating gluconeogenesis and glycolysis to ensure net glucose production by hepatocytes during periods of food deprivation (Wu and Self, 2005). Third, glutamate and aspartate mediate the transfer of reducing equivalents across the mitochondrial membrane and thus regulate glycolysis and cellular redox state (Brosnan, 2001). Fourth, arginine and phenylalanine up-regulate expression of GTP cyclohydrolase-I expression and activity, thereby increasing the availability of tetrahydrobiopterin for NO synthesis from arginine and for the hydroxylation of aromatic amino acids (Shi et al., 2004). The arginine-NO pathway can also be modulated by a number of other amino acids (including taurine, lysine, glutamate, and homocysteine) to exert their physiological and pathological effects (Wu and Meininger, 2002). Fifth, arginine or its metabolites up-regulate expression of key proteins and enzymes (e.g., AMP-activated protein kinase and peroxisome proliferator-activated receptor γ coactivator-1α) responsible for mitochondrial biogenesis and substrate oxidation, thereby reducing excess fat mass in obese animals (Fu et al., 2005; Jobgen et al., 2006). Sixth, methionine, glycine, and serine play an important role in one-carbon metabolism and, thus, the methylation of proteins and DNA, thereby regulating gene expression and protein activity (Stead et al., 2006). Finally, coordination of amino acid metabolism among the liver, skeletal muscle, intestine, and immune cells maximizes glutamine availability for renal ammoniagenesis and therefore the regulation of acid-base balance in animals (Curthoys and Watford, 1995).

**Immune functions**

*Glutamine, arginine, and cysteine*: Protein deficiency has long been known to impair immune functions and increases the susceptibility to disease in animals. However, only in the past 15 years, have the underlying cellular and molecular mechanisms begun to unfold. A dietary deficiency of protein reduces the availability of most amino acids in plasma, particularly glutamine, arginine, tryptophan, and cysteine (Wu et al., 1999). The roles of glutamine, arginine, and cysteine in enhancing the immune function have been well established (Field et al., 2000; Wu et al., 2004). For example, glutamine is a major fuel for lymphocytes (Wu et al., 1991) and is essential for their proliferation and function (Field et al., 2002). This amino acid also enhances the phagocytic activity of macrophages, cytokine production by T-lymphocytes, and antibody generation by B-lymphocytes (Parrybillings et al., 1990; Field et al., 2002). The availability of cysteine is a major factor that limits the synthesis of glutathione, the most abundant low-molecular weight thiol and a key antioxidant (Wu et al., 2004d). Thus, dietary supplementation with N-acetyl-L-cysteine (a stable precursor of cysteine) is highly effective in enhancing immune functions under various disease states (Grindle et al., 2001). Of note, a large amount of NO synthesized from arginine by inducible NO synthase is cytotoxic to pathogenic microorganisms and virus (Bronte and Zanovello, 2005). Therefore, this free radical is a key mediator of the immune response in animals. Dietary supplementation with arginine enhances the immune status of milk-fed piglets (Kim et al., 2004a) and pregnant sows (Kim et al., 2006). In the course of one of our experiments to study the effect of dietary supplementation with 1.0% L-arginine-HCl or 1.7% L-alanine (isonitrogenous control) on pregnancy outcome in
gilt, a disease outbreak (swine dysentery) occurred on our research farm. Interestingly, all 6 control gilts died, but all of the 6 arginine-supplemented gilts were healthy and successfully completed the pregnancy. Although the number of gilts in the trial was relatively small, the results of this unplanned "natural" experiment do provide powerful evidence for an important role of arginine in the immunity.

Tryptophan and proline: There has been growing interest in recent years in the role of tryptophan and proline in immune functions. There is a progressive decline in plasma levels of tryptophan in pigs with chronic lung inflammation (Melchior et al., 2003). Catabolism of tryptophan appears to be critical for the functions of both macrophages and lymphocytes. Oral administration of tryptophan has been reported to enhance the innate immune response (Esteban et al., 2004). Interestingly, anthranilic acid (a metabolite of tryptophan via the indoleamine 2,3 dioxygenase pathway) inhibits the production of proinflammatory T-helper-1 cytokines and prevents autoimmune neuroinflammation (Platten et al., 2005). Most recently, Ha et al. (2005) discovered that a lack of proline catabolism via proline oxidase due to a deficiency of intestinal proline oxidase impairs gut immunity. The major mediator derived from proline oxidation is H$_2$O$_2$, which is cytotoxic to pathogenic bacteria and is also a signaling molecule. It can be surmised that a high activity of proline oxidase in the porcine placenta (Wu et al., 2005) and the piglet small-intestine (Wu, 1997) may play a crucial role in protecting these organs from infections during the critical periods of fetal and neonatal development.

**FUNCTIONAL FATTY ACIDS**

One of the most interesting findings in recent lipid nutrition research is the role of omega-3 fatty acids (O3FA) in both humans and animals. Their potential benefits in improving health and preventing certain diseases have now been widely recognized (Simopoulos, 1991; Rice, 1999; Wu and Meinunger, 2002). However, unlike omega-6 fatty acids (O6FA), smaller amounts of O3FA are found in the typical grain-based animal feeds. Although studies with livestock have been limited, dietary supplementation with O3FA holds great promise in improving the reproductive performance of sows (Table 3).

Nutritional characteristics of omega-3 and 6 fatty acids

Both O3FA and O6FA are polyunsaturated fatty acids (PUFA) and can be distinguished from each other based on the location of the first double bond from the methyl end. Among PUFA, $\omega$-linolenic acid (ALA; 18:3 n-3) and linoleic acid (LA; 18:2 n-6) are classified as nutritionally essential fatty acids (EFA) because mammals cannot synthesize them. ALA and LA are the precursors of other PUFA that are both nutritionally and physiologically important. ALA can be converted to EPA (20:5 n-3, also known as eicosapentaenoic acid) and DHA (22:6 n-3, also known as docosahexaenoic acid), whereas LA can be converted to arachidonic acid (ArA, 20:4 n-6) (Figure 1). Thus, animals can obtain DHA and EPA either directly from the diet or by *de novo* synthesis from dietary ALA.

LA and ALA can be obtained from grains and vegetable oils, whereas EPA and DHA are predominantly found in marine products. Both O3FA and O6FA are metabolically and functionally distinct, are not interchangeable, and may have opposing physiological functions (Simopoulos, 1991). These PUFA give rise to different types of eicosanoids, which play important roles in the regulation of inflammatory reactions, blood pressure, and platelet aggregation (McCown and Bistrian, 2003; Muskiet et al., 2004). In addition, O3FA and O6FA are essential constituents of plasma membranes in the brain (Sathy, 1985; Innis, 1991; Crawford 2002; Muskiet et al., 2004), central nervous system (Cole et al., 2005), and vascular systems (Al et al., 1995), making them critical components during rapid tissue formation (i.e., gestation and fetal growth).

**Omega-3 fatty acid in sow diets**

*Maternal omega-3 fatty acid intake and transfer to progeny:* Several studies have shown that fatty acid composition in sow's diets affects that of sow milk and nursing piglets. Taubholt et al. (1993) demonstrated that feeding sows diets supplemented with cod liver oil from 107 d of gestation to weaning increased EPA and DHA contents in colostrum and milk. However, no differences were observed in piglet weight gain and overall morbidity. Arbuckle and Innis (1993) reported that dietary supplementation with fish oil to sows between d 4 before parturition and d 15 postpartum increased milk DHA and EPA contents but had no effect on ArA. These authors also observed that DHA content was higher, but ArA content was lower, in the plasma, liver, red blood cell (RBC), brain, and synaptic plasma membrane of piglets from sows fed high-DHA diets. Interestingly, the fish oil treatment did not affect DHA or ArA concentrations in the brain and retina of piglets, suggesting a tissue-specific response. Other studies have also shown that maternal supplementation of O3FA reduced ArA content in the liver, but not in the brain of newborn piglets (Rooke et al., 2001). Further, Buzinet et al. (2003) reported that high maternal intake of ALA (flax seed oil) increased both ALA and DHA content in sow's milk and neonatal tissues (including the brain, liver, and carcass). Similarly, Cooke et al. (1998) found that feeding sow's diets containing tuna oil during late gestation and during the first week of lactation increased O3FA but reduced O6FA content in new-born piglets. O3FA
concentrations in colostrum and milk were also increased in response to the maternal dietary supplementation with tuna oil (Rooke et al., 1998).

Available evidence suggests that dietary supplementation with O3FA and O6FA is effective in increasing their availability in the porcine conceptus. For example, Rooke et al. (1999, 2000) noted an increase in plasma DHA in fetal umbilical cord at birth when sows were fed diets containing tuna oil. These results suggest that PUFA can cross the placenta into the fetal circulation. Also, other researchers (Brazle et al., 2005; Brazle et al., 2006) reported a marked increase in O3FA concentrations in the porcine conceptus during early gestation when maternal diets were supplemented with O3FA. Further, Fritsche et al. (1993a) have demonstrated that inclusion of fish oil in sow's diets resulted in elevated levels of O3FA in milk as well as both maternal and neonatal plasma. In contrast, some studies suggested that there was little or no transfer of fatty acids across the porcine placenta during late gestation (Thulin et al., 1989; Ramsay et al., 1991). However, this conclusion is solely based on the measurement of fatty acid concentrations in plasma, which depends not only on the entry of O3FA or O6FA into the umbilical vein but also their utilization and oxidation by the fetus. Notably, Rooke et al.

Figure 1. Biosynthesis of long-chain polyunsaturated fatty acids and eicosanoids from essential fatty acids (Modified from Uauy and Castillo, 2003).
Omega-3 fatty acids and eicosanoid production: As mentioned earlier, both ArA and EPA are precursors of eicosanoids (such as prostaglandins, thromboxanes, and leukotrienes), which play critical roles in inflammatory and immune responses (Figure 1). However, unlike those synthesized from EPA, eicosanoids derived from ArA are generally pro-inflammatory, potent platelet aggregators, and vasoconstrictors (Muskiet et al., 2004). Furthermore, competition occurs between ArA and EPA for eicosanoid synthesis at the cyclooxygenase and lipoygenase levels (Simopoulos, 1991). Thus, the balance between O3FA and O6FA may determine the type of eicosanoids produced, and therefore the response of animals to eicosanoid synthesis. Fritsche et al. (1993b) reported that substituting menhaden fish oil for lard as a source of fat in sow's diets during late gestation and lactation substantially increased concentrations of O3FA (i.e. EPA) in immune cells of nursing pigs and reduced in vitro eicosanoid release by alveolar macrophages. Studies with humans and animals have also demonstrated that O3FA and O6FA modulate the production of pro-inflammatory cytokines. Compelling evidence shows highly beneficial effects of O3FA in improving the host immunity under a number of inflammatory conditions (Robinson et al., 1993; Grimbble, 1998). Thus, the ability of EPA to competitively inhibit eicosanoid synthesis from ArA is an important factor for its anti-inflammatory effects. Studies have also suggested that O3FA intake may improve resistance to infections disease by altering cytokine and/or eicosanoid synthesis (Anderson and Fritsche, 2002). Finally, some findings suggest that O3FA delays the onset of parturition, thereby increasing gestation length in sows (Olson et al., 1992; Edwards and Pike, 1997; Rooke et al., 2001c), possibly by reducing intrauterine production of prostaglandins such as PGF2α, an eicosanoid synthesized from ArA (Antzen et al., 1998; Mattos et al., 2000; Rooke et al., 2001c).

Omega-3 fatty acids and litter size: The original work of Webel et al. (2003) has led to growing interest in the role of O3FA in improving pregnancy outcome in pigs. These researchers found that the inclusion of O3FA in sow’s diets during lactation and post-weaning period increased the litter size by 0.6 piglet in comparison with the control group. Most recently, Spencer et al. (2004) reported a similar increase in litter size when sows were fed diets supplemented with O3FA between d 30 prior breeding and farrowing. The increase in litter size was associated with a decrease in the piglet birth weight (1.42 vs. 1.37 kg/pig, p<0.05; compared to the control group), without changes in the distribution of low-birth-weight piglets. Consistent with this finding, Rooke et al. (2001c) reported that sows fed diets supplemented with salmon oil produced lighter pigs at birth but these piglets had a higher pre-weaning survival rate than the control group. Additionally, a mechanism for the beneficial effect of supplementation with O3FA to sow’s diets involves an increase in embryonic survival (Webel et al., 2003).

Omega-3 fatty acids and behavioral response: With the high O3FA content of the brain (Sastry, 1985; Muskiet et al., 2004), it is likely that these fatty acids have significant impacts on brain development and function and thus behavior. DHA is especially important for the development and proper functioning of brain in neonates (Crawford, 2000). Rooke et al. (2001b) found that piglets from sows fed diets containing mena oil had a more active suckling behavior immediately after birth, which contributes to their enhanced growth during the entire lactation period. Further, Ng and Innis (2003) reported that fat composition in the diet had significant effects on piglet behavior, which may result from a change in the metabolism of dopamine and other neurotransmitters (Delion et al., 1994; Zimmer et al., 2000). In support of this notion, piglets fed milk formula containing ALA and DHA had higher serotonin concentrations than piglets fed formula without ALA and DHA (Owens and Innis, 1998). Serotonin has also been implicated in a variety of neural functions, including feeding, sleep, and cognition (McEntee and Crook, 1991). However, further investigations are required to determine positive behavioral changes of piglets in response to maternal O3FA supplementation.

CONCLUSION

Amino acids and fatty acids display remarkable metabolic and regulatory versatility. They serve as essential precursors for the synthesis of a variety of molecules with enormous importance, and also regulate metabolic pathways and processes vital to the health, growth, development, reproduction, and functional integrity of animals. The current sow feeding program aims at providing amino acids for optimum protein synthesis. However, in view of the crucial regulatory roles of functional amino acids, their supplementation to the sow’s diet can be highly beneficial for enhancing production performance. Additionally, typical grain-based sow’s diets contain low levels of O3FA but high levels of O6FA, which leads to a deficiency of O3FA and an imbalance in the proportions of these EFA and their derivatives, thus
negatively impacting piglet survival and immune functions. These findings underline the practical importance of an adequate supply and balance of EFA during gestation, lactation and piglet growth. Further research is required to provide accurate recommendations for formulating sow’s diets with optimal amounts of functional amino acids and fatty acids.

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