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INVITED REVIEW

L-Glutamate nutrition and metabolism in swine

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Abstract

L-Glutamate (Glu) has traditionally not been considered as a nutrient needed in diets for humans and other animals (including swine) due to the unsubstantiated assumption that animals can synthesize sufficient amounts of Glu to meet their needs. The lack of knowledge about Glu nutrition has contributed to suboptimal efficiency of global livestock production. Over the past 25 years, there has been growing interest in Glu metabolism in the pig, which is an agriculturally important species and also a useful model for studying human biology. Because of analytical advances in its analysis, Glu is now known to be a highly abundant free amino acid in milk and intracellular fluid, a major constituent of food and tissue proteins, and a key regulator of gene expression, cell signaling, and anti-oxidative reactions. Emerging evidence shows that dietary supplementation with 2% Glu maintains gut health and prevents intestinal dysfunction in weanling piglets, while enhancing their growth performance and survival. In addition, the inclusion of 2% Glu is required for dietary arginine to maximize the growth performance and feed efficiency in growing pigs, whereas dietary supplementation with 2% Glu reduces the loss of skeletal muscle mass in endotoxin-challenged pigs. Furthermore, supplementing 2% Glu to a corn- and soybean-meal-based diet promotes milk production by lactating sows. Thus, an adequate amount of dietary Glu as a quantitatively major nutrient is necessary to support maximum growth, development, and production performance of swine. These results also have important implications for improving the nutrition and health of humans and other animals.

Keywords Amino acids · Function · Growth · Physiology · Requirement

Abbreviations

AA	Amino acid
BW	Body weight
CP	Crude protein
GDH	Glutamate dehydrogenase
Gln	L-Glutamine
Glu	L-Glutamate
α-KG	α-Ketoglutarate
mTOR	Mechanistic target of rapamycin
NRC	National Research Council

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Introduction

L-Glutamate (Glu) is one of the most abundant amino acids (AAs) in food and animal tissues, and has received growing interest from nutritionists due to its enormous roles in metabolism and physiology (Blachier et al. 2009; Brosnan and Brosnan 2013; Hu et al. 2017; Wu 2018). Historically, the definition of "nutrient requirement" referred to the amount of a nutrient in the diet necessary to prevent metabolic disorders that result in impaired growth and even death of animals (Maynard et al. 1979). To date, in human nutrition, as well as the modern livestock industries (McDonald et al. 2011; Wu 2018), nutrient requirement is assessed to optimize the health, growth, development, and productivity of the organisms. Of particular note, Glu has recently been considered as a nutritionally essential AA for intestinal and whole-body homeostasis in neonates (Hou and Wu 2017; Rezaei et al. 2013a). In the case of animal agriculture, meat and egg producers must also take into account such factors as market weight, feed cost, maintenance cost, feed efficiency, genetic strain, as well as industry and environmental sustainability, when deciding whether to supplement animal

feed with Glu or other AAs. An increase in feed efficiency, calculated as body weight (BW) gain/feed intake, can reduce the costs of producing market-weight swine (Patience et al. 2015). Thus, consideration of what constitutes a nutrient requirement includes economic, environmental, and biological or physiologic factors. Because the pig is anatomically, physiologically and biochemically similar to the human, and is also an agriculturally important species, this review focuses on Glu metabolism, nutrition and safety in swine.

Glutamate metabolism in pigs

Knowledge of Glu metabolism in pigs provides a foundation for understanding the basis of Glu nutrition. Glu was traditionally not recognized as a nutritionally essential AA for any age of pigs, because it was thought to be synthesized sufficiently in the body (Maynard et al. 1979). However, modern breeds of pigs grow faster, gain more lean tissues, and gestate more fetuses (Strathe et al. 2017; Weber et al. 2015) and, therefore, have greater requirements for Glu, when compared with previous breeds (Wu et al. 2014). Results of recent studies have shown that: (1) dietary Glu is a major energy substrate in the small intestine of pigs (Reeds et al. 2000; Reeds et al. 1996) and (2) sufficient provision of dietary Glu can enhance villus height and whole-body growth in weanling pigs (Rezaei et al. 2013a). In addition, Glu can improve barrier and anti-oxidative functions in porcine small-intestinal epithelial cells (Jiao et al. 2015). Similarly, dietary supplementation with Glu plus aspartate can alleviate oxidative stress in weaned piglets challenged with hydrogen peroxide (Duan et al. 2016). Furthermore, Kang et al. (2017) reported that dietary supplementation with 2% glutamate alleviated muscle protein loss by activating mechanistic target of rapamycin (mTOR) and inhibiting the expression of proinflammatory factors. Collectively, these findings indicate important nutritional and physiological roles of Glu in pigs. To date, adequate provision of dietary Glu is particularly important in the pig industry, because low-protein diets, which are currently used to reduce the excretion of nitrogenous wastes from swine, do not sufficiently supply Glu or its AA precursors (Hou et al. 2016). Thus, there is an urgent need to reevaluate the dietary Glu requirements of modern breeds of pigs during their nursery, weaning, growing-finishing, gestating and lactating periods. To achieve this goal, it is imperative to fully understand Glu metabolism (synthesis and catabolism) in pigs.

Glutamate synthesis in pigs

Nearly all cells are capable of forming Glu from Gln, BCAAs, alanine, and aspartate via different enzymes (e.g., phosphate-activated glutaminase, Gln:fructose-6-phosphate transaminase, BCAA transaminase, Glu-pyruvate transaminase; and Glu-oxaloacetate transaminase). However, net synthesis of Glu occurs in a cell- and tissue-specific manner. H.A. Krebs described in 1935 the conversion of Gln into Glu via glutaminase in animal tissues containing mitochondria. In pigs, glutaminase (a mitochondrial enzyme) exists in two isoforms (liver and kidney types) that are encoded by two different genes and differ in biochemical properties. Phosphate-activated glutaminase in extrahepatic tissues and cells is the kidney type (Krebs 1935). Differences in catalytic kinetics and regulation between kidney- and liver-type glutaminases were originally identified by H.A. Krebs in 1935. Specifically, liver-type glutaminase absolutely requires NH_3 for activation, has high K_m for Gln and high affinity for phosphate, and is not affected by low Glu concentration. In contrast, kidney-type glutaminase does not require NH_3 for activation, has low K_m for Gln and low affinity for phosphate, is subject to inhibition by low Glu concentration. Another enzyme that can generate Glu from Gln is Gln:fructose-6-phosphate transaminase (cytosolic), which is particularly abundant in red blood cells and endothelial cells (Wu et al. 2001). This reaction may be the major source of Glu in cells (e.g., mammalian red blood cells) that lack mitochondria and do not take up extracellular Glu. The endogenous sources of Glu in pigs are shown in Fig. 1.

In animals, including pigs, BCAAs donate an amino group to α-KG to form Glu, with glucose being the major source of α-KG (Li et al. 2009). The activity of BCAA transaminase varies greatly among different cell types, with the skeletal muscle and liver possessing relatively high and

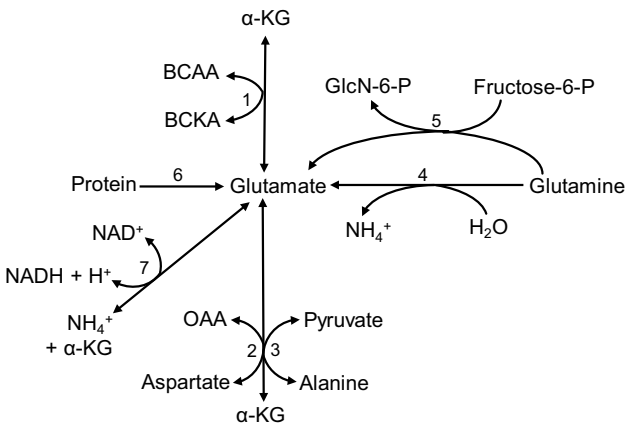

Fig. 1 Endogenous sources of glutamate in pig tissues. Adapted from Wu (2018). Enzymes that catalyze the indicated reactions are: 1, branched-chain amino acid transaminase; 2, glutamate–oxaloacetate transaminase; 3, glutamate-pyruvate transaminase; 4, phosphate-activated glutaminase; 5, glutamine:fructose-6-phosphate transaminase; 6, enzymes for intracellular protein degradation; and 7, glutamate dehydrogenase. BCAA, branched-chain amino acids; BCKA, branched-chain α-ketoacids; GlcN-6-P, glucosamine-6-phosphate; α-KG, α-ketoglutarate; OAA, oxaloacetate

very low activity, respectively. Furthermore, the transamination of alanine or aspartate with α-KG generates Glu, and these pathways are widely spread in animal tissues (Wu 2013). Finally, glutamate dehydrogenase can catalyze the synthesis of Glu from α-KG and ammonia. Thus, pigs can form Glu from dietary AAs. However, endogenous synthesis of Glu, which is estimated to be 419 mg/kg BW/day (Fig. 2), may not be sufficient for the maximum growth and feed efficiency of young pigs, particularly under stress conditions such as weaning and infections (Hou et al. 2016).

Abundance of Glu in sow's milk and pig tissues

It was recognized in the late 2000s that previous investigators had failed to determine the content of protein-bound Glu in sow's milk; therefore, studies were initiated to quantify free and protein-bound Glu in sow's colostrum and milk on days 1–28 of lactation (Haynes et al. 2009). We have shown

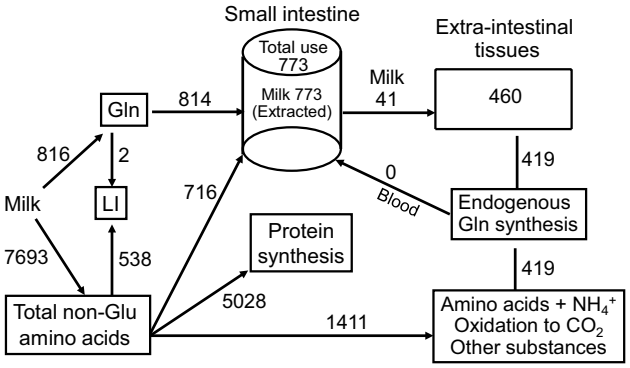

Fig. 2 Whole-body synthesis of glutamate in young pigs. Values are expressed as mg/kg BW/day. The pig (7.92 kg BW) consumes 816 mg Glu/kg BW/day from milk [true ileal digestibility of Glu = 99.7% (Mavromichalis et al. 2001)] and gains 293 g BW/day. The total content of AAs in the milk is 50 g/L (Kim and Wu 2004) and milk intake by piglets is 170 mL/kg BW/days (Wang et al. 2008). True ileal digestibility of non-Glu AAs is 93% (Mavromichalis et al. 2001). There is no net flux of arterial plasma Glu into the small intestine (Wu et al. 1994). Utilization of dietary (milk) Glu by the small intestine in first pass is 773 mg/kg BW/day (814 × 95% = 773) (Wu et al. 2010), with the total use of Glu by the small intestine being 773 mg/kg BW/day. The entry of dietary (milk) Glu into portal vein is 41 mg/kg BW/day (814 × 5% = 41). Utilization of non-Glu AAs in the body is calculated on the basis of the following: intake of non-Glu AAs from milk (7693 mg/kg BW/day; Wu et al. 2010), non-Glu AAs entering large intestine (538 mg/kg BW/day = 7693 × 7% = 538), amount of non-Glu AA available to the small intestine (7155 mg/kg BW/day = 7693 − 538 = 7155), the rate of degradation of non-Glu AAs by the small intestine [10% of non-Glu AAs in the lumen of SI; 716 mg/kg BW/day = 7155 × 10% = 716 (Wu et al. 2011)], need for non-Glu AA for whole-body protein synthesis (5028 mg/kg BW/day), and the amount of non-Glu AA available for oxidation and AA synthesis in the body = 1411 mg/kg/day (7155 − 716 − 5028 = 1411). To meet the needs for Glu for utilization by extraintestinal tissues [460 mg/kg BW/day (Wu et al. 2010)], endogenous synthesis of Glu = 419 mg/kg BW/day (460 − 41 = 419). *LI* large intestine

that concentrations of free Glu in sow's milk increase from 0.15 mM on day 1 (the day of farrowing) to 1.1 mM on day 8 of lactation, and are relatively constant, thereafter (Wu and Knabe 1994). Consistent with a decline in milk protein content in the first week of lactation, concentrations of protein-bound Glu in sow's milk also decrease between days 1 and 8 of lactation, and then remain relatively constant through day 28 of lactation (Wu et al. 2011). On all days of lactation, Glu is the second most abundant peptide-bound AA in sow's milk, only slightly after proline (Haynes et al. 2009; Wu 2013). In post-weaning pigs, Glu intake from typical plant (e.g., corn- and soybean meal)-based diets fed 14–20% crude protein (CP) is the second highest only after Gln (Wu et al. 2014). This is also the case with wheat-based diets (Wu et al. 2011).

Despite the high intake of dietary Glu by pre- and post-weaning pigs, concentrations of this AA in their plasma are relatively low (50–100 μM), when compared with most AAs (Flynn et al. 2000). This is because about 95–97% of dietary Glu is degraded by the small intestine of pigs (Stoll and Burrin 2006; Wu et al. 2010). However, Glu is the third most abundant AA in the body protein of pigs after glycine and proline (Hou et al. 2016). Thus, there must be active pathways for Glu synthesis in all ages of pigs, and these pathways will be discussed in the following section.

Synthesis of Glu from Gln and BCAAs plus α-KG in the extraintestinal tissues of pigs

(a) Small intestine. Although several metabolic pathways can potentially form Glu from Gln and branched-chain AAs (BCAAs) (Fig. 1), Glu merely serves as an intermediate of these reactions in the small intestine. In the case of glutaminase, the Gln-derived Glu is further converted into α-KG, which is oxidized to CO_2 in mitochondria. In the case of BCAA transaminase, the Glu that is formed from BCAAs and α-KG is rapidly transaminated with pyruvate or oxaloacetate to form alanine or aspartate, with α-KG being regenerated (Wu 1998). This transamination-coupled reaction does not result in Glu production. There is little net production of Glu by the small intestine of pigs (Hou et al. 2016; Reeds et al. 1996; Wu et al. 1994).

(b) Liver In growing pigs, the liver has net uptakes of basic and most neutral AAs from the portal vein at different proportions of their net portal-vein fluxes, but a net release of Glu (35 g/kg of ingested feed) (Wu 2018). Periportal hepatocytes do not appear to take up extracellular Glu but release this AA. Although perivenous hepatocytes take up extracellular Glu, the liver shows net release of Glu. When pigs are fed a regular diet, their liver receives little dietary Glu from the portal vein as noted previously, but takes up a net amount of Gln (6.4 g/kg of ingested feed) from the portal vein, and releases Glu as a result of hepatic AA metabolism.

Hepatic degradation of BCAAs is limited due to a low activity of BCAA transaminase in pigs (Li et al. 2009). In addition, oxidation of Gln at physiological plasma concentrations (e.g., 0.5 to 1 mM) is limited in the liver (Watford 2015). Thus, the major sources of Glu in the liver are neither Gln nor BCAAs, but are likely alanine, proline, phenylalanine and asparagine that are extracted from the portal vein in the largest amounts by the liver (Wu 2018).

(c) Skeletal muscle Skeletal muscle represents 40–45% of the total body weight and, therefore, plays an important role in Glu synthesis in animals. Glu is the second most abundant α-AA in the skeletal muscles of pre- and post-weaning pigs, with concentrations being 5–10 mM (Wu 2013). In muscle, BCAA transaminase produces Glu and BCKAs from BCAAs and α-KG, and glutaminase also hydrolyzes Gln into Glu (Wu et al. 2011). Intramuscular synthesis of Glu is insufficient to meet Glu requirement by muscle, because pig skeletal muscle has a net uptake of Glu (0.49–0.72 μmol/kg BW/min) from the arterial blood to support tissue growth (Ytrebo et al. 2006). In the skeletal muscle, Glu is utilized for the synthesis of proteins, Gln, alanine and aspartate. Thus, exogenous or endogenous provision of a large amount of Glu can promote intramuscular DNA synthesis (Liu et al. 2002) and the rapid gain of lean tissues (Rezaei et al. 2013a) in growing pigs.

(d) Kidneys The kidney has a high rate of glomerular infiltration rate (GFR) and may potentially play a role in Glu synthesis. The kidneys possess BCAA transaminase activity for the production of Glu and BCKAs from BCAAs and α-KG. However, a high renal activity of GDH rapidly converts Glu into ammonia and α-KG to prevent an accumulation of Glu (an inhibitor of renal glutaminase). Based on ammonia assays, Krebs (1935) reported that the porcine kidney homogenates did not have the activity of glutaminase for Glu production. However, Kvamme et al. (1970) identified the presence of phosphate-activated glutaminase in the porcine renal cortex and purified this enzyme. In healthy young pigs (25–30 kg), renal synthesis of Glu is insufficient to meet Glu requirement by the kidneys, because these animals exhibit a net renal uptake of Glu (Ytrebo et al. 2006; Junco et al. 1991).

(e) Mammary gland BCAAs undergo extensive transamination in mammary tissue (Li et al. 2009). Thus, the uptake of BCAAs by porcine mammary glands (76 g/day on Day 13–20 of lactation) is much greater than their excretion in milk protein (46 g/day) (Lei et al. 2012). In contrast, the output of Glu plus Gln in sow's milk is less than the uptake of these two AAs by the mammary glands (Lei et al. 2012). This necessitates the net production of both Glu and Gln by the mammary glands of lactating sows. Quantitatively, the lactating porcine mammary gland catabolizes 30 g BCAAs/day (40% of the BCAAs taken up from arterial plasma), with nitrogenous products being Glu, Gln, alanine and aspartate (Li et al. 2009). There is evidence that in vivo uptake of BCAAs by mammary tissue is essential for its synthesis of Glu (Matsumoto et al. 2013). The synthesis of Glu and Gln compensates for their inadequate uptake from the arterial blood by the lactating mammary gland and contributes to the high abundance of these two AAs in sow's milk (Lei et al. 2012).

(f) Placenta The uptake of Glu by the uterus of gestating sows meets at most 46% of Glu required by the growing fetuses during late pregnancy (Hou et al. 2016). Thus, the placenta and fetal tissues must synthesize at least 54% of Glu needed by the fetuses. We found that the porcine placenta (e.g., on days 20–110 of gestation) extensively degrades BCAAs through transamination with α-KG to form Glu (Self et al. 2004), with some of the Glu being released into the fetal circulation (Wu et al. 2013). The synthesis of Glu explains the observation that Glu is the second most abundant free AA and the third most abundant protein-bound AA in the porcine placenta (Wu et al. 2017).

(g) Other tissues Other porcine tissues, including the brain, lungs, heart, adipose tissue and lymphoid organs, generate Glu from: (1) Gln via glutaminase, and (2) BCAAs and α-KG via BCAA transaminase, as noted previously. These tissues, except for the brain, also extract Glu from the arterial blood. Quantitative data on Glu synthesis by the brain, lungs, heart, adipose tissue and lymphoid organs are not available. However, there is evidence that Glu synthesis by the lungs is insufficient to meet their needs for Glu, because the lungs of growing pigs exhibit a net uptake of a large amount of Glu (0.88–1.54 μmol/kg BW/min), which is almost twice the value for the hind-leg muscle (Ytrebo et al. 2006). As noted previously, the liver is a major endogenous source of Glu in the blood circulation of pigs.

Evidence for inadequate Glu synthesis and the need of exogenous Glu by porcine small-intestinal cells

Optimal gut health is fundamental to optimal whole-body health, as well as maximum growth performance and feed efficiency in swine. However, within the first few days post weaning, feed intake is usually limited (< 10% of pre-weaning dry matter intake) and intestinal atrophy along with intestinal oxidative stress occurs. The deficiencies of multiple nutrients, including Glu, contribute to this weaning-associated growth depression syndrome. We have used a porcine enterocyte culture model to determine roles of Glu in intestinal epithelial cells (Jiao et al. 2015). The culture medium contained physiological concentrations of BCAAs, Gln and other AAs found in the pig plasma. We reported that, compared with 0 mM Glu, 0.5-, 1-, and 2 mM Glu enhanced cell growth by 13–37% at 24 h in a concentration-dependent manner. In addition, 0.5 mM Glu increased transepithelial electrical resistance (TEER) by 58% at 24 h

and by 98% at 48 h. These effects of Glu were associated with increases in the mRNA abundance of Glu transporter (solute carrier family 1 member 1, SLC1A1) by 30–130% and in the protein abundance of excitatory amino acid transporter 3 (EAAT3) by 19–34%. In response to oxidative stress induced by 1 mM diquat, 0.5 mM Glu enhanced the viability, TEER, and membrane integrity of enterocytes by increasing the abundance of the tight junction proteins, including occludin, claudin-3, zonula occludens (ZO)-2, and ZO-3. Collectively, these results indicate that Glu plays an important role in mucosal barrier function by enhancing cell growth, maintaining membrane integrity, and the expression of tight-junction proteins in response to oxidative stress. Therefore, intestinal synthesis of Glu is inadequate when its substrates [e.g., Gln, BCAAs and glucose (the major source of α-KG)] are limited (e.g., under weaning and other stress conditions), and effective measures should be taken to prevent a dietary deficiency of Glu.

Glutamate catabolism in pigs

Multiple enzymes initiate Glu degradation in a cell- and tissue-specific manner (Wu 2013). Transamination plays an important role in initiating the degradation of Glu to yield α-KG, which is either further oxidized to CO_2 and H_2O or converted into glucose, depending on the physiological and nutritional status. Glu-pyruvate transaminase and Glu-oxaloacetate transaminase are abundant in both mitochondria and the cytoplasm of most mitochondria-containing cells, particularly hepatocytes, enterocytes, cells of the immune system, and kidneys.

In addition to transamination, dehydrogenation of glutamate by Glu dehydrogenase (GDH) results in the production of α-KG plus ammonia in multiple tissues (Wu 2013). Although GDH catalyzes the interconversion of Glu into α-KG and ammonia, this reaction results in the production of either ammonia or glutamate in animal cells (e.g., hepatocytes and renal tubules) depending on the physiological concentrations of substrates and products (Treberg et al. 2010). GDH is a major enzyme that directly produces ammonia from AA catabolism in animals. Interestingly, this enzyme is allosterically activated by L-leucine, which has important implications for the regulation of Glu catabolism and hormone secretion. In tissues (e.g., skeletal muscle, heart, and small intestine) other than the liver, pancreas and kidneys, GDH activity is low and is not a quantitatively significant source of ammonia.

Decarboxylation of Glu by Glu decarboxylase produces GABA in tissues (Wu 2013). This enzyme is particularly abundant in the brain and the pancreas. In mammals, Glu decarboxylase exists in two isoforms, which are encoded by two different genes: *GAD1* (the brain) and *GAD2* (the pancreas). GABA is further degraded to either succinate by succinate semialdehyde dehydrogenase or γ-hydroxybutyrate. In the brain, the production and catabolism of GABA occur in neurons and glial cells, respectively. These highly cell-specific events play an important role in neurotransmission. Data on quantitative utilization of plasma Glu in young pigs are summarized in Fig. 3.

(a) Small intestine Besides protein synthesis, the small intestine of pigs utilize Glu via several metabolic pathways (Wu 2013). Studies involving the cannulation of the jejunal artery and jejunal vein of 14- and 21-day-old suckling piglets, as well as 29- to 58-day-old pigs weaned at 21 days of age have shown that their small intestine does not take up Glu from arterial blood (Wu et al. 1994). However, in enterocytes from the small intestine of these pigs, Glu is extensively degraded to mainly CO_2, alanine and aspartate via Glu transaminases, and, to a lesser extent, citrulline, proline and arginine via P5C synthase (Wu et al. 1994; Wu and Knabe 1995). Endogenous synthesis of citrulline and

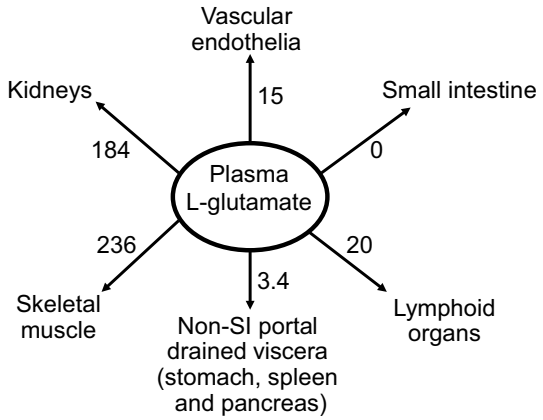

Fig. 3 Utilization of circulating glutamate by major organs of young pigs fed a milk-protein diet. Values in the figure are expressed as mg Glu/kg BW/day. The pig (7.92 kg BW) consumes 816 mg Glu/kg BW/day from milk [true ileal digestibility of Glu = 99.7% (Mavromichalis et al. 2001)] and gains 293 g BW/day. The total content of AA in the milk is 50 g/L (Kim and Wu 2004). There is no net flux of arterial plasma Glu into the small intestine (Wu et al. 1994). Rate of extraction of Glu by the non-SI portal-drained viscera is 3.4 mg/kg BW/day (Reeds et al. 1996). Glu utilization by skeletal muscle is calculated on the basis of the following: mass of skeletal muscle (3.17 kg; 40% of BW), protein gain in skeletal muscle (2.22 g/kg BW/day), Glu content in muscle protein (8.12 g/100 g protein), concentration of free Glu in skeletal muscle (470 mg/kg wet tissue), and Glu oxidation [0.034 mmol Glu/kg muscle/h; determined at 0.15 mM Glu (G. Wu, unpublished data)]. Glu utilization by kidneys is 184 mg/kg BW/day (Ytrebo et al. 2006). Glu utilization by whole-body lymphocytes is calculated on the basis of 1.43×10^{10} cells/kg BW (Lydyard and Grossi 1989) and the rate of Glu utilization by lymphocytes [0.41 nmol/10^6 cells/h; determined at 0.15 mM Glu (G. Wu, unpublished data)]. Glu utilization by vascular endothelia is based on the number of endothelial cells [1.5×10^9/kg BW (Wu and Thiagarajan 1996)] and the rate of Glu utilization in endothelial cells [2.86 nmol Glu/10^6 cells/h; determined at 0.15 mM Glu (G. Wu, unpublished data)]. *SI* small intestine

arginine in enterocytes, which involves both the mitochondria and the cytosol (Wu and Morris 1998), plays an important role in maintaining arginine homeostasis in milk-fed piglets (Flynn and Wu 1996) and in post-weaning, growing pigs (Wu et al. 1997). Dietary Glu, aspartate, and Gln plus arterial Gln provide approximately 80% of ATP to the small-intestinal mucosa in pigs (Reeds et al. 2000). Blachier et al. (1999) reported that the rate of oxidation of 2 mM Glu to CO_2 in enterocytes of 60-kg pigs was similar to that of 2 mM Gln. Consistent with a low-GDH activity, there is limited production of ammonia from Glu or monosodium glutamate (MSG) by pig enterocytes (Blachier et al. 1999).

Results of in vivo isotopic and kinetic studies indicate that 95–97% of the orally administered Glu at a regular intake level (0.5 g Glu/kg BW/day) is utilized by the small intestine of pigs during first-pass metabolism, with only 3–5% of enteral Gln entering the portal vein (Reeds et al. 1996; Wu et al. 2010). The small intestine has such a high capacity to catabolize dietary Glu that even oral administration of Glu at four times its normal dietary intake (Janeczko et al. 2007) or dietary supplementation with 4% MSG (2 g MSG/kg BW/day) (Rezaei et al. 2013a) results in only a transient, approximately 75% increase in circulating levels at 1 h after feeding. Under these conditions, the concentrations of Glu in pig plasma remain low. When MSG alone was rapidly administered to 60-kg pigs (0.33 g MSG/pig/day), an approximately 100% increase in Glu concentrations in arterial and portal vein plasma were observed at 1 h after administration without any adverse effect on pigs (Blachier et al. 1999). This further supports the notion that dietary components can affect Glu catabolism by the small intestine and the whole body (Daabees et al. 1994; Stegink et al. 1973). Due to the extensive utilization of dietary Glu by the pig small intestine, Glu in the body is derived primarily from *de novo* synthesis in insulin-sensitive tissues (skeletal muscle, heart, liver, and adipose tissue), the brain and kidneys, and, to a much lesser extent, from the diet (Wu 2013; Curthoys and Watford 1995).

(b) Liver In the pig liver, GDH can degrade Glu that is derived from the metabolism of other AAs into ammonia and α-KG (Wu 2018). Ammonia is detoxified as urea via the hepatic urea cycle, and α-KG's metabolic fate (e.g., for glucose synthesis or ATP production) depends on the physiological state of pigs. Glu is also metabolized to form alanine and aspartate via transamination (Wu 2013). In the liver of growing pigs, the rate of Glu uptake plus synthesis exceeds the rate of Glu degradation, resulting in its release from this organ.

(c) Skeletal muscle The rate of deamination of Glu in skeletal muscle is low. This is because of a low activity of GDH in this tissue. Less than 15% of Glu utilized by the pig skeletal muscle is oxidized to CO_2. Production of protein, Gln, alanine and aspartate is the major pathway for Glu utilization in skeletal muscle, which amounts to 0.49–0.72 μmol/kg BW/min (Ytrebo et al. 2006). Thus, the carbon skeleton of Glu is well conserved in the muscle, which may be considered as a major sink of dietary AAs.

(d) Kidneys A high-renal activity of GDH rapidly converts Glu into ammonia and α-KG. Based on the rate of renal Glu extraction by pigs (39 μmol/min per 100 ml GFR per kidney) (Junco et al. 1991) and the GFR of 1.115 mL/kg BW/min per kidney) in pigs (Link et al. 1985), the rate of Glu utilization by both kidneys in pigs is estimated to be 0.87 μmol/kg BW/min. The pathway of GDH contributes to a net release of ammonia (1.8–2.4 μmol/kg BW/min) from the kidneys in growing pigs (Junco et al. 1991; Ytrebo et al. 2006). The Glu-derived α-KG can be oxidized to CO_2, which reacts with H_2O to form H_2CO_3 under the action of carbonic anhydrase. H_2CO_3 is in equilibrium with $H^+ + HCO_3^-$. The latter is reabsorbed by renal tubules into the blood.

Glutamate nutrition in pigs

Results of recent studies indicate that dietary supplementation with Glu to conventional diets can improve the growth or production performance of modern breeds of pigs. Thus, there have been suggestions that Glu is a conditionally essential AA for weanling pigs (Rezaei et al. 2013a; Watford 2015) and lactating sows (Wu et al. 2014). Based on published work, Wu et al. (2014) and Hou et al. (2016) have recommended the minimal content of Glu in diets for gestating, lactating, nursing, weanling, and growing-finishing swine. Hou and Wu (2017) concluded that the term "nutritionally nonessential AAs" is a misnomer in nutritional sciences and could be replaced with "AAs synthesizable in animals". This is a major paradigm shift in swine AA nutrition.

Glu nutrition in sow-reared pigs

Quantitative data on Glu utilization by the small intestine and extra-intestinal tissues of sow-reared piglets are summarized in Table 1. About 95% of milk Glu is extracted by the piglet small intestine in the first pass, and only about 5% of milk Glu enters the portal vein. Oxidation to CO_2 for ATP production is the major pathway for intestinal Glu metabolism. Skeletal muscle and kidneys are two major extra-intestinal tissues for Glu utilization via protein synthesis and mitochondrial oxidation pathways, respectively, in growing pigs (Table 2). BCAAs and non-BCAA AAs in milk are ultimately nitrogenous substrates for Glu synthesis in suckling piglets (Table 3). Due to no net synthesis of Glu by the small intestine and negligible uptake of Glu by the small intestine from the arterial blood, milk-derived Glu is essential for the growth, integrity and function of this tissue. Oral administration of monosodium glutamate [MSG; 0, 0.06, 0.5, or 1 g/kg BW/day for 21 days] beginning immediately

Table 1 Utilization of glutamate by the small intestine (SI) of sow-reared 21- to 35-day-old pigs

Variable	Amount (g/day)
Glu provision from milk to the SI[a]	6.44
Amount of milk Glu entering the portal vein[b]	0.32
Utilization of total milk Glu by the SI[b]	6.12
Glu needed for accretion of intracellular constituent proteins[c]	0.13
Glu needed for production of mucin proteins exported by SI into the intestinal lumen[d]	0.046
Glu needed for production of membrane-bound mucin proteins in the SI mucosa[e]	0.31
Glu metabolized to CO_2, amino acids plus lactate, and glutathione[f]	5.95

[a]Calculated according to Wu et al. (2014): Glu content in whole milk = 4.80 g/L; milk intake = 1.345 L/day (170 mL/kg BW/day; average of days 21 and 35; days 21 = 190 mL/kg BW/day; days 28 = 170 mL/kg BW/day; days 35 = 150 mL/kg BW/day); Glu intake from whole milk = 816 mg/kg BW/day (6.46 g/day; 4.80 × 1.345 *L* = 6.46); true ileal Glu digestibility = 99.7%; availability of dietary Glu to the SI = 6.44 g/day (6.46 × 99.7% = 6.44 g/days); average body weight of pigs = 7.92 kg

[b]Calculated according to Hou et al. (2016), Reeds et al. (1996) and Wu et al. (2010): the rate of utilization of dietary Glu by the SI = 95% of enteral intake; utilization of dietary Glu by the SI = 6.12 g/day (6.46 × 99.7% × 95% = 6.12); the flux of plasma Glu into the SI = 0.00. A negligible amount of Glu is formed from intestinal metabolism of AAs in pigs

[c]Calculated according to Wang et al. (2008): small-intestinal weight gain = 11.1 g/day; protein content in the small intestine = 13.9%; Glu content in proteins of small-intestinal tissues = 8.57 g/100 g protein; Glu needed for accretion of intracellular constituent proteins = 0.13 g/day (11.1 × 13.9% × 8.57% = 0.13)

[d] Calculated according to Lien et al. (1997) and Nichols and Bertolo (2008): the rate of mucin proteins exported into the small-intestinal lumen = 0.14 g/kg BW/day; production of mucin protein exported into the small-intestinal lumen = 1.11 g/day (0.14 × 7.92 = 1.11); Glu content in mucins = 4.1% (4.1 g/100 g mucin protein); Glu needed for production of exported mucin protein = 0.046 g/day (1.11 × 4.1% = 0.046)

[e]Calculated according to Lien et al. (1997) and Satchithanandam et al. (1990): SI mucosa weight = 76 g (25% of SI weight; 25% × 302 g = 76 g); protein content in the SI mucosa = 14%; mucin protein content in the SI mucosa = 76 mg/g mucosa protein (7.6%); membrane-bound mucin protein in the SI mucosa = 0.81 g (76 × 14% × 7.6% = 0.81); fractional rate of synthesis of membrane-bound mucin protein in the SI = 414%/day; membrane-bound mucin protein synthesized by the SI = 3.35 g/day (0.81 × 414% = 3.35); Glu needed for production of membrane-bound mucin protein = 0.14 g/day (3.35 × 4.1% = 0.14); Glu needed for production of membrane-bound mucin = 0.18 g/day (0.04 + 0.14 = 0.18); Glu needed for production of intestinal protein = 0.31 g/day (0.13 + 0.18 = 0.31)

[f]Calculated according to Reeds et al. (1997), Stoll et al. (1999) and Wu et al. (unpublished data): oxidation to CO_2 = 3.09 g/day (5.95 × 52% = 3.09); ornithine, citrulline and arginine synthesis = 0.32 g/day (5.95 × 5.4% = 0.32); proline synthesis = 0.31 g/day (5.95 × 5.2% = 0.31); alanine plus lactate synthesis = 0.62 g/day (5.95 × 10.4% = 0.62); glutathione synthesis = 0.60 mmol GSH/kg BW/day, with 1 mol glutathione containing 1 mol Glu (MW of Glu = 147); Glu required for GSH synthesis = 0.70 g/day (0.60 × 147 × 7.92 = 698 mg); synthesis of other nitrogenous substances (e.g., Asp and Asn) = 0.45 g/day (5.95 × 7.5% = 0.45); other organic acids (α-KG, malate, pyruvate, and succinate) = 0.46 g/day (5.95 × 7.7% = 0.46)

after birth enhanced the expression of Glu receptors and Glu transporters in the stomach and jejunum of sow-reared piglets (Zhang et al. 2013). There are reports that addition of 5 g MSG to 1 kg creep feed (starter diet) can increase the feed consumption of suckling pigs by 36% on Day 18 after farrowing, but does not affect their body weight at weaning (Gatel and Guion 1990). It remains to be determined whether milk-born Glu is sufficient for the maximal growth of sow-reared piglets, particularly low-birth-weight piglets.

Glu nutrition in weanling pigs

There is growing interest in Glu nutrition in weanling pigs. Zimmerman (1975) reported that supplementing 3.36% Glu to a corn- and soybean meal-based low-protein diet (16% CP) for 28 days enhanced daily weight gain by 12% in pigs weaned at 21 days of age without affecting the feed:gain ratio. Of interest, Glu supplementation had no effect on the growth of older pigs weaned at 31 days of age to a corn- and soybean meal-based diet containing 18% CP for 9 days before being fed a 16% CP diet for 21 days (Zimmerman 1975). Thus, a 16% CP diet does not supply sufficient Glu to weanling pigs. Similarly, Gatel and Guion (1990) found that dietary supplementation with 0.5% MSG to the weanling diet increased daily food intake by 10% and daily BW gain by 7%. Interestingly, the effect of MSG was greater in piglets with a weaning weight less than 8.5 kg than those with a weaning weight of ≥ 8.5 kg. This may be because small piglets are more susceptible to

Table 2 Utilization of glutamate by extra-small intestinal tissues in sow-reared 21- to 35-day-old piglets

Variable	Amount (g/day)
Glu utilization by extra-small intestinal tissues	3.64
Glu utilization by non-SI parts of the portal-drained viscera (PDV)[a]	0.027
Glu utilization by skeletal muscle[b]	1.87
Glu utilization by kidneys[c]	1.46
Glu utilization by lymphocytes[d]	0.16
Glu utilization by the vascular endothelium[e]	0.12
Glu utilization by the small intestine (from Table 1)	6.12
Requirement of Glu by the whole body[f]	9.76

[a]Calculated according to Reeds et al. (1996): the rate of extraction of Glu by non-SI PDV, 0.96 μmol/kg BW/h (0.023 mmol/kg BW/day); the extraction of Glu by non-SI PDV, 0.027 g/day (0.023 × 147 × 7.92/1000 = 0.027)

[b]Calculated according to Wu et al. (2007) and Wu, G. (unpublished data): the mass of skeletal muscle = 3.17 kg (40% of 7.92 kg BW); the gain of skeletal muscle = 117 g/day (293 g × 40% = 117 g); the concentration of true protein in skeletal muscle = 15.0%; total proteins in skeletal muscle = 476 g (3.17 kg × 15% = 0.476 kg); protein gain in skeletal muscle = 17.6 g/day (117 × 15% = 17.6); Glu content in muscle proteins = 8.12 g/100 g protein [13.4% × (1/1.650) = 8.12%]; the amount of Glu in muscle proteins = 38.5 g (8.12% × 474 = 38.5); free Glu in skeletal muscle = 3.22 mmol/kg wet tissue; free Glu gain in skeletal muscle = 55 mg/day (0.117 kg × 3.22 × 147 = 55); Glu needed for muscle protein gain = 1.433 g/day (17.6 × 8.12% = 1.43); Glu oxidation in skeletal muscle = 0.38 g/day (determined with 0.15 mM [1 − ^{14}C]glutamate, 0.034 ± 0.004 nmol Glu/mg muscle/h = 0.034 mmol/kg muscle/h × 24 × 147 × 3.17 kg = 0.38 g/day); total Glu needed for muscle growth = free Glu gain + Glu in muscle protein gain + Glu oxidation = 1.87 g/day (0.055 + 1.433 + 0.38 = 1.87)

[c]Calculated according to Junco et al. (1991) and Link et al. (1985): extraction of Glu by kidneys = 870 nmol/kg BW/min (1.25 mmol/kg BW/day), or 1.46 g/day (1.25 × 147 × 7.92/1000 = 1.46)

[d]Calculated according to Lydyard and Grossi (1989) and Wu, G. (unpublished data): the number of lymphocytes in the 7.92-kg body = 1.13 × 10^{11}/pig (1.43 × 10^{10}/kg BW); Glu utilization by lymphocytes = 0.41 nmol/10^6 cells/h at 0.15 mM extracellular Glu; 0.16 g/day (0.048 × 24 × 0.113 × 147/1000 = 0.16 g)

[e]Calculated according to Wu and Thiagarajan (1996) and Wu, G. (unpublished data): the number of endothelial cells (EC) in the 7.92-kg pig = 1.19 × 10^{10} cells (1.5 × 10^9 endothelial cells/kg BW); Glu utilization in EC = 2.86 ± 0.22 nmol Glu/10^6 cells/h at 0.15 mM extracellular Glu; 0.12 g/day (2.86 × 24 × 1.19 × 10^4 × 147/10^6 = 0.12)

[f]Calculated as: SI + extra-SI tissues (non-SI PDV + skeletal muscle + kidneys + lymphocytes + vascular endothelium) = 6.12 + 3.64 = 9.76 g/day

stress and metabolic abnormalities than larger piglets at weaning (Wu et al. 2006).

Intestinal dysfunction of weanling piglets is a major concern of swine producers worldwide (Wu et al. 2014). For optimal intestinal health and growth, weanling pigs (21–35 days of age) should receive at least the same quantity of dietary Glu as their age-matched sow-reared counterparts. However, weanling pigs usually have a reduced rate of feed intake during the first week post weaning, compared with suckling piglets (Wu et al. 2014). Thus, the corn- and soybean meal-based weaning diet provides only about 50% of Glu needed by the small intestine of weanling piglets (Table 4). Clearly, dietary supplementation with Glu is necessary for their well-being. This is particularly important for weanling piglets that fed a diet contaminated with mycotoxins (Duan et al. 2014).

Rezaei et al. (2013a) conducted a study to assess the efficacy of dietary supplementation with Glu in postweaning pigs. Piglets were weaned at 21 days of age to a corn- and soybean meal-based diet (21% CP) supplemented with 0, 0.5, 1, 2, or 4% MSG. MSG was added to the basal diet at the expense of cornstarch. At 42 days of age (21 days after weaning), blood samples (10 mL) were obtained from the jugular vein of pigs/group at 1 and 4 h after feeding for AA analysis. Feed intake was not affected by dietary supplementation with 0–2% MSG and was 15% lower in pigs supplemented with 4% MSG, compared with the 0% MSG group. Compared with the control, dietary supplementation with 1, 2 and 4% MSG dose-dependently increased plasma concentrations of Glu, Gln, and many other AAs (including lysine, methionine, phenylalanine and leucine), daily BW gain, and feed efficiency in postweaning pigs. At day 7 post weaning, dietary supplementation with 1–4% MSG also increased jejunal villus height, DNA content, and anti-oxidative capacity. The MSG supplementation dose-dependently reduced the incidence of diarrhea during the first week after weaning. Similar results have been reported by other investigators (Lin et al. 2014). Likewise, supplementing creep feeds with Glu plus Gln can improve intestinal and immunological health in weanling piglets (Cabrera et al. 2013). These data indicate that dietary supplementation with up to 4% MSG improves growth performance in postweaning pigs, and support the view that Glu is a conditionally essential AA for weanling pigs (Table 5).

Glu nutrition in growing-finishing pigs

Reducing dietary intake of protein is an effective means to minimize nitrogen excretion by pigs during the growing and finishing periods. Kirchgessner et al. (1993) conducted experiments to evaluate a role of dietary supplementation with 1–4% Glu to low-protein diets on pig growth and carcass quality. The content of CP in the diets of grower pigs (30–60 kg BW) and finisher pigs (60–90 kg BW) was 12 and 10%, respectively. All diets contained the same amount of nutritionally essential AAs. Compared with the positive control (17% CP in the grower period and 14% CP in the finisher period), daily weight gain and feed conversion were reduced by up to 13% with the low-protein diet during the grower period despite similar feed

Table 3 Availabilities of milk BCAAs and non-BCAA amino acids (NBAAs) for glutamate synthesis in the extra-intestinal tissues of sow-reared 21- to 35-day-old piglets

Variable	Amount
Availability of milk BCAAs for glutamate synthesis in extra-intestinal tissues	1.97 g/day
Accretion of total BCAAs in the body[a]	6.48 g/day
Content of total BCAAs in the whole milk[b]	9.28 g/L
Total milk BCAAs entering into the portal vein[c]	8.45 g/day
Total milk BCAAs available for Glu synthesis[d]	1.97 g/day
Amount of Glu synthesized from milk BCAAs[e]	2.24 g/day
Availability of milk non-BCAA amino acids for glutamate synthesis in extra-intestinal tissues	4.5 g/day
Accretion of total non-BCAA amino acids in the body[f]	34.8 g/day
Accretion of Glu in the body[g]	3.69 g/day
Content of non-BCAA amino acids in the whole milk[h]	40.7 g/L
Total milk non-BCAA amino acids entering into the portal vein[i]	39.3 g/day
Total milk non-BCAA amino acids available for Glu synthesis (39.3 − 34.8 = 4.5 g/day)	4.5 g/day
Maximum amount of Glu synthesized from milk non-BCAA amino acids[j]	3.67 g/day
Maximum amount of Glu synthesized from milk AAs in extra-intestinal tissues (2.24 + 3.67 = 5.91)	5.91 g/day

[a]Calculated according to Mavromichalis et al. (2001) and Wu et al. (2014): the content of leucine in body proteins = 7.1 g/100 g protein; the content of isoleucine in body proteins = 3.9 g/100 g protein; the content of valine in body proteins = 4.7 g/100 g protein; the content of total BCAAs in body proteins = 15.7 g/100 g protein (7.1 + 3.9 + 4.7 = 15.7); the content of protein in the body = 14.1 g/100 g BW; leucine accretion in the body = 2.93 g/day (293 g × 7.1% × 14.1% = 2.93); isoleucine accretion in the body = 1.61 g/day (293 g × 3.9% × 14.1% = 1.61); valine accretion in the body = 1.94 g/day (293 g × 4.7% × 14.1% = 1.94); total BCAA accretion in the body = 6.48 g/day (2.93 + 1.61 + 1.94 = 6.48)

[b]Calculated according to Kim and Wu (2004): the content of leucine in the whole milk = 4.46 g/L; the content of isoleucine in the whole milk = 2.28 g/L; the content of valine in the whole milk = 2.54 g/L; the content of total BCAAs in the whole milk = 9.28 g/L (4.46 + 2.28 + 2.54 = 9.28)

[c]Calculated according to Mavromichalis et al. (2001), and Stoll and Burrin (2006): leucine digestibility = 91%; isoleucine digestibility = 90%; valine digestibility = 87%; leucine in the small-intestinal lumen entering the portal vein = 75%; isoleucine in the small-intestinal lumen entering the portal vein = 77%; valine in the small-intestinal lumen entering the portal vein = 69%; the amount of milk leucine entering into the portal vein = 4.09 g/day (4.46 × 1.345 × 91% × 75% = 4.09); the amount of milk isoleucine entering into the portal vein = 2.13 g/day (2.28 × 1.345 × 90% × 77% = 2.13); the amount of milk valine entering into the portal vein = 2.05 g/day (2.54 × 1.345 × 87% × 75% = 2.23); the amount of total BCAAs entering into the portal vein = 8.27 g/day (4.09 + 2.13 + 2.23 = 8.45)

[d]Total BCAAs available for Glu synthesis = 1.97 g/day (8.45 − 6.48 = 1.97)

[e]Calculated according to the molecular weights of intact leucine, isoleucine, valine and glutamate: (4.09 − 2.93) × 147/131 + (2.13 − 1.61) × 147/131 + (2.23 − 1.94) × 147/117 = 2.24 g/day

[f]Calculated according to Wu et al. (2014): 84.3 g NBAAs/100 g protein; the accretion of NBAAs in the body = 34.8 g/day (293 g × 14.1% × 84.3% = 34.8)

[g]Calculated according to Haynes et al. (2009), Li et al. (2011) and Wu et al. (2014): body protein = 1117 g (14.1% × 7920 g = 1117); Glu content in body proteins = 8.57 g/100 g protein [14.1% × (1/1.645) = 8.57%]; Glu in body proteins = 84.1 g (8.57% × 1117 = 95.7); concentration of free Glu in blood = 0.15 mmol/L; volume of blood = 554 mL (7 mL/100 g BW × 7920 g = 554); free Glu in blood = 0.012 g (0.15 mmol/L × 147/1000 = 0.012); the content of free Glu in body tissues = 3.53 mmol/kg wet tissue; free Glu in body tissues = 4.11 g (3.53 × 7.92 × 147/1000 = 4.11); total Glu in the body = 99.8 g (95.7 + 0.012 + 4.41 = 99.8); daily Glu accretion in the body = 3.69 g/day (99.8 × 293 g/7920 g = 3.69)

[h]Calculated according to Wu et al. (2014): Content of NBAAs in whole milk = Total AAs − BCAAs = 50 − 9.28 = 40.7 g/L

[i]Calculated according to Mavromichalis et al. (2001) and Wu et al. (2014): digestibility of milk NBAAs, 95%; milk Glu not entering the portal vein: 6.12 g/day; NBAAs in the small-intestinal lumen entering the portal vein, 85%; milk Glu entering the portal vein: 0.32 g/day; total milk non-BCAA amino acids entering into the portal vein (40.7 g/L × 1.345 × 95% − 6.12) × 85% + 0.32 = 39.3 g/day

[j]Calculated according to the average molecular weights of non-BCAA amino acids (molecular weight = 120 Da): 4.5 g/day × 120/147 = 4.5 g/day

intake. With increasing the amount of Glu supplementation, weight gains and feed conversion were improved in a dose-dependent manner. However, pigs fed the low protein diet supplemented with 4% Glu still exhibited a lower daily weight gain and a lower feed efficiency, compared with the positive control group. This result suggests that pigs need biosynthesizable AAs other than Glu for achieving maximal growth. Of note, low-protein diet increased fat deposition in the body, but this effect was ameliorated or fully reversed by dietary Glu supplementation. Fickler et al. (1995) reported that the inclusion of 2% Glu was required for dietary arginine to maximize the growth performance and feed efficiency in growing pigs. Likewise, Le Floc'h et al. (1994) found that adding 2.62% Glu plus 1% MSG to a threonine-deficient (0.42% threonine) and low-protein (12.6% CP) diet for growing-finishing pigs

Table 4 Needs for supplemental glutamate by the 21- to 35-day-old weanling pig to maintain the function of the small intestine[a]

Variable	Amount
Crude protein content in the corn- and soybean meal-based diet[b]	21.47%
Optimal provision of total Glu to the weanling pig[c]	6.44 g/day
Glu content in the diet[d]	1.76%
Availability of Glu from the weaning diet to the small intestine[e]	3.33 g/day
Supplemental Glu needed in the weaning diet based on the need of the Weanling pig's small intestine (6.44 − 3.33 = 3.11 g/day)	3.11 g/day
Content of supplemental Glu in the diet[f]	1.30%

[a]Body weight = 7.24 kg (d 21 = 5.86 kg; day 35 = 8.62 kg); BW gain = 197 g/day; feed intake = 33.2 g/kg BW/day (240 g/day); small-intestine weight, 38 g/kg BW (Wang et al. 2008)

[b]Calculated according to Wu et al. (2014): corn content in the diet = 55.8%; soybean meal content in the diet = 36.6%; crude protein content in the corn = 7.22%; crude protein content in soybean meal = 47.64%; crude protein content in the diet = 21.47% (55.8% × 7.22% + 36.6% × 47.64% = 21.47%)

[c] Based on Glu provision from milk to the small intestine of the sow-reared 21- to 35-day-old piglet (Table 1)

[d] Calculated according to Li et al. (2011): Glu content in the corn = 0.32%; Glu content in soybean meal = 4.31%; Glu content in the diet = 1.76% (55.8% × 0.32% + 36.6% × 4.31%)

[e]Calculated according to Wu et al. (2014): Glu intake from the diet = 4.22 g/day (240 g/day × 1.76% = 4.22); Digestibility of Glu in dietary protein = 79%; availability of Glu from the diet to the small intestine = 3.33 g/day (4.22 × 79% = 3.33) or 460 mg/kg BW/day (3.33/7.24 × 1000 = 460)

[f]Calculated according to the feed intake of 240 g/day: (3.11/240) × 100 = 1.30%

Table 5 Safety of dietary supplementation with Glu or MSG in weanling, growing-finishing, gestating and lactating swine

Body weight (BW) or age of pigs (days) [kg BW or days]	CP or Glu content in basal diet (%)		Supplemental Glu or MSG in diet	Days of supplementation	Any adverse effects	References
	CP	Glu[†]				
Weanling piglets						
5.5–13.5 kg (days 21–42)	21	1.9	0.5–4% MSG	21	None	Rezaei et al. (2013a)
4.7–13 kg (days 21–49)	16	1.5	3.36% Glu	28	None	Zimmerman (1975)
5.6–12 kg (days 31–61)	18	1.7	3.36% Glu	9	None	Zimmerman (1975)
	16	1.5	3.36% Glu	21	None	Zimmerman (1975)
Days 25–55	18	1.6	3% MSG	30	None	Kong et al. (2015)
Days 28–42	18	1.7	1% Glu	14	None	Liu et al. (2002)
Days 30–58[‡]	19	1.7	2% Glu	28	None	Kang et al. (2017)
7.5–12 kg (days 28–41)	22	2.0	0.5% MSG	13	None	Gatel and Guion (1990)
Growing-finishing pigs						
30–90 kg	10–12	1.1–1.3	1–4% Glu	~ 120	None	Kirchgessner et al. (1993)
77–120 kg	13	1.2	1% Glu	60	None	Hu et al. (2017)
Gestating sows	15	1.3	0.15% Glu	30	None	Bignell (2014)
Lactating sows	18	1.5	1–2% MSG	21	None	Rezaei et al. (2013b)
Lactating sows	23.5	2.2	1% Glu or 1.15% MSG	21	None	Hewitt and van Barneveld (2012)

[†]Except for the analyzed value in Rezaei et al. (2013a, 2013b), other values were calculated on the basis of Glu content in feed ingredients (Li et al. 2011)

[‡]Pigs were challenged with LPS

CP crude protein, *Glu* glutamic acid, *MSG* monosodium glutamate

(40–100 kg BW) increased daily weight gain and gain:feed ratio by 18% and 10%, respectively, compared with pigs fed the basal diet without Glu or MSG supplementation. Furthermore, as noted previously, dietary supplementation with 2% Glu can reduce the loss of muscle mass in growing pigs challenged with LPS (Kang et al. 2017). These results indicate an important role for Glu in modulating lipid and protein metabolism in swine.

In growing-finishing pigs, a major concern is that excessive amounts of subcutaneous white adipose tissue (e.g., backfat) are naturally deposited in market-weight pigs fed a conventional finishing diet (NRC 2012). Notably, supplementing 3% MSG to a corn- and soybean meal-based diet can beneficially reduce triglyceride concentrations in the plasma and the white adipose tissue of growing pigs (Kong et al. 2015). Likewise, dietary supplementation with 1% Glu beneficially increases the intramuscular fat deposition and improves the meat color without affecting the subcutaneous fat mass in growing-finishing pigs (Hu et al. 2017). This beneficial effect of Glu is achieved likely through increasing lipolysis and reducing lipogenesis in white adipose tissue, as well as stimulating the oxidation of fatty acids and glucose in skeletal muscle (Kong et al. 2015). Additionally, dietary Glu may inhibit the degradation of nutritionally essential AAs in the small intestine (Rezaei et al. 2013a). Thus, Glu can regulate energy partitioning in the body to favor white-fat reduction and lean-tissue gain. This is nutritionally and economically important, as meat production is the main goal of the swine industry.

Glu nutrition in gestating pigs

Modern high prolific sows ovulate 20–30 oocytes, but can deliver only 10–15 live-born piglets at term (Ji et al. 2017; Town et al. 2005). There is a positive relationship between uterine capacity and fetal mortality (Bazer et al. 2014). The greatest restraint on litter size in pigs is placental development and function in early gestation and uterine capacity during all periods of gestation (Bazer et al. 1988). Among domestic animals, pigs exhibit the most severe naturally occurring intrauterine growth restriction, and 76% of these compromised piglets do not survive to weaning (Wu et al. 2006). As noted previously, Glu is a major substrate for the synthesis of arginine in most mammals, including pigs. This is nutritionally and physiologically important for the following reasons. First, both polyamines and nitric oxide (products of Arg) play a key role in placental angiogenesis and growth in mammals (Wu et al. 2013). Second, dietary Arg is insufficient for maximal embryonic/fetal survival or growth in pigs (Wu et al. 2017). Third, Glu contributes an amino group for the conversion of 4-hydroxyproline (a product of collagen degradation) into glycine (a nutritionally essential amino acid for young pigs and possibly gestating dams) in the major tissues of swine (Wu 2018).

The growth of the placenta and the fetus is very rapid during the first-half and second-half of pregnancy, respectively. This requires provision of large amounts of Glu. On day 40 of gestation (term = 114 days), in fetal pig allantoic fluid, Glu (2.4 mM) is the fourth most abundant AA (Wu et al. 1996). This suggests an important role of Glu in porcine fetal growth and development. In modern pig production, maternal feed intake is restricted (e.g., 2–2.5 kg per day) to prevent the development of overweight or obesity during gestation. In gilts fed 2 kg of a corn- and soybean meal-based diet containing 12.2% CP, dietary Glu entering the portal vein can meet only 18% of its uterine uptake during the late gestation, which is associated with a high rate of low-birth-weight piglets (Wu et al. 2006). Endogenous synthesis of AAs, including Glu, may be inadequate for optimal pregnancy outcome in pigs (Ji et al. 2017; Hou et al. 2016). Of note, dietary supplementation with Gln, which is metabolized in maternal tissues and fetuses to form Glu, can alleviate uterine growth restriction in gilts and sows (Wu et al. 2011). Thus, there is a suggestion that Glu is a conditionally essential AA for gestating swine (Watford 2015).

Glu nutrition in lactating sows

A role of dietary Glu in lactation is indicated by the fact that its metabolic product, Arg, is essential to blood flow to mammary glands and milk production by lactating mammals, such as sows (Kim and Wu 2009). Work on Glu nutrition in lactating sows is very limited in the literature. Studies with sows have shown that the lactating mammary gland increases milk production as dietary CP intake is increased from 14 to 18% (Manjarin et al. 2014). The lactating sow fed a corn- and soybean meal-based diet containing 18% CP loses approximately 0.5 kg BW (80 g protein) per day between days 1 and 21 of lactation (Mateo et al. 2008), which is equivalent to 15% of dietary AA entering the portal vein (Hou et al. 2016). Thus, dietary protein intake in the current feeding program is substantially insufficient for milk protein production by prolific sows. Dietary Glu entering the portal vein can meet only 8% of Glu output in porcine milk (Hou et al. 2016). Although the lactating sow mobilizes its protein stores to provide Glu for milk production, this capacity has a physiological limit because an excessive loss of body protein is not compatible with health or survival (Wu et al. 2014). Thus, lactating sows may not be able to synthesize sufficient Glu for supporting maximal milk production. This view is supported by several lines of evidence from studies with lactating sows. First, dietary supplementation with 1% Gln (a precursor of Glu) enhances milk production by sows (Wu et al. 2011), Gln concentration in milk (Manso et al. 2012; Wu et al. 2011), as well as the growth and survival of piglets (Wu et al. 2014). Likewise, supplementing Glu plus Gln to the diet of lactating sows increased the concentrations of lipids in colostrum and mature milk (Santos de Aquino et al. 2014). Second, supplementing 1 and 2% MSG to a corn- and soybean meal-based diet (containing 18% CP) for lactating sows increased: (a) milk production, as well as the concentrations of free and peptide-bound AAs in milk; (b) growth and survival of suckling piglets; and (c) efficiency of feed utilization for lactation (Rezaei et al.

2013b). Third, compared with the control group without any supplementation, supplementing 1.15% MSG to a sorghum- and wheat-based diet (containing 23.5% CP) for lactating sows enhanced milk yield and the preweaning growth of piglets by 9% (Hewitt and van Barneveld 2012).

Safety of Glu supplementation in pigs

Dietary Glu is extensively catabolized in young, growing-finishing, gestating, and lactating pigs (Hou et al. 2016). We found that 7- to 21-day-old low-birth-weight and normal-birth-weight piglets reared by sows could well tolerate the oral administration of 2 g of Glu/kg BW/day during a 2-week experimental period (Wu G, unpublished data). Rezaei et al. (2013a) assessed the safety of Glu supplementation in pigs between 21 and 42 days of age, based on general observations (e.g., behavior, skin health, and hair), feed intake, growth, body composition, as well as hematological and blood chemistry tests. In this study, piglets were fed a typical corn- and soybean meal-based diet (containing 1.91% Glu) supplemented with 0, 0.5, 1, 2 and 4% MSG (equivalent to 0, 0.432, 0.864, 1.73 and 3.46% Glu, respectively) for 21 days. The supplemental doses of 0, 0.5, 1, 2, and 4% MSG provided pigs with 0, 175, 332, 659 and 1263 mg Glu/kg BW/day, respectively, beyond the amount of Glu in the basal diet (710–789 mg/kg BW/day) at the feed intake of 36.5–41.3 g/kg BW/day. Hematological variables at 1 and 4 h after feeding were: (a) the numbers of white blood cells, red blood cells, and platelets; (b) blood hemoglobin, blood pH, plasma protein, and fibrinogen; (c) mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume; and (d) percentages of neutrophils, lymphocytes, monocytes, and eosinophils. Serum chemistry at 1 and 4 h after feeding included the concentrations of: (a) total serum protein, albumin, and globulins; (b) total bilirubin, amino acids, glucose, urea, ammonia, creatinine, free fatty acids, triglyceride, and cholesterol; (c) sodium, chloride, calcium, phosphorus, and magnesium; (d) alkaline phosphatase, alanine transaminase, aspartate transaminase, creatine kinase, and lactate dehydrogenase. All the variables in standard hematology and clinical chemistry tests, as well as gross and microscopic structures, did not differ among all the five groups of pigs. These results indicate that dietary supplementation with up to 4% MSG is safe in post-weaning pigs, while improving their growth performance and feed efficiency.

In studies involving 10- to 20-kg (Chung and Baker 1992) and 20- to 50-kg pigs (Wang and Fuller 1989) fed purified diets containing 10% glutamic acid, no adverse effects on their growth or health were observed. Long-term supplementation with 1–4% Glu to diets for growing-finishing pigs (30–90 kg BW) was also safe (Kirchgessner et al. 1993). Likewise, no adverse effects were reported for post-weaning pigs, growing-finishing pigs, gestating sows, or lactating sows fed diets supplemented with various amounts of Glu or MSG for 14–120 days (Table 5). Based on these results, we suggest that pigs at all production stages can tolerate well dietary supplementation with at least 2% Glu without any adverse effects.

In summary, extensive research over the past 25 years has identified Glu as one of the most abundant AAs in sow's milk and swine diets. However, nearly all of the dietary Glu is catabolized by the small intestine during the first pass, and endogenous synthesis via inter-organ metabolism of AAs is crucial for maintaining Glu homeostasis in the whole body. At the cellular level, Glu is physiologically essential for the synthesis of proteins and other nitrogenous substances (including glutathione and arginine) with key metabolic functions in the body. Thus, this nutrient plays an important role in improving the health, survival, growth, development, lactation, and reproduction of swine. Compelling evidence shows that Glu is a nutritionally essential AA for weanling pigs to both maintain normal intestinal physiology and enhance efficiency in the utilization of dietary protein for gut and whole-body growth. Additionally, recent findings indicate that adequate amounts of dietary Glu are necessary to support maximum lactation and reproduction performance in pigs. Glu is truly a functional AA and a dietarily essential AA in swine nutrition. All of this new knowledge should be taken into consideration in revising the current version of NRC (2012)-recommended requirements of AAs for swine to formulate balanced diets in various phases of production. These results also have important implications for improving the nutrition of humans and other animals.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics statement This article reviews published studies and does not require either the approval of animal use or human consent.

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