Amino Acids (2013) 45:463–477
DOI 10.1007/s00726-013-1493-1

INVITED REVIEW

Glycine metabolism in animals and humans: implications for nutrition and health

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Received: 1 April 2013 / Accepted: 2 April 2013 / Published online: 25 April 2013

Abstract Glycine is a major amino acid in mammals and other animals. It is synthesized from serine, threonine, choline, and hydroxyproline via inter-organ metabolism involving primarily the liver and kidneys. Under normal feeding conditions, glycine is not adequately synthesized in birds or in other animals, particularly in a diseased state. Glycine degradation occurs through three pathways: the glycine cleavage system (GCS), serine hydroxymethyltransferase, and conversion to glyoxylate by peroxisomal D-amino acid oxidase. Among these pathways, GCS is the major enzyme to initiate glycine degradation to form ammonia and CO_2 in animals. In addition, glycine is utilized for the biosynthesis of glutathione, heme, creatine, nucleic acids, and uric acid. Furthermore, glycine is a significant component of bile acids secreted into the lumen of the small intestine that is necessary for the digestion of dietary fat and the absorption of long-chain fatty acids. Glycine plays an important role in metabolic regulation, anti-oxidative reactions, and neurological function. Thus, this nutrient has been used to: (1) prevent tissue injury; (2) enhance anti-oxidative capacity; (3) promote protein synthesis and wound healing; (4) improve immunity; and (5) treat metabolic disorders in obesity, diabetes, cardiovascular disease, ischemia-reperfusion injuries, cancers, and various inflammatory diseases. These multiple beneficial effects of glycine, coupled with its insufficient de novo synthesis, support the notion that it is a conditionally essential and also a functional amino acid for mammals (including pigs and humans).

Keywords Glycine · Synthesis · Metabolism · Function · Nutrition

Abbreviations

AGT	Alanineglyoxylate aminotransferase
GCS	Glycine cleavage enzyme system
GlyR	Glycine receptor
IL	Interleukin
IR	Ischemia-reperfusion
SHMT	Serine hydroxymethyltransferase
TDH	Threonine dehydrogenase

Introduction

There is a rich history of glycine (aminoacetic acid) research, which dates back to 1820 when it was first isolated from acid hydrolysates of protein (i.e., gelatin) by the French chemist H. Braconnot (see Meister 1965 for review). Glycine was found to be as sweet as glucose and, hence, its name was derived from the Greek word "glykys" meaning sweet. In 1838, G.J. Mulder reported that this amino acid could also be obtained from gelatin and meat using alkaline hydrolysis with potassium hydroxide. In 1845, V. Dessaignes identified glycine as a component of hippuric acid. One year later, the correct composition of glycine was determined independently by three chemists: E.N. Horsford, A. Laurent, and G.J. Mulder. The structure

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of glycine was established by A. Cahours in 1857 and it was synthesized chemically from ammonia and monochloroacetic acid in 1858.

Glycine is the simplest amino acid in nature and has no D or L chemical configuration (Wu et al. 2013). It is a major constituent in extracellular structural proteins (collagen and elastin) in animals (Wu 2009). Glycine has traditionally been classified as a "nutritionally nonessential amino acid" for mammals (including humans, pigs and rodents) due to the presence of its endogenous synthesis in the body (Darling et al. 1999; Wu 2010b). However, available evidence shows that the amount of glycine synthesized in vivo is insufficient to meet metabolic demands in these species (Jackson 1991; Melendez-Hevia et al. 2009; Rezaei et al. 2013a; Wu 2010a, b). Although mild insufficiency of glycine is not threatening for life, a chronic shortage may result in suboptimal growth, impaired immune responses, and other adverse effects on health and nutrient metabolism (de Koning et al. 2003; Lewis et al. 2005; Matilla et al. 2002). Of particular note, as for birds (e.g., chickens), dietary glycine is essential for fetal (Jackson et al. 2002) and neonatal (Wu and Knabe 1994) development, because fetuses and neonates cannot synthesize sufficient glycine to meet optimal requirements (Cetin et al. 1995; Paolini et al. 2001). Therefore, glycine should be considered as a conditionally essential amino acid for mammals to support maximum growth (Wu et al. 2013). The major objective of this article is to provide an overview of the recent advances in glycine metabolism in animals and humans, as well as its important implications for nutrition and health.

Glycine synthesis in animals and humans

Earlier nutritional and isotopic studies led to the discovery that glycine is synthesized in mammals, including pigs (Mertz et al. 1952), rats (Arnstein and Neuberger 1953), and humans (Watts and Crawhall 1959). Specifically, these investigations showed that: (1) young animals could grow even though the diet did not contain glycine and (2) ^{15}N-glycine was greatly diluted in physiological fluids (e.g., plasma) due to the formation of new unlabeled glycine in the body. In the meantime, biochemical studies with rats established that glycine could be formed from: (1) *serine* (Arnstein and Keglevic 1956; Shemin 1946) via serine hydroxymethyltransferase (SHMT) (Shemin 1950), (2) *choline* via the formation of sarcosine (Soloway and Stetten 1953) and (3) *threonine* (Chao et al. 1953) via the threonine dehydrogenase pathway (Dale 1978; Hartshorne and Greenberg 1964). Subsequent studies identified the presence of these three pathways for glycine synthesis in other animals, including pigs (Ballèvre et al. 1990; Walsh and Sallach 1966). Recent studies indicate that glyoxylate (Melendez-Hevia et al. 2009) and hydroxyproline (Wu et al. 2011a) are substrates for glycine synthesis in animals. In young adult men consuming daily 44 kcal energy and 1.5 g protein per kg body weight, the rate of whole-body glycine synthesis is 116 mg/ kg body weight/day, which is reduced in response to decreased intake of both nutritionally essential and nonessential amino acids (Yu et al. 1985). Rates of whole-body glycine synthesis are 1.99 and 1.29 g/kg BW/day, respectively, in fed young and adult rats (Arnstein and Neuberger 1953). This is consistent with a higher metabolic rate in rodents than in humans.

Synthesis of glycine from serine

SHMT catalyzes the formation of glycine from serine, which is derived from the diet or endogenous synthesis from glucose and glutamate (Fig. 1). SHMT is a pyridoxal phosphate- and tetrahydrofolate-dependent enzyme. It is present in both the cytoplasm and mitochondria in mammalian cells. The mitochondrial SHMT (mSHMT or SHMT2) appears to be ubiquitous and responsible for the bulk of glycine synthesis in most cell types, whereas the cytosolic SHMT (cSHMT or SHMT1) occurs primarily in the liver and kidneys and is less active in catalyzing the conversion of serine to glycine than SHMT2 (Girgis et al. 1998; Narkewicz et al. 1996; Stover et al. 1997). SHMT1 and SHMT2 are encoded by distinct genes. Emerging evidence shows that mSHMT, rather than cSHMT, is a major source of tetrahydrofolate-activated C_1 units in hepatocytes (MacFarlane et al. 2008). In the reaction catalyzed by SHMT, a C_1 unit is transferred from C-3 of serine to tetrahydrofolate, yielding glycine and N^5-N^{10}-methylene tetrahydrofolate (Stover et al. 1997). The latter is a source of the methyl group for some methylation reactions (Mudd et al. 2001). Specifically, N^5-N^{10}-methylene tetrahydrofolate is used by: (1) N^5-N^{10}-methylene tetrahydrofolate reductase to generate N^5-methyl-tetrahydrofolate; (2) N^5-N^{10}-methylene tetrahydrofolate dehydrogenase to generate N^5-N^{10}-methylene-tetrahydrofolate; (3) by thymidylate synthase to form 2′-deoxythymidylate (Melendez-Hevia et al. 2009; Wang et al. 2012). All of these reactions result in the regeneration of tetrahydrofolate to ensure its availability for the formation of glycine from serine. Note that there are tissue, species, and development-related differences in SHMT expression among animals (Lewis et al. 2005).

Synthesis of glycine from threonine

In some biochemistry textbooks, it is stated that threonine is degraded by SHMT to produce glycine and acetaldehyde (Rawn 1989; Lehninger et al. 1993) and that SHMT and threonine aldolase are identical (Schirch and Gross 1968).

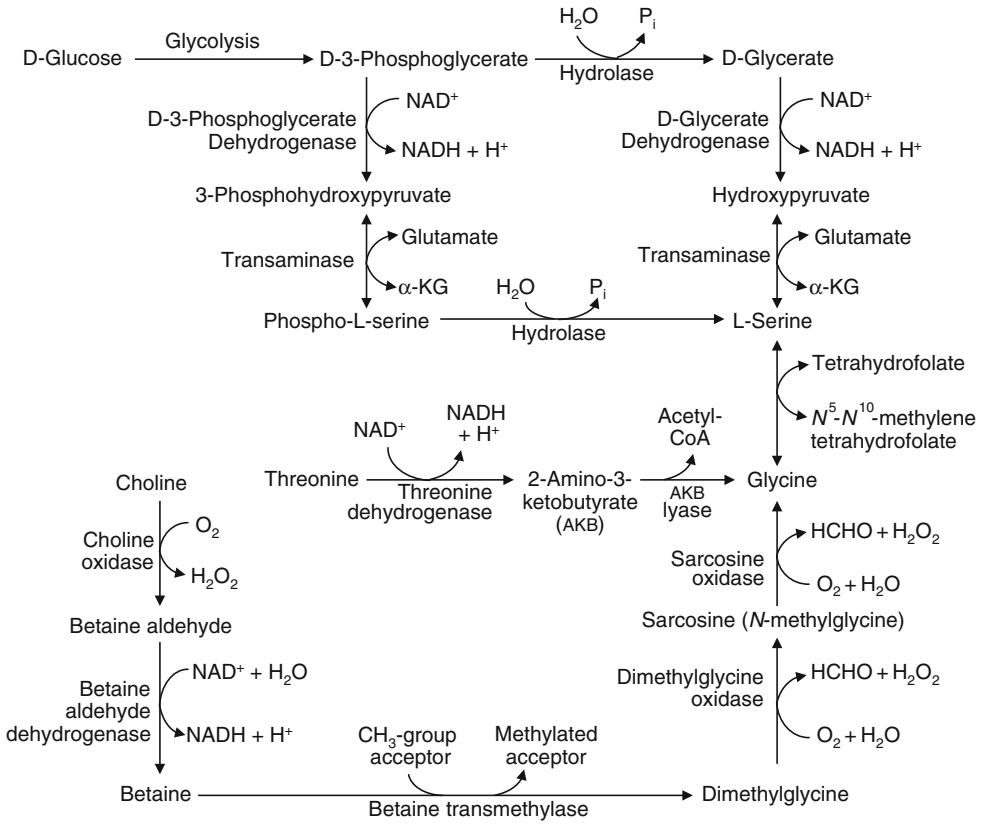

Fig. 1 Synthesis of glycine from glucose and glutamate, serine, choline, and threonine in animals. The quantitative importance of glycine synthesis from these substrates may depend on species, developmental stage, and their dietary availability. *α-KG* α-Ketoglutarate

However, it has recently been clarified that although SHMT from the liver of some animals has a low activity of threonine aldolase, the two enzymes are distinct in terms of both biochemical and immunochemical properties (Ogawa et al. 2000; Yeung 1986). In rats, pigs, cats, and chickens, threonine dehydrogenase is the major enzyme for initiating ~80 % threonine degradation (Ballèvre et al. 1990; Bird and Nunn 1983; Davis and Austic 1994; Hammer et al. 1996; House et al. 2001), with glycine as a co-product (Fig. 1). However, there are reports that threonine dehydrogenase is responsible for only 7–11 % of threonine degradation in adult humans (Darling et al. 2000) and that virtually no threonine is converted to glycine in full-term infants (Parimi et al. 2005). Moreover, threonine is only a minor source of glycine in milk-fed piglets and in post-weaning pigs fed a conventional corn- and soy-bean meal-based diet (Wu et al. 2010) due to the limited supply of threonine from the diets. Clearly, the quantitative importance of glycine synthesis from threonine may depend on species, developmental stage, and dietary availability. When dietary intake of threonine is limited, this amino acid is not a significant source of glycine in the body (Le Floc'h et al. 1995; Wu et al. 2010).

Synthesis of glycine from choline

In adult rats, ~40–45 % of the ingested choline can be metabolized to form glycine and the value can increase up to 70 % when dietary level of choline is low (Soloway and Stetten 1953). The oxidative degradation of choline to glycine provides methyl groups in mammalian tissues (Wu et al. 2013). After the conversion of choline to betaine by choline dehydrogenase and betaine aldehyde dehydrogenase (Zhang et al. 1992), the three methyl groups of choline can be made available for converting: (1) homocysteine into methionine using betaine as the methyl donor by betaine-homocysteine methyltransferase (Finkelstein et al. 1982), while generating dimethylglycine, (2) dimethylglycine into sarcosine (*N*-methylglycine) by dimethylglycine dehydrogenase, and (3) sarcosine into glycine by sarcosine dehydrogenase (Porter et al. 1985). The last two enzymes are mitochondrial flavoenzymes with widespread distribution [e.g., in the liver, lung, pancreas, kidneys, thymus, and oviduct (Bergeron et al. 1998)]. Sarcosine and glycine are interconvertible through transmethylation (Fig. 1). In this glycine–sarcosine cycle, sarcosine dehydrogenase plays a key role in regulating the ratio of S-adenosylmethionine to S-adenosylhomocysteine. Thus, the ratio of

S-adenosylmethionine to S-adenosylhomocysteine is considered to affect reactions involving methyl transfer in cells (Yeo and Wagner 1994). It should be borne in mind that because the content of choline in diets is relatively low (usually < 0.1 % on an as-fed basis), its contribution to glycine synthesis is quantitatively low in animals.

Glycine synthesis from glyoxylate

Glyoxylate is an additional source of glycine through transamination primarily utilizing alanine as the donor of the amino group (Fig. 2). Alanine:glyoxylate aminotransferase (AGT) is quantitatively the most important enzyme responsible for the nearly irreversible transfer of the amino group from alanine to glyoxylate, yielding glycine and pyruvate (Thompson and Richardson 1967). There are two isozymes of AGT in mammals, designated as AGT1 and AGT2 (Noguchi et al. 1978). They are different proteins based on their different biochemical properties (e.g., molecular weight, isoelectric point, structure, immunological characteristics and kinetics), but have the same ability to catalyze the production of glycine from glyoxylate (Lee et al. 1995).

Hepatic levels of the AGT1 protein are relatively high in primates (humans, baboons, and marmosets), carnivores (cats and dogs), and lagomorphs (rabbits), but very low in rodents (rats, mice, hamsters, and guinea pigs), pigs, cattle, and sheep (Danpure et al. 1990; Takada and Noguchi 1982). The intracellular distribution of AGT1 is dependent upon animal species. For example, based on subcellular fractionation and immunocytochemical techniques, hepatic AGT1 has been reported to be present entirely in peroxisomes in humans, rabbits, and guinea pigs but exclusively in mitochondria in carnivores (e.g., cats and dogs) (Danpure et al. 1989, 1990). Interestingly, hepatic AGT1 is localized in both peroxisomes and mitochondria in several rodents (e.g., rats, mice, and hamsters) (Danpure 1997; Danpure et al. 1990; Takada and Noguchi 1982). Of particular note, AGT1 is a dual-functional enzyme (also known as serine-pyruvate transaminase/AGT), allowing for its metabolic roles in both glyoxylate detoxification and gluconeogenesis (Xue et al. 1999). In humans, mutations that result in the mistargeting of the human AGXT1 protein from peroxisomes to mitochondria cause primary hyperoxaluria type 1, an autosomal recessive disorder of oxalate metabolism (Danpure et al. 1989). This disease is characterized by increased oxalate production from glyoxylate, reduced conversion of glyoxylate to glycine, elevated levels of alanine, and hyperoxaluria (Danpure and Jennings 1986; Danpure et al. 1989). Emerging evidence shows that the two homologues of the mitochondrial AGT1, alanine transaminase and phosphoserine aminotransferase can transaminate glyoxylate to glycine with a relatively high efficiency, using L-glutamate and L-alanine as the amino-group donor (Donini et al. 2009).

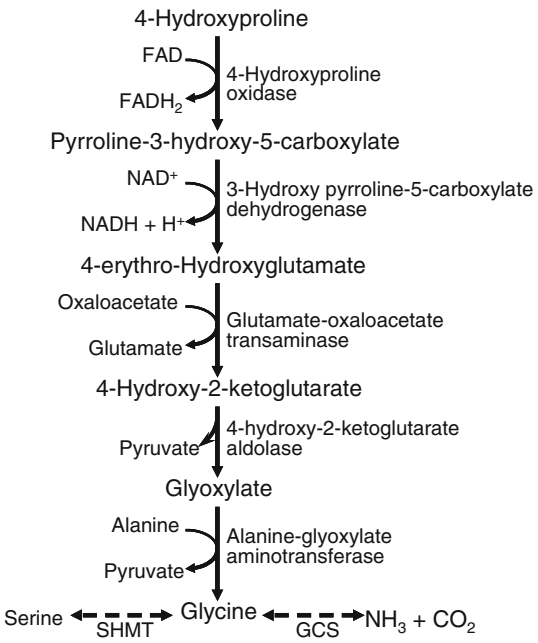

Fig. 2 Synthesis of glycine from 4-hydroxyproline in the kidneys of piglets. All the enzymes required for glycine synthesis from Hyp are present in the kidneys. Glycine may be converted into serine by SHMT or degraded to NH_3 and CO_2 by GCS, with the regeneration of tetrahydrofolate, an essential cofactor for SHMT. Thus, GCS is coupled with SHMT for glycine catabolism. The GCS enzyme favors glycine oxidation (Lowry et al. 1985b), but not glycine synthesis from ammonia plus CO_2 (Lowry et al. 1985a)

AGT2, a mitochondrial enzyme (Takada and Noguchi 1982), is the major isoform of the hepatic AGT in rodents (rats, mice, hamsters, and guinea pigs), pigs, cattle, and sheep, and is found primarily in the kidneys of animals (Danpure 1997). AGT2 is expressed at high levels in the liver and kidneys of rats, pigs and sheep, but plays a minor role in glyoxylate metabolism in carnivores (Noguchi and Takada 1979; Noguchi et al. 1978). AGT2 is virtually absent from the human liver (Danpure 1997), but is likely expressed at a relatively high level in the human kidneys. Interestingly, recent studies indicate that AGT2 can metabolize asymmetric dimethylarginine via transamination to α-keto-δ-(*N*,*N*-dimethylguanidino)valeric acid (Rodionov et al. 2010), thereby linking glycine with the metabolism of methylarginines (inhibitors of nitric oxide synthesis) in cells.

Glyoxylate can be produced through three pathways: (1) oxidation of glycolate by peroxisomal glycolate oxidase; (2) deamination of glycine by peroxisomal D-amino acid oxidase; and (3) metabolism of hydroxyproline in mitochondria with 4-hydroxy-2-ketoglutarate as an intermediate (Holmes and Assimos 1998). Humans and other animals (e.g., cattle, chickens, rats, sheep, and swine) normally have negligible dietary intake of glycolate, which is a

metabolite in higher plants and the green algae at the content of < 1 mg/kg fresh weight (Sarkar and Choudhuri 1981). Likewise, the formation of glyoxylate from glycine via peroxisomal D-amino acid oxidase does not result in a net synthesis of glycine. Thus, hydroxyproline is the main source of glyoxylate in carnivores, and it accounts for 11.5 % of amino acids in collagen of all animals (Neuman and Logan 1950). Note that collagen represents ~30 % of total protein in the body (Wu et al. 2011a, b). Interestingly, there is a suggestion that hydroxyproline is a source of glycine in animals (Lowry et al. 1985a; Ruiz-Torres and Kurten 1976).

Quantitative analysis of glycine synthesis

Let us use the swine as an animal model to do quantitative analysis of glycine synthesis in the whole body. Glycine is the most abundant amino acid in the plasma of postnatal pigs (0.9–1.2 mM) (Flynn et al. 2000; Wu et al. 1994). This is in striking contrast to all other studied mammals whose plasma contains 0.2–0.3 mM glycine (Lowry et al. 1985a). Paradoxically, we (Wu and Knabe 1994) and others (Davis et al. 1994) reported a relatively low concentration of glycine in sow's milk. Based on glycine content in whole milk and metabolic requirements for glycine by piglets, we estimated that the intake of glycine from sow's milk provides at most only 20 % of the glycine required by the 7-day-old pig (Table 1). Thus, 80 % of the glycine needed by the neonate must be provided through endogenous synthesis, and this synthetic pathway must be very active in young pigs. For example, the rate of whole-body glycine synthesis must be at least 0.71 g/kg BW/day in 14-day-old pigs to meet their metabolic needs (Wu et al. 2010).Likewise, in the 30-day-old postweaning pig (7.8 kg body weight) fed a typical corn- and soybean meal-based diet, at least 54 % of the glycine needed for tissue protein synthesis must be derived from endogenous synthesis (Wu 2010b).

Table 1 Relative contributions of milk versus endogenous synthesis to meet glycine requirement of piglets

	Amounts of glycine (mg/kg BW/day)
Glycine provision from sow's milk	311
Milk intake (0.78 L/day; 1.12 g/L of whole milk)[a]	349
Undigestible glycine in sow's milk (11 %)[b]	38
Glycine requirements for growth and metabolic function	≥1,515
Body weight gain (200 g/day; 27.2 g protein)[a]	1,216
Glycine oxidation to urea and carbon dioxide[c]	96
Glycine utilization for creatine synthesis[d]	46
Glycine utilization for purine synthesis[e]	112
Glycine utilization for conjugation of bile acid[f]	16
Glycine utilization for hepatic glutathione synthesis[g]	13
Glycine utilization for hippuric acid production[h]	11
Glycine utilization for heme synthesis[i]	5
Glycine needed from endogenous synthesis	≥1,204

[a] Wu et al. (2004a)

[b] Mavromichalis et al. (2001)

[c] Rivera-Ferre et al. (2006)

[d] Brosnan et al. (2009)

[e] Hellwing et al. (2007)

[f] Harada et al. (1988), Hafkenscheid and Hectors (1975)

[g] Reeds et al. (1997)

[h] Kristensen et al. (2009)

[i] Matrone et al. (1960)

Published results indicate that: (1) glycine synthesis from choline plus threonine contributes ≤6 % of glycine needed by the young pig, and (2) production of glycine from dietary serine represents ≤7 % of total glycine synthesis (Table 2). At this time, substrates for ≥88 % of the endogenous synthesis of glycine in milk-fed pigs are unknown (Table 2). Of particular interest, Lowry et al. (1985a) reported that the perfused rat kidney converted 4-hydroxyproline (a product of collagen degradation) to glycine via 4-hydroxyproline oxidase, but the contribution of 4-hydroxyproline to whole-body glycine synthesis has not been studied in any animal species. This potentially is a novel pathway for glycine synthesis (Fig. 2), which has not been described in any biochemistry or nutrition textbooks (Lewis 2001; Newsholme and Leech 2010), may be quantitatively important in young pigs. Experimental data are required to test this hypothesis.

Glycine degradation in animals and humans

A substantial amount of glycine is catabolized in the small intestine (Wu et al. 2010). For example, ~30 % of dietary glycine is degraded by the small intestine of young pigs during the first pass into the portal vein. The major responsible cell types are likely various strains of bacteria in the intestinal lumen (Dai et al. 2010, 2011, 2012). Catabolism of glycine occurs in animals through three pathways: (1) decarboxylation and deamination by glycine the cleavage enzyme system (GCS), (2) conversion into serine by SHMT, and (3) conversion into glyoxylate by D-amino acid oxidase. D-amino acid oxidase in the liver and kidneys has a relatively low affinity for glycine, and oxidation to glyoxylate plays an insignificant role in glycine degradation (Thureen et al. 1995). When ^{15}N-glycine was

Table 2 Endogenous synthesis of glycine in young pigs

Substrate	Glycine synthesis (mg/kg BW/day)
Total synthesis of glycine	≥1,204
Dietary serine[a]	81
Choline (via sarcosine)[b]	36
Threonine (via threonine dehydrogenase)[c]	33
Unknown substrates	≥1,054

[a] Wu et al. (2010)

[b] Based on concentrations of choline in sow's milk (3.12 mmol/L; Donovan et al. 1997)

[c] Average of the values of 43 and 22 mg/kg BW/day reported by Ballèvre et al. (1991) and Le Floc'h et al. (1995), respectively. This value (33 mg/kg BW/day) is similar to the value of 31 mg/kg BW/day based on the availability of dietary threonine for catabolism in the piglet (Wu et al. 2010)

orally administered into young adult men, the ^{15}N enrichments relative to ^{15}N-glycine in plasma were as follows: serine, 54 %; urea, 20 %; glutamine/glutamate amino-N, 15 %; alanine, 7 %; leucine, isoleucine, valine, ornithine, proline, and methionine, 3–8 % (Matthews et al. 1981). Thus, rapid interconversion of glycine and serine occurs in man, and the ^{15}N from these two amino acids actively participates in transamination reactions via the formation of glutamate. Similar results have been reported for adult rats (Schadereit et al. 1986).

The glycine cleavage system

The mitochondrial GCS is widely distributed in the animal kingdom and is the major enzyme responsible for glycine degradation in the body (dos Santos et al. 2001; Kikuchi et al. 2008; Lowry et al. 1985b). Interestingly, this enzyme complex has been reported to be absent from neurons (Sato et al. 1991). The GCS requires tetrahydrofolate/N^5,N^{10}-methylene tetrahydrofolate and catalyzes the reversible interconversion of glycine into serine (Fig. 1). The physiological significance of the GCS in glycine catabolism is epitomized by its defect in humans, leading to extremely high levels of glycine in plasma and neurological disorders referred to as glycine encephalopathy (also known as nonketotic hyperglycinemia) (Conter et al. 2006). This is the second most common inborn error of amino acid metabolism after phenylketonuria.

The GCS is a complex enzyme system composed of three proteins and one carrier protein (Kikuchi et al. 2008): (1) a pyridoxal phosphate-containing protein or glycine decarboxylase (P protein); (2) aminomethyltransferase (T protein); (3) dihydrolipoamide dehydrogenase (L protein); and (4) the hydrogen carrier protein or a lipoic acid-containing protein (H protein) (Fig. 3). The GCS catalyzes a completely reversible reaction, with its first step being the decarboxylation of glycine by P protein that uses H protein as a co-substrate. Then, the aminomethyl moiety bounded to the lipoic acid of H protein acts as an intermediate that is degraded to methylene tetrahydrofolate and ammonia through the catalysis of T protein, while generating a dithiol form of the H protein. At the last step, the dithiol form of the H protein is disulfurated by the catalysis of L protein with NAD^+ as a co-substrate (Fig. 3). Glucagon, high protein diets, and metabolic acidosis increase hepatic GCS activity and glycine degradation in mammals (Jois et al. 1989; Lowry et al. 1985b). In contrast, in humans, elevated levels of fatty acids in plasma inhibit the rate of glycine appearance (owing to whole-body protein degradation and de novo synthesis) and does to appear to affect oxidation of glycine to CO_2 (Dasarathy et al. 2009).

Metabolism through the formation of serine by SHMT

As noted previously, SHMT catalyzes the reversible action of serine formation from glycine and a one-carbon unit donated by N^5-N^{10}-methylene tetrahydrofolate. Nearly 50 % of the N^5-N^{10}-methylene tetrahydrofolate generated by the GCS contributes to serine formation from glycine (Lamers et al. 2007). Approximately, 30 and 50 % of the extracellular glycine is directed to serine biosynthesis in primary cultures of ovine fetal hepatocytes and mid-gestation fetal hepatocytes, respectively, with net utilization of glycine for serine production (Narkewicz et al. 1996; Thureen et al. 1995). Similar results have been reported for the rat kidneys (Lowry et al. 1985b). Interestingly, in adult rats, circulating levels of serine do not appear to exhibit a dose-dependent increase in response to glycine supplementation (Shoham et al. 2001). Similar results were found for pigs (Fig. 4). Given a much larger metabolic pool of glycine than serine in the body, the moderate increase in plasma serine concentrations despite a two to threefold elevation in glycine suggests that conversion of glycine to serine may not be a major pathway for glycine utilization in these animals.

Multiple pathways compete for glycine, providing a complex picture of its utilization via inter-organ coordination (Wu et al. 2013). In humans, serine biosynthesis through SHMT accounts for 41 % of whole-body glycine flux (Lamers et al. 2007). It should be borne in mind that glycine can be either converted into serine by SHMT or degraded to NH_3 and CO_2 by the GCS, with the regeneration of tetrahydrofolate, an essential cofactor for SHMT. Thus, GCS is coupled with SHMT for glycine catabolism (Fig. 5). Based on intracellular concentrations of substrates and products, and its enzyme kinetics, the GCS favors glycine oxidation rather than glycine synthesis from ammonia plus CO_2 (Kikuchi et al. 2008; Lowry et al. 1985a, b). Thus,

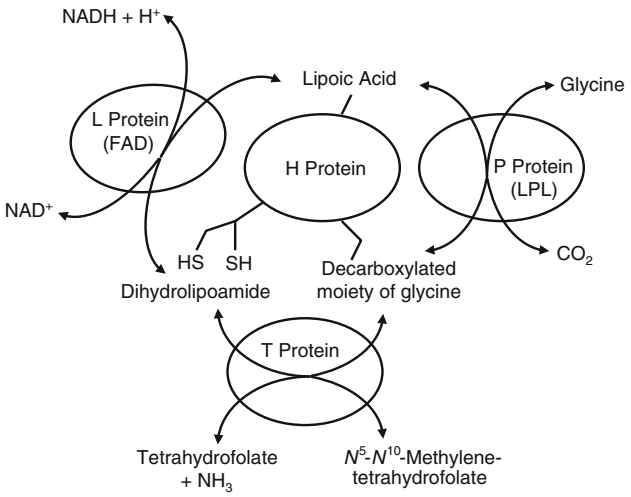

Fig. 3 Sequential reactions of enzymes in the glycine cleavage system in animal cells. First, glycine dehydrogenase (*P protein*) catalyzes glycine decarboxylation in the presence of a lipoic acid-binding protein (*H protein*). Second, the decarboxylated moiety of glycine is deaminated by a tetrahydrofolate-dependent enzyme (aminomethyltransferase; *T protein*), with the production of dihydrolipoamide. Third, dihydrolipoamide is reduced by an NAD^+-dependent and FAD-requiring dihydrolipoamide dehydrogenase (*L protein*), which is the common E3 protein component of the α-ketoacid dehydrogenase complex. Adapted from Wu et al. (2013)

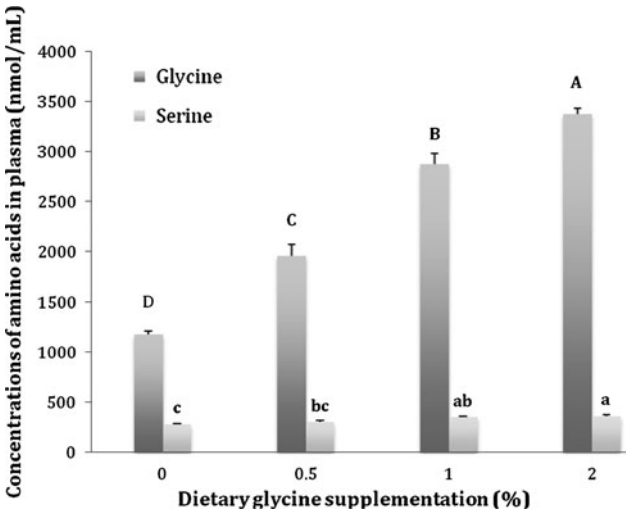

Fig. 4 Concentrations of glycine and serine in the plasma of growing pigs. Values are mean ± SEM, $n = 6$. Pigs were weaned at 21 days of age to a corn- and soy-bean meal-based diet (Wu et al. 1996) containing 0.88 % glycine and 0.79 % serine (Li et al. 2011), and then received dietary supplementation with 0, 0.5, 1 or 2 % glycine for 21 days. During the 21-day trial, food intake did not differ ($P > 0.05$) among the three groups of pigs and was 51 ± 2 g/kg BW/day (mean ± SEM, $n = 18$). At 42 days of age, blood samples were obtained from the jugular vein at 1.5 h after feeding for analysis of amino acids in plasma (Yao et al. 2012). Results were analyzed by one-way analysis of variance and the Student-Newman–Keuls multiple comparison (Wei et al. 2012). *A–D* For glycine concentrations, means with different superscript letters differ ($P < 0.05$). *a–c* For serine concentrations, means with different superscript letters differ ($P < 0.05$)

direct synthesis of glycine from NH_4^+, CO_2, N^5-N^{10}-methylene tetrahydrofolate and NADH is insignificant in animals (Meister 1965).

Physiological functions of glycine

Glycine has crucial roles in nutrition and metabolism (Table 3). First, glycine represents 11.5 % of total amino acids and 20 % of amino acid nitrogen in body proteins (Wu et al. 2010). Protein synthesis accounts for 80 % of whole-body glycine needs by growing animals [e.g., piglets (Table 1)]. In collagen (a fibrous structural protein), glycine is required at every third position so that the assembly of the triple helix of the protein has the glycine residue at the interior of the helix, where there is no space for a larger side group than the glycine's single hydrogen atom in the side chain. Within enzymes, glycine provides flexibility for their active sites (Yan and Sun 1997). Second, there are multiple pathways for glycine utilization to generate glutathione, creatine, purines (RNA and DNA), heme (hemoglobins), and serine (Hall 1998). Creatine participates in muscle and nerve energy metabolism, whereas glutathione is the most abundant low-molecular-weight thiol (0.5–10 mM) and the major anti-oxidant in cells (Wu et al. 2004b). In addition, DNA synthesis and, therefore, protein synthesis and cell proliferation depend on purines, whereas heme-containing proteins are crucial for oxygen

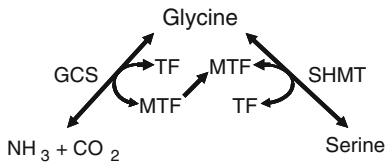

Fig. 5 The coupling of the GCS with SHMT for glycine catabolism in animals. *GCS* glycine cleavage system, *MTF* N^5-N^{10}-Methylene tetrahydrofolate, *SHMT* serine hydroxymethyltransferase, *TF* Tetrahydrofolate

transport and the mitochondrial electron transport system (Dai et al. 2013).

Third, glycine is the major amino acid for the conjugation of bile acids in mammals (e.g., pigs and humans), thereby playing a key role in the digestion and absorption of lipids and lipid-soluble vitamins (Hafkenscheid and Hectors 1975). Fourth, through glycine-gated chloride channels in leukocytes and macrophages, glycine modulates intracellular Ca^{2+} levels, thereby regulating the production of cytokines, generation of superoxide, and immune function (Zhong et al. 2003). Fourth, glycine is a neurotransmitter in the central nervous system, thereby regulating behavior, food intake, and whole-body homeostasis (Rajendra et al. 1997). Collectively, glycine plays an

important role in metabolism, growth, development, immunity, cytoprotection, and survival of animals and humans.

Amelioration of metabolic syndrome in obesity and diabetes

Obesity is one of the most severe public health problems in the twenty first century, with increasing prevalence in both adults and children (Barness et al. 2007; Wu et al. 2012). This metabolic disorder increases the risk for type II diabetes and premature death (Trujillo and Scherer 2006). Several cardiovascular studies have reported that the regional accumulation of body fats is a significant risk factor for cardiovascular diseases, and intra-abdominal fat obesity has a much closer association with disorders of glucose and lipid metabolism than subcutaneous fat obesity (Despres et al. 1990). Interestingly, concentrations of glycine in plasma are reduced in obese and diabetic subjects (Felig et al. 1969; Satterfield et al. 2012; Wijekoon et al. 2004). Growing evidence shows that glycine supplementation may be a novel therapy for obesity and type II diabetes. Specifically, dietary supplementation with glycine decreases concentrations of free fatty acids and triglycerides, as well as adipocyte size and adiposity in an animal model of intra-abdominal obesity (Alvarado-Vasquez et al. 2003; El Hafidi et al. 2004), while inhibiting nonenzymatic glycation of lens proteins and hemoglobin in diabetic rats (Alvarado-Vasquez et al. 2003; Ramakrishnan and Sulochana 1993) and in type-2 diabetic patients (Carvajal Sandoval et al. 1999) and in type-1 diabetic rats (Bahmani et al. 2012). The beneficial effects of glycine in obesity and type 2 diabetes therapy can result from: (1) improved insulin sensitivity (Gannon et al. 2002), (2) increased anti-oxidative and anti-inflammatory capacity (Cruz et al. 2008; Garcia-Macedo et al. 2008; Sekhar et al. 2011), and (3) normalization of secretion of triglyceride-rich very low-density lipoproteins from the liver by triggering neuronal transmission in the dorsal vagal complex through the *N*-methyl-D-aspartate receptor (Yue et al. 2012).

Cytoprotection

Ischemia-reperfusion (IR) injury refers to cellular damage induced reperfusion of previously viable ischemic tissues and often occurs in surgeries, such as organ transplantation, resection, cardiopulmonary bypass, sepsis, and renal artery angioplasty (Collard and Gelman 2001). Most recently, glycine has been shown to protect cells from IR injury in various organs, including the liver, kidney, lung, intestine and skeletal muscle. For example, glycine minimizes reperfusion injury in a rat model of low-flow and reflow liver perfusion (Zhong et al. 1996). In addition, during the harvest of an organ and after liver transplantation, intravenous administration of glycine can blunt liver necrosis induced by reperfusion and prevent disturbances to the

Table 3 Physiological functions of glycine in animals and humans

	Direct action of glycine or the functions of its metabolites
Direct action of glycine	Protein synthesis (particularly accounting for 1/3 of amino acids in collagen and elastin); inhibition of calcium influx through activation of the glycine-gated channel in the cell membrane; inhibitory neurotransmitter in the central nervous system; co-agonist with glutamate for *N*-methyl-D-aspartate receptor receptors; anti-oxidant; anti-inflammation; one-carbon-unit metabolism; conjugation with bile acids
Function of glycine metabolites Serine	Protein synthesis, one-carbon-unit metabolism, and gluconeogenesis; conversion into choline via a series of reactions requiring methionine; conversion into ethanolamine through formation of phosphatidylserine; synthesis of D-serine (a neurotransmitter) in the brain
Porphyrins and heme	Hemoproteins (e.g., hemoglobin, myoglobin, catalase, and cytochrome c); production of carbon monoxide (a signaling molecule); storage of iron in the body
Bilirubin	Natural ligand of aryl hydrocarbon receptor in the cytoplasm
Creatine[a]	Antioxidant; anti-viral; anti-tumor; energy metabolism in heart, skeletal muscle, and brain; neurological and muscular development and function
Glutathione[b]	Free radical scavenger; anti-oxidant; cell metabolism (e.g., formation of leukotrienes, mercapturate, glutathionylspermidine, glutathione-nitric oxide adduct and glutathionylproteins); signal transduction; regulation of gene expression; apoptosis; cellular redox; immune response
Nucleic acids[c]	Coding for genetic information; gene expression; cell cycle and function; protein and uric acid synthesis; lymphocyte proliferation; facilitation of wound healing
Uric acid	Antioxidant; the major end product of amino acid oxidation in avian species

Adapted from Wu et al. (2013)

[a] Requiring arginine, methionine, and glycine as substrates

[b] Requiring cysteine, glutamate, and glycine as substrates

[c] Requiring glutamine, aspartate, and glycine as substrates

hepatic microcirculation (Schemmer et al. 1999). Glycine can also ameliorate hepatic IR injury after partial hepatectomy and improve the regeneration of the remnant liver (Ito et al. 2008). When rats are subjected to a brief period of renal ischemia (15 min), dietary supplementation of glycine can improve glomerular filtration rate, alleviate tubular injury, and reduce free radical production (Yin et al. 2002). However, glycine is not effective in attenuating severe renal injury induced by a longer period of ischemia (Yin et al. 2002). In addition, glycine preconditioning can protect mitochondrial viability during pulmonary IR injury (Sommer et al. 2012) and intestinal hemorrhages (Petrat et al. 2011), and normalize arterial blood pressure during IR injury to the small intestine (Petrat et al. 2011). Furthermore, in a canine model of IR injury, perfusion (15 min) with 2.2 % glycine can preserve skeletal muscle function, while decreasing edema and muscle necrosis (Ascher et al. 2001).

The cytoprotective effect of glycine is also associated with reduced apoptosis in a variety of organs. In particular, glycine prevents apoptosis of endothelial cells induced by the lack of vascular endothelial growth factor (Zhang et al. 2000) through: (1) down-regulating expression of pro-apoptotic proteins (Bax and caspase-3) and up-regulating expression of anti-apoptotic protein (Bcl-2) in mesenteric IR injury (Jacob et al. 2003), (2) attenuating the increase of nuclear factor-κB phosphorylation (Pal et al. 2012), and (3) blocking the opening of a permeability death "channel" on the cell membrane (Estacion et al. 2003). These mechanisms may explain, in part, the observation that glycine inhibits pathological angiogenesis associated with tumor growth in rodent models of carcinogenesis (Amin et al. 2003). Thus, glycine may be a useful nutrient for chemoprevention, the treatment of carcinoma (Yamashina et al. 2007) and atherosclerosis (McCarty et al. 2009), and improvement of embryonic survival (Gao et al. 2009; Guay et al. 2002).

Experimental evidence supports a role for glycine in improving cardiovascular function, particularly, in offspring who have experienced malnutrition in utero. During pregnancy, de novo synthesis of glycine is inadequate to meet its requirement for fetal growth and development (Jackson et al. 1997). Epidemiological evidence shows a close association between small size at birth and a higher risk of developing cardiovascular diseases, especially hypertension, during adult life (Huxley et al. 2000). Animal studies indicate that maternal low-protein diets during gestation result in abnormal cardiovascular development and hypertension in offspring, and these problems can be prevented by supplementing glycine to their postnatal diets (Brawley et al. 2004; Jackson et al. 2002). Glycine may act by: (1) activating the glycine-gated chloride channel [also known as glycine receptor (Pfeiffer and Betz 1981)], suppressing the agonist-induced opening of L-type voltage-dependent calcium channels to attenuate Ca^{2+} influx and its intracellular concentrations in endothelial cells (Yamashina et al. 2001); (2) enhancing the availability of nitric oxide in the vasculature by reducing its oxidation in a glutathione-dependent mechanism (Wu and Meininger 2002); (3) stimulating the *N*-methyl-D-aspartate receptor, leading to nitric oxide-dependent vasodilatation (Slomowitz et al. 2004); and (4) augmenting glutathione synthesis in cells (Wu et al. 2004b).

Anti-inflammatory responses

Glycine has been proposed to be an anti-inflammatory and immunomodulatory agent (Wheeler et al. 1999; Zhong et al. 2003) and to affect the sensitivity of tumor cells to methotrexate, an inhibitor of dihydrofolate reductase (Vazquez et al. 2013). Thus, it has been used as a therapeutic nutrient to treat many different kinds of inflammation-associated diseases, such as hemorrhagic (Ikejima et al. 1996) and endotoxic shock (Zhong et al. 1999), alcoholic liver disease (Yamashina et al. 2005), gastric ulcer (Tariq and Al Moutaery 1997), arthritis (Li et al. 2001), and melanoma tumors (Rose et al. 1999b). Available evidence shows that dietary supplementation with glycine reduces inflammatory reactions, morbidity, and mortality in pathogen-infected animals (Li et al. 2007). The underlying mechanisms are multiple and synergistic, and mainly involve: (1) activation of the glycine receptor (i.e., the glycine-gated chloride channel) in leukocytes and (2) suppression of activation of a variety of immunocytes, including macrophages and monocytes (Li et al. 2007).

The glycine receptor occurs in wide varieties of cells and is comprised of three distinct subunits: (1) α (48 kDa), a ligand binding subunit; (2) β (58 kDa), a structural subunit; and (3) gephyrin (93 kDa), a cytoplasmic anchoring protein (Pfeiffer and Betz 1981; Rajendra et al. 1997). Taurine and β-alanine can also activate the glycine receptor, but have a much lower effect than glycine (Rajendra et al. 1995). As alluded to previously, glycine induces an influx of chloride into cells and, therefore, hyperpolarization on the plasma membrane, leading to reduced entry of calcium into cells (McCarty et al. 2009). An inhibitor of the glycine receptor, strychnine, reverses these effects of glycine (Ikejima et al. 1997). There is also evidence that glycine inhibits the production of proinflammatory cytokines [e.g., tumor necrosis factor-α, interleukin-1β (IL-1β) and IL-6, and enhances IL-10 (an anti-inflammatory cytokine)] by activated macrophages and other leukocytes (Spittler et al. 1999), as well as pathological proliferation of T-lymphocytes (Stachlewitz et al. 2000). Furthermore, glycine can exert anti-inflammatory effects during endothelial inflammation through inhibiting

activation of nuclear factor-κB, degradation of inhibitor κBα, expression of E-selectin, and production of IL-6 (Hasegawa et al. 2012).

The basic research on glycine to enhance the anti-inflammatory capacity of cells has been translated into nutritional practices involving animal models. First, dietary supplementation with 0.5 % glycine is now commonly used to: (1) prevent the infiltration of inflammatory cells, edema, synovial hyperplasia in joints, injuries in experimental arthritis, and lung inflammation in rats (Li et al. 2001; Wheeler et al. 2000) and (2) inhibit tumor growth in rodents (Amin et al. 2003; Rose et al. 1999a, 1999b). Second, dietary glycine protects the intestine against the harmful effects of radiotherapy in cancer treatment. For example, supplementation of glycine at a dose of 0.65 g/kg per day for 14 days has a superior protective effect on the irradiated colon wall in rats exposed to abdominal irradiation (de Aguiar Picanco et al. 2011). Third, glycine supplementation mitigates the adverse effects of some agents (e.g., lipopolysaccharide, peptidoglycan polysaccharide, and peroxisome proliferators) on enhanced secretion of cytokines, activation of proteases, and increased apoptosis in various animal models (Rose et al. 1999a; Spittler et al. 1999; Li et al. 2001). Although it is convenient to use glycine as an isonitrogenous control in nutritional experiments because of its relatively high content of nitrogen, this practice is undesirable and inappropriate.

Animal growth and development

Birds (e.g., chickens) actively produce uric acid via a glycine-dependent pathway and cannot synthesize sufficient glycine to meet metabolic needs (Baker 2009). Therefore, glycine must be included in diets to support maximum growth and development of avian species. Dietary glycine content for maximum growth and feed conversion efficiency in 7- to 20-day-old broilers has been reported to be approximately 1.0 % (Corzo et al. 2004). In contrast, glycine was previously thought to be a nutritionally nonessential amino acid for mammals, including humans and pigs (see Wu 2010a, b for review). However, based on the dietary intake of glycine and the need of glycine for tissue protein synthesis, Wu (2010a, b) has proposed that glycine is a nutritionally essential amino acid for sow-reared piglets and postweaning pigs that *normally* do not synthesize sufficient glycine under conventional feeding conditions. In support of this view, Powell et al. (2011) found that the rate of glycine synthesis in 20–50 kg pigs fed a low-protein diet (a 5 % unit reduction in crude protein content) may not be adequate for their maximum growth performance. These authors further reported that dietary supplementation with 0.52 % glycine can increase average daily gain and feed efficiency of growing pigs to the levels observed for pigs fed the normal protein diet (Powell et al. 2011). However, dietary supplementation with 1.7 % glycine had no positive effects on growth performance likely because of an adverse effect on the transport and utilization of neutral amino acids in the body.

Safety and toxicity of glycine supplementation

Appropriate doses of supplemental glycine (e.g., up to 2 % in the diet for young pigs) are generally safe for animals based on food intake, behavior, as well as physiological parameters in plasma and urine (Wu 2009). However, like all other nutrients, excessive amounts of glycine in diets can cause amino acid imbalances and toxicity (Wu et al. 2013). For example, intraperitoneal administration of 6.6 g glycine/kg BW/day reduces the survival of adult mice receiving irrigating fluid, as compared to the lower doses of 3.3 and 4.5 g glycine/kg BW/day (Olsson et al. 1997). In addition, intravenous administration of 1.5 g glycine/kg body weight over 90 min increases intracranial pressure and myocardial damage in young pigs, compared with 3 and 5 g mannitol/kg body weight over 90 min (Sandfeldt et al. 2001). In addition, in adult rats, dietary supplementation with 3.2 g glycine/kg BW/day for 2 weeks induces abnormal changes in glial cell morphology in the hippocampus and cerebellum (Shoham et al. 1999). Similarly, dietary supplementation with 5 g glycine/kg BW/day for 3 and 5 months reduces the density of class B, N-type Ca^{2+} channels in the parietal cortex and hippocampus of adult rats (Shoham et al. 2001). Furthermore, the body weight of rats receiving dietary supplementation with 5 g glycine/kg BW/day was lower compared with the control group after 3 months of treatment (Shoham et al. 2001). Therefore, caution should be taken in dietary supplementation of glycine to animals and humans.

Conclusion and perspectives

Glycine has multiple physiological functions in animals and humans. It is a major component of collagen and elastin, which are the most abundant proteins in the body. Glycine is the precursor of various important metabolites of low molecular weight, such as porphyrins, purines, glutathione, heme, and creatine. As an inhibitory neurotransmitter in the central nervous system and as an anti-oxidant, glycine has anti-inflammatory, immunomodulatory and cytoprotective roles in both nervous and peripheral tissues. Like many other "nutritionally nonessential amino acids", glycine may play a role in regulation of epigenetics (Phang et al. 2013; Wang et al. 2012). Thus, glycine is a truly a functional amino acid in animal nutrition (Wu et al. 2013).

Endogenous synthesis of glycine is *normally* insufficient in avian species. Therefore, glycine is classified as a nutritionally essential amino acid for birds (including chickens and ducks) and it must be included in their diets to meet the metabolic needs. Growing evidence shows that mammals may not adequately synthesize glycine during gestation and the neonatal period and under certain conditions. Like arginine, glutamine and glutamate for weaning pigs (Geng et al. 2011; Rezaei et al. 2013b; Wu et al. 1996, 2004a, 2011b), glycine should be classified as a conditionally essential amino acid for humans (Jackson 1991) and other animals, including piglets (Rezaei et al. 2013a). Dietary supplementation with an appropriate dose of glycine is effective in ameliorating metabolic disorders in patients with obesity, diabetes, cardiovascular disease, ischemia-reperfusion injuries, various inflammatory diseases, and cancers. Glycine can also improve neurological function and quality of sleep (Bannai and Kawai 2012). The underlying mechanisms responsible for the effects of glycine remain to be fully elucidated. While caution should be taken in developing a safe dose and method of administration in dietary supplementation and clinical therapy, glycine holds great promise in improving growth, health, and well-being in both animals and humans.

Acknowledgments Work in our laboratories was supported by the National Basic Research Program of China (Grant 2013CB127302), National Research Initiative Competitive Grants from the Animal Reproduction Program (2008-35203-19120) and Animal Growth & Nutrient Utilization Program (2008-35206-18764) of the USDA National Institute of Food and Agriculture, AHA (10GRNT4480020), Texas A&M AgriLife Research (H-8200), the National Natural Science Foundation of China (No. u0731001, 30810103902, 30928018, 30972156, 31172217 and 31272450), China Postdoctoral Science Foundation (2012T50163), Chinese Universities Scientific Funds (No. 2012RC024), and the Thousand-People Talent program at China Agricultural University. Important contributions of our graduate students and colleagues to the recent development of the field are gratefully appreciated.

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

References

Alvarado-Vasquez N, Zamudio P, Ceron E et al (2003) Effect of glycine in streptozotocin-induced diabetic rats. Comp Biochem Physiol C Toxicol Pharmacol 134:521–527

Amin K, Li J, Chao WR et al (2003) Dietary glycine inhibits angiogenesis during wound healing and tumor growth. Cancer Biol Ther 2:173–178

Arnstein HR, Keglevic D (1956) A comparison of alanine and glucose as precursors of serine and glycine. Biochem J 62:199–205

Arnstein HR, Neuberger A (1953) The synthesis of glycine and serine by the rat. Biochem J 55:271–280

Ascher E, Hanson JN, Cheng W et al (2001) Glycine preserves function and decreases necrosis in skeletal muscle undergoing ischemia and reperfusion injury. Surgery 129:231–235

Bahmani F, Bathaie SZ, Aldavood SJ et al (2012) Glycine therapy inhibits the progression of cataract in streptozotocin-induced diabetic rats. Mol Vis 18:439–448

Baker DH (2009) Advances in protein-amino acid nutrition of poultry. Amino Acids 37:29–41

Ballèvre O, Cadenhead A, Calder AG et al (1990) Quantitative partition of threonine oxidation in pigs: effect of dietary threonine. Am J Physiol 259:E483–E491

Ballèvre O, Buchan V, Rees WD et al (1991) Sarcosine kinetics in pigs by infusion of [1-^{14}C]sarcosine: use for refining estimates of glycine and threonine kinetics. Am J Physiol 260:E662–E668

Bannai M, Kawai N (2012) New therapeutic strategy for amino acid medicine: glycine improves the quality of sleep. J Pharmacol Sci 118:145–148

Barness LA, Opitz JM, Gilbert-Barness E (2007) Obesity: genetic, molecular, and environmental aspects. Am J Med Genet A 143A:3016–3034

Bergeron F, Otto A, Blache P et al (1998) Molecular cloning and tissue distribution of rat sarcosine dehydrogenase. Eur J Biochem 257:556–561

Bird MI, Nunn PB (1983) Metabolic homoeostasis of L-threonine in the normally-fed rat. Importance of liver threonine dehydrogenase activity. Biochem J 214:687–694

Brawley L, Torrens C, Anthony FW et al (2004) Glycine rectifies vascular dysfunction induced by dietary protein imbalance during pregnancy. J Physiol 554:497–504

Brosnan JT, Wijekoon EP, Warford-Woolgar L et al (2009) Creatine synthesis is a major metabolic process in neonatal piglets and has important implications for amino acid metabolism and methyl balance. J Nutr 139:1292-1297

Carvajal Sandoval G, Medina Santillan R et al (1999) Effect of glycine on hemoglobin glycation in diabetic patients. Proc West Pharmacol Soc 42:31–32

Cetin I, Marconi AM, Baggiani AM et al (1995) In vivo placental transport of glycine and leucine in human pregnancies. Pediatr Res 37:571–575

Chao FC, Delwiche CC, Greenberg DM (1953) Biological precursors of glycine. Biochim Biophys Acta 10:103–109

Collard CD, Gelman S (2001) Pathophysiology, clinical manifestations, and prevention of ischemia-reperfusion injury. Anesthesiology 94:1133–1138

Conter C, Rolland MO, Cheillan D et al (2006) Genetic heterogeneity of the GLDC gene in 28 unrelated patients with glycine encephalopathy. J Inherit Metab Dis 29:135–142

Corzo A, Kidd MT, Burnham DJ et al (2004) Dietary glycine needs of broiler chicks. Poult Sci 83:1382–1384

Cruz M, Maldonado-Bernal C, Mondragon-Gonzalez R et al (2008) Glycine treatment decreases proinflammatory cytokines and increases interferon-gamma in patients with type 2 diabetes. J Endocrinol Invest 31:694–699

Dai ZL, Zhang J, Wu G, Zhu WY (2010) Utilization of amino acids by bacteria from the pig small intestine. Amino Acids 39:1201–1215

Dai ZL, Wu G, Zhu WY (2011) Amino acid metabolism in intestinal bacteria: links between gut ecology and host health. Front Biosci 16:1768–1786

Dai ZL, Li XL, Xi PB et al (2012) Metabolism of select amino acids in bacteria from the pig small intestine. Amino Acids 42:1597–1608

Dai ZL, Wu ZL, Yang Y et al (2013) Nitric oxide and energy metabolism in mammals. BioFactors. doi:10.1002/biof.1099

Dale RA (1978) Catabolism of threonine in mammals by coupling of L-threonine 3-dehydrogenase with 2-amino-3-oxobutyrate-CoA ligase. Biochim Biophys Acta 544:496–503

Danpure CJ (1997) Variable peroxisomal and mitochondrial targeting of alanine: glyoxylate aminotransferase in mammalian evolution and disease. BioEssays 19:317–326

Danpure CJ, Jennings PR (1986) Peroxisomal alanine:glyoxylate aminotransferase deficiency in primary hyperoxaluria type I. FEBS Lett 201:20–24

Danpure CJ, Cooper PJ, Wise PJ et al (1989) An enzyme trafficking defect in two patients with primary hyperoxaluria type 1: peroxisomal alanine/glyoxylate aminotransferase rerouted to mitochondria. J Cell Biol 108:1345–1352

Danpure CJ, Guttridge KM, Fryer P et al (1990) Subcellular distribution of hepatic alanine:glyoxylate aminotransferase in various mammalian species. J Cell Sci 97:669–678

Darling PB, Dunn M, Sarwar G et al (1999) Threonine kinetics in preterm infants fed their mothers' milk or formula with various ratios of whey to casein. Am J Clin Nutr 69:105–114

Darling PB, Grunow J, Rafii M et al (2000) Threonine dehydrogenase is a minor degradative pathway of threonine catabolism in adult humans. Am J Physiol 278:E877–E884

Dasarathy S, Kasumov T, Edmison JM et al (2009) Glycine and urea kinetics in nonalcoholic steatohepatitis in human: effect of intralipid infusion. Am J Physiol 297:G567–G575

Davis AJ, Austic RE (1994) Dietary threonine imbalance alters threonine dehydrogenase activity in isolated hepatic mitochondria of chicks and rats. J Nutr 124:1667–1677

Davis TA, Nguyen HV, Garciaa-Bravo R et al (1994) Amino acid composition of human milk is not unique. J Nutr 124:1126–1132

de Aguiar Picanco E, Lopes-Paulo F, Marques RG et al (2011) L-arginine and glycine supplementation in the repair of the irradiated colonic wall of rats. Int J Colorectal Dis 26:561–568

de Koning TJ, Snell K, Duran M et al (2003) L-serine in disease and development. Biochem J 371:653–661

Despres JP, Moorjani S, Lupien PJ et al (1990) Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. Arteriosclerosis 10:497–511

Donini S, Ferrari M, Fedeli C et al (2009) Recombinant production of eight human cytosolic aminotransferases and assessment of their potential involvement in glyoxylate metabolism. Biochem J 422:265–272

Donovan SM, Mar MH, Zeisel SH (1997) Choline and choline ester concentrations in porcine milk throughout lactation. J Nutr Biochem 8:603–607

dos Santos Fagundes I, Rotta LN, Schweigert ID et al (2001) Glycine, serine, and leucine metabolism in different regions of rat central nervous system. Neurochem Res 26:245–249

El Hafidi M, Perez I, Zamora J et al (2004) Glycine intake decreases plasma free fatty acids, adipose cell size, and blood pressure in sucrose-fed rats. Am J Physiol Regul Integr Comp Physiol 287:R1387–R1393

Estacion M, Weinberg JS, Sinkins WG et al (2003) Blockade of maitotoxin-induced endothelial cell lysis by glycine and L-alanine. Am J Physiol 284:C1006–C1020

Felig P, Marliss E, Cahill GF Jr (1969) Plasma amino acid levels and insulin secretion in obesity. N Engl J Med 281:811–816

Finkelstein JD, Martin JJ, Harris BJ et al (1982) Regulation of the betaine content of rat liver. Arch Biochem Biophys 218: 169–173

Flynn NE, Knabe DA, Mallick BK et al (2000) Postnatal changes of plasma amino acids in suckling pigs. J Anim Sci 78:2369–2375

Gannon MC, Nuttall JA, Nuttall FQ (2002) The metabolic response to ingested glycine. Am J Clin Nutr 76:1302–1307

Gao HJ, Wu G, Spencer TE et al (2009) Select nutrients in the ovine uterine lumen: I. Amino acids, glucose and ions in uterine lumenal flushings of cyclic and pregnant ewes. Biol Reprod 80:86–93

Garcia-Macedo R, Sanchez-Munoz F, Almanza-Perez JC et al (2008) Glycine increases mRNA adiponectin and diminishes pro-inflammatory adipokines expression in 3T3-L1 cells. Eur J Pharmacol 587:317–321

Geng MM, Li TJ, Kong XF et al (2011) Reduced expression of intestinal *N*-acetylglutamate synthase in suckling piglets: a novel molecular mechanism for arginine as a nutritionally essential amino acid for neonates. Amino Acids 40:1513–1522

Girgis S, Nasrallah IM, Suh JR et al (1998) Molecular cloning, characterization and alternative splicing of the human cytoplasmic serine hydroxymethyltransferase gene. Gene 210: 315–324

Guay F, Matte JJ, Girard CL et al (2002) Effect of folic acid and glycine supplementation on embryo development and folate metabolism during early pregnancy in pigs. J Anim Sci 80:2134–2143

Hafkenscheid JC, Hectors MP (1975) An enzymic method for the determination of the glycine/taurine ratio of conjugated bile acid in bile. Clin Chim Acta 65:67–74

Hall JC (1998) Glycine. JPEN J Parenter Enteral Nutr 22:393–398

Hammer VA, Rogers QR, Freedland RA (1996) Threonine is catabolized by L-threonine 3-dehydrogenase and threonine dehydratase in hepatocytes from domestic cats (Felis domestica). J Nutr 126:2218–2226

Harada E, Kiriyama H, Kobayashi E et al (1988) Postnatal development of biliary and pancreatic exocrine secretion in piglets. Comp Biochem Physiol A 91:43–51

Hartshorne D, Greenberg DM (1964) Studies on liver threonine dehydrogenase. Arch Biochem Biophys 105:173–178

Hasegawa S, Ichiyama T, Sonaka I et al (2012) Cysteine, histidine and glycine exhibit anti-inflammatory effects in human coronary arterial endothelial cells. Clin Exp Immunol 167:269–274

Hellwing ALF, Tauson AH, Skrede A et al (2007) Bacterial protein meal in diets for pigs and minks: comparative studies on protein turnover rate and urinary excretion of purine base derivatives. Arch Anim Nutr 61:425–443

Holmes RP, Assimos DG (1998) Glyoxylate synthesis, and its modulation and influence on oxalate synthesis. J Urol 160:1617–1624

House JD, Hall BN, Brosnan JT (2001) Threonine metabolism in isolated rat hepatocytes. Am J Physiol Endocrinol Metab 281:E1300–E1307

Huxley RR, Shiell AW, Law CM (2000) The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. J Hypertens 18:815–831

Ikejima K, Iimuro Y, Forman DT et al (1996) A diet containing glycine improves survival in endotoxin shock in the rat. Am J Physiol 271:G97–G103

Ikejima K, Qu W, Stachlewitz RF et al (1997) Kupffer cells contain a glycine-gated chloride channel. Am J Physiol 272:G1581–G1586

Ito K, Ozasa H, Noda Y et al (2008) Effect of non-essential amino acid glycine administration on the liver regeneration of partially hepatectomized rats with hepatic ischemia/reperfusion injury. Clin Nutr 27:773–780

Jackson AA (1991) The glycine story. Eur J Clin Nutr 45:59–65

Jackson AA, Persaud C, Hall M et al (1997) Urinary excretion of 5-L-oxoproline (pyroglutamic acid) during early life in term and preterm infants. Arch Dis Child Fetal Neonatal Ed 76:F152–F157

Jackson AA, Dunn RL, Marchand MC et al (2002) Increased systolic blood pressure in rats induced by a maternal low-protein diet is reversed by dietary supplementation with glycine. Clin Sci (Lond) 103:633–639

Jacob T, Ascher E, Hingorani A et al (2003) Glycine prevents the induction of apoptosis attributed to mesenteric ischemia/reperfusion injury in a rat model. Surgery 134:457–466

Jois M, Hall B, Fewer K et al (1989) Regulation of hepatic glycine catabolism by glucagon. J Biol Chem 264:3347–3351

Kikuchi G, Motokawa Y, Yoshida T et al (2008) Glycine cleavage system: reaction mechanism, physiological significance, and hyperglycinemia. Proc Jpn Acad Ser B 84:246–263

Kristensen NB, Norgaard JV, Wamberg S et al (2009) Absorption and metabolism of benzoic acid in growing pigs. J Anim Sci 87:2815–2822

Lamers Y, Williamson J, Gilbert LR et al (2007) Glycine turnover and decarboxylation rate quantified in healthy men and women using primed, constant infusions of [1,2–$^{13}C_2$]glycine and [$^{2}H_3$]leucine. J Nutr 137:2647–2652

Le Floc'h N, Obled C, Sève B (1995) In vivo threonine oxidation rate is dependent on threonine dietary supply in growing pigs fed low to adequate levels. J Nutr 125:2550–2562

Lee IS, Muragaki Y, Ideguchi T et al (1995) Molecular cloning and sequencing of a cDNA encoding alanine-glyoxylate aminotransferase 2 from rat kidney. J Biochem 117:856–862

Lehninger A, Nelson DL, Cox MM (1993) Principles of biochemistry, 2nd edn. Worth Publishers, New York, p 526

Lewis AJ (2001) Amino acids in swine nutrition. In: Lewis AJ, Southern L (eds) Swine nutrition, 2nd edn. CRC Press, New York, pp 131–150

Lewis RM, Godfrey KM, Jackson AA et al (2005) Low serine hydroxymethyltransferase activity in the human placenta has important implications for fetal glycine supply. J Clin Endocrinol Metab 90:1594–1598

Li X, Bradford BU, Wheeler MD et al (2001) Dietary glycine prevents peptidoglycan polysaccharide-induced reactive arthritis in the rat: role for glycine-gated chloride channel. Infect Immun 69:5883–5891

Li P, Yin YL, Li DF et al (2007) Amino acids and immune function. Br J Nutr 98:237–252

Li XL, Rezaei R, Li et al (2011) Composition of amino acids in feed ingredients for animal diets. Amino Acids 40:1159-1168

Lowry M, Hall DE, Brosnan JT (1985a) Hydroxyproline metabolism by the rat kidney: distribution of renal enzymes of hydroxyproline catabolism and renal conversion of hydroxyproline to glycine and serine. Metabolism 34:955–961

Lowry M, Hall DE, Brosnan JT (1985b) Increased activity of renal glycine-cleavage-enzyme complex in metabolic acidosis. Biochem J 231:477–480

MacFarlane AJ, Liu X, Perry CA et al (2008) Cytoplasmic serine hydroxymethyltransferase regulates the metabolic partitioning of methylenetetrahydrofolate but is not essential in mice. J Biol Chem 283:25846–25853

Matilla B, Mauriz JL, Culebras JM et al (2002) Glycine: a cell-protecting anti-oxidant nutrient. Nutr Hosp 17:2–9

Matrone G, Thomason EL Jr, Burn CR (1960) Requirement and utilization of iron by the baby pig. J Nutr 72:459–465

Matthews DE, Conway JM, Young VR et al (1981) Glycine nitrogen metabolism in man. Metabolism 30:886–893

Mavromichalis I, Parr TM, Gabert VM et al (2001) True ileal digestibility of amino acids in sow's milk for 17-day-old pigs. J Anim Sci 79:707–713

McCarty MF, Barroso-Aranda J, Contreras F (2009) The hyperpolarizing impact of glycine on endothelial cells may be anti-atherogenic. Med Hypotheses 73:263–264

Meister A (1965) Biochemistry of amino acids. Academic Press, New York

Melendez-Hevia E, De Paz-Lugo P, Cornish-Bowden A et al (2009) A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. J Biosci 34:853–872

Mertz ET, Beeson WM, Jackson HD (1952) Classification of essential amino acids for the weanling pig. Arch Biochem Biophys 38:121–128

Mudd SH, Cerone R, Schiaffino MC et al (2001) Glycine *N*-methyltransferase deficiency: a novel inborn error causing persistent isolated hypermethioninaemia. J Inherit Metab Dis 24:448–464

Narkewicz MR, Thureen PJ, Sauls SD et al (1996) Serine and glycine metabolism in hepatocytes from mid gestation fetal lambs. Pediatr Res 39:1085–1090

Neuman RE, Logan MA (1950) The determination of hydroxyproline. J Biol Chem 184:299–306

Newsholme E, Leech T (2010) Functional biochemistry in health and disease. Wiley, West Sussex

Noguchi T, Takada Y (1979) Peroxisomal localization of alanine: glyoxylate aminotransferase in human liver. Arch Biochem Biophys 196:645–647

Noguchi T, Okuno E, Takada Y et al (1978) Characteristics of hepatic alanine-glyoxylate aminotransferase in different mammalian species. Biochem J 169:113–122

Ogawa H, Gomi T, Fujioka M (2000) Serine hydroxymethyltransferase and threonine aldolase: are they identical? Int J Biochem Cell Biol 32:289–301

Olsson J, Sandfeldt L, Hahn RG (1997) Survival after high-dose intraperitoneal infusion of glycine solution in the mouse. Scand J Urol Nephrol 31:119–121

Pal PB, Pal S, Das J et al (2012) Modulation of mercury-induced mitochondria-dependent apoptosis by glycine in hepatocytes. Amino Acids 42:1669–1683

Paolini CL, Marconi AM, Ronzoni S et al (2001) Placental transport of leucine, phenylalanine, glycine, and proline in intrauterine growth-restricted pregnancies. J Clin Endocrinol Metab 86:5427–5432

Parimi PS, Gruca LL, Kalhan SC (2005) Metabolism of threonine in newborn infants. Am J Physiol Endocrinol Metab 289:E981–E985

Petrat F, Drowatzky J, Boengler K et al (2011) Protection from glycine at low doses in ischemia-reperfusion injury of the rat small intestine. Eur Surg Res 46:180–187

Pfeiffer F, Betz H (1981) Solubilization of the glycine receptor from rat spinal cord. Brain Res 226:273–279

Phang JM, Liu W, Hancock C (2013) Bridging epigenetics and metabolism: role of non-essential amino acids. Epigenetics 8(3):231–236

Porter DH, Cook RJ, Wagner C (1985) Enzymatic properties of dimethylglycine dehydrogenase and sarcosine dehydrogenase from rat liver. Arch Biochem Biophys 243:396–407

Powell S, Bidner TD, Payne RL et al (2011) Growth performance of 20- to 50-kilogram pigs fed low-crude-protein diets supplemented with histidine, cystine, glycine, glutamic acid, or arginine. J Anim Sci 89:3643–3650

Rajendra S, Lynch JW, Pierce KD et al (1995) Mutation of an arginine residue in the human glycine receptor transforms beta-alanine and taurine from agonists into competitive antagonists. Neuron 14:169–175

Rajendra S, Lynch JW, Schofield PR (1997) The glycine receptor. Pharmacol Ther 73:121–146

Ramakrishnan S, Sulochana KN (1993) Decrease in glycation of lens proteins by lysine and glycine by scavenging of glucose and possible mitigation of cataractogenesis. Exp Eye Res 57:623–628

Rawn JD (1989) Biochemistry. Carolina Biological Supply, North Carolina, p 470

Reeds PJ, Burrin DG, Stoll B et al (1997) Enteral glutamate is the preferential source for mucosal glutathione synthesis in fed piglets. Am J Physiol 273:E408–E415

Rezaei R, Wang WW, Wu ZL et al (2013a) Biochemical and physiological bases for utilization of dietary amino acids by young pigs. J Anim Sci Biotech 4:7

Rezaei R, Knabe DA, Tekwe CD et al (2013b) Dietary supplementation with monosodium glutamate is safe and improves growth performance in postweaning pigs. Amino Acids 44:911–923

Rivera-Ferre MG, Aguilera JF, Nieto R (2006) Differences in whole-body protein turnover between Iberian and Landrace pigs fed adequate or lysine-deficient diets. J Anim Sci 84:3346–3355

Rodionov RN, Murry DJ, Vaulman SF et al (2010) Human alanine-glyoxylate aminotransferase 2 lowers asymmetric dimethylarginine and protects from inhibition of nitric oxide production. J Biol Chem 285:5385–5391

Rose ML, Cattley RC, Dunn C et al (1999a) Dietary glycine prevents the development of liver tumors caused by the peroxisome proliferator WY-14,643. Carcinogenesis 20:2075–2081

Rose ML, Madren J, Bunzendahl H et al (1999b) Dietary glycine inhibits the growth of B16 melanoma tumors in mice. Carcinogenesis 20:793–798

Ruiz-Torres A, Kurten I (1976) Is there a recycling of hydroxyproline? Experientia 32:555–556

Sandfeldt L, Riddez L, Rajs J et al (2001) High-dose intravenous infusion of irrigating fluids containing glycine and mannitol in the pig. J Surg Res 95:114–125

Sarkar U, Choudhuri MA (1981) Effects of some oxidants and antioxidants on senescence of isolated leaves of sunflower with special reference to glycolate content, glycolate oxidase, and catalase activities. Can J Botany 59:392-396

Sato K, Yoshida S, Fujiwara K et al (1991) Glycine cleavage system in astrocytes. Brain Res 567:64–70

Satterfield MC, Dunlap KA, Keisler DH et al (2012) Arginine nutrition and fetal brown adipose tissue development in diet-induced obese sheep. Amino Acids 43:1593–1603

Schadereit R, Krawielitzki K, Herrmann U (1986) ^{15}N transamination in the administration of various tracer substances. 1. Whole body studies in rats. Arch Tierernahr 36:783–792

Schemmer P, Bradford BU, Rose ML et al (1999) Intravenous glycine improves survival in rat liver transplantation. Am J Physiol 276:G924–G932

Schirch L, Gross T (1968) Serine transhydroxymethylase. Identification as the threonine and allothreonine aldolases. J Biol Chem 243:5651–5655

Sekhar RV, McKay SV, Patel SG et al (2011) Glutathione synthesis is diminished in patients with uncontrolled diabetes and restored by dietary supplementation with cysteine and glycine. Diabetes Care 34:162–167

Shemin D (1946) The biological conversion of L-serine to glycine. J Biol Chem 162:297–307

Shemin D (1950) Some aspects of the biosynthesis of amino acids. Cold Spring Harb Symp 14:161–167

Shoham S, Javitt DC, Heresco-Levy U (1999) High dose glycine nutrition affects glial cell morphology in rat hippocampus and cerebellum. Int J Neuropsychopharmacol 2:35–40

Shoham S, Javitt DC, Heresco-Levy U (2001) Chronic high-dose glycine nutrition: effects on rat brain cell morphology. Biol Psychiatry 49:876–885

Slomowitz LA, Gabbai FB, Khang SJ et al (2004) Protein intake regulates the vasodilatory function of the kidney and NMDA receptor expression. Am J Physiol Regul Integr Comp Physiol 287:R1184–R1189

Soloway S, Stetten D Jr (1953) The metabolism of choline and its conversion to glycine in the rats. J Biol Chem 204:207–214

Sommer SP, Sommer S, Sinha B et al (2012) Glycine preconditioning to ameliorate pulmonary ischemia reperfusion injury in rats. Interact Cardiovasc Thorac Surg 14:521–525

Spittler A, Reissner CM, Oehler R et al (1999) Immunomodulatory effects of glycine on LPS-treated monocytes: reduced TNF-alpha production and accelerated IL-10 expression. FASEB J 13: 563–571

Stachlewitz RF, Li X, Smith S et al (2000) Glycine inhibits growth of T lymphocytes by an IL-2-independent mechanism. J Immunol 164:176–182

Stover PJ, Chen LH, Suh JR et al (1997) Molecular cloning, characterization, and regulation of the human mitochondrial serine hydroxymethyltransferase gene. J Biol Chem 272: 1842–1848

Takada Y, Noguchi T (1982) Subcellular distribution, and physical and immunological properties of hepatic alanine: glyoxylate aminotransferase isoenzymes in different mammalian species. Comp Biochem Physiol B 72:597–604

Tariq M, Al Moutaery AR (1997) Studies on the antisecretory, gastric anti-ulcer and cytoprotective properties of glycine. Res Commun Mol Pathol Pharmacol 97:185–198

Thompson JS, Richardson KE (1967) Isolation and characterization of an L-alanine: glyoxylate aminotransferase from human liver. J Biol Chem 242:3614–3619

Thureen PJ, Narkewicz MR, Battaglia FC et al (1995) Pathways of serine and glycine metabolism in primary culture of ovine fetal hepatocytes. Pediatr Res 38:775–782

Trujillo ME, Scherer PE (2006) Adipose tissue-derived factors: impact on health and disease. Endocr Rev 27:762–778

Vazquez A, Tedeschi PM, Bertino JR (2013) Overexpression of the mitochondrial folate and glycine-serine pathway: a new determinant of methotrexate selectivity in tumors. Cancer Res 73:478–482

Walsh DA, Sallach HJ (1966) Comparative studies on the pathways for serine synthesis in animal tissues. J Biol Chem 241: 4068–4076

Wang JJ, Wu ZL, Li DF et al (2012) Nutrition, epigenetics, and metabolic syndrome. Antioxid Redox Signal 17:282–301

Watts RWE, Crawhall JC (1959) The first glycine metabolic pool in man. Biochem J 73:277–286

Wei JW, Carroll RJ, Harden KK et al (2012) Comparisons of treatment means when factors do not interact in two-factorial studies. Amino Acids 42:2031–2035

Wheeler MD, Ikejema K, Enomoto N et al (1999) Glycine: a new anti-inflammatory immunonutrient. Cell Mol Life Sci 56:843–856

Wheeler MD, Rose ML, Yamashima S et al (2000) Dietary glycine blunts lung inflammatory cell influx following acute endotoxin. Am J Physiol 279:L390–L398

Wijekoon EP, Skinner C, Brosnan ME et al (2004) Amino acid metabolism in the Zucker diabetic fatty rat: effects of insulin resistance and of type 2 diabetes. Can J Physiol Pharmacol 82:506–514

Wu G (2009) Amino acids: metabolism, functions, and nutrition. Amino Acids 37:1–17

Wu G (2010a) Recent advances in swine amino acid nutrition. J Anim Sci Biotech 1:49–61

Wu G (2010b) Functional amino acids in growth, reproduction and health. Adv Nutr 1:31–37

Wu G (2013) Amino acids: biochemistry and nutrition. CRC Press, Boca Raton

Wu G, Knabe DA (1994) Free and protein-bound amino acids in sow's colostrum and milk. J Nutr 124:415–424

Wu G, Meininger CJ (2002) Regulation of nitric oxide synthesis by dietary factors. Annu Rev Nutr 22:61–86

Wu G, Borbolla AG, Knabe DA (1994) The uptake of glutamine and release of arginine, citrulline and proline by the small intestine of developing pigs. J Nutr 124:2437–2444

Wu G, Meier SA, Knabe DA (1996) Dietary glutamine supplementation prevents jejunal atrophy in weaned pigs. J Nutr 126: 2578–2584

Wu G, Knabe DA, Kim SW (2004a) Arginine nutrition in neonatal pigs. J Nutr 134:2783S–2790S

Wu G, Fang YZ, Yang S et al (2004b) Glutathione metabolism and its implications for health. J Nutr 134:489–492

Wu G, Bazer FW, Burghardt RC et al (2010) Functional amino acids in swine nutrition and production. In: Doppenberg J, van der Aar

P (eds) Dynamics in animal nutrition. Wageningen Academic Publishers, The Netherlands, pp 69–98

Wu G, Bazer FW, Burghardt RC et al (2011a) Proline and hydroxyproline metabolism: implications for animal and human nutrition. Amino Acids 40:1053–1063

Wu G, Bazer FW, Johnson GA et al (2011b) Important roles for L-glutamine in swine nutrition and production. J Anim Sci 89: 2017–2030

Wu G, Imhoff-Kunsch B, Girard AW (2012) Biological mechanisms for nutritional regulation of maternal health and fetal development. Paediatr Perinat Epidemiol 26(Suppl 1):4–26

Wu G, Wu ZL, Dai ZL et al (2013) Dietary requirements of "nutritionally nonessential amino acids" by animals and humans. Amino Acids 44:1107–1113

Xue HH, Sakaguchi T, Fujie M et al (1999) Flux of the L-serine metabolism in rabbit, human, and dog livers. Substantial contributions of both mitochondrial and peroxisomal serine:pyruvate/alanine:glyoxylate aminotransferase. J Biol Chem 274:16028–16033

Yamashina S, Konno A, Wheeler MD et al (2001) Endothelial cells contain a glycine-gated chloride channel. Nutr Cancer 40: 197–204

Yamashina S, Ikejima K, Enomoto N et al (2005) Glycine as a therapeutic immuno-nutrient for alcoholic liver disease. Alcohol Clin Exp Res 29(11 Suppl):162S–165S

Yamashina S, Ikejima K, Rusyn I et al (2007) Glycine as a potent anti-angiogenic nutrient for tumor growth. J Gastroenterol Hepatol 22(Suppl 1):S62–S64

Yan BX, Sun YQ (1997) Glycine residues provide flexibility for enzyme active sites. J Biol Chem 272:3190–3194

Yao K, Yin YL, Li XL et al (2012) Alpha-ketoglutarate inhibits glutamine degradation and enhances protein synthesis in intestinal porcine epithelial cells. Amino Acids 42:2491–2500

Yeo EJ, Wagner C (1994) Tissue distribution of glycine *N*-methyltransferase, a major folate-binding protein of liver. Proc Natl Acad Sci USA 91:210–214

Yeung YG (1986) L-threonine aldolase is not a genuine enzyme in rat liver. Biochem J 237:187–190

Yin M, Zhong Z, Connor HD et al (2002) Protective effect of glycine on renal injury induced by ischemia-reperfusion in vivo. Am J Physiol Renal Physiol 282:F417–F423

Yu YM, Yang RD, Matthews DE et al (1985) Quantitative aspects of glycine and alanine nitrogen metabolism in postabsorptive young men: effects of level of nitrogen and dispensable amino acid intake. J Nutr 115:399–410

Yue JT, Mighiu PI, Naples M et al (2012) Glycine normalizes hepatic triglyceride-rich VLDL secretion by triggering the CNS in high-fat fed rats. Circ Res 110:1345–1354

Zhang J, Blusztajn JK, Zeisel SH (1992) Measurement of the formation of betaine aldehyde and betaine in rat liver mitochondria by a high pressure liquid chromatography-radioenzymatic assay. Biochim Biophys Acta 1117:333–339

Zhang Y, Ikejima K, Honda H et al (2000) Glycine prevents apoptosis of rat sinusoidal endothelial cells caused by deprivation of vascular endothelial growth factor. Hepatology 32:542–546

Zhong Z, Jones S, Thurman RG (1996) Glycine minimizes reperfusion injury in a low-flow, reflow liver perfusion model in the rat. Am J Physiol 270:G332–G338

Zhong Z, Enomoto N, Connor HD et al (1999) Glycine improves survival after hemorrhagic shock in the rat. Shock 12:54–62

Zhong Z, Wheeler MD, Li X et al (2003) L-Glycine: a novel antiinflammatory, immunomodulatory, and cytoprotective agent. Curr Opin Clin Nutr Metab Care 6:229–240