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REVIEW ARTICLE

Advances in protein–amino acid nutrition of poultry

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Abstract The ideal protein concept has allowed progress in defining requirements as well as the limiting order of amino acids in corn, soybean meal, and a corn–soybean meal mixture for growth of young chicks. Recent evidence suggests that glycine (or serine) is a key limiting amino acid in reduced protein [23% crude protein (CP) reduced to 16% CP] corn–soybean meal diets for broiler chicks. Research with sulfur amino acids has revealed that small excesses of cysteine are growth depressing in chicks fed methionine-deficient diets. Moreover, high ratios of cysteine:methionine impair utilization of the hydroxy analog of methionine, but not of methionine itself. A high level of dietary L-cysteine (2.5% or higher) is lethal for young chicks, but a similar level of DL-methionine, L-cystine or N-acetyl-L-cysteine causes no mortality. A supplemental dietary level of 3.0% L-cysteine (7× requirement) causes acute metabolic acidosis that is characterized by a striking increase in plasma sulfate and decrease in plasma bicarbonate. *S*-Methylmethionine, an analog of *S*-adenosylmethionine, has been shown to have choline-sparing activity, but it only spares methionine when diets are deficient in choline and(or) betaine. Creatine, or its precursor guanidinoacetic acid, can spare dietary arginine in chicks.

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Abbreviations

Cys	Cysteine
CP	Crude protein
DDGS	Distillers dried grain with solubles
GAA	Guanidinoacetic acid
Met	Methionine
OH-M	DL-2-hydroxy-4-(methylthio) butyric acid
SAA	Sulfur amino acid
SMM	*S*-Methylmethionine

Introduction

This review will focus on recent developments and progress in protein–amino acid nutrition of poultry, i.e., broilers, layers, broiler breeders, and turkeys. The ideal protein concept (Mitchell 1964) was first put into practice with swine (ARC, Agriculture Research Council 1981; Baker 1997; Chung and Baker 1992a, b, c; Cole 1980; Wang and Fuller 1989, 1990). Subsequently, an ideal pattern of amino acids, with amino acids ratioed to lysine, was proposed and tested in broiler chicks by Baker and Han (1994). Some of the Illinois ideal ratios were subsequently tested and revised (Baker et al. 2002; Emmert and Baker 1997). Other workers also have proposed ideal amino acid ratios for broiler chickens (Mack et al. 1999). Knowledge of digestible amino acid requirements as well as amino acid digestibilities in common feed ingredients fed to poultry are viewed as important tools in advancing knowledge in amino acid nutrition and metabolism of poultry.

Substituting amino acids for intact protein

Approximately 90% of diets for poultry in the U.S. is comprised of corn and soybean meal. Because the cost of these key ingredients has increased markedly in recent years, keen interest exists in feeding reduced protein corn–soybean meal diets that contain supplemental amino acids. The rapid rise of corn-based ethanol production has resulted in a 27% crude protein (CP) by-product ingredient, distillers dried grain with solubles (DDGS). For poultry, this ingredient is markedly deficient in bioavailable lysine and tryptophan. Increasingly, DDGS is being used to replace some of the corn and soybean meal in poultry diets.

It has been known for well over 20 years that there are limits to how much intact protein can be replaced by free amino acids in terms of achieving maximal weight gain and feed efficiency of broiler chicks. Edmonds et al. (1985) reported that a 24% CP methionine-fortified corn–soybean meal diet (positive control) reduced to 16% CP (corn at 8% CP replacing soybean meal at 48% CP) would not produce optimal growth performance of young chicks, even when fortified with all suspect limiting amino acids. Work at the University of Georgia showed the same results (Fancher and Jensen 1989a, b, c; Pinchasov et al. 1990). Waldroup et al. (1976) and Han et al. (1992) observed that a 19% low CP diet fortified with limiting amino acids (methionine, lysine, threonine, valine, arginine) would produce optimal performance of young chicks. Fernandez et al. (1994) subsequently determined the order of amino acid limitation in both corn and dehulled soybean meal for chicks during the period 8–22 days posthatching. For corn, the limiting order was (1) lysine, (2) threonine, (3) tryptophan, (4) arginine, valine and isoleucine (equally 4th limiting), (5) sulfur amino acid (SAA), (6) phenylalanine + tyrosine, and (7) histidine. The order of limiting amino acids in soybean meal was (1) SAA, (2) threonine, (3) lysine and valine (equally 3rd limiting), (4) nonspecific amino nitrogen, and (5) histidine.

A breakthrough occurred in achieving optimal performance of young broiler chicks receiving an amino acid fortified 16% CP diet when Dean et al. (2006) discovered that glycine plus essential amino acids was necessary for obtaining performance with the low CP diet that would equal a 22% CP corn–soybean meal positive-control diet. The Dean et al. (2006) work suggested that an amino acid fortified 16% CP diet required at least 2.44% glycine + serine. Because avian species excrete uric acid as an end product of nitrogen metabolism, and because every mole of uric acid synthesized requires 1 mol of glycine, it would seem that high protein rather than low protein intakes would require more glycine. Thus, the glycine (or serine) response being as efficacious as a full array of dispensable amino acids (including glycine) for chicks fed low protein diets is surprising.

Ideal amino acid ratios for broiler chicks

Amino acid requirements ratioed to lysine have become a popular means of expressing requirements, particularly since factors such as protein accretion potential (i.e., bird strain) and dietary energy density have little effect on the ideal ratios. However, period of growth (i.e., age), gender, and criterion of response can have important effects on a particular ratio. Extensive studies with lysine, for example, have shown that males have higher requirements than females, and maximal feed efficiency (i.e., gain:feed ratio) requires a higher dietary level of lysine than maximal body weight gain (Dozier III et al. 2008; Garcia et al. 2006; Han and Baker 1993, 1994; Mack et al. 1999). The Met requirement for maximal feed conversion efficiency may also be higher than the need for maximal weight gain (Mack et al. 1999). One would think that if sex and criterion of response affect both lysine and SAA requirements, all other indispensable amino acids would be similarly affected. However, this appears not to be the case. Baker et al. (2002) in studying lysine, tryptophan, threonine, isoleucine, and valine requirements of young male chicks found that only lysine was required in higher concentration for maximal gain:feed than for maximal weight gain. Earlier work with threonine and tryptophan also showed that the requirement of broiler chicks was similar for both maximal weight gain and maximal feed efficiency (Rosa et al. 2001a, b; Shan et al. 2003). Moreover, in the threonine and tryptophan studies of Rosa et al. (2001a, b) the requirement for males and females was similar. That the lysine requirement is affected by gender but other amino acids are not affected adds a complicating factor to use of ideal ratios for broiler chicks. Thus, for separate-sex feeding, female chicks having a 10% lower lysine requirement than male chicks means that females would need to have ratios (to lysine) for all other indispensable amino acids adjusted upwards by approximately 10%. The simplest solution to this gender difference in ratios is to use the male (gain:feed) requirement for lysine together with the male ideal ratios, i.e., for both sexes. This suggests also, that there is no practical or economic advantage to separate-sex feeding.

Because protein gain as a percentage of total body weight gain decreases as growing chicks advance in both age and weight, requirements (% of diet) for all amino acids decrease with age and weight. The NRC (1994) model shows these decreasing requirements in three growth periods: starter phase (0–3 weeks), grower phase (3–6 weeks) and finisher phase (6–8 weeks). Emmert's laboratory at the University of Arkansas used the ideal ratio concept to propose phase-feeding programs in which two or more diets could be blended multiple times during the 6 to 8-week feeding period of broiler chicks (Pope and Emmert 2001, 2002; Pope et al. 2002, 2004; Warren and Emmert 2000). Due to maintenance:protein accretion considerations, ideal ratios for certain amino acids (SAA, threonine, tryptophan) may increase, but only slightly, as birds advance in age and weight.

Bregendahl et al. (2008) conducted an extensive study on true digestible amino acid requirements of laying hens, and concluded that with a lysine requirement (for maximal egg mass) of 538 mg/day the ideal ratios (% of lysine) would be 94% for SAA, 79% for isoleucine, 93% for valine, 77% for threonine, and 22% for tryptophan. These ratios, particularly that for tryptophan:lysine are higher than ratios used for growth of broilers. The Bregendahl et al. (2008) study represents a “first attempt” to find ideal amino acid ratios for laying hens. Undoubtedly, these estimated ratios will be revised and refined in the years ahead.

Work from the University of Alberta has focused on determining amino acid requirements, and ultimately ideal amino acid ratios (i.e., requirements ratioed to lysine), for pre-lay broiler-breeder pullets that average 20 weeks of age and weigh 3 kg (Coleman et al. 2003; Tabiri et al. 2002). Indirect L-[1-(14C)] phenylalanine indirect oxidation methodology has been used to estimate requirements, and thus far an estimate of 0.49% of the diet (366 mg/day) for lysine has been made. Requirements of broiler-breeder pullets have been unknown up to this point, so the work being done in the Korver/Ball laboratory at the University of Alberta will greatly aid our understanding of protein–amino acid needs in this class of poultry.

Dose-response studies with sulfur amino acids

There are numerous instances where it is desirable to construct assay diets that are specifically deficient in either Met or cyst(e)ine per se. Often overlooked in Met dosing bioassays is the profound effect dietary cyst(e)ine concentration can have on the magnitude of growth responses to Met (Baker and Dilger 2008, 2009). With diets singly deficient in Met [i.e., excess dietary cyst(e)ine] throughout the Met dosing range, every incremental dose of Met produces a marked growth response that is attributable not only to Met but also to Met allowing a portion (equal to each Met dose) of the excess dietary cyst(e)ine to be used. On the other hand, in basal diets where Met and cyst(e)ine are equally deficient, each dose of Met is partitioned 50:50 to furnish both Met and, via transsulfuration, Cys. The Met portion used for Cys biosynthesis is 100% efficient on a molar basis, but it is only 81% efficient on a weight or dietary concentration basis (Baker 2006; Graber and Baker 1971). Hence, the magnitude of response to Met when cyst(e)ine is also deficient is less than half as great as that occurring when Met is singly deficient throughout the Met dosing range (Baker and Dilger 2008, 2009).

With cyst(e)ine dose-response studies, similar pitfalls exist. When cyst(e)ine is always singly deficient throughout a dosing range for Cys or cystine, each dose of cyst(e)ine will allow an equal increment of Met to also be used. In cyst(e)ine dosing studies such as this, however, it is important for Met to be set at its minimal requirement (i.e., no excess) established in a bioassay diet with deficient Met and excess cyst(e)ine. Clearly, if Met and cyst(e)ine are equally deficient, Cys (or cystine) supplementation will not elicit a growth response. Often the case in practice, however, are dietary conditions where cyst(e)ine is more deficient than Met, but Met is also deficient. In these cases, responses to cyst(e)ine will be curvilinear rather than linear.

Growth or protein accretion responses to Met when administered to animals consuming a protein-free diet have intrigued researchers for well over 50 years (Allison et al. 1947; Lubaszewska et al. 1973; Muramatsu and Okumura 1979; Muramatsu et al. 1986; Okumura and Muramatsu 1978; Yoshida and Moritoki 1974; Yokogoshi and Yoshida 1976, 1979, 1981). In 1999, Webel and Baker (1999) provided evidence that the Met response in chicks fed a protein-free diet was not due to Met per se but instead was due to Met furnishing Cys via transsulfuration. Thus, nitrogen accretion responses to cyst(e)ine supplementation were as great as those obtained from Met supplementation. This suggests that Cys is the 1st limiting amino acid for utilization of endogenous amino acids.

Sulfur amino acid precursors

The precursor role of Met and Cys have been reviewed previously (Baker 1994, 2006; Baker and Dilger 2009). Also, food components and body metabolites that have Met and (or) Cys sparing activity have been reviewed. Recent evidence involving small excesses of cyst(e)ine in Met-deficient diets has revealed that as little as 0.10% supplemental cyst(e)ine is growth depressing in chicks fed Met-deficient diets (Dilger and Baker 2007a). Cyst(e)ine:Met imbalances of this type also affect the efficiency of DL-2-hydroxy-4-(methylthio) butyric acid (i.e., OH-M) as a precursor of Met. Efficacy of OH-M relative to DL-Met has been controversial for well over 40 years (Baker and Boebel 1980; Boebel and Baker 1982; Christensen and Anderson 1980; Jansman et al. 2003; Katz and Baker 1975; Sauer et al. 2008; Scott et al. 1966; Vazquez-Anon et al. 2006). Recent work in our laboratory on OH-M efficacy is discussed below.

The bioassays shown in Tables 1, 2 and 3 (Dilger and Baker 2008a) were done in batteries using male chicks obtained from the cross of New Hampshire males and Columbian females. Other details of allotment and feeding procedures were the same as those described previously (Dilger and Baker 2007a, b). Two Met and SAA-deficient diets were employed. The purified basal diet used in Assay 1 was analyzed to contain 20.3% CP, 0.12% Met, and 0.05% cyst(e)ine, and its complete description has been published (Dilger and Baker 2007a, b; Dilger et al. 2007a, b). The other SAA-deficient diet (Assays 2 and 3) was an amino acid-fortified corn (57.5%) and peanut meal (27.5%) diet analyzed to contain 19.0% CP, 0.22% Met, and 0.23% cyst(e)ine (Dilger and Baker 2008a). All bioassays except Assay 1 (12 days in length) were of 9-day duration, i.e., from 8 to 17 days posthatch. Ingredients used in all diets were from the same source and batch, and all ingredients were analyzed for CP, Met, cyst(e)ine, and lanthionine. The latter was assumed to have a cyst(e)ine bioavailability of 30% (Robbins et al. 1980; Baker et al. 1981).

The two Met precursor compounds evaluated were feed-grade DL-Met (Degussa) and feed-grade DL-OH-Met, Ca (Novus). Product guarantees of 99% for DL-Met and 84% for DL-OH-Met (Ca) were assumed for these commercially available Met precursor compounds. However, after conducting Assay 1, analytical and bioassay evaluation of purity for DL-Met (Dilger et al. 2007a; Dilger and Baker 2008a) indicated that this compound was not different from 100% pure and efficacious relative to pure L-Met. Thus, a 100% value was assumed for feed-grade DL-Met in Assays 2 and 3. We did not have similar information for DL-OH-Met (Ca), so in Assays 2 and 3 we continued to use the 84% value for DL-OH-Met (Ca) in comparisons with DL-Met. In Assays 2 and 3, 0.10% excess cyst(e)ine was evaluated as a factor affecting DL-M and OH-M utilization. Cyst(e)ine was provided by L-cystine in Assay 2 and by 3.54% feather meal in Assay 3. The addition of 3.54% feather meal in Assay 3 furnished 0.160% cyst(e)ine, 0.046% lanthionine, and 0.018% methionine. Based on previous work (Baker et al. 1981; Han and Parsons 1990; Robbins et al. 1980), we calculated that the cyst(e)ine + lanthionine contributed by 3.54% feather meal provided 0.10% bioavailable cyst(e)ine.

Table 1 Slope-ratio assessment of DL-OH-Met (Ca) relative to DL-Met in chicks fed a purified basal diet containing 0.12% methionine and 0.40% cyst(e)ine (Assay 1)

Supplement addition		Weight gain (g)[b]	Gain:feed (g/kg)[c]
Met source[a]	Level (mg/kg)		
None	0	46	302
DL-M	404	82	438
DL-M	808	146	541
DL-M	1,212	242	684
OH-M	476	65	379
OH-M	952	115	508
OH-M	1,429	185	599
SEM		10.5	16.9

Values are means of five pens of three male chicks during a 12-day feeding period from 8 to 20 days posthatch; average initial weight was 107 g; Dilger and Baker (2008a)

DL-M, DL-Met; *OH-M*, DL-OH-Met (Ca)

[a] The three additions of OH-M were isosulfurous to those of DL-M, assuming purity values of 99% for feed-grade DL-M and 84% for feed-grade OH-M

[b] Multiple linear regression of gain (Y in g) on supplemental sulfur intake (X in mg) from DL-M (X_1) and OH-M (X_2) was: $Y = 40.2 + 2.245\ X_1 + 1.766\ X_2$; $R^2 = 0.97$. The ratio of slopes (percent, relative to DL-M) was 78.7% (95% CI: 70.6–86.7) for OH-M

[c] Multiple linear regression of gain:feed (Y in g/kg) on supplemental sulfur intake (X in mg) from DL-M (X_1) and OH-M (X_2) was: $Y = 368.8 + 42.15\ X_1 + 33.86\ X_2$; $R^2 = 0.93$. The ratio of slopes (percent, relative to DL-M) was 80.3% (95% CI: 65.2-95.3) for OH-M

Table 2 Effect of excess cyst(e)ine on the efficacy of DL-OH-Met (Ca) relative to DL-Met for chicks fed a corn–peanut meal diet (Assay 2)

Supplement addition[a]			Weight gain (g)[c]	Gain:feed (g/kg)
Met source	Met, mg/kg	Cys, %		
None	0	0	105^{z}	441^{y}
DL-M	465	0	169^{x}	544^{x}
OH-M	554	0	163^{x}	538^{x}
None	0	0.10	93^{z}	453^{y}
DL-M	465	0.10	168^{x}	565^{x}
OH-M	554	0.10	149^{y}	535^{x}
SEM[b]			4.9	12.8

Values are means of five pens of four male chicks during a 9-day feeding period from 8 to 17 days posthatch; average initial weight was 103 g; Dilger and Baker (2008a)

[a] The corn–peanut meal basal diet contained by analysis 0.22% Met and 0.23% cyst(e)ine. DL-Met (DL-M) and DL-OH-Met, Ca (OH-M) were supplemented at isosulfurous levels, assuming purity values of 100% for feed-grade DL-M and 84% for feed-grade OH-M; cyst(e)ine was supplemented as L-cystine

[b] Mean values with unlike superscript letters (x, y, z) are different ($P < 0.05$)

[c] O vs. cystine ($P < 0.05$); DL-M vs. OH-M ($P < 0.05$); 0 vs. Met ($P < 0.01$)

Assay 1 (Table 1) was a slope-ratio bioassay done using the purified diet, with the basal diet for this assay (Table 1) modified to contain 0.12% Met and 0.40% cyst(e)ine (Dilger and Baker 2008a). Multiple linear regression analysis (Kratzer and Littell 2006; Littell et al. 1997) of weight gain and gain:feed as a function of supplemental sulfur intake resulted in an average (gain and gain:feed) OH-M bioefficacy value of 79.5%, equivalent to 66.8% on

Table 3 Effect of excess cysteine provided by feather meal on the efficacy of DL-OH-Met (Ca) relative to DL-Met for chicks fed a corn–peanut meal diet (Assay 3)

Supplement addition[a]			Weight gain (g)[c,d]	Gain:feed (g/kg)[c,e]
Met source	Met (mg/kg)	Cys (%)		
None	0	0	86^{y}	421^{y}
DL-M	465	0	130^{v}	528^{v}
OH-M	554	0	120^{v}	498^{x}
None	0	0.10 (FM)	60^{z}	398^{z}
DL-M	465	0.10 (FM)	108^{x}	531^{v}
OH-M	554	0.10 (FM)	90^{y}	492^{x}
SEM[b]			3.9	6.7

Values are means of five pens of four male chicks during a 9-day feeding period from 8 to 17 days posthatch; average initial weight was 99 g; Dilger and Baker (2008a)

[a] The corn–peanut meal basal diet contained by analysis 0.22% Met and 0.23% cyst(e)ine. DL-Met (DL-M) and DL-OH-Met, Ca (OH-M) were supplemented at isosulfurous levels assuming purity values of 100% for feed-grade DL-M and 84% for feed-grade OH-M; cyst(e)ine was supplemented as 0.10% bioavailable cyst(e)ine provided by feather meal (FM)

[b] Mean values with unlike superscript letters (v, x, y, z) are different ($P < 0.05$)

[c] O vs. Met ($P < 0.01$); DL-M vs. OH-M ($P < 0.01$)

[d] 0 vs. Cys as FM ($P < 0.01$)

[e] 0 vs. Met × 0 vs. Cys as FM ($P < 0.08$)

a supplemental compound basis. Thus, with a single deficiency of Met (i.e., excess cyst(e)ine), OH-M bioefficacy was clearly inferior to DL-M. Other reviews have come to a similar conclusion, although cyst(e)ine:Met ratio was not considered as a factor (Baker 1994; Baker 2006; Jansman et al. 2003).

Assay 2 (Table 2) was done using the SAA-deficient corn–peanut meal diet containing 0.22% Met and 0.23% cyst(e)ine. Based on NRC (1994) SAA digestibility estimates, the basal diet for this assay as well as for Assay 3 contained 0.19% digestible Met and 0.19% digestible cyst(e)ine. Statistical analysis of data in Table 2 indicated that the main effects of cystine addition and Met source (DL-M vs. OH-M) were significant ($P < 0.05$) for weight gain, but not gain:feed. The growth performance difference between Met sources was greater in the presence than in the absence of the 0.10% L-cystine supplement.

Assay 3 (Table 3) was similar to Assay 2, both containing a 3 × 2 factorial arrangement of treatments, but the cyst(e)ine supplement in Assay 3 was provided by feather meal replacing corn starch in the corn–peanut meal diet. In all cases the 3.54% feather meal addition depressed ($P < 0.01$) weight gain. It also decreased gain:feed in diets unsupplemented with Met. Both gain and feed efficiency were greater ($P < 0.01$) in chicks fed DL-M than in those fed an isosulfurous level of OH-M, regardless of cyst(e)ine supplementation. Nonetheless, the weight gain advantage for DL-M over OH-M was greater in the presence (16.7%) than absence (7.7%) of excess cyst(e)ine. A smaller difference existed for gain:feed, with the advantage for DL-M vs. OH-M being 7.3% in the presence and 5.7% in the absence of excess cyst(e)ine.

We believe that previous evidence (Boebel and Baker 1982; Christensen and Anderson 1980; Katz and Baker 1975; Scott et al. 1966) together with the results presented in Tables 1, 2, and 3 herein point to the conclusion that cyst(e)ine:Met ratio in a given assay diet can have marked effects on the bioefficacy of either free acid or Ca salt forms of DL-OH-Met relative to DL-Met. In 2006, two swine papers were published wherein the free acid form of DL-OH-Met was compared to DL-Met (Kim et al. 2006; Yi et al. 2006). In the Kim et al. (2006) work, their SAA-deficient basal diet contained a cyst(e)ine:Met ratio of 1.90, and they reported a DL-OH-Met bioefficacy value of only 64% (compound basis) relative to DL-Met. Yi et al. (2006), on the other hand, used a SAA-deficient basal diet that was approximately equal in bioavailable Met and cyst(e)ine—and they reported a DL-OH-Met bioefficacy value of over 100% (compound basis) relative to DL-Met. Vazquez-Anon et al. (2006) used a multiple linear regression model to evaluate DL-OH-Met and DL-Met in broiler chick experiments. They found that dietary cyst(e)ine level was a statistically significant parameter in the model—for DL-OH-Met but not for DL-Met. It is our opinion that cyst(e)ine:Met ratio is a more important consideration than diet type (purified vs. practical) or degree of Met deficiency (severe vs. marginal) in comparisons of DL-OH-Met vs. DL-Met bioefficacy. More work is needed on both source and level of excess dietary cyst(e)ine concerning their effects on DL-OH-Met utilization.

Pharmacologic effects of cysteine

It is well established the modest excesses of SAA, particularly Cys, can have marked pharmacologic effects on trace-mineral utilization (Baker and Czarnecki-Maulden 1987). Thus, at a supplemental level of 0.40% of the diet (roughly twice the requirement), L-Cys increases gut absorption of dietary Zn and Fe, but decreases gut absorption of Cu (Greger and Mulvaney 1985; Hortin et al. 1991; Layrisse et al. 1984; Persia et al. 2004; Robbins and Baker 1980a, b; Taylor et al. 1986). The negative effects of Cys supplementation on Cu absorption and positive effects on Cu excretion are much more marked than those which can be accomplished with isosulfurous levels of either Met or cystine (Baker and Czarnecki-Maulden 1987). In fact, hepatologists treating Wilson's disease (Persia et al. 2004; Walshe 1956) and Indian childhood cirrhosis (Tanner et al. 1979) use L-Cys therapy to minimize the Cu toxicity associated with these diseases. In an animal model of Cu toxicity, Persia et al. (2004) showed that pharmacologic Cys supplementation was far more effective than pharmacologic Zn or ascorbate in reducing liver Cu accumulation.

Cysteine is, in fact, a rather potent reducing agent in addition to its capacity of being capable of either chelating or complexing trace elements. With pentavalent organic arsenic (As), supplemental L-Cys (0.40% of diet) via its reducing-agent bioactivity causes conversion of pentavalent organic As to trivalent organic As. This latter compound is 100 times more toxic than pentavalent organic As (Czarnecki et al. 1984a). This result is of significance to both human and poultry nutrition. For humans, Cys or Cys-based drugs (e.g., D-penicillamine) are typically used to treat As poisonings—and they work for inorganic As toxicities. But for organic pentavalent As poisonings, such as those caused by contaminated sea food (Chapman 1926; Coulson et al. 1935), use of Cys compounds could be lethal. For poultry, the coccidiostat Roxarsone (3-nitro-4-hydroxyphenylarsonic acid) is used, and this compound is a pentavalent organic arsenical whose toxicity is exacerbated by pharmacologic Cys (Czarnecki et al. 1984a). Interestingly, roxarsone toxicity in poultry is ameliorated by pharmacologic Cu consumption (Czarnecki and Baker 1982a, 1984, 1985; Czarnecki et al. 1984b).

Cobalt, cadmium, and selenium toxicities are also affected by pharmacologic Cys ingestion. The reader is referred to other sources for more details on these Cys × trace mineral interactions (Czarnecki and Baker 1982b; Kennedy 1968; Klaassen 1980; Lowry and Baker 1989; Southern and Baker 1981).

Sulfur amino acid toxicity, with emphasis on cysteine

Large dietary excesses of Met have been well studied due to interest in the resulting homocysteinemia and biochemical lesions, e.g., splenic hemosiderosis (Baker 2006). Among the indispensable amino acids, Met is well established as being the most growth depressing when fed at supplemental levels well above the dietary requirement (Baker 2006; Edmonds and Baker 1987a, b; Harper et al. 1970; Muramatsu et al. 1971). Far less is known about effects of excess cyst(e)ine ingestion. Both the reduced (Cys) and oxidized (cystine) forms of cyst(e)ine support animal growth equally when provided in a cyst(e)ine deficient and Met adequate diet (Baker 2006). However, prior to our recent work (Dilger et al. 2007b; Dilger and Baker 2008b), a direct comparison of graded (excess) doses of L-Cys, L-cystine, and N-acetyl-L-Cys had not been made.

At dietary supplemental levels of 2.5–3.0% of the diet, L-Cys, L-cystine, and N-acetyl-L-Cys were found to be modestly (and equally) growth depressing for young chicks, but an isosulfurous level of DL-Met was far more growth depressing than any of the cyst(e)ine compounds (Dilger et al. 2007b). No mortality occurred in chicks fed 2.5% supplemental DL-Met, L-cystine, or N-acetyl-L-Cys, but 50% mortality occurred within the first 5 days of feeding 2.5% supplemental L-Cys. Adding as little as 0.05% H_2O_2 to the drinking water prevented mortality, and this suggested that the reducing-agent activity of L-Cys was somehow involved in the lethality. Remarkably, these same excess doses of cyst(e)ine compounds, when tested in rats and pigs, revealed no mortality from L-Cys in these mammalian species.

A 72-h time-course study was subsequently conducted wherein serial blood and liver samples were taken from chicks fed a control corn–soybean meal diet or this same diet supplemented with 3.0% L-Cys (Dilger and Baker 2008b). Beginning at 12-h and extending throughout the 72-h dosing period of chicks receiving 3.0% L-Cys, plasma bicarbonate decreased and plasma sulfate increased (fourfold), resulting in a marked increase in anion gap. Interestingly, plasma total protein, albumin, and inorganic P remained stable during the entire 72 h of sampling and were unaffected by excess L-Cys ingestion. This is deemed important because these three bio-markers constitute an estimated two-thirds of the anion gap estimate (Constable 2000).

It appears that excess dietary L-Cys causes acute and lethal metabolic acidosis in chicks, but not in pigs or rats. We have not tested the effects of a similar dose of L-cystine or N-acetyl-L-Cys in chicks to prove that the nonlethal effects of these compounds will not cause the same degree of metabolic acidosis. Noteworthy is the fact that the 3.0% supplemental L-Cys dose caused a striking rise (over twofold) in plasma free cystine that was much greater in magnitude than the 30% increase in plasma free Cys.

The lethality of L-Cys in chickens is striking and unique for a dietary amino acid in excess. No other amino acid at six to seven times the requirement causes the acute mortality that is seen with excess L-Cys. Why this occurs in chicks, but not in rats or pigs is puzzling. One cannot help but wonder if uric acid rather than urea production in the avian is somehow involved, particularly since uric acid, like Cys, has reducing-agent activity.

S-Methylmethionine

S-Methylmethionine (SMM) is an analog of *S*-adenosylmethionine, with a methyl group substituted for the adenosyl group. This compound is unique to plants and is found in considerable quantity in several vegetable-based foods, including soybeans and soybean meal (Augspurger et al. 2005; Grunau and Swiader 1991; Kovatscheva and Popova 1977). It is an active participant in the Met cycle in plants (Ranocha et al. 2001). Radiolabeling experiments have suggested that the methyl group(s) of SMM are available for choline or creatine biosynthesis, but not for Met biosynthesis (Stekol 1955). Anecdotal evidence also suggests that SMM may ameliorate fatty liver caused by choline deficiency (Matsuo et al. 1980). Quantitative feeding studies to ascertain choline and Met-sparing bioefficacy had not been undertaken until our recent experiments with L-SMM (Augspurger et al. 2005).

We developed a soy-protein isolate semipurified diet that was devoid of choline (also SMM) and deficient in Met. When the diet was made singly deficient in choline or in both choline and Met, dietary SMM produced a marked growth response in young chicks. However, when the diet was adequate in choline and singly deficient in Met, SMM supplementation did not elicit a response. Thus, it appears that the remethylation of homocysteine to Met via betaine-homocysteine methyltransferase prefers betaine as a methyl donor and that methyl from SMM may be used only if choline or betaine is inadequate in the diet. That SMM can apparently methylate phosphatidylethanolamine to form choline is important and may explain why choline responses in chicks and pigs fed corn–soybean meal diets have been variable. Thus, soybean meal contains not only choline and betaine, but also 0.165% SMM (Augspurger et al. 2005). Because choline and creatine biosynthesis are thought to account for the majority of the methyl demand from *S*-adenosylmethionine, it seems likely that SMM will also be found capable of methylating guanidinoacetate to form creatine.

Guanidinoacetate, creatine, and arginine

Ringel et al. (2008a, b) have proposed that guanidinoacetate (GAA), a precursor of creatine, has potential as a feed additive for broiler chicks. As little as 0.06% supplemental GAA added to all-vegetable diets was shown to improve weight gain and feed efficiency. Our interest in GAA and creatine has been centered on the potential of these compounds to spare dietary arginine. A large body of avian work in the 1960s had shown that casein was markedly deficient in arginine (but rich in lysine) for chick growth. Thus, use of this casein-based diet produced a plethora of lysine-arginine antagonism papers, and not only supplemental arginine, but also creatine was able to elicit a growth response in these high lysine-low arginine casein-based diets (Allen et al. 1972; Austic and Nesheim 1972; Austic and Scott 1975; Fisher et al. 1956a, b; Jones et al. 1967; Robbins and Baker 1981; Waterhouse and Scott 1961; Wietlake et al. 1954).

Creatine itself is not an ideal feed additive due to its instability and cost. Guanidinoacetate, however, is stable, and at a supplemental level of 0.06–0.12% of the diet it is cost effective. Because GAA is an immediate precursor of creatine, requiring only a methyl group transfer from *S*-adenosylmethionine (or SMM), it should spare dietary arginine in the same manner as creatine. Our unpublished data confirm that 0.12% supplemental GAA (or isomolar levels of creatine) added to a 20% protein arginine-deficient casein diet yields a marked growth response in young chicks. Time will tell if GAA sparing of arginine has practical significance in poultry nutrition. Amino acid fortified low protein corn–soybean meal diets for broiler chicks are deficient in not only Met, lysine, and threonine (1st three limiting amino acids) but also in arginine and valine, which are equally 4th limiting (Han et al. 1992).

Stress and requirements for and utilization of amino acids

Batal and Parsons (2002) have provided evidence that newly hatched chicks are not developmentally able to efficiently digest protein, carbohydrates, and fat during the first 10–14 days of life. They evaluated lysine digestibility and metabolizable energy (ME) utilization of a simple casein diet and a complex corn–soybean meal diet at 0–2, 3–4, 7, 14, and 21 days posthatching. Lysine digestibility and ME yield of the casein diet was little affected by age, but these criteria were improved rather markedly with age up to 10–14 days of age in chicks receiving the corn–soybean meal diet. This early stressful growth period in young chicks has been a source of emphasis in recent years, and Bartell and Batal (2007) have recently shown that addition of 1.0% glutamine to a corn–soybean meal diet will improve indices of intestinal health and increase body weight gain of young chicks.

Recent stress-related research from Japan has focused on individual amino acid additions for neonatal chicks. Nakashima et al. (2007) has reported beneficial effects on muscle proteolysis from leucine or ketoisocaproate administration. This group (Nakashima et al. 2008) has also found interesting effects from glycine administration. Other work has been directed at minimizing stress levels in neonatal chicks by administering alanine (Kurauchi et al. 2008), arginine (Suenaga et al. 2008a, b), proline (Hamasu et al. 2008), or serine (Asechi et al. 2008).

How does generalized stress due to heat exposure (Han and Baker 1993; Shan et al. 2003) or disease (Klasing and Barnes 1988; Webel et al. 1998a, b) affect amino acid requirements and utilization of young chicks. The evidence would suggest that although marked anorexia can be induced by either heat stress or experimentally induced *E. coli* infection (i.e., LPS induced), the amino acid requirements remain rather constant expressed in terms of dietary concentration (i.e., % of diet or % of ME intake). The requirements for individual amino acids, in fact, decrease when expressed on a mg/day intake basis. Also, the Webel et al. (1998a, b) work evaluated the efficiency of using lysine, threonine, and arginine for protein accretion. With graded intakes of these amino acids, plots of protein accretion against digestible amino acid intake showed straight-line responses up to the point of maximal protein accretion. With or without *E. coli* endotoxin (LPS) administration (every other day for 11 days), the regression lines below requirement for (−) and (+) LPS were both linear and parallel, and this indicates that utilization efficiency of these amino acids was not only constant (i.e., no diminishing returns) but also was unaffected by LPS administration.

Webel et al. (1997) used young pigs to evaluate the sequence of events during the first 24 h following a challenge dose of LPS. The pigs had been feed deprived for 12 h before receiving the i.p. injection of LPS, and they remained in a fasted state for the 24-h post-dosing study period. Blood samples were collected at 0, 2, 4, 8, 12, and 24 h after the LPS injection. At 2 h, plasma TNF-α was elevated tenfold, and at 4 h post-injection, cortisol was also elevated tenfold, but interleukin 6 was elevated 200-fold. These elevations in cortisol and proinflammatory cytokines in diseased or immunologically challenged pigs are thought to be the cause of reduced feed intake and growth (Johnson 2002; Kelley et al. 1994; Klasing and Johnstone 1991). In the Webel et al. (1997) study, plasma urea nitrogen was increased almost threefold at 8 and 12 h post LPS injection, i.e., following the cytokine responses, and this is indicative of a catabolic response to the LS challenge.

McFarlane et al. (1989a, b, c) studied multiple stressors in young chicks, including heat, coccidiosis, aerial ammonia, and stray voltage in the pen. Remarkably, when these stressors, all of which caused some degree of anorexia, were imposed singly or in various combinations, the decreases in feed intake and growth were additive and equal to the sum of each stressor imposed singly. Hyun et al. (1998) did a similar study in pigs and imposed heat, crowding, and mixing as stressors. They also found that these stress agents produced additive decreases in feed intake and growth, roughly a 10% decrease for each independent stressor, but a 30% decrease when all three stressors were imposed together. Clearly, anorexia in sick or stressed animals has benefits. When Murray and Murray (1979) infected mice with *Listeria*, they noted a marked decrease in voluntary food intake. However, when they force fed these infected mice to the same intake as control noninfected mice, nearly 100% of the force-fed mice died, whereas only 50% mortality occurred in infected mice that were not force fed. This indicates that anorexia is an adaptive response to disease stress that is both necessary and beneficial. Due to the reduced feed intake, attempts to increase the level of individual or multiple amino acids in the diet to achieve the same intake as that occurring in unstressed animals may do more harm than good.

Considerable controversy has existed regarding whether the efficiency of use (for protein and/or amino acid accretion) of amino acids above maintenance is constant (Baker et al. 1996; Batterham 1994; Batterham et al. 1990; Chung and Baker 1992b; Edwards III et al. 1997, 1999; Heger et al. 2002, 2003; Velu et al. 1971, 1972) or variable with diminishing returns (Gahl et al. 1991; Heger and Frydrych 1985; Miller and Payne 1961) in growing animals fed graded levels (from near 0 to near optimal) of a limiting amino acid. Other work had suggested constant utilization of a complete amino acid mixture or of various intact proteins (Emmert et al. 2000; Hegsted and Neff 1970). Apart from this controversy, it is important to note that the available evidence points to the conclusion that utilization efficiencies of individual essential amino acids are different (Adeola 1995; Baker et al. 1996; Batterham 1994; Chung and Baker 1992b; Edwards III et al. 1997, 1999). Batterham (1994), for example, calculated efficiency values (above maintenance) of 75, 64, and 38% for lysine, threonine, and tryptophan, respectively. These were pig values and were based on recovering (retaining) absorbed amino acids in whole-body protein. Heger et al. (2002, 2003) also found tryptophan to be least efficiently utilized among individual amino acids fed to pigs.

The efficiency work discussed above suggests that even when an indispensable amino acid is consumed below its required level and with all other amino acids adequate, true digestible (absorbed) levels of these amino acids are retained with surprisingly low efficiencies. Why? Does the need for glucose via gluconeogenesis pull amino acids away from protein accretion (Pascual et al. 1997). Regardless, the phenomenon of "inefficiency of amino acid use for protein accretion" appears to be a valid concept and one which confounds those who are interested in modeling amino acid requirements. Most of the studies on efficiency of amino acid use involved casein or casein–amino acid mixtures, and it has been shown that true digestibilities of free amino acids and the amino acids in casein are not different from 100% (Chung and Baker 1992c). Thus, the low efficiencies of recovering (in whole-body protein) digestible (absorbed) amino acids does not involve digestibility phenomena.

Protein quality of oilseed products, with emphasis on soy

Soybean meal furnishes a majority of the amino acids in most poultry diets. Moreover, further processed soy products are often used in nutrition research studies with poultry. Boling-Frankenbach et al. (2001) completed 9-day protein efficiency ratio (PER) studies at 10% dietary CP in which soybean meal PER was compared to the PER obtained with several other protein sources (Table 4). The PER values shown in Table 4 are revealing in that canola meal, in fact, was found to have a higher PER protein quality than soybean meal. This resulted from the fact that the lysine deficiency (% of CP) of canola meal is less severe than the SAA deficiency of soybean meal. The PER comparisons also illustrate how superior both soybean meal and canola meal are relative to other oilseed meals such as cottonseed meal and peanut meal. Moreover, relative to soybean meal, poultry feedstuffs such as meat and bone meal and corn gluten meal are very inferior in protein quality. The data in Table 4 also illustrate how merely looking at body weight gain can result in misleading conclusions regarding protein quality. Casein, for example, is higher in ME than either soybean meal or canola meal, and this causes a lower food intake in chicks fed casein. Hence, based on weight gain, one might conclude that casein is less than half as efficacious as soybean meal. However, when dividing by CP intake, the lesser food intake produced by casein is taken into account such that a more realistic protein quality value for casein relative to soybean meal and canola meal is obtained. Nonetheless, the severe arginine deficiency of casein (more deficient than SAA) for chicks results in a surprisingly low PER value. With rats or pigs, the protein quality of casein relative to soybean meal would be higher.

Emmert and Baker (1995) performed chick protein quality (PER) studies with four different processed soy products: dehulled soybean meal (SBM, 49% CP), soy-protein concentrate (SPC, 63.9% CP), functional soy-protein isolate (FSPI, 82.4% CP), and edible soy-protein isolate (ESPI, 85.0% CP). These soy products are often used in nutrition research studies with laboratory animals, but a direct comparison of their protein quality features had never been carefully made. Soy concentrates are used in meat products, baked goods, and certain dairy products. Soy isolates are typically used in beverages, soups, gravies, meats, baked goods, and cheeses. To obtain ESPI from FSPI, the latter is treated with H_2O_2 to reduce bacterial counts, and ESPI is then typically used for enteral products and infant formulas.

At 10% CP and without amino acid supplementation, average chick PER values [gain (g)/CP intake (g)] obtained by Emmert and Baker (1995) were 3.54 for SBM, 3.24 for SPC, 3.14 for FSPI, and 2.78 for ESPI. Addition of the 1st limiting amino acid (methionine) or the 1st and 2nd limiting amino acids (methionine and threonine) brought about increases in PER, as expected, and essentially eliminated the PER differences among the soy sources that were observed when fed without amino acid supplementation. These results emphasize the fact that not all soy sources have the same protein quality. Thus, in going from soy flour to SPC, hexane extraction and alcohol washes are involved which remove lipids and oligosaccharides. Further processing of SPC to SPI involves alkaline extraction and centrifugation (to remove cotyledons), followed by acid precipitation (to remove soy whey, a product rich in both SAA and threonine). Washes with H_2O_2 are then used to convert FSPI to ESPI. The analytical results (amino acid analysis) obtained with the four soy products evaluated by Emmert and Baker (1995) were predictive of how the products would rank in PER feeding studies.

Table 4 Protein quality assessment of various intact proteins as measured by protein efficiency ratio (PER) in young chicks

Protein source[a]	Limiting amino acid	Weight gain (g)	PER[b]
Canola meal (37.1% CP)	Lysine	129	3.98
Soybean meal (48.4% CP)	SAA	107	3.75
Casein (88.3% CP)	Arginine	51	3.01
Cottonseed meal (44.1% CP)	Lysine	41	2.41
Peanut meal (43.0% CP)	Lysine	39	2.24
Meat and bone meal (49.0% CP)	SAA, tryptophan	37	2.03
Corn gluten meal (62.9% CP)	Lysine	14	1.31
Pooled SEM		2.5	0.08

Adapted from Boling-Frankenbach et al. (2001). Data are mean values of four pens of four male chicks during the period 8–17 days posthatch

[a] All ingredients were fed at 10% CP and as the sole source of protein in a cornstarch-dextrose purified diet

[b] Weight gain (g)/CP intake (g)

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