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Betaine supplementation can optimize use of methionine, choline in diets

ABSTRACT

Findings relative to betaine supplementation of diets provide poultry feed formulators an attractive way to optimize their use of methionine and choline. Betaine provides the most efficient way to supply methyl groups in the diet and decreases the need for choline and methionine to meet this function.

By ERKKI VIRTANEN and GARY RUMSEY

Betaine, methionine and choline, along with the vitamin co-enzymes vitamin B_6, folic acid and vitamin B_{12}, are the principal sources of methyl groups in the diet of animals and humans. Although no nutritional recommendations on the methyl group needs of animals have been established because of the strategic role of methylation in the nervous, immune, renal and cardiovascular systems, it is agreed that both growing and mature animals require a constant supply of methyl groups (du Vigneaud, 1952; Newberne, 1993). Methyl groups are needed for synthesizing several physiologically essential compounds such as methionine, carnitine, creatine, phospholipids, adrenal hormones, RNA and DNA (Baker, 1984; Friedel et al., 1989; Smolin and Benevenga, 1989; Frontiera et al., 1994). A deficit of methyl groups is the only dietary

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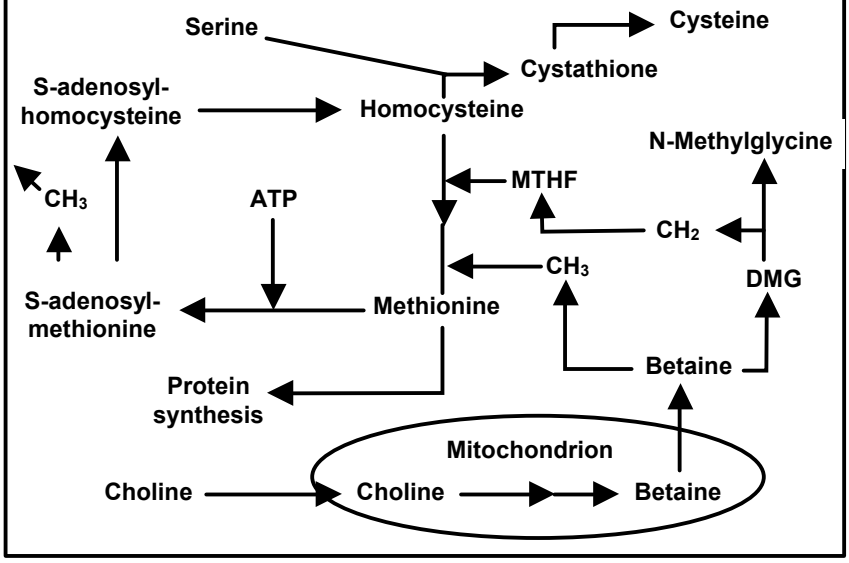
FIGURE



Metabolic relationship between betaine, choline and methionine

TABLE

Methionine/betaine interaction trials with broiler chicks under various levels of coccidial challenge[1,2]

Research site	Days on trial	Basal level of methionine, %, st/gr/fi	Added choline ppm,st/gr/fi	Added DL-methionine %	Added betaine %	Final bodyweight kg	Final feed/gain
Colorado Quality	47	0.38/0.37/0.30	520/510/360	-	-	2.336[b]	1.808[ab]
Research, Inc. -	47	0.38/0.37/0.30	520/510/360	0.15	-	2.380[a]	1.792[a]
clean[3]	47	0.38/0.37/0.30	520/510/360	-	0.075	2.372[a]	1.788[a]
Colorado Quality	47	0.42/0.42/0.35	520/510/360	-	-	2.339[ab]	1.841[bc]
Research, Inc. -	47	0.42/0.42/0.35	520/510/360	0.10	-	2.380[a]	1.792[a]
clean[3]	47	0.42/0.42/0.35	520/510/360	-	0.05	2.350[ab]	1.804[ab]
Colorado Quality	47	0.38/0.37/0.30	520/610/360	-	-	2.276[c]	1.875[d]
Research, Inc. -	47	0.38/0.37/0.30	520/610/360	0.15	-	2.325[b]	1.846[c]
challenge[4]	47	0.38/0.37/0.30	520/610/360	-	0.075	2.310[bc]	1.835[bc]
Colorado Quality	47	0.42/0.42/0.35	520/510/360	-	-	2.291[c]	1.853[c]
Research, Inc. -	47	0.42/0.42/0.35	520/510/360	0.10	-	2.325[bc]	1.846[c]
challenge[4]	47	0.42/0.42/0.35	520/510/360	-	0.05	2.317[bc]	1.823[b]
Georgia Poultry	42	0.40/0.36/0.31	360/360/180	-	-	2.110x	1.932x
Research, Inc. -	42	0.40/0.36/0.31	360/360/180	0.15	-	2.170[y]	1.902[z]
Challenge[5]	42	0.40/0.36/0.31	360/360/180	-	0.05	2.132[xy]	1.915[y]
	42	0.40/0.36/0.31	360/360/180	-	0.075	2.165[y]	1.905[z]
	42	0.40/0.36/0.31	360/360/180	-	0.10	2.163[y]	1.902[z]

[1]Commercial corn-soy diets with 22-23, 20 and 18% protein in the starter, grower and finisher diets, respectively
[2]Common superscript letters indicate non-significant (P>0.05) differences between treatments
[3]Challenge minimized by using clean litter. The 4-point scale for measuring lesion score was <0.3
[4]Mild inoculation via the feed with a mixture of *Eimeria tenelle, E. maxima* and *E. acervulina.* Lesion score was 0.8-1.6 at 21 days
[5]Moderate inoculation via the feed with a mixture of *E. tenella, E. maxima* and *E. acervulina.* Lesion score was 1.3-1.8 at 21 days

deficiency that by itself appears to be carcinogenic (Rogers, 1993.)

There is some confusion among nutritionists concerning the relative physiological roles of the above-mentioned compounds in methylation reactions (Jackson, 1996)(Figure). S-adenosyl-methionine (SAM), synthesized from methionine and adenosine phosphate, is the primary methyl donor in virtually all metabolic systems (du Vigneaud, 1939; Finkelstein, 1990). Before methionine can donate its methyl, it must be converted to SAM. It was the metabolic mobility of the methyl group of methionine that led to its being described as biologically labile (Mudd and Poole, 1975). Additional labile methyl groups can be derived from betaine as well as the methylated form of folic acid, 5-methyltetrahydrofolate (THF, Mudd et al., 1980).

All three methyl groups of betaine serve as methyl donors in converting homocysteine to methionine, wherein the organism is maintained in a heightened state of methylation potential (Frontiera et al., 1994). In the reaction catalyzed by the betaine-homocysteine methyltransferase (BHMT) enzymatic pathway, betaine transfers one of its three methyl groups (a labile methyl group in this instance) directly to homocysteine and in so doing, forms methionine and dimethylglycine (Finkelstein, 1990). The aforementioned dimethylglycine is then catabolized to one carbon units from which labile methyl groups in the form of THF are derived by de novo formation. It is the labile methyl group of THF that serves as the methyl donor for the enzyme 5-methyltetrahydrofolate-homocysteine methyltransferase (FHMT), the second and alternate pathway for synthesizing methionine from homocysteine.

Summarily, it appears betaine donates one of its methyl groups directly to homocysteine to form methionine in the BHMT reaction while the remaining two betaine methyls indirectly participate in the methylation of homocysteine to methionine via the FHMT pathway. The activity of the FHMT reaction is much less than the activity of the BHMT pathway in several animal species, including the chick (Baker and Czarnecki, 1985; Saunders and McKinlay, 1989). Enough evidence has been accumulated to support the importance of betaine dependent methylation (Storch et al., 1991). Furthermore, the BHMT pathway is the only means for the degradation of betaine (and choline) as well as being the principal regulator of methionine production.

BHMT's activity is increased at both ends of the spectrum of methionine intake (Smolin and Benevenga, 1989). The activity of this enzyme appears to be a significant means of maintaining methionine concentrations during periods of inadequate methionine intake as well as for the removal of excess homocysteine following excessive methionine intake (Finkelstein et al., 1982).

Because its methyl groups are not labile, choline, per se, is not a methyl donor. The methyls of choline become labile only after the two-step mitochondrial oxidation via betaine aldehyde to betaine (Mann et al., 1938). There is some direct evidence on the efficiency of this conversion based on the work of Stekol et al. (1953a, 1953b, 1957), which have been confirmed by findings from our research laboratories (Tiihonen, Cultor Technology Center communications). It appears that a labelled methyl group from betaine is much more efficiently transferred to methionine or creatine than the methyl group from choline. Baker and Czarnecki (1985) reported, in their research to quantify the efficacy of homocysteine as a methionine precursor, that betaine, but not choline, enhanced the homocysteine to methionine pathway.

While total dietary sulfur amino acids significantly affected the activity of the BHMT pathway of methionine generation (Finkelstein et al., 1986), the activity of choline oxidase appeared to be unaffected (Molitoris and Baker, 1976). There are marked differences between choline and betaine in their effects on BHMT activity; while 0.2% dietary choline produced a non- significant 36% increase in BHMT activity, 0.2% betaine produced a corresponding significant 213% increase (Finkelstein, 1983). Research findings from our laboratories show that, unlike betaine, dietary choline is rapidly incorporated into body lipids, thereby rendering it relatively unavailable for hepatic methylations, (Tiihonen, Cultor Technology Center communications).

How much of the dietary methionine is required for methylation? Predicated on the assumption of a highly efficient conversion of choline to betaine, Frontiera et al. (1994) estimated from the data of Mudd et al. (1975; 1980), that humans require about 0.35 mmol/kg bodyweight per day of methyl groups and that about 0.05 mmol/kg bodyweight per day (about 14%) of this requirement is obtained from dietary choline after it is converted to betaine. Estimates on the methylation requirements of chicks are unavailable, but the work of Saunderson and MacKinlay (1990) suggests that a major part of dietary methionine is converted to SAM.

It has been suggested that about 90% of the chick's need for transmethylation must be furnished by methionine in the form of SAM (D. H. Baker, personal communication). Under abiotic stresses such as disease, the need for SAM is likely to increase, because methylation reactions are needed for building immune defense mechanisms as well as the synthesis of polyamines, which play a role in tissue repair processes (Tsiagbe et al., 1987a, 1987b). The Tsiagbe group observed the methionine requirement for maximum growth was below the requirement for maximum antibody response and that dietary choline was without effect on the immune variables studied.

It is important that SAM be recirculated back into methionine for protein synthesis. Whereas homocysteine may be remethylated to methionine by either BHMT or FHMT, it can also be metabolized via a unidirectional transsulfuration reaction to cystathionine, which is ultimately catalyzed to aketobutyrate and cysteine (Frontiera et al., 1994). Finkelstein (1990) reported that about 45% of homocysteine was converted to cystathionine in rats fed a balanced diet. Mudd and Poole (1975) estimated that 53% of the available homocysteine was converted to cystathionine in human males fed a balanced diet, but declined to 20% following the feeding of a methionine-deficient diet.

This finding suggests that significant amounts of methionine may be "lost" to cyst(e)ine synthesis under methionine-deficient conditions. It has also been demonstrated that the cyst(e)ine content of a diet can affect the animal's requirement for methionine and that a percentage of the total sulfur amino acids requirement of the chick, pig and rat that can be supplied by cystine or cysteine (Smolin and Benevenga, 1989). Finkelstein and Mudd (1967) showed that dietary cyst(e)ine supplementation resulted in significantly higher levels of BHMT activity, even when dietary methionine was adequate.

They concluded that the metabolic effect of these changes may be enhanced methionine retention and diminished transsulfuration. It should be noted that no dietary source for homocysteine is needed to improve methionine availability because homocysteine is produced from the methionine (SAM) used in methylation (Finkelstein, 1990).

Being the first limiting amino acid, the practical implications of improving methionine retention are the most obvious in the poultry nutrition arena. We have run a number of studies with broiler chicks using marginally methionine deficient (20-25%) practical corn-soy diets (Table). The trials have been run under practical conditions on built-up litter, the birds thereby being exposed to a normal level of pathogen challenges and the diets supplemented with commonly accepted ionophoric coccidiostats and growth promoters. The data from all trials shows a significant response to added methionine in growth or feed/gain or both. The performance of broilers supplemented with either 0.10-0.15% methionine or 0.050-0.075% betaine were similar except for the single trial where birds fed the 0.05% betaine diet exhibited significantly better feed/gain than those birds fed the 0.1% methionine diet.

All diets were supplemented with recommended commercial levels of choline which were in accord with National Research Council (1994) recommendations. Therefore, the conclusion of Jackson (1996) that betaine can spare methionine only in choline-deficient diets lacks credibility. Our data presented here are also in agreement with the findings of Finkelstein et al. (1983), as well as Baker and Czarnecki (1985), whose data indicate that choline was ineffective in stimulating BHMT activity.

Most probably, the requirement for SAM would be minimized and there would be less need for efficient recovery of homocysteine in a pathogen and challenge-free laboratory environment. This may also be true for birds fed diets low in cyst(e)ine because under the aforementioned conditions, there would be a diminished need to spare methionine with supplemental methyl donors. Under practical field conditions, the need for methionine for SAM generation is very likely increased as is the need for methionine recovery through homocysteine methylation.

Our data show that under practical field conditions, betaine is more effective in promoting growth and feed efficiency than methionine, provided the dietary levels of methionine *are not* more limiting than in the studies cited here.

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KEY WORDS

Betaine, Betafin (Poultry), methionine, choline, methyl donor