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BETAFIN®

- Natural product
- The most efficient methyl donor for animal nutrition
- Specific benefits through its osmotic function

About the author

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Continuing the debate: betaine, methionine and choline

Continuing our discussion on the nutritional value of methionine, choline and betaine, Dr Virtanen supplies his views on the metabolic importance and the dietary effects that these compounds have on the performance of poultry

THE BIOCHEMICAL RELATIONSHIPS of methyl donors and their role in practical feed formulation have been recently studied and discussed both in scientific papers and industry magazines (Virtanen and Rosi 1995, Schutte et al. 1995, Virtanen and Remus 1996, Dudley Cash 1996, Rostagno and Pack 1996, Virtanen and Rumsey 1996). The most recent review by Dr. Annison was published in the October 1996 issue of Feed Milling International.

Whereas our view on the roles of betaine, methionine and choline in the methylation metabolism has been presented in more detail elsewhere (Virtanen and Rumsey, Feedstuffs, October 7, 1996), Dr. Annison's article deserves some comments.

Activated methionine, SAM, is the primary methyl donor

S-adenosylmethionine (SAM), synthesised from methionine and adenosine phosphate, is the primary methyl donor in virtually all metabolic systems (du Vigneaud 1939, Finkelstein 1990). Methylation is not needed to produce SAM from methionine as indicated by Fig.2 of Dr. Annison's article. However, the only way to recycle SAM back to methionine is via the transmethylation cycle, where the final step is the methylation of homocysteine to methionine. In this reaction, betaine is the major methyl donor in the chick (Saunderson and McKinlay 1990).

A large part of methionine is used to produce SAM, and needs to be recycled to methionine to be available for protein synthesis.

A major part of dietary methionine is used for methylation. Frontiera et al. (1994) estimated from the data of Mudd et al. (1975, 1980) that the requirement for methyl groups in the human exceeds the dietary intake of methionine. Estimates on the methylation requirements of chicks are unavailable, but the work of Saunderson and McKinlay (1990) suggests that a major part of methionine is converted to SAM. Research at our laboratory (Tiihonen, Cultor Technology Center communications) demonstrates that the concentration of SAM in the chicken's liver is about the same or higher than that of methionine (Table 1). Interestingly, generation of SAM increased in this study when the chicks were challenged with coccidia, which can be explained by the elevated need for SAM for immune responses and tissue repair (Tsiagbe et al. 1987 a,b).

Hence it is evident that the chick needs a high methylation capacity to recycle methionine used for methylation back to methionine. Let us make a rough calculation: the chick's dietary requirement for methionine is 5200 ppm during its three first weeks of life (NRC).

FIGURE 1 Metabolic relationship between betaine, choline and methionine

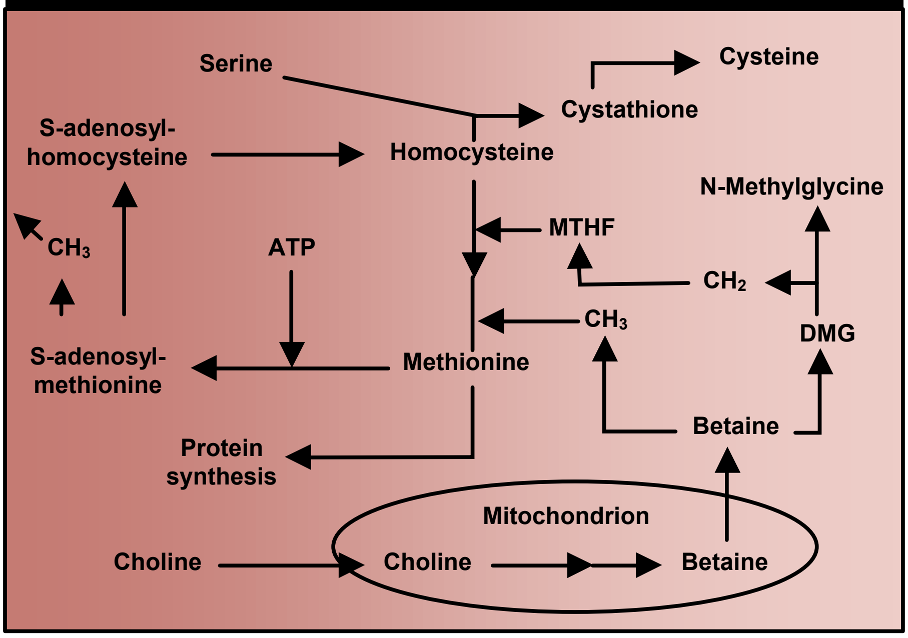

TABLE 1 **Effect of dietary treatment and coccidiosis challenge on the concentration (nmol/g wet tissue) of free methionine and S-adenosylmethionine (SAM) in broiler liver. Dietary choline content was 1400ppm and salinomycin was used as the coccidiostat**

	0.52 per cent Methionine	0.40 per cent Methionine	0.40 per cent Methionine + 0.06 per cent Betaine
Methionine	70	67	69
SAM	73	51	66
SAM, challenged*	118	97	100

** Moderate coccidiosis challenge through oral inoculation*

The corresponding figure for choline is 1300 ppm. Assuming that 60 per cent of the choline is required for other purposes than methylation (e.g. synthesis of phosphatidylcholine and acetylcholine, see Lowry et al 1987), 520 ppm would be available for methylation. Even if this amount was fully available for methylation, it would be theoretically able to directly methylate 675 ppm homocysteine (equimolar to 520 ppm choline) to methionine, and some more indirectly through methylating folate. These values are below the estimated need for methionine as methyl donor.

> ***"Routine additions of choline into commercial broiler diets are far below the levels of the chick's requirement for methylation"***

What is the evidence on the methylation value of choline?

Choline is not a methyl donor, because its methyl groups are not labile, i.e. metabolically available for methylation. Choline is a precursor of a methyl donor, betaine. Conversion of choline to betaine requires its active uptake by mitochondria and two-step oxidation via betaine aldehyde. While it is clear that this conversion *qualitatively* takes place in the chick, there is sparsely data on the *quantitative* efficacy of the conversion. Stekol et al. (1953 a,b; 1957) demonstrated that a labile methyl group from betaine methylated three-four times more efficiently homocysteine to methionine than a methyl group from choline in chicks. In creatine synthesis, the methyl group of betaine was about ten times more efficient. Finkelstein (1983) reported that in the rat 0.2 per cent betaine added to a purified 22 per cent amino acid diet stimulated the homocysteine methylating enzyme (BHMT) about six times more than 0.2 per cent choline (213 per cent vs. 36 per cent increase in BHMT activity). The preliminary data from our laboratory indicate similar differences in the methylation efficacy of betaine vs. choline. The difference may not be explained only by inefficient oxidation of choline but also by incorporation of choline into phospholipids in the gut tissue, making it less available for conversion (Tiihonen, Cultor Technology Center communications). Moreover, ionophores commonly used in poultry feeds may inhibit conversion of choline to betaine (Tyler et al. 1979). Emmert et al. (1996) reported that betaine and choline produce similar increases in BHMT activity in the chicken liver; however, those of their diets which were moderately deficient in methionine were supplemented with excess amounts (2500-5600 ppm) of these compounds. Hence it is evident that routine additions of choline into commercial broiler diets are far below the level of the chick's requirement for methylation, especially when environmental challenges increase the need for methylation.

Why similar kinds of experiments on the methionine sparing effect of betaine produce different results?

The importance of the recycling of methionine depends on two major factors.

1. The requirement of methionine for methylation, which is affected by environmental conditions, especially pathogen challenge
2. The availability of cyst(e)ine: If cyst(e)ine becomes limiting in the metabolism, a significant part of homocysteine needs to be converted to cyst(e)ine, and not available for methylation to methionine.

TABLE 2 **Growth performance (1 to 47 days) of broilers fed a basal, methionine-deficient diet or the basal diet supplemented with 1.5g DL-methionine or 0.75g betaine/kg. The level of choline was 1650 ppm, 1550 ppm and 1320 ppm in starter, grower and finisher, respectively. The broilers were fed with a clean (Treatments 1 – 3) or a coccidia-inoculated diet (Treatments 4 – 6)**

Coccidia challenge	Diet	Body weight kg	Feed:gain	Mortality per cent
No	Basal	2.336^{ABC}	1.808^{AB}	4.1^{A}
No	Basal + Met	2.380^{D}	1.792^{A}	4.1^{A}
No	Basal +Bet	2.372^{D}	1.788^{A}	3.2^{A}
Yes	Basal	2.276^{A}	1.875^{D}	2.3^{A}
Yes	Basal +Met	2.325^{BC}	1.846^{C}	2.0^{A}
Yes	Basal +Bet	2.310^{ABC}	1.835^{BC}	4.3^{A}

Finnsugar's experiments

Our experiments using practical corn-soya or wheat-barley-soya diets demonstrate that betaine can spare a significant part of methionine under practical growing conditions, also with diets supplemented with higher than 'adequate' levels of choline. Dr. Annisons has misinterpreted the data of Virtanen and Rosi (1995, Table 2).

It needs to be stressed that the dietary uptake of homocysteine is marginal, hence betaine can only spare the part of methionine which can be potentially lost in the transmethylation cycle. Our experiments and the work of Pesti et al. (1979) demonstrate that about 25 per cent of the chick's methionine requirement can be spared with betaine, when the birds are raised in practical conditions and fed practical corn-soya diets.

Rostagno and Pack (1996) reported that betaine had no methionine sparing effect in their experiment. Their basal diet was low in cysteine and contained methionine about 60 per cent of the chick's requirement. The experiment was run under clean, non-stress conditions. In this experiment, the need of methionine for methylation was obviously minimised and the need of homocysteine for cyst(e)ine synthesis maximised, resulting in minimal need for methionine recycling. Under these circumstances it is natural that betaine plays a minor role in methionine metabolism. The same conditions largely apply to the study of Schutte et al. (1995).

Although minimising environmental challenges may follow the principles of traditional nutrition research, our view is that it is not an applicable way for the determination of methionine and methylation requirement in commercial broiler diets. With pathogen challenges normally present in broiler houses, a higher level of methylation is needed to prevent loss of methionine in transmethylation. Without an effective methyl donor, additional methionine only produces accumulation of homocysteine, a toxic intermediate of the methionine metabolism. This may explain why methionine responses in practical conditions are far below those reported by Schutte et al. (1995) and Rostagno & Pack (1996).

"Although minimising environmental challenges may follow the principles of traditional research, our view is that it is not an applicable way for the determination of methionine and methylation requirement in commercial broiler diets"

What are the physiological roles of betaine?

It is self-evident that betaine is not able to replace methionine as a structural part in proteins, and can only increase methionine availability through its methyl donor function. However, in contrast to the claim of Annison that "betaine has a single role in metabolism as intermediate of choline metabolism", there is extensive literature demonstrating the importance of betaine in the maintenance of osmotic balance, especially in hyperosmotically stressed organisms and cells (see e.g. Yancey et al. 1982, Burg 1994, Petronini et al. 1994.) Interestingly, animal cells appear to have limited capability to respond to osmotic stress by increasing oxidation of choline to betaine (Björköv 1991, Burg 1992), and are hence more dependent on uptake of exogenous betaine.

The osmotic properties of betaine have been widely utilised in the salmon industry (see e.g. Clarke et al. 1994). Recent research indicates that the osmotic effects of betaine significantly improve the resistance of gut eptihelium against coccidial infection in chicks (Augustine et al. 1996, Remus 1996).

Key words:
Betafin (poultry), Betafin, betaine, methionine, choline, methyl donor, broiler, cysteine,