The Keto Acid of Methionine Is a Safe and Efficacious Substitute for Dietary L-Methionine: The Answer from Chick Bioassays

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In this issue of The Journal of Nutrition, Dilger et al. (1) provide evidence for the safety and efficacy of 2-keto-4-(methylthio)butyric acid (Keto-Met) as a precursor of L-methionine (L-Met) in chicks. They carefully demonstrate that Keto-Met, provided as the calcium salt, is highly efficacious, with isosulfurous levels of Keto-Met producing growth that averaged 88–96% of that obtained with L-Met. They further show that, when excess levels are fed, Keto-Met is no more toxic than L-Met. This study is the most recent in a career-long series of studies from David Baker’s laboratory on the efficacy and safety of replacing sulfur amino acids with various analogs in the diets of chicks, pigs, and rats.

To maintain nitrogen balance or support growth, minimal amounts of each of the essential amino acids in the l-configuration are required. The true requirement for essential amino acids, however, appears largely to be reducible to a requirement for their carbon skeletons. Most of these carbon skeletons, or keto acids, can be converted to l-amino acids by transamination reactions catalyzed by enzymes present in animal tissues. The efficacy reported for the replacement of dietary L-Met by Keto-Met (1) indicates that Keto-Met undergoes highly efficient transamination to L-Met, with little loss of this carbon skeleton due to oxidative decarboxylation and further catabolism. The essentially complete conversion of Keto-Met to Met, at least under normal physiological and dietary conditions, is also suggested by the high efficiency of the methionine salvage pathway in returning the methylthio moiety of methylthioadenosine, which is formed as a by-product of polyamine synthesis, to the methionine pool via Keto-Met as an intermediate (2,3).

The ability to convert Keto-Met to L-Met almost certainly underlies the ability of many species to effectively use D-Met or DL-2-hydroxy-4-(methylthio)butyric acid (DL-OH-Met) as a source of L-Met. Synthetic DL-Met and DL-OH-Met are used extensively in practical diets for poultry and other animals to increase the level of sulfur amino acids, which are frequently limited in the protein sources of these diets (4). Conversion of either D-Met or DL-OH-Met to L-Met requires the stereospecific oxidation of the 2-carbon to yield Keto-Met followed by the transamination of Keto-Met to L-Met. D-Met is oxidatively deaminated to Keto-Met by D-amino acid oxidase in peroxisomes (5,6); D-OH-Met is oxidized to Keto-Met by D-2-hydroxy acid dehydrogenase in mitochondria; and L-OH-Met is oxidized to Keto-Met by 1-2-hydroxy acid oxidase in peroxisomes (7–9). Keto-Met is then converted to L-Met by transfer of the α-amino group from a donor amino acid, a reaction that can be catalyzed by several aminotransferases (10). Rangel-Lugo and Austic (10) demonstrated that chick tissue homogenates were capable of using many different amino donors for the transamination reactions converting Keto-Met to L-Met, with branched-chain amino acids and glutamate being among the best donors.

The careful design of diets and feeding studies is critical to the analysis of the replacement value of an amino acid analog for an essential l-amino acid. In studies of methionine analogs, one must consider that the total sulfur amino acid requirement can be met by Met alone or by a mixture of Met and cyst(e)ine (11). For their bioassays of Keto-Met, Dilger et al. (1) used 2 approaches: 1) supplementing a cysteine-adequate purified amino acid diet with graded levels of Keto-Met (~40–70% of the Met requirement) to yield a linear growth response and then comparing this response to that obtained with isosulfurous levels of Met by a standard slope-ratio analysis, and 2) supplementing a low-protein corn-soybean meal-peanut meal diet that was deficient in methionine (2.5 g/kg) and total sulfur amino acids [5.0 g/kg Met + cyst(e)ine] with a single level of Keto-Met (a level isosulfurous to 0.5 g/kg Met) to yield a total sulfur amino acid level near but slightly below the requirement and then comparing the growth response to a standard curve obtained by supplementing the same diet with a range of l-Met levels (0, 0.25, 0.5, or 0.75 g/kg). The latter method is less precise for determining relative efficacy but more closely parallels the situation encountered within the food animal industry in which grossly adequate diets are supplemented to maximize growth.

In chicks, as in many other animals, voluntary food intake is particularly sensitive to imbalances and ratios of one amino acid to another (12–14). Not surprisingly, food intake was low in chicks fed the basal diet and increased markedly with each addition of Met or Keto-Met over the range used in the slope-ratio analysis (1). Thus, growth response in the bioassay may have been due to either, or both, the increased concentration of the limiting amino acid in the food or the increase in total food intake. One way to at least partially address this issue is to use...
gain:food instead of weight gain as the outcome of interest. Despite as much as a 119% increase in food intake by the chicks supplemented with Keto-Met, Dilger et al. (1) obtained similar efficacy values for Keto-Met when they were calculated based on gain:food as when they were calculated based on weight gain.

The assessment of safety is particularly important for methionine analogs because methionine is considered to be the most toxic of the dietary essential amino acids, causing both growth reduction and tissue damage (13–15). Deposition of iron (hemosiderin) in the spleen is a consistent feature of methionine toxicity, and the splenic iron content generally increases in parallel with growth reduction (15). To test the safety of Keto-Met relative to l-Met, Dilger et al. (1) added excess l-Met (15 or 30 g/kg) or the isosulfurous amount of Keto-Met to a nutritionally adequate corn-soybean meal basal diet. The growth-depressing and food intake-depressing effects of excess Keto-Met, as well as splenic iron deposition (which was grossly depressing and food intake-depressing effects of excess Keto-Met), were similar to those obtained with isosulfurous levels of l-Met (1). Thus, Keto-Met in the chick diet had toxic effects that were comparable to those produced by an isosulfurous level of l-Met.

Methionine toxicity is believed to be due to catabolism of excess methionine by a nonspecific transamination “pathway” in which Met is first converted to Keto-Met and then oxidatively decarboxylated to 3-methylthiopropionate (16). Thus, the observation that Keto-Met was no more toxic than l-Met seems to suggest that even large amounts of dietary Keto-Met can be readily converted to l-Met by the chick, i.e., that Keto-Met, provided as such, was no more likely than Met itself to lead to production of noxious metabolites or that the equilibrium of transamination reactions lies in favor of Met synthesis over that of Keto-Met.

Keto-Met is clearly an effective precursor of Met, yet it has not been used much, probably due to the lack of economical commercial sources. Both DL-Met and DL-OH-Met (e.g., Alimet, Novus International), however, are available and currently used to supplement animal foods. DL-Met is not used for supplementation of human foods because humans and other primates use the D-isomer of methionine inefficiently compared with other animals (17–19). On the other hand, DL-OH-Met is currently being used in an enteral product (Ketosteril, Fresenius Kabi) marketed for use, in conjunction with a low protein diet, by patients with chronic renal insufficiency. Given the efficacy and safety of Keto-Met relative to l-Met in the chick, it seems likely that future studies will demonstrate the usefulness of Keto-Met as a methionine analog in the diets of other animals and of humans.

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**Literature Cited**


