Minimizing Amino Acid Catabolism Decreases Amino Acid Requirements

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The processes of natural selection shape the efficiency of nutrient use by animals, with some being especially thrifty while others are wasteful. An examination of the widely divergent amino acid economies of different species vividly illustrates this basic nutritional principle. The domestic cat evolved as a carnivore and has a very high maintenance requirement for dietary amino acids. The cat’s very high basal rate of amino acid catabolism, also referred to as minimal, obligatory, or inevitable catabolism, results in the diversion of essential amino acids from protein synthesis and increases the dietary requirement for amino acids (1). Conversely, species that specialize on consuming very low protein foods like fruits or nectars are exceptionally thrifty in their use of dietary amino acids, because they are able to shut down endogenous losses and have maintenance requirements that are 5- to 10-fold less than that of cats (2,3). Omnivores, including pigs, chickens, and humans, are intermediate in maintenance amino acid needs.

Feed, particularly dietary protein, dominates the cost of producing meat and eggs, so any unnecessary catabolism of amino acids has important economic implications. Urinary nitrogen loss due to amino acid catabolism also leads to environmental degradation due to contamination of ground water and lakes. In fact, odors and nitrogen pollution from animal manures limit animal production in many parts of the world. Furthermore, ammonia vapors from manures negatively affect animal health and welfare.

Lysine is the most limiting amino acid in cereal grain-based diets fed to growing pigs and fish and is 2nd most limiting for poultry. Thus, lysine requirements are a primary determinant of the level of protein and the cost of animal feeds. Lysine is irreversibly catabolized in the liver and the initial regulatory steps are catalyzed by the bifunctional protein, ω-aminoadipic semialdehyde synthase (AASS). This enzyme possesses both lysine ketoglutarate reductase and saccharopine dehydrogenase catalytic activities. In the November 2008 issue of The Journal of Nutrition, Cleveland et al. (4) demonstrated that partial knockdown of AASS mRNA in murine hepatic cells using RNA interference decreases lysine oxidation and lysine requirement. In this novel study, short hairpin RNA complementary to AASS mRNA were stably transfected into a murine hepatocyte cell line. AASS mRNA and protein abundance were markedly reduced, resulting in enzyme activities that were about one-half of wild-type levels. Importantly, these changes in enzyme activity permitted the cells to proliferate maximally at lower levels of media lysine. Titration of media lysine levels demonstrated that the lysine requirement decreased by 26%. Clearly, a sizable part of the lysine requirement of these cells is due to obligatory catabolism of lysine.

The magnitude of savings that might occur by decreasing basal lysine catabolism in pigs and poultry is considerable. The overall efficiency that absorbed lysine is used for protein accretion in young growing chicks and pigs is between 70 and 80% (5–7). Radiotracer studies indicated that basal oxidation of lysine accounts for much of this loss in young pigs (8). The proof of concept article by Cleveland et al. (4) heralds the use of RNA interference to improve the efficiency of dietary amino acid utilization in livestock and aquaculture species, permitting feeding to be formulated to contain lower levels of protein. Although the manipulation of amino acid requirements of animals has been accomplished by traditional genetic selection procedures (9), this has not been widely applied due to the difficulty of assessing an individual animal’s requirement (10) in order to apply selection. Thus, RNA knockdown technology provides a direct avenue toward an important goal in food animal production.

Use of any new technology, including RNA interference, in food animals must overcome a battery of consumer, ethical, and technological barriers. Technological barriers will likely prove to be the easiest to overcome. Stable integration of interfering RNA into mice can now be done using commercially available kits; Peterson et al. (11) recently integrated a transgene for interfering RNA against an endogenous retrovirus into pigs. The impact of reduced lysine catabolism on the health and wellbeing of animals possessing diminished AASS activity will be a major consideration for consumer acceptance. For example, it is possible that tolerance to high levels of dietary lysine will be diminished. Humans with familial hyperlysinemia caused by defective AASS enzymes accumulate very high levels of lysine in blood and tissues, leading in some cases to developmental and neuromuscular manifestations if high lysine diets are consumed. Because of economic and environmental reasons, most farmed animals are fed minimal levels of lysine, but careful research should ensure that animal welfare is not impaired if higher protein diets are mistakenly fed. It is likely that lysine intolerance will not be an issue, because the RNA interference approach lends itself to partial knockdowns where gene function is reduced but not eliminated. This was clearly shown by Cleveland et al. (4), where the magnitude of AASS mRNA knockdown was dependent on the specific short hairpin RNA construct used and the number of constructs that were transfected. Additionally, their study indicates post-transcriptional regulation of the remaining AASS. This
regulation could facilitate lysine homeostasis despite a lower rate of basal catabolism. An additional concern for animal nutritionists is the effect of decreased flux through lysine oxidation on the availability of other metabolic intermediates that might be needed in metabolism. Lysine is unique among amino acids in that its catabolic pathway is not known to uniquely supply any metabolic precursors. This certainly would not be the case if RNA knockout technology were applied to dampen the oxidation of methionine, which supplies many critical metabolic intermediates during its catabolism. A final potential nutritional concern relates to the antagonism caused by high levels of plasma lysine on the metabolism of arginine. Although this antagonism would not be likely with commercial diets, it illustrates that nutritionists will need to be aware of subtle phenotypic differences that might accompany the manipulation of nutritional genotypes.

Literature Cited