Upregulation of AGAT as a Possible Target in Molecular Nutrition

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Dear Editor,

L-arginine:glycine amidinotransferase (AGAT; EC 2.1.4.1) is a key enzyme in the biosynthesis of creatine, a natural amino acid derivative that plays a major role in temporal and spatial energy buffering. AGAT catalyzes the first and rate-limiting step in creatine synthesis, by transferring an amidino group from arginine to the N^α -amine of glycine, to yield L-ornithine and guanidinoacetic acid (GAA). AGAT is a tissue-specific enzyme, predominantly expressed in the human kidney and pancreas, but also located in the liver, heart, brain, and testis. AGAT activity appears to be deficient in various medical conditions, including inherited cerebral creatine deficiency syndrome-3 (CCDS3, or AGAT deficiency), end-stage kidney disease, stroke, and vitamin E shortfall [1], all characterized by the low levels of creatine and clinical indices of impaired bioenergetics. For instance, circulating GAA and creatine levels, and renal AGAT activity were significantly lower in a chronic renal failure model, with elevated blood urea nitrogen suggestive of kidney damage [2]. Having this in mind, primary and secondary AGAT deficits thus highlight the enzyme as a sensible molecular target for various nutritional compounds aimed to upregulate its activity and recover energy metabolism.

A literature search, however, revealed an evident shortage of nutraceuticals capable to upregulate AGAT

activity. While many nutritional agents are found to downregulate AGAT activity (e.g., creatine, L-arginine, GAA, ornithine) [1], only cysteine has been identified so far as a possible stimulator of AGAT function. Cysteine (2R-2-amino-3-sulfanylpropanoic acid) is a nonessential amino acid required for the synthesis of proteins and nonprotein compounds, including coenzyme A and glutathione. A seminal paper by Walker [3] evaluated the potential of various sulfhydryl compounds to modulate AGAT activity using in vitro hog and rat kidney samples. Cysteine appears to reverse the inhibition of AGAT (induced by L-canavanine and L-ornithine), with relative AGAT activity revived for 3% to 103 points (i.e., a relative activity of 100 represents 11 μ mol of arginine formed by the reaction). This perhaps suggests that cysteine instigates AGAT function, a feature that might have promising therapeutic potential in pathologies with mildly downregulated AGAT activity.

However, no clinical trials known to the author have evaluated if dietary cysteine induces AGAT stimulation. A recent double-blind placebo-controlled crossover trial has found that a single dose of cysteine derivative (2,400 mg of *N*-acetyl-L-cysteine, NAC) improved biomarkers of brain creatine metabolism (e.g., glutamate/glutamine-to-creatine ratio) in patients with schizophrenia [4]. These data provide preliminary evidence that NAC mod-

ulates human brain bioenergetics, and AGAT upregulation might be involved. More studies are needed to validate the possible role of dietary cysteine in AGAT upregulation in a clinical environment, accounting for organ-specific responses and different administration protocols, also to discover and scrutinize other nutraceuticals that might stimulate AGAT, a worthwhile target in molecular nutrition and biomedicine.

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