

“Failure to Thrive” as a Vegan – Could Supplemental Carninutrients Help?

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Abstract

Flesh foods are rich in certain physiologically essential, nutritionally non-essential metabolic cofactors – dubbed “carninutrients” – which, when employed as supplements, have shown efficacy for treating certain health disorders and for promoting optimal physical and mental performance. Carnitine, taurine, creatine, and carnosine are prominent carninutrients; long-chain omega-3 fats, although not cofactors, might also be considered carninutrients. Although these compounds are synthesized endogenously, they are also absorbed from the diet, and their tissue levels tend to be lower in vegetarians than in omnivores. About a third of former vegetarians report that they abandoned vegetarianism owing to their impression that they failed to experience robust health while vegetarian. B12 or iron deficiency, which are readily correctible, may account for some of these cases. The down-regulation of IGF-I activity associated with vegan diets – of key importance to the cancer-preventive properties of such diets – conceivably could be a factor in other cases; a higher protein intake would remedy this. But consideration should be given to the possibility that comprehensive carninutrient supplementation could be symptomatically beneficial in some vegetarians; this could be assessed in double-blind studies. Vegetarians who develop clinical syndromes reported to respond to carninutrient supplementation would likely be prime candidates for such supplementation.

Carninutrients Can Promote Health and Optimal Performance

Flesh foods are a rich source of certain physiologically essential, but nutritionally non-essential metabolic cofactors which are not provided by plant-derived foods, notably carnitine, taurine, creatine, and carnosine; these have been described as “carninutrients”.¹ These agents play key metabolic roles in skeletal muscle, heart, and the brain. Dairy products and eggs, staples of many vegetarian diets, provide only trace amounts of these compounds. Although vegans can synthesize these within their bodies from precursors provided by vegan diets, these agents are reasonably well absorbed when ingested in foods or supplements. Hence, body stores of these carninutrients can be boosted to some extent by oral administration. For each of these carninutrients, rodent studies, and to a more limited extent clinical studies, have demonstrated that supplementation can provide benefits to health or physical capacities, at least under certain circumstances.²⁻²⁵ The clinical utility of carnitine or carnitine esters is well established in early age-related cognitive dysfunction, diabetes, and intermittent claudication; in patients who have sustained a previous myocardial infarction, supplemental carnitine lessens mortality and reduces risk for arrhythmias and angina.^{2-4, 7} Although taurine has received limited clinical evaluation – primarily in congestive heart failure, where it has proved efficacious - it exerts anti-atherosclerotic, anti-hypertensive, and platelet-stabilizing activities potentially beneficial for cardiovascular health.^{1, 8-13} The greater aggregability of platelets in vegetarians as opposed to omnivores may reflect sub-optimal taurine status.¹ Supplemental creatine can improve muscle performance in exercises involving rapid repeated contractions and improve the effectiveness of resistance training; it also may favorably impact cognitive performance in some circumstances, and is reported to improve memory, specifically in vegetarians.¹⁴⁻¹⁷

However, supplemental creatine does not appear to improve cardiac function in heart failure.^{26, 27} Boosting muscle carnosine levels via supplementation with its precursor beta-alanine aids performance in vigorous anaerobic exercise; this agent may also have potential for cardioprotection.^{21, 24, 28}

These findings evidently reflect the fact that body stores of these agents are often functionally sub-saturating; in regard to carnitine and creatine, this appears to be true among many of the elderly.^{17, 29, 30} It is logical to expect that this sub-saturation may be most common or significant in vegans, as they do not ingest these agents in their diets and are wholly dependent on endogenous synthesis. Indeed, for each of these carnitrients, there is evidence that plasma levels or tissue stores are lower in vegans and vegetarians than in omnivores.^{1, 31-42}

Why Do Some Vegans Report “Failure to Thrive”?

Advocates of vegan or vegetarian diets often hear from people who claim that they made an earnest effort to eat a plant-based diet, but that they simply did not experience robust health when they did so – resulting in their return to their former omnivore ways. An informal survey by CBS News in 2005 found that 3 times as many people described themselves as ex-vegetarians as current vegetarians – implying that only a minority of self-described vegetarians stick with their diet in the long term. An internet survey of former vegetarians found that 35% blamed chronic poor health for their return to an omnivore diet.⁴³ What could be the basis for such a perception?

Informed vegans are aware that their diets lack vitamin B12, and therefore supplement with this nutrient. However, a high proportion of citations under the key word “vegan” in PubMed pertain to vegans who have developed symptomatic B12 deficiency. Some former vegetarians who report malaise while following a primarily vegan vegetarian diet may in fact have become B12 deficient.⁴⁴

In young women, an exacerbation of latent iron deficiency may sometimes be responsible for their malaise; heme iron from flesh foods is more efficiently and reliably absorbed than non-heme iron, and body iron stores tend to be notably lower in vegans/vegetarians than in omnivores.^{45, 46} When this is the problem, it can be readily diagnosed and corrected with supplemental iron.

Some lapsed vegans complain that they experienced excessive weight loss on a vegan diet. The tendency for whole-food vegan diets to promote healthful weight loss is in fact one key reason why many people become vegan in the first place.^{47, 48} However, certain restricted versions of vegan diets – such as raw food vegan diets, devoid of grains, beans, or tubers – may often be unduly low in total calories, leading to a degree of weight loss perceived as cosmetically undesirable. The solution here is to include unrestricted amount of grains, beans, and tubers in one’s diet.

It is also conceivable that the down-regulation of systemic IGF-I and possibly mTORC1 activities, consequent to a vegan diet rather low in certain essential amino acids (most notably methionine and lysine), may have adverse symptomatic consequences in some people. This down-regulation is thought to be largely responsible for the much lower risk for “Western” cancers enjoyed by certain quasi-vegan non-Western cultures, and also has potential for slowing the aging process.⁴⁹⁻⁵⁴ If a reduction in IGF-I activity does contribute to the “failure to thrive” phenomenon reported by some lapsed vegans, high-quality protein from dairy foods or eggs, or a higher intake of plant proteins (high soy intakes increase IGF-I in vegans^{50, 55}) would be expected to remedy the problem.

In some instances, a person may develop a temporary illness, unrelated to diet, while eating a vegetarian diet. If the person suspects his diet as the cause, goes back to omnivore eating, and his illness then resolves (which it would have anyway), he may falsely attribute his illness to his former vegetarian diet.

Carninutrient Supplementation for Vegetarians

But consideration should also be given to the possibility that supplemental intakes of carninutrients could be symptomatically beneficial in many vegans who report that they simply don't feel as good – or who experience specific symptoms – since they adopted a vegan diet. If a sufficient cohort of such people could be gathered together for a clinical study – or perhaps recruited via the internet – it should be possible to do a placebo-controlled test of this hypothesis. If this hypothesis were sustained, an avenue would be available for maximizing the number of people who could stick with a vegan diet. Such a diet is clearly very beneficial in numerous ways for health, the environment, and our fellow animals.⁵⁶ There does not appear to be any reason to suspect that increased intakes of carnitine, taurine, creatine, and carnosine are in any way responsible for the health risks associated with flesh-rich diets; saturated fat, high-quality protein, heme iron, bioavailable phosphate, and mutagens produced by high-temperature cooking of flesh foods (e.g. heterocyclic amines) may be key mediators of these. In contrast, moderate elevations of carninutrient stores emerge as health protective in the research literature, and supplemental intakes of these compounds, at least in non-massive doses in subjects with adequate renal function, do not produce side effects. (An exception in regard to the carnosine precursor beta-alanine is noted below.)

Carnosine – the dipeptide beta-alanyl-L-histidine - is found primarily in muscle, heart, and neurons, where it functions to buffer changes in pH during rapid muscular or neuronal activity; it also has versatile antioxidant activity.^{57, 58} Beta-alanine availability, but not that of histidine, is rate-limiting for carnosine synthesis in muscle and likely other tissues as well, which is why supplemental beta-alanine is employed to boost tissue carnosine stores. Moreover, in most humans, carnosine in plasma is degraded so rapidly by carnosinase that the functional consequences of joint ingestion of beta-alanine and histidine are little different than those of ingesting intact carnosine.⁵⁹ Supplemental beta-alanine has the drawback that a bolus intake of beta-alanine in excess of 800 mg tends to produce transitory “pins and needles” paresthesias during the peak of plasma concentrations; these can be avoided by administering the daily beta-alanine in divided doses, or using a time-release preparation.⁶⁰ This also should aid tissue retention of beta-alanine. Supplemental orotate can also boost beta-alanine availability, as it is converted to beta-alanine within the liver.^{61, 62} This may play a role in the reported utility of magnesium orotate administration in cardiac disorders.⁶³⁻⁶⁵

Histidine and Long-Chain Omega-3 as Supplements for Vegetarians

Even though supplemental histidine does not increase carnosine synthesis, histidine itself has metal-chelating, antioxidant, and anti-inflammatory properties that are potentially beneficial, as rodent and clinical studies are starting to reveal.⁶⁶⁻⁷⁰ Flesh-rich diets tend to be especially rich in histidine, owing to their high carnosine contents; hence, histidine supplementation, with or without beta-alanine, might be more likely to benefit vegans than omnivores.

Also pertinent is the fact that vegan diets – and indeed any diets devoid of fish or brain tissue – tend to be low in the long-chain omega-3 fatty acids that play a key structural role in the brain and retina, and that diminish risk for cardiac sudden death.⁷¹ Ample intakes of these special fats also can have useful anti-

inflammatory and anti-carcinogenic activities, especially in the context of diets relatively low in omega-6 fats.⁷²⁻⁷⁵ And some epidemiology suggests that a lifetime of ample omega-3 status may provide a measure of protection from age-related cognitive dysfunction, macular degeneration, and clinical depression.⁷⁶⁻⁸² Vegan diets with meaningful levels of terrestrial alpha-linolenic acid enable a certain limited endogenous synthesis of long-chain omega-3s, but fish or fish oil ingestion is associated with notably higher tissue levels of these fats. Hence, long-chain omega-3s, although they do not function as cofactors, might be considered carninutrients. Vegan admirers of the China Study, which provided important evidence for the protective merits of plant-based diets, should be aware that this study also correlated increased fish consumption with improved health outcomes, likely reflecting a protective role of long-chain omega-3s.⁸³

Vegans can now obtain DHA supplements manufactured from certain algae, but these are greatly more expensive than fish oil per unit omega-3.⁸⁴ Flaxseed genetically modified to produce stearidonic acid - more efficiently converted to long-chain omega-3s than is alpha-linolenic acid⁸⁵ - could represent a more cost-effective way for vegans to achieve superior omega-3 status, but unfortunately such a product is not yet commercially available.⁸⁶ It is clear that declining fish stocks will ultimately prove inadequate as a growing portion of the world's population wishes to ingest fish oil; stearidonic acid from bioengineered plants may represent a practical and cost-effective solution to this problem.

Concluding Comments

A peculiarity of the flesh-derived nutrients discussed here is that, although they each play a key role in muscle function (not surprising, as they are richly supplied by flesh foods), they are also important constituents of neurons and the brain. It's not inconceivable that subtle impairments of brain function reflecting suboptimal levels of carninutrients might contribute to the malaise reported by some ex-vegetarians.^{7, 17, 87-92}

Whether or not dietary deprivation of carninutrients plays a role in the "failure to thrive" phenomenon reported by some ex-vegetarians, clinicians should be aware that tissue stores of these cofactors are likely to be somewhat decreased in long-term vegetarians. Hence, such people may be prime candidates for carninutrient supplementation when they present with ailments that are reported to respond to such supplementation. In particular, vegetarians who develop heart disorders might benefit from supplementation with carnitine, taurine, precursors of carnosine, and omega-3 oils.

In closing, it is crucial to note that there is *no evidence* that the net impact of transitioning from an omnivore to a vegan diet is a reduction in perceived health. A great many people who become vegans report robust or improved health, and are often delighted with the spontaneous weight loss and marked improvements in risk factors that this transition typically entails. And, in the long term, whole-food vegan diets can be expected to reduce risk for a wide range of common health disorders, including coronary disease, diabetes, and many types of cancer. However, no diet is perfect in every particular for every individual. If some individuals genuinely feel subpar on a vegan diet, it is important to find ways to correct this - precisely because such diets have such valuable long-term impacts on health, the ecology, and animal welfare.

References

- (1) McCarty MF. Sub-optimal taurine status may promote platelet hyperaggregability in vegetarians. *Med Hypotheses* 2004;63(3):426-33.
- (2) DiNicolantonio JJ, Lavie CJ, Fares H, Menezes AR, O'Keefe JH. L-carnitine in the secondary prevention of cardiovascular disease: systematic review and meta-analysis. *Mayo Clin Proc* 2013 June;88(6):544-51.
- (3) Vidal-Casariago A, Burgos-Pelaez R, Martinez-Faedo C et al. Metabolic effects of L-carnitine on type 2 diabetes mellitus: systematic review and meta-analysis. *Exp Clin Endocrinol Diabetes* 2013 April;121(4):234-8.
- (4) Brass EP, Koster D, Hiatt WR, Amato A. A systematic review and meta-analysis of propionyl-L-carnitine effects on exercise performance in patients with claudication. *Vasc Med* 2013 February;18(1):3-12.
- (5) Malaguarnera M, Gargante MP, Russo C et al. L-carnitine supplementation to diet: a new tool in treatment of nonalcoholic steatohepatitis--a randomized and controlled clinical trial. *Am J Gastroenterol* 2010 June;105(6):1338-45.
- (6) Zhou X, Liu F, Zhai S. Effect of L-carnitine and/or L-acetyl-carnitine in nutrition treatment for male infertility: a systematic review. *Asia Pac J Clin Nutr* 2007;16 Suppl 1:383-90.
- (7) Montgomery SA, Thal LJ, Amrein R. Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. *Int Clin Psychopharmacol* 2003 March;18(2):61-71.
- (8) Murakami S. Taurine and atherosclerosis. *Amino Acids* 2012 December 8.
- (9) Abebe W, Mozaffari MS. Role of taurine in the vasculature: an overview of experimental and human studies. *Am J Cardiovasc Dis* 2011;1(3):293-311.
- (10) Ito T, Schaffer SW, Azuma J. The potential usefulness of taurine on diabetes mellitus and its complications. *Amino Acids* 2012 May;42(5):1529-39.
- (11) Yamori Y, Taguchi T, Hamada A, Kunimasa K, Mori H, Mori M. Taurine in health and diseases: consistent evidence from experimental and epidemiological studies. *J Biomed Sci* 2010;17 Suppl 1:S6.
- (12) Xu YJ, Arneja AS, Tappia PS, Dhalla NS. The potential health benefits of taurine in cardiovascular disease. *Exp Clin Cardiol* 2008;13(2):57-65.
- (13) Militante JD, Lombardini JB. Treatment of hypertension with oral taurine: experimental and clinical studies. *Amino Acids* 2002;23(4):381-93.
- (14) Moon A, Heywood L, Rutherford S, Cobbold C. Creatine Supplementation: Can it Improve Quality of Life in the Elderly without Associated Resistance Training? *Curr Aging Sci* 2013 December;6(3):251-7.

- (15) Allen PJ. Creatine metabolism and psychiatric disorders: Does creatine supplementation have therapeutic value? *Neurosci Biobehav Rev* 2012 May;36(5):1442-62.
- (16) Gualano B, Roschel H, Lancha-Jr AH, Brightbill CE, Rawson ES. In sickness and in health: the widespread application of creatine supplementation. *Amino Acids* 2012 August;43(2):519-29.
- (17) Rawson ES, Venezia AC. Use of creatine in the elderly and evidence for effects on cognitive function in young and old. *Amino Acids* 2011 May;40(5):1349-62.
- (18) Sestili P, Martinelli C, Colombo E et al. Creatine as an antioxidant. *Amino Acids* 2011 May;40(5):1385-96.
- (19) Candow DG. Sarcopenia: current theories and the potential beneficial effect of creatine application strategies. *Biogerontology* 2011 August;12(4):273-81.
- (20) Candow DG, Chilibeck PD. Potential of creatine supplementation for improving aging bone health. *J Nutr Health Aging* 2010 February;14(2):149-53.
- (21) Culbertson JY, Kreider RB, Greenwood M, Cooke M. Effects of beta-alanine on muscle carnosine and exercise performance: a review of the current literature. *Nutrients* 2010 January;2(1):75-98.
- (22) Hoffman JR, Emerson NS, Stout JR. beta-Alanine supplementation. *Curr Sports Med Rep* 2012 July;11(4):189-95.
- (23) Quesnele JJ, Laframboise MA, Wong JJ, Kim P, Wells GD. The Effects of Beta Alanine Supplementation on Performance: A Systematic Review of the Literature. *Int J Sport Nutr Exerc Metab* 2013 August 5.
- (24) Stvolinsky SL, Dobrota D. Anti-ischemic activity of carnosine. *Biochemistry (Mosc)* 2000 July;65(7):849-55.
- (25) Hipkiss AR. Would carnosine or a carnivorous diet help suppress aging and associated pathologies? *Ann N Y Acad Sci* 2006 May;1067:369-74.
- (26) Carvalho AP, Rassi S, Fontana KE, Correa KS, Feitosa RH. Influence of creatine supplementation on the functional capacity of patients with heart failure. *Arq Bras Cardiol* 2012 July;99(1):623-9.
- (27) Wallis J, Lygate CA, Fischer A et al. Supranormal myocardial creatine and phosphocreatine concentrations lead to cardiac hypertrophy and heart failure: insights from creatine transporter-overexpressing transgenic mice. *Circulation* 2005 November 15;112(20):3131-9.
- (28) Sale C, Saunders B, Harris RC. Effect of beta-alanine supplementation on muscle carnosine concentrations and exercise performance. *Amino Acids* 2010 July;39(2):321-33.
- (29) Pistone G, Marino A, Leotta C, Dell'Arte S, Finocchiaro G, Malaguarnera M. Levocarnitine administration in elderly subjects with rapid muscle fatigue: effect on body composition, lipid profile and fatigue. *Drugs Aging* 2003;20(10):761-7.

- (30) Malaguarnera M, Cammalleri L, Gargante MP, Vacante M, Colonna V, Motta M. L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial. *Am J Clin Nutr* 2007 December;86(6):1738-44.
- (31) Delanghe J, De Slypere JP, De BM, Robbrecht J, Wieme R, Vermeulen A. Normal reference values for creatine, creatinine, and carnitine are lower in vegetarians. *Clin Chem* 1989 August;35(8):1802-3.
- (32) Lombard KA, Olson AL, Nelson SE, Rebouche CJ. Carnitine status of lactoovovegetarians and strict vegetarian adults and children. *Am J Clin Nutr* 1989 August;50(2):301-6.
- (33) Etzioni A, Levy J, Nitzan M, Erde P, Benderly A. Systemic carnitine deficiency exacerbated by a strict vegetarian diet. *Arch Dis Child* 1984 February;59(2):177-9.
- (34) Laidlaw SA, Shultz TD, Cecchino JT, Kopple JD. Plasma and urine taurine levels in vegans. *Am J Clin Nutr* 1988 April;47(4):660-3.
- (35) Rana SK, Sanders TA. Taurine concentrations in the diet, plasma, urine and breast milk of vegans compared with omnivores. *Br J Nutr* 1986 July;56(1):17-27.
- (36) Benton D, Donohoe R. The influence of creatine supplementation on the cognitive functioning of vegetarians and omnivores. *Br J Nutr* 2011 April;105(7):1100-5.
- (37) McCormick VM, Hill LM, Macneil L, Burke DG, Smith-Palmer T. Elevation of creatine in red blood cells in vegetarians and nonvegetarians after creatine supplementation. *Can J Appl Physiol* 2004 December;29(6):704-13.
- (38) Burke DG, Chilibeck PD, Parise G, Candow DG, Mahoney D, Tarnopolsky M. Effect of creatine and weight training on muscle creatine and performance in vegetarians. *Med Sci Sports Exerc* 2003 November;35(11):1946-55.
- (39) Lukaszuk JM, Robertson RJ, Arch JE et al. Effect of creatine supplementation and a lacto-ovo-vegetarian diet on muscle creatine concentration. *Int J Sport Nutr Exerc Metab* 2002 September;12(3):336-48.
- (40) Harris RC, Wise JA, Price KA, Kim HJ, Kim CK, Sale C. Determinants of muscle carnosine content. *Amino Acids* 2012 July;43(1):5-12.
- (41) Baguet A, Everaert I, De NH et al. Effects of sprint training combined with vegetarian or mixed diet on muscle carnosine content and buffering capacity. *Eur J Appl Physiol* 2011 October;111(10):2571-80.
- (42) Everaert I, Mooyaart A, Baguet A et al. Vegetarianism, female gender and increasing age, but not CNDP1 genotype, are associated with reduced muscle carnosine levels in humans. *Amino Acids* 2011 April;40(4):1221-9.
- (43) Herzog H. Why do most vegetarians go back to eating meat? *Psychology Today* . 2011.
Ref Type: Magazine Article

- (44) Pawlak R, Parrott SJ, Raj S, Cullum-Dugan D, Lucus D. How prevalent is vitamin B(12) deficiency among vegetarians? *Nutr Rev* 2013 February;71(2):110-7.
- (45) Reddy S, Sanders TA. Haematological studies on pre-menopausal Indian and Caucasian vegetarians compared with Caucasian omnivores. *Br J Nutr* 1990 September;64(2):331-8.
- (46) Alexander D, Ball MJ, Mann J. Nutrient intake and haematological status of vegetarians and age-sex matched omnivores. *Eur J Clin Nutr* 1994 August;48(8):538-46.
- (47) Ornish D. *Eat More, Weigh Less: Dr. Dean Ornish's Life Choice Program for Losing Weight Safely While Eating Abundantly*. New York: Harper; 1997.
- (48) McCarty MF. Dietary saturate/unsaturate ratio as a determinant of adiposity. *Med Hypotheses* 2010 July;75(1):14-6.
- (49) Allen NE, Appleby PN, Davey GK, Key TJ. Hormones and diet: low insulin-like growth factor-I but normal bioavailable androgens in vegan men. *Br J Cancer* 2000 July;83(1):95-7.
- (50) Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. *Cancer Epidemiol Biomarkers Prev* 2002 November;11(11):1441-8.
- (51) McCarty MF. Insulin and IGF-I as determinants of low "Western" cancer rates in the rural third world. *Int J Epidemiol* 2004 August;33(4):908-10.
- (52) Fontana L, Weiss EP, Villareal DT, Klein S, Holloszy JO. Long-term effects of calorie or protein restriction on serum IGF-1 and IGFBP-3 concentration in humans. *Aging Cell* 2008 October;7(5):681-7.
- (53) McCarty MF. A low-fat, whole-food vegan diet, as well as other strategies that down-regulate IGF-I activity, may slow the human aging process. *Med Hypotheses* 2003 June;60(6):784-92.
- (54) McCarty MF, Barroso-Aranda J, Contreras F. The low-methionine content of vegan diets may make methionine restriction feasible as a life extension strategy. *Med Hypotheses* 2009 February;72(2):125-8.
- (55) Dewell A, Weidner G, Sumner MD et al. Relationship of dietary protein and soy isoflavones to serum IGF-1 and IGF binding proteins in the Prostate Cancer Lifestyle Trial. *Nutr Cancer* 2007;58(1):35-42.
- (56) Robbins J. *Diet for a New America*. New York: HJ Kramer; 1998.
- (57) Boldyrev AA, Aldini G, Derave W. Physiology and pathophysiology of carnosine. *Physiol Rev* 2013 October;93(4):1803-45.
- (58) Kohen R, Yamamoto Y, Cundy KC, Ames BN. Antioxidant activity of carnosine, homocarnosine, and anserine present in muscle and brain. *Proc Natl Acad Sci U S A* 1988 May;85(9):3175-9.
- (59) Everaert I, Taes Y, De HE et al. Low plasma carnosinase activity promotes carnosinemia after carnosine ingestion in humans. *Am J Physiol Renal Physiol* 2012 June 15;302(12):F1537-F1544.

- (60) Decombaz J, Beaumont M, Vuichoud J, Bouisset F, Stellingwerff T. Effect of slow-release beta-alanine tablets on absorption kinetics and paresthesia. *Amino Acids* 2012 July;43(1):67-76.
- (61) Aonuma S, Hama T, Tamaki N, Okumura H. Orotate as a beta-alanine donor for anserine and carnosine biosynthesis, and effects of actinomycin D and azauracil on their pathway. *J Biochem* 1969 August;66(2):123-32.
- (62) Traut TW, Loechel S. Pyrimidine catabolism: individual characterization of the three sequential enzymes with a new assay. *Biochemistry* 1984 May 22;23(11):2533-9.
- (63) Rosenfeldt FL. Metabolic supplementation with orotic acid and magnesium orotate. *Cardiovasc Drugs Ther* 1998 September;12 Suppl 2:147-52.
- (64) Geiss KR, Stergiou N, Jester, Neuenfeld HU, Jester HG. Effects of magnesium orotate on exercise tolerance in patients with coronary heart disease. *Cardiovasc Drugs Ther* 1998 September;12 Suppl 2:153-6.
- (65) Stepura OB, Martynow AI. Magnesium orotate in severe congestive heart failure (MACH). *Int J Cardiol* 2009 May 1;134(1):145-7.
- (66) Feng RN, Niu YC, Sun XW et al. Histidine supplementation improves insulin resistance through suppressed inflammation in obese women with the metabolic syndrome: a randomised controlled trial. *Diabetologia* 2013 May;56(5):985-94.
- (67) Andou A, Hisamatsu T, Okamoto S et al. Dietary histidine ameliorates murine colitis by inhibition of proinflammatory cytokine production from macrophages. *Gastroenterology* 2009 February;136(2):564-74.
- (68) Farshid AA, Tamaddonfard E, Yahyae F. Effects of histidine and N-acetylcysteine on diclofenac-induced anti-inflammatory response in acute inflammation in rats. *Indian J Exp Biol* 2010 November;48(11):1136-42.
- (69) Mong MC, Chao CY, Yin MC. Histidine and carnosine alleviated hepatic steatosis in mice consumed high saturated fat diet. *Eur J Pharmacol* 2011 February 25;653(1-3):82-8.
- (70) Kasaoka S, Tsuboyama-Kasaoka N, Kawahara Y et al. Histidine supplementation suppresses food intake and fat accumulation in rats. *Nutrition* 2004 November;20(11-12):991-6.
- (71) Leaf A. Prevention of sudden cardiac death by n-3 polyunsaturated fatty acids. *J Cardiovasc Med (Hagerstown)* 2007 September;8 Suppl 1:S27-S29.
- (72) Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. *Exp Biol Med (Maywood)* 2008 June;233(6):674-88.
- (73) Zheng JS, Hu XJ, Zhao YM, Yang J, Li D. Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. *BMJ* 2013;346:f3706.
- (74) Kantor ED, Lampe JW, Peters U, Vaughan TL, White E. Long-Chain Omega-3 Polyunsaturated Fatty Acid Intake and Risk of Colorectal Cancer. *Nutr Cancer* 2013 September 20.

- (75) Fernandez E, Chatenoud L, La VC, Negri E, Franceschi S. Fish consumption and cancer risk. *Am J Clin Nutr* 1999 July;70(1):85-90.
- (76) Yurko-Mauro K. Cognitive and cardiovascular benefits of docosahexaenoic acid in aging and cognitive decline. *Curr Alzheimer Res* 2010 May;7(3):190-6.
- (77) Fotuhi M, Mohassel P, Yaffe K. Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association. *Nat Clin Pract Neurol* 2009 March;5(3):140-52.
- (78) Christen WG, Schaumberg DA, Glynn RJ, Buring JE. Dietary omega-3 fatty acid and fish intake and incident age-related macular degeneration in women. *Arch Ophthalmol* 2011 July;129(7):921-9.
- (79) Chong EW, Kreis AJ, Wong TY, Simpson JA, Guymer RH. Dietary omega-3 fatty acid and fish intake in the primary prevention of age-related macular degeneration: a systematic review and meta-analysis. *Arch Ophthalmol* 2008 June;126(6):826-33.
- (80) Freeman MP. Omega-3 fatty acids in major depressive disorder. *J Clin Psychiatry* 2009;70 Suppl 5:7-11.
- (81) McNamara RK. Long-chain omega-3 fatty acid deficiency in mood disorders: rationale for treatment and prevention. *Curr Drug Discov Technol* 2013 September;10(3):233-44.
- (82) Sanhueza C, Ryan L, Foxcroft DR. Diet and the risk of unipolar depression in adults: systematic review of cohort studies. *J Hum Nutr Diet* 2013 February;26(1):56-70.
- (83) Wang Y, Crawford MA, Chen J et al. Fish consumption, blood docosahexaenoic acid and chronic diseases in Chinese rural populations. *Comp Biochem Physiol A Mol Integr Physiol* 2003 September;136(1):127-40.
- (84) Doughman SD, Krupanidhi S, Sanjeevi CB. Omega-3 fatty acids for nutrition and medicine: considering microalgae oil as a vegetarian source of EPA and DHA. *Curr Diabetes Rev* 2007 August;3(3):198-203.
- (85) Walker CG, Jebb SA, Calder PC. Stearidonic acid as a supplemental source of omega-3 polyunsaturated fatty acids to enhance status for improved human health. *Nutrition* 2013 February;29(2):363-9.
- (86) Ruiz-Lopez N, Haslam RP, Venegas-Caleron M et al. The synthesis and accumulation of stearidonic acid in transgenic plants: a novel source of 'heart-healthy' omega-3 fatty acids. *Plant Biotechnol J* 2009 September;7(7):704-16.
- (87) El IA, Shen CH, L'Amoreaux WJ. Neuroprotective role of taurine during aging. *Amino Acids* 2013 October;45(4):735-50.
- (88) Yamano E, Tanaka M, Ishii A, Tsuruoka N, Abe K, Watanabe Y. Effects of chicken essence on recovery from mental fatigue in healthy males. *Med Sci Monit* 2013;19:540-7.

- (89) Herculano B, Tamura M, Ohba A, Shimatani M, Kutsuna N, Hisatsune T. beta-alanyl-L-histidine rescues cognitive deficits caused by feeding a high fat diet in a transgenic mouse model of Alzheimer's disease. *J Alzheimers Dis* 2013;33(4):983-97.
- (90) Ma J, Xiong JY, Hou WW et al. Protective effect of carnosine on subcortical ischemic vascular dementia in mice. *CNS Neurosci Ther* 2012 September;18(9):745-53.
- (91) Corona C, Frazzini V, Silvestri E et al. Effects of dietary supplementation of carnosine on mitochondrial dysfunction, amyloid pathology, and cognitive deficits in 3xTg-AD mice. *PLoS ONE* 2011;6(3):e17971.
- (92) Cederholm T, Salem N, Jr., Palmblad J. omega-3 fatty acids in the prevention of cognitive decline in humans. *Adv Nutr* 2013 November;4(6):672-6.