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Milk protein loses its crown?

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In the time of a plague it seems appropriate to consider the issue of what has been termed a trilemma: that of environmental sustainability and human health linked by global diets (1). In this context a transition from animal-source to plant-based foods has been advocated given that healthy plant-based diets are more sustainable and associated with lower risk of noncommunicable diseases (2). Alternative protein sources are at the core of the discussion, especially meat replacement (3), because of the longstanding and deep-seated emotional and cultural place of meat in the Western world, not least because of its organoleptic qualities [the fourth N in the 4N behavioral theory for rationalization of meat consumption: meat eating is *natural*, *normal*, *necessary*, and *nice* (4)]. Although there is a long list of well-known and widely consumed alternative plant proteins, all plant proteins attract a legacy view of their inferiority in terms of the quality of their proteins. This originates from early demonstrations of the inability of both cereal and legume protein on their own to support animal growth, because of low lysine in all cereals, low tryptophan in maize, and a marginal limitation of sulfur amino acids for legumes, especially in growth trials in rats with a high requirement for cysteine for hair growth. In fact the amino acid profile of cereals and legumes is dominated by one or a few individual storage proteins, e.g., lysine-poor gluten, 80% of wheat protein, and sulfur amino acid–poor vicilins, 35% of soybean proteins. Increasing the relative amounts of cytoplasmic (as in the germ) to storage proteins results in a more balanced profile as with the Quality Protein Maize hybrid with ≤90% higher concentrations of limiting amino acids (5) which was shown to support infant height-growth as the sole source of protein and energy many years ago (6). For other plant-protein sources without storage proteins, such as green leaves (e.g., spinach), aquatic plants (duckweed), marine microalgae (e.g., chlorella), the cyanobacterium (blue-green algae) spirulina, and mycoproteins (Mycos), their amino acid profile is much more balanced (7). Moreover, they are abundant: duckweed is said to be the fastest-growing plant on the planet. The downsides of some of these plant protein sources are their potentially low digestibility and their antinutritional factors which can adversely influence their safety (although these are offset by many of their secondary metabolites acting as phytoprotectants, enabling them to mediate disease protection). Of the noncereal, nonlegume plant-protein sources which we eat, most of them have high protein:energy ratios (e.g., 0.45:1 and 0.55:1 for spinach and mushrooms, respectively) but with little energy: i.e., a 25-g protein portion would require 1 kg of spinach and >300 g of mushrooms. The more energy-dense quinoa, the pseudo-cereal sacred food of the Incas with edible seeds and leaves, considered by NASA for self-sustaining space flight (8), would provide 25 g of protein with a balanced amino acid profile and 650 kcal from 150 g, making it closer to a more complete plant food (9) (although some feel that it has limited culinary attributes making it hard to satisfy the fourth N). Thus, entirely plant-based diets of cereals, legumes, and mixed vegetables can deliver a balanced amino acid profile, as demonstrated by the normal height growth of judiciously micronutrient-supplemented vegan children breastfed for most of their first year (10). However, for many, what such diets do not deliver are the high-protein foods with the mouth-feel and taste of meat, eggs, or cheese enjoyed by meat-eating populations.

Whereas the search for meat replacements focuses on satisfying the organoleptic properties of meat, in fact—as identified previously (11) from a strictly nutritional viewpoint—milk replacement is arguably more challenging, in terms of both its nutrient provision (i.e., calcium, iodine, vitamin B-12, riboflavin, and protein) and its current consumption rate, at least in Northern Europe. Furthermore, milk protein has become important in the context of the postprandial stimulation of muscle protein synthesis (MPS). Thus, after the first demonstration 4 decades ago that the postprandial stimulation of MPS by dietary protein was measurable by stable isotopes and muscle biopsy (12), subsequent work identified the postprandial aminoacidemia, especially that of leucine, as the important dietary protein signaling mechanism for MPS, now known to act via the sestrin leucine sensor which activates the protein kinase mammalian target of rapamycin complex 1 (mTORC1) to increase protein synthesis (13). The high leucine content of milk, especially of whey protein (14), which is rapidly digested and absorbed after its oral consumption (15), has resulted in milk protein becoming the dietary protein standard against which the quality of dietary proteins can be judged through their ability to stimulate MPS in vivo (16).

In this issue of *The American Journal of Clinical Nutrition*, a potential meat replacer, a single-cell fungal Myco, is reported

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to stimulate MPS to a greater extent than milk protein in both rested and exercised leg muscle of healthy young men (17). The filamentous microfungus *Fusarium venenatum* is attractive as a meat replacer because it can be grown in continuous culture to produce a high-fiber (β-glucan and chitin), protein-dense (>50% energy) product with a favorable fatty acid profile (mainly PUFAs), with high concentrations of zinc and selenium, with an iron concentration about the same as that of chicken but with no vitamin B-12, which can be processed to make various meat replacers (18). However, its production method (on a glucose substrate with the need to reduce the high RNA content to acceptable low concentrations) results in a product currently more costly than meat (19), although alternative cheaper production methods utilizing pea-processing by-products have been described (20). Myco has been widely available for some time as various meat product replacers. Importantly, its amino acid composition is similar to animal-source foods in terms of its total essential amino acids (46%), lysine, the sulfur amino acids, and tryptophan, although its leucine content is similar to meat and egg and 15% lower than milk (21). Monteyne et al. (17) report mixed MPS in young men who consumed a single bolus drink of Myco or milk protein matched to provide similar leucine contents. This leucine matching resulted in 20% more protein and more than twice the energy content in the Myco compared with the milk drink, which the authors discount as potential explanations of the better postprandial response of MPS to the Myco drink. In any case, as often observed in these clinical studies of in vivo MPS, the CVs of the measurements are high (50%–80%) and the numbers of subjects low so that the potential for both type 1 and 2 errors is high. For example, the postprandial insulin response (another important initiator of signal transduction to mTORC1) involved a mean AUC for the Myco which was more than twice that of milk but is described as not different ($P > 0.05$), and the greater increase in MPS with the Myco was mainly because fasted MPS rates were somewhat lower for the Myco subjects, because postprandial rates after Myco and milk were not different ($P = 0.093$). Although it is probably premature to conclude that milk protein has lost its crown as the protein of choice for muscle building, nevertheless the studies do show that mycoprotein is an effective stimulator of MPS, which is an important milestone in the development of this novel food. What would be worthwhile are studies looking at MPS in subjects on traditional vegan diets of cereals, pulses, and vegetables, to establish whether the third of the 4Ns of meat consumption rationalization (*necessary*) is valid.

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