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Designing medical foods for inherited metabolic disorders: why intact protein is superior to amino acids

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Phenylketonuria and tyrosinemia are inherited metabolic disorders characterized by high blood levels of phenylalanine (Phe) or tyrosine (Tyr), due to mutations in genes affecting Phe and Tyr metabolism, respectively. The primary management is a lifelong diet restricted in protein from natural foods in combination with medical foods comprised mixtures of synthetic amino acids. Compliance is often poor after childhood leading to neuropsychological sequela. Glycomacropeptide, an intact 64 amino acid glycophosphopeptide isolated from cheese whey, provides a new paradigm for the management of phenylketonuria and tyrosinemia because glycomacropeptide contains no Phe and Tyr in its pure form, and is also a prebiotic. Medical foods made from glycomacropeptide have been used successfully for the management of phenylketonuria and tyrosinemia. Preclinical and clinical studies demonstrate that intact protein from glycomacropeptide provides a more acceptable and physiologic source of defined protein compared to amino acids in medical foods. For example, harmful gut bacteria were reduced, beneficial short chain fatty acids increased, renal workload decreased, protein utilization increased, and bone fragility decreased using intact protein versus amino acids. Advances in biotechnology will propel the transition from synthetic amino acids to intact proteins for the management of inherited metabolic disorders.

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Introduction

Inherited metabolic disorders (IMDs) are genetic disorders that are often identified based on excessive amounts of specific intermediary metabolites that accumulate due to enzyme deficiency. Detection of IMD in newborn screening programs has expanded in the last decade because of improved technology using tandem mass spectroscopy and a greater capacity for genotyping [1]. The major categories of IMD detected by newborn screening include disorders affecting the metabolism of amino acids, organic acids and the oxidation of fatty acids. The treatment of individuals diagnosed with these disorders often involves nutritional management with medical foods comprised synthetic mixtures of amino acids (AAs); approximately 75 IMD require management with AA medical foods. A medical food is defined by the United States Food and Drug Administration as a 'food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation' (United States Food and Drug Administration; http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/).

Phenylketonuria (PKU, OMIM 261600), caused by a deficiency of hepatic phenylalanine hydroxylase (PAH EC 1.14.16.1) activity that catalyzes the conversion of Phe to Tyr, is the first human genetic disease to have effective programs for newborn screening and treatment [2]. A low-Phe diet restricted in protein from natural foods and supplemented with AA medical food, and since 2010 glycomacropeptide (GMP) medical foods, is the cornerstone of treatment to prevent profound cognitive impairment in individuals with PKU [3,4]. Lifelong adherence to the low-phe PKU diet in combination with AA medical foods is poor and new options are needed. GMP medical foods comprised primarily intact protein provide a safe and acceptable option for the nutritional management of PKU with fewer side effects and improved acceptability compared with AA medical foods [5••].

This review highlights evidence supporting the advantages of using intact dietary protein for IMD, with emphasis on the use of GMP medical foods in the nutritional management of PKU. Considerations in the biotechnology needed to attain intact proteins with specific amino acid profiles suitable for manufacture of medical foods for IMD are discussed.

Intact protein enables production of a variety of palatable foods

Medical foods made with intact dietary protein are superior to formulations of synthetic AAs because of improved

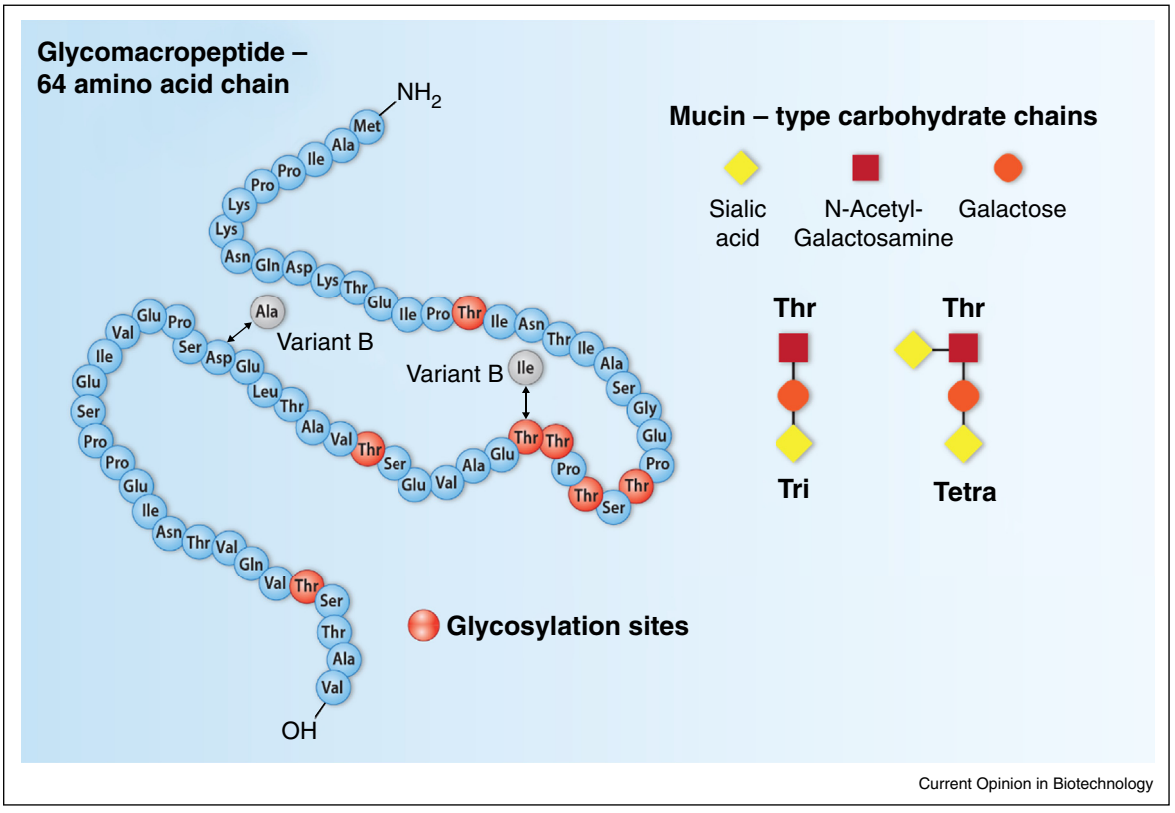
odor and taste as well as functional properties suitable for the production of a variety of foods. Moreover, nutritionally complete GMP medical foods made with the intact protein GMP supplemented with limiting AAs provide a more physiologic source of low-Phe protein than AA medical foods for the nutritional management of PKU with respect to gastrointestinal health, satiety, protein metabolism and bone development.

Prebiotic properties of glycomacropeptide support gastrointestinal health

Glycomacropeptide or caseinomacropeptide is a bioactive 64-amino acid glycophosphopeptide derived from κ-casein in bovine milk that is produced during the manufacture of cheese, when rennet (chymosin) cleaves the C-terminal of κ-casein between Phe 105–Met 106 releasing GMP into the cheese whey and precipitating para-κ-casein to form cheese [6], Figure 1. The unique AA profile of GMP with an absence of aromatic amino acids (Phe, Tyr and Trp) enables the formulation of medical foods for PKU and tyrosinemia. GMP is an acidic peptide (isoelectric point below 4) that is hydrophilic and heat stable, with good functional properties for formulation of a variety of foods including beverages, baked goods and gelled products such as puddings [7]. GMP has a high degree of glycosylation with mucin-type carbohydrate chains resulting in prebiotic properties in mice [8•]. Positive prebiotic effects include changes in the intestinal microbiota to reduce harmful sulfate-reducing bacteria and synthesis of short-chain fatty acids (SCFA) that lower colonic pH and prevent colonization with infectious bacteria [8•,9].

The human gut contains trillions of commensal bacteria referred to as the intestinal microbiota. Diet and other environmental factors are known to affect the composition of the intestinal microbiota, potentially resulting in dysbiosis as a meditator of chronic diseases such as Type 2 diabetes mellitus and inflammatory bowel disease [9]. Children with PKU were noted to have distinct taxonomic

Figure 1



Structure of glycomacropeptide (GMP), a bioactive glycosylated peptide released from κ-casein during cheesemaking. GMP is a unique peptide lacking aromatic amino acids and thus has been isolated from whey for use in medical foods for the management of phenylketonuria and tyrosinemia. Bovine GMP represents a heterogenous group of 64 amino acid peptides due to genetic variance (variants A and B) and post-translational modification, including phosphorylation at serine residues and *O*-glycosylation at threonine residues. The primary structure of bovine variant A is shown; the 2 sites corresponding to mutational differences in the B variant are indicated. Glycosylated forms of GMP include five different mucin-type carbohydrate chains containing N-acetylneuraminic acid (sialic acid), N-acetylgalactosamine, or galactose. The majority of glycosylated GMP molecules include trisaccharide and tetrasaccharide chains as shown.
Adapted from Sawin *et al.* [8•].