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Review

Mannose metabolism: More than meets the eye

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ABSTRACT

Mannose is a simple sugar with a complex life. It is a welcome therapy for genetic and acquired human diseases, but it kills honeybees and blinds baby mice. It could cause diabetic complications. Mannose chemistry, metabolism, and metabolomics in cells, tissues and mammals can help explain these multiple systemic effects. Mannose has good, bad or ugly outcomes depending on its steady state levels and metabolic flux. This review describes the role of mannose at cellular level and its impact on organisms.

Contents

1. Introduction

Nearly all studies of mammalian sugar metabolism focus exclusively on glucose because of its central role in energy generation, storage and regulation. In medicine, glucose is also the focus because of diabetes and obesity. Other hexoses (mannose and galactose) receive relatively little attention in metabolic studies. These monosaccharides can be converted into glucose for catabolism or be derived from glucose for glycan biosynthesis.

Mannose occurs in multiple glycoconjugates. For nearly 40 years [1], [2-^{3}H]-mannose ([2-^{3}H]-Man) served as convenient biosynthetic label for mannose-containing glycans, helping to elucidate and quantify multiple biosynthetic pathways. The label is highly specific: catabolism of [2-^{3}H]-Man releases ^{3}HOH, which is immediately diluted into an ocean of H_2O so other hexoses are not labeled.

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When mannose became an effective therapeutic for glycosylation-deficient patients [2], it called for a more in-depth understanding of mannose metabolism at both the cellular and organismic levels. Mannose can be a life saving therapeutic and a non-antibiotic treatment for selected bacterial infections [3], but in other situations it can be lethal [4] or teratogenic [5], underscoring the importance of stringent regulation of mannose metabolism. In this review, we will discuss mannose origins, metabolism, fate in cells, animals and humans, and its therapeutic applications.

2. Mannose chemistry

D-Mannose is the 2-epimer of glucose and exists primarily as sweet-tasting α-(67%) or as a bitter-tasting β-(33%) anomer of the pyranose [6,7]; furanose forms comprise <2%. Mannose is ~5x as active as glucose in non-enzymatic glycation [8], which may explain why evolution did not favor it as a biological energy source. In the laboratory, mannose can be generated by oxidation of mannitol or by base-catalyzed epimerization of glucose through fructose [9]. L-Mannose is not normally used in biological systems; however, its structural similarity to naturally occurring L-rhamnose enables some plant enzymes to use L-mannose as an unnatural substrate *in vitro* [10]. Mutant strains of *Aerobacter aerogenes* can use it as a sole carbon and energy source [11].

3. Occurrence, origins and dietary sources of mannose

Mannose occurs in microbes, plants and animals. Free mannose is found in small amounts in many fruits such as oranges, apples and peaches [12] and in mammalian plasma at 50–100 μM [13]. More often, mannose occurs in homo-or hetero-polymers such as yeast mannans (α-mannose) where it can account for nearly 16% of dry weight [14] or in galactomannans [15]. Ivory nuts, composed of β-mannans (sometimes called vegetable ivory) are quite hard and used for carving and manufacturing buttons. In fact, ivory nut shavings were the original industrial source of mannose [16].

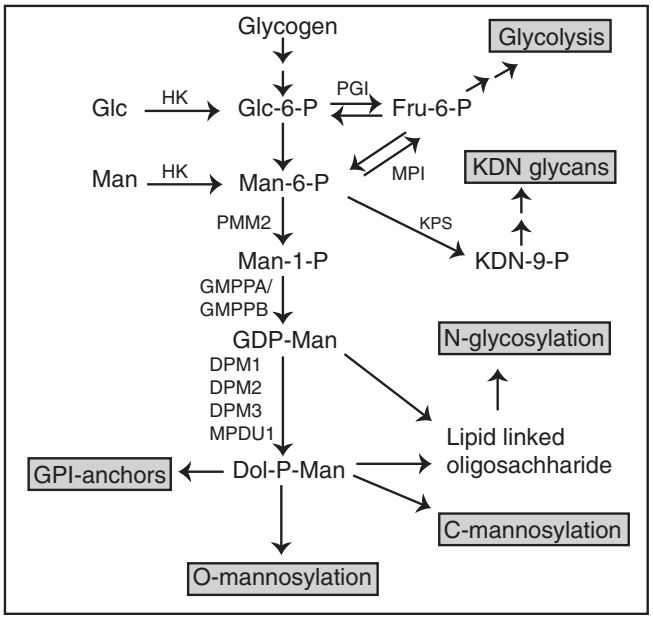

Fig. 1. Mannose metabolic pathway: Man, mannose; Glc, glucose; HK, hexokinase; MPI, phosphomannose isomerase; PMM2, phosphomannomutase; GMPP (A/B), GDP-mannose pyro-phosphorylase (A/B); PGI, phosphoglucose isomerase; KPS, KDN-9-phosphate synthase; Man-6-P, mannose-6-phosphate; Fru-6-P, fructose-6-phosphate, Glc-6-P, glucose-6-phosphate; GDP-Man, GDP-mannose; Dol-P-Man, dolichol phosphate mannose; DPM, Dol-P-Man synthase.

Coffee beans, fenugreek and guar gums are rich sources of galactomannans [17], but these plant polysaccharides are not degraded in the mammalian GI tract and, therefore, provide very little bio-available mannose for glycan synthesis. These polysaccharides are partially digested by anaerobic bacteria in the colon [18]. Small amounts of bio-available mannose occur in glycoproteins.

4. Mannose metabolism in cells

Mannose is transported into mammalian cells via facilitated diffusion hexose transporters of the *SLC2A* group (GLUT) present primarily on the plasma membrane. Various cell lines transport 6.5–23.0 nmols/hr/mg protein [19], but no mannose-specific or -preferential transporters have been reported among the 14 distinct GLUT transporters found in humans [20]. Most studies of GLUT substrate specificity assess only transport of glucose and fructose, but very rarely mannose transport. Several reports describe SGLT-like mannose transporters in the intestine and kidney, where they could deliver free mannose from the diet or recover it from the urine [21]. To date, there is no evidence for the physiological importance of these transporters. Within the cell, mannose is phosphorylated by hexokinase (HK) to produce mannose-6-phosphate (Man-6-P), which serves as a common substrate for three competing enzymes. It is either catabolized by phosphomannose isomerase (MPI) or directed into N-glycosylation via phosphomannomutase (PMM2). Another minor pathway utilizes mannose for synthesis of 2-keto-3-deoxy-D-glycero-D-galacto-nononic acid (KDN), a sialic-acid related molecule found in fish and mammals [22] (Fig. 1). The fate of Man-6-P largely depends on the ratio of MPI to PMM2 within a cell [19] – higher ratio leads to greater catabolism, while lower ratio favors the glycosylation pathway. PMM2-derived mannose-1-phosphate (Man-1-P) is then incorporated into several glycosylation intermediates including GDP-mannose (GDP-Man), GDP-fucose, and dolichol phosphate mannose (Dol-P-Man). These intermediates then contribute to N-glycosylation, O-glycosylation, C-mannosylation, and GPI anchor synthesis (Fig. 1).

GPI anchors play a significant role in protein sorting, trafficking and dynamics. All GPI-anchors share a common core structure H_2-N(CH_2)2OPO_3H-6Manα1->2Manα1->6Manα1->4GlcNα1->6Myo-Ino1-phospholipid [23]. The mannosyltransferases use Dol-P-Man. O-Mannose-based glycans are well known in yeast [24], but only identified 35 years ago in a mixture of unidentified brain proteoglycans [25]. Now, it is known that ER resident Protein O-mannosyl transferases 1 and 2 (POMT1 and POMT2) use Dol-P-Man to add mannose to serine and threonine residues, and the glycan is further extended by other monosaccharides in ER and Golgi [26]. Functional mutations in O-Mannose glycosylation are known to cause muscular dystrophies called α-dystroglycanopathies, since the major substrate protein is α-dystroglycan [27]. More recent studies show that a series of cadherins are also major carriers of O-mannose glycans [28]. C-mannosylation also uses Dol-P-Man to add mannose to C2 of tryptophan. The C-mannosyl transferase in the ER recognizes a consensus motif WXXW [29]. GPI anchors, O- and C-mannosylation have been reviewed extensively [29–33]. Since the majority of mannose is used for N-glycosylation, we will focus on it.

Mannose is the major monosaccharide component of N-glycans and relies on ample supply of Man-6-P, Man-1-P, GDP-Man, and Dol-P-Man for synthesis of lipid linked oligosaccharides (LLOs). The first five mannose residues are added on the cytoplasmic face of ER using GDP-Man. The glycan is then flipped to the luminal side via a flippase [34] and extended by four more mannose residues and glucose. This $Man_9Glc_3GlcNAc_2$ glycan is transferred to newly synthesized proteins soon after they emerge from the translocon or