

Nonglucose Carbohydrates and Infant Nutrition and Metabolism¹

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See related article: Brown et al., J. Nutr. 1648-52, 2009

Human milk is the ideal nutrient for growing babies in the first few months after birth. A number of studies have confirmed the advantages of maternal milk over cow milk-based infant formula for protecting against diarrheal illness and respiratory infection, influencing cognitive development, and possibly preventing chronic disease (1). The mechanism and the physiological basis for the superiority of maternal milk continues to be examined. Use of new and sophisticated analytical methods have shown that a number of biologically active compounds, such as nonglucose carbohydrates, oligosaccharides, and PUFA, are present in significant quantities in maternal milk and are either not present or are present in low quantities in infant formula (2–4). The biologic and metabolic roles of these compounds in the baby remains to be examined. In the current issue of *The Journal of Nutrition*, Brown et al. (5) quantified the kinetics of 2 nonglucose carbohydrates present in human milk, mannose and inositol, in late preterm infants using stable isotopic tracers. They conclude that the daily utilization rates [assuming it to be equal to the rate of their appearance (Ra)] of mannose and inositol are much higher than what could be obtained from the ingested milk. The authors suggest that both mannose and inositol must be synthesized endogenously in significant quantities to meet the infant's daily requirement.

Mannose, an epimer of glucose, is a ubiquitous component of mammalian serum (usual concentration, 28–100 $\mu\text{mol/L}$) (6). It is actively transported across the cell membranes by a specific, high-affinity transporter. Within the cell, it is phosphorylated to form mannose-6-phosphate catalyzed by hexokinase. Mannose-6-phosphate can either participate in the biosynthesis of a number of glycoproteins (major fate) and glycopospholipids or may enter the glycolytic pathway at the level of fructose-6-phosphate. However, because the activity of phosphomannose isomerase is low, the entry of mannose into the glycolytic pathway and therefore its contribution to the synthesis of glycogen or glucose is low. Mannose is fairly rapidly absorbed from the gut. Parenterally administered mannose is rapidly cleared from the circulation in healthy humans and rats without causing a significant change in blood glucose concentration (7–9). Brusati et al. (10) demonstrated a significant uptake of mannose by the fetus from the maternal circulation in normal human pregnancy, suggesting a significant role for mannose during development. The usual

sources of mannose are dietary (certain fruits like apples, peaches, and oranges) or the salvage of mannose released by the degradation of preformed glycoproteins (8).

Inositol, a 6-carbon sugar, is present in several tissues as myoinositol. It is synthesized in the liver, kidney, brain, testes, and mammary gland from D-glucose. Glucose-6-phosphate, formed following phosphorylation of glucose, is cyclized to form inositol-1-phosphate, which is then dephosphorylated by inositol-1-phosphatase to produce inositol. Inositol is present in high concentrations in tissues relative to plasma concentration and exists in its free form or as a phosphorylated derivative [reviewed in (11)]. It has been shown to participate in transmembrane signaling, eicosinoid synthesis, and the secretion of lipoprotein. Inositol is present in high concentrations in human milk as compared with infant formula (2,3). However, supplementation of inositol to preterm infants has not been shown to have any significant impact on growth or neonatal morbidity (12).

Because of the limit in the number of blood samples that can be obtained from the small babies, Brown et al. (13,14) took advantage of the so-called multiple infusion start time or the overlapping (staggered) infusion of multiple tracer isotopomers protocol. This technique allows procurement of data reflecting multiple different time points from a single blood sample. This is important and other investigators should take advantage of this methodology, particularly in view of the increasingly restrictive propensity among institutional review boards and health care providers toward nonbeneficial research in infants and children. Could the short duration of the study (2 h), the very large variation in plasma concentration or the pool size of these carbohydrates, and the use of one compartment model and therefore the potential lack of tracer equilibrium have resulted in overestimation of the rate of appearance. The answer is probably not. As discussed above, the intracellular pools of both these carbohydrates are much larger than the extracellular concentrations. A lack of equilibrium would only result in less dilution and a higher tracer enrichment in the plasma compartment and therefore would result in an underestimation of the rate of turnover. Perhaps the major limitation of the present study, which is true for all studies of the neonate, is the duration of fasting. Because current clinical practices dictate that the babies be fed frequently (every 3 h in the present study), the neonates are never in a true fasting or postprandial state. Therefore the present data could not be strictly considered to reflect the fasting state. As many of these compounds are extensively extracted in the splanchnic compart-

¹ Author disclosure: Satish Kalhan, no conflicts of interest.

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ment during the first pass, there is no significant change in their plasma concentration in response to feeding, yet the administered tracers would be diluted in the splanchnic circulation. Thus, the Ra represents a sum of both the endogenous Ra and a varying contribution of the absorbed carbohydrate entering the portal/splanchnic circulation. A third variable contributing to the estimated total rate of appearance is that from the preformed products (glycoproteins, etc.) via futile cycling (8). Only carefully performed studies in babies and adults, with novel tracer methodologies and compartmental analysis, would allow us to further refine these models and provide estimates of the contribution of these different sources.

The study by Brown et al. (5) is extremely important and provides us an initial insight into the metabolism and nutritional requirement of mannose and inositol. They clearly demonstrate that such studies can be performed in small babies and provide important scientific data required to examine the biological role of these nutrients in vivo. Such data are important not only for the understanding of basic biology of these nutrients, but also for developing strategies for nutritional management of the newborn infant.

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