Impact Of Human Milk Oligosaccharide (HMO) In Neonates

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Abstract—Human milk oligosaccharides (HMOs) represent a highly heterogeneous class of carbohydrates which are widely accepted to be beneficial for breast fed infants because of their assumed anti-inflammatory, anti-infective and immune stimulating properties. Human milk oligosaccharides (HMOs) are known to be prebiotics which is stimulating the growth of beneficial intestinal bacteria, and act as receptor analogs by inhibiting the binding of pathogens with cell surface glycans. In addition, the development of a balanced intestinal microflora system plays an important role in modulating the postnatal immune system. And this article also describes about the various local effects and systemic effects of human milk oligosaccharide (HMO). The glyobiology of the oligosaccharide and its impact study is reviewed.

Key words—human milk oligosaccharide (HMO), prebiotic, Anti-adhesive, glyobiology, probiotic, host epithelial cell, neonates.

I. Introduction

Human Milk Oligosaccharide (HMO) is the premiere prebiotics for the neonates. Human Breast milk is rich in oligosaccharides and act as a source of commensal and probiotic bacteria which seems to play an important role in gut colonization and modulation of the infant gut [1]. Human milk oligosaccharide (HMO) plays an important role in protecting neonates from pathogenic micro-organism especially the enteric bacteria. This is due to their ability to act as soluble receptors that inhibit the bacteria binding to their host cell target ligands. HMO not only acts as substrates for specific bacterial species, but also resembles their adhesion molecules or ligands which may enable them to directly affect gut maturation or influence inflammatory processes.

A. Human milk oligosaccharide

In breast-fed babies, Human milk is often the sole dietary source for the first few months of life. It contains all the nutrients necessary for the infant to thrive, but also ingredients that may provide health benefits beyond those of traditional nutrients. Human milk oligosaccharides (HMO) comprise part of these functional ingredients and nearly 1 Litre of mature human milk contains approximately 5–10 g unbound oligosaccharides, and over one hundred and thirty different HMO have been identified.

Oligosaccharide is the third most abundant component of human milk. Human milk oligosaccharides play a clinical role in protecting the neonates from infant diarrhea as a result of Campylobacter, caliciviruses, and diarrhoea of all causes in the breast-fed infants [2].

<table>
<thead>
<tr>
<th>Micro nutrients</th>
<th>Human milk (g/l)</th>
<th>Bovine milk (g/l)</th>
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<tbody>
<tr>
<td>Protein</td>
<td>10</td>
<td>35</td>
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<td>Fat</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Lactose</td>
<td>65</td>
<td>45</td>
</tr>
<tr>
<td>Oligosaccharide</td>
<td>5–10*</td>
<td>0.05</td>
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The building blocks of Human milk oligosaccharides are the 5 monosaccharides such as D-glucose (Glc), D-galactose (Gal), N-acetylglucosamine (GlcNAc), L-Fucose (Fuc), and sialic acid [(N-acetyl neuraminic acid (Neu5Ac)]. HMO act as a potential probiotic and immunogenic compounds which is resistant to low pH and resistant to pancreatic and brush border enzymes.
The important functions of human milk oligosaccharides are Prebiotic, Anti-adhesive, Anti-Microbial and Glycome modifications. At present the modern methods have been developed for the analysis of oligosaccharide. Mass spectrometry and Nano flow liquid chromatography allow rapid profiling for saccharide composition. There are nearly 200 different oligosaccharides in human milk while in other mammals number is less than 50 and often less than 20. Only trace amounts of these oligosaccharides are present in mature bovine milk and, as a consequence, it is low in bovine milk–based infant formula. Recent advances in glycobiology and nutrition which includes the use of stable isotopes, frontal-affinity chromatography, glycan microarrays, MS, and automated solid-phase carbohydrate synthesis, will help verify hypotheses and unravel the mysteries behind HMO.

II. Effects of HMO

A. Local effects

Once the human milk is ingested into the human system, HMO can withstand the low pH in the gut and resist degradation through enzymes from the pancreas and brush border membrane [3, 4]. Therefore, intact HMO rinses the infant's esophagus, stomach, and small intestine before they serve as nutrients for colon bacteria. As in [5] it was reported about the prebiotic effects of HMO showing that a mixture of HMO which promotes the growth of Bifidobacterium bifidum.

Other oligosaccharides, structurally different from those in human milk, have also been added to the infant formula to mimic potential prebiotic effects as in [6, 7].

Adhesion to the host's epithelial surface is essential for the virulence of most pathogenic microorganisms, e.g. Campylobacter jejuni, Escherichia coli, Vibrio cholera, and Shigella and Salmonella strains and C. jejuni, is one of the most predominant causes of diarrhoea worldwide. The adhesion-related virulence factors are often lectins, carbohydrate-binding proteins, which dock to oligosaccharides on the epithelial cell surface. These carbohydrate-binding determinants are also often part of HMO, suggesting that HMO serve as soluble ligand analogs, block pathogen adhesion, and protect breast-fed infants against infections and diarrhea [8]. Fucosylated HMO will inhibit the growth of Campylobacter species binding to human intestinal mucosa [9]. Antimicrobial effects of HMO were also described for calicivirus diarrhea [10] and infections with heat-stable enterotoxin of E. coli as in [11].

HMO may change the glycome of intestinal epithelial cells. 3’'sialyllactose (3’SL) is one of the predominant sialylated HMO which reduces the expression of various glycosyltransferases, which diminishes the content of cell surface sialic acid, fucose, and galactose. Such glycoalx modifications may alter the ability of certain pathogens to adhere. 3’SL exposure of Caco-2 cells reduces the adhesion of enteropathogenic E. coli (EPEC) by 50% [12].

HMO rinses the laryngopharyngeal region and may also reduce pathogen adhesion at the entry to the upper respiratory tract. Human milk inhibits adhesion of Streptococcus pneumoniae and Haemophilus influenzae to human pharyngeal mucosa. These pathogens attach to sialylated glycans on the host's epithelium and are responsible for most of the otitis media cases and respiratory tract infections in newborn infants [13]. Sialylated glycans are also part of HMO and may partially account for the beneficial effects of human milk as in [14].

B. Systemic effects

HMO is partially absorbed intact in the infant's intestine and appears in the urine of breast-fed, but not formula-fed infants. HMO serves as anti-adhesive receptor analogs for urinary pathogens. And the appearance of HMO in the urine indirectly proves their presence in the systemic circulation. They may alter protein-carbohydrate interactions also on a systemic level. Selectins, for example, are involved in cell-cell interactions in the immune system [15]. P-selectin is also involved in the formation of platelet-neutrophil complexes (PNC), a subpopulation of highly activated neutrophils primed for adhesion, phagocytosis, and enhanced production of reactive oxygen species (ROS) [16]. HMO inhibit leukocyte adhesion at sites of inflammation and reduce formation of highly active PNCs, they may contribute to the

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**Fig. 1. Structure of HMO**
protection of breast-fed infants against NEC and other inflammatory diseases as in [17], [18].

1) Control of amebiasis: Breast-fed infants are at lower risk to develop such devastating disorders such as amebiasis or necrotizing enterocolitis (NEC) and worldwide, approximately 50 million people are infected with E. histolytica, resulting in nearly 100,000 deaths annually. E. histolytica resides in the colon, where it used as a specific Gal/GalNAclectin to attach to and destroy the host’s epithelial cells. Here, the specific HMO but also Galactooligosaccharides (GOS) prevent E.histolytica attachment and cytotoxicity. These results suggest that HMO contribute to the lower incidence of amebiasis in breast-fed infants compared to formula-fed infants.

III. Bioactive HMO

HMO is a heterogenic group of at least 130 different compounds. Which of these oligosaccharides interact with a given lectin is currently unknown and as per the above recent methods we can profile the HMO glycome and describe inter-individual differences as well as intra-individual changes during the time of lactation. Once individual “bioactive” HMO is identified, they can be chemically synthesized and used to supplement infant formula for clinical trials. The recent development of automated solid-phase oligosaccharide synthesis has been a milestone for efficient and fast chemical HMO synthesis [19].

Some of the natural sources of HMO like oligosaccharide were Goat’s milk is a rich source of HMO-like oligosaccharides and may be suitable for supplementing formula. These oligosaccharides separate as by-products in goat cheese production and can be isolated by membrane technology on a large scale [20].

IV. In-Vitro studies on effect of HMO

The effect of the human milk oligosaccharide fraction (HMOS) on infant fecal microbiota cultured in vitro was investigated to determine the prebiotic activity of HMO. It supplemented cultures which is developed significantly at lower pH and after fermentation, HMO supplemented cultures contained higher lactic acid concentrations. HMO supplemented microbiota contained significantly more Bifidobacteria and Lactobacillus sp. By this activity the use of HMO supplemented microbiota will significantly decrease the number of E. coli, Clostridium perfringens, and Clostridium difficile. When HMO is supplemented in-vitro, then the growth of Bifidobacteria and Lactobacilli were stimulated, and it inhibits the growth of clostridial pathogens. HMOS also inhibit binding by C. perfringenstio intestinal epithelial cells. These changes in microbiota community composition are highly reminiscent of differences in microbiota of breastfed infants relative to microbiota of prematurely weaned infants [21].

A.Carbohydrates as future anti-adhesion drugs for infectious diseases

Sharon Nathan, (2006) Adhesion of pathogenic organisms to host tissues is the prerequisite for the initiation of the majority of infectious diseases. In many systems, it is mediated by lectins present on the surface of the infectious organism that bind to complementary carbohydrates on the surface of the host tissues. Lectins-deficient mutants often lack the ability to initiate infection. The bacterial lectins are typically in the form of elongated submicroscopic multi-subunit protein appendages, known as fimbriae (or pili). Soluble carbohydrates recognized by the bacterial surface lectins block the adhesion of the bacteria to animal cells in vitro. And type 1 fimbriated E.Coli has been inhibited by aromatic α-mannosides and this is 1000 times more active due to the presence of hydrophobic region next to the monosaccharide-binding site of the fimbriae. The suitable sugars will also inhibit the binding property with the cells of carbohydrate-specific toxins, among them those of Shigelladsenteriae Type 1, and of the homologous Verotoxins of E. coli, specific for galabiose. The above data provide clear proof for the feasibility of anti-adhesion therapy of infectious diseases using CHO.

V. Benefits of breast-feeding compared to formula feeding

- Less diarrhea
- Fewer and less severe episodes of infection
- Higher intelligence
- Less necrotizing enterocolitis
- Less atopy
- Possible protection from sudden infant death syndrome
- Long term health effects

VI. Conclusion

There is increasing evidence that HMOs are of particular importance for the infant health. Functions which are discussed include anti-adhesive and anti-inflammatory effects, role as probiotics and it has an influence on brain development or preventive effects with regard to certain diseases and this oligosaccharide influence the composition of intestinal micro biota and allow the growth of bifidobacterium and lactobacillus organism. It is obvious to conclude that HMO has wider functional importance in the biological system and to maintain the infants in healthy state of being.

VII. Reference


