Sialic acid, an important component of human milk oligosaccharides, has multiple bioactives

Sialic acid molecules occur on all cell surfaces and on most secreted proteins of vertebrates, mediating or modulating a variety of normal and pathological processes (Varki, 2008). The highest concentration of sialic acid occurs in the brain where it plays an important role in brain development, and in the function of the nervous system.

There are two major sialic acids which occur in nature, derivatives of the nine-carbon sugar, neuraminic acid. N-acetylneuraminic acid (Neu5Ac) is an important sialic acid in humans (Figure 1). It occurs in many human body fluids including saliva, gastric juice, serum, urine, tears, and human milk. However, sialic acids rarely occur free in nature. They are more commonly present as components of oligosaccharide chains of mucins, glycoproteins, and glycolipids.

In addition, several viral pathogens (including human influenza virus and avian influenza virus) use sialylated proteins as receptors. Interruption of sialic acid biosynthesis is lethal in embryonic mice, and more subtle mutations in sialic acid metabolism result in a variety of diseases in humans (Schnaar et al., 2014).

Human milk is a major dietary source of sialic acid (Neu5Ac) where it is attached to the terminal end of free oligosaccharides. Sialic acid is an intriguing molecule because of its simultaneous presence in large amounts in both human milk and human brain tissue.

Sialic acid might be a conditionally essential nutrient in infancy because of a high demand coupled with a limited capacity for endogenous synthesis. The unusually large amounts of sialic acid in human milk may be an important exogenous source of sialic acid for the human infant. Furthermore, because of the genetic difference between human and non-human mammals, infant formula based on cow’s milk does not contain any significant quantities of Neu5Ac. Further studies are needed to test the hypothesis that sialic acid in human milk is indeed

Figure 1. N-Acetylneuraminic acid (Neu5Ac).
a conditional essential nutrient that could be important for human infants to reach their full genetic potential. Most non-human mammals do not have the sialic acid N-Acetyleneuraminic acid (Neu5Ac), but they have another sialic acid, N-glycolyneuraminic acid (Neu5Gc) (Figure 2). Humans cannot synthesize Neu5Gc because the human gene to encode for production of Neu5Gc was eliminated long ago, although curiously it is found in apes, our closest evolutionary neighbours. Trace amounts of the non-human sialic acid, Neu5Gc, can be found in adult humans, but these come from consumption of animal tissues in the human diet. The main sources are red meats such as lamb, pork, and beef. It is not found in poultry and only in trace amounts in fish. This confirms that Neu5Gc is mainly found in foods of mammalian origin.

**Sialic acids in the brain**

Sialic acid is now recognised as being very important in supporting the central nervous system and brain growth. It is a structural and functional component of brain gangliosides and glycoproteins. Cortical tissue from human brain has 2–4 times more sialic acid than that of seven other mammals, including our closest relative, the chimpanzee (Wang et al., 1998).

Brain ganglioside sialic acid has implications for evolutionary development and intellectual capacity. The sialic acid moieties of gangliosides and glycoproteins in the frontal cortex play both a structural and functional role and probably participate in a variety of cellular events, such as cell recognition, adhesion in cell-to-cell contact formation, receptor binding and modulation, immunological properties, and bio-signal transduction. Neural cell membranes contain 20 times more sialic acid than other types of membranes, indicating that sialic acid has a clear role in neural structure (Wang and Brand-Miller, 2003).

Further experimental evidence for the role of sialic acid in brain development has shown that the administration of exogenous sialic acid to pigs through supplementation of the feed with 3’- or 6’-sialyllactose can enrich ganglioside sialic acid content in the cerebellum of neonatal pigs (Jaciobi et al., 2016). Administration of exogenous sialic acid to rat pups increased brain ganglioside and glycoprotein sialic acid concentrations, and improved learning performance (Morgan and Winick, 1980). It is quite likely that brain sialic acid plays an important role in brain development and learning ability.

Because of the high sialic acid content in human milk, breast-fed infants at 5 months of age have nearly twice the amount of total salivary sialic acid compared with formula-fed infants. The brain sialic acid concentration in breast-fed infants was also significantly higher than that of formula-fed infants, as observed in babies who died from sudden infant death syndrome (Wang, 2012). Low levels of oligosaccharides similar in structure to those found in human milk are present in the blood of infants, which would be necessary to supply sialic acid to the developing brain (Goehringer et al., 2014). Moreover, sialic acid in human milk is highest during early lactation, a time when the brain is taking up sialic acid most rapidly (Svennerholm et al., 1989). It seems highly likely human milk is a source of sialic acid that can be absorbed into brain tissue.

The higher level of ganglioside and protein-bound sialic acid in brain frontal cortex of breast-fed infants has important implications. These findings support the hypothesis that an exogenous source of sialic acid in human milk may contribute significantly to greater sialylation of gangliosides and glycoproteins in body fluids, tissues and brain glycoconjugates in breast-fed infants and contribute to the observed neurological and intellectual advantages of breastfeeding over formula feeding.

It is clear that formula-fed infants will not receive significant amounts of human sialic acid compared to breast-fed infants. Possibly there is a case to study the addition of sialic acid to infant formulas.

**Sialic acid and infectious disease**

Harmful bacteria, viruses, and other pathogens use cell surface carbohydrates as sites for recognition and binding to their target host cell which is the first step in infection. Oligosaccharide sequences frequently containing sialic acid occur on mucins which can act as ‘decoys’ for microorganisms and parasites. Pathogenic organisms attempting to gain access to mucosal membranes to cause infection might first encounter their oligosaccharide ligands attached to soluble mucins. Upon binding to these sequences in the mucins, they are swept away by ciliary action, leaving the mucosal cell untouched. The potential of sialic acids as antimicrobials is clearly enormous.

Sialic containing oligosaccharides in human milk can act as highly specific receptors for a variety of viruses, bacteria, and parasites. Both free and bound sialylated oligosaccharides in human milk prevent the binding of rotavirus and cholera toxin associated with infant diarrhoea, as well as *Escherichia coli* strains associated with neonatal meningitis and sepsis (Smilowitz et al., 2014). An understanding of the role that sialic acid plays in the pathogenicity of infectious microorganisms is...
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crucial for disease management. Sialic acid levels in blood are also used as a marker of the acute-phase protein response. Some acidic glycoproteins, for example, fibronogen and haptoglobin, have sialic acid as the terminal sugar and they increase markedly in response to cell injury. In type II diabetes, the circulating sialic acid concentration is elevated in comparison with non-diabetic subjects (Cook et al., 1990).

There is an interesting aspect to the different sialic acids found in human and non-human mammals. Human cells normally do not have the sialic acid Neu5Ac on their surface. This should render humans resistant to microbial pathogens that require cell surface Neu5Gc for invasion. This could explain the apparent lack of susceptibility of humans to certain domestic livestock pathogens that use Neu5Gc to invade cells and generate infection. Conversely, the excess of cell surface sialic acid, NeuAc, in humans could render them more susceptible to microbial pathogens that use Neu5Ac to support invasion. However, in this case it would be interesting to determine if administration of human sialic acid would set up a competition for binding the pathogen where it could bind to free sialic acid and then be safely removed by ciliary action from the gastrointestinal tract.

Sialic acid and the immune system

The immunoglobulin IgG has general anti-inflammatory properties when administered intravenously, and has been widely used to treat autoimmune diseases, including immune thrombocytopenia, rheumatoid arthritis, and systemic lupus erythematosus. The anti-inflammatory activity of IgG depends upon the presence of sialic acid in the Fc fragment of the immunoglobulin. Removal of the terminal sialic acid from the Fc fragment abolishes the anti-inflammatory activity. Conversely, enrichment of the sialylated fraction of IgG enhances this activity (Anthony et al., 2008).

Sialic acids and cancer

During malignant transformation of cells, glycosylation is heavily altered compared with healthy tissue. One key change of malignant tissue is an increase of the non-human sialic acid, Neu5Gc, instead of normal Neu5Ac into cell surface glycans. The non-human sialic acid Neu5Gc occurs in the glycan structures of many human tumours. Indeed, cancer cells metabolically incorporate exogenous Neu5Gc, originating from red meat and milk products in the diet. For humans, Neu5Gc-containing antigens are immunogenic and this may promote tumour growth. Low doses of anti-Neu5Gc antibodies sustain Neu5Gc-positive tumours in Neu5Gc-deficient mice by triggering a chronic inflammation that helped tumour growth (Julien and Delannoy, 2014). Thus, Neu5Gc maybe the missing link between red meat consumption and the risk of cancer, particularly colorectal cancer, an association that so far appears unique to humans.

Since Neu5Gc uses the same biochemical pathways as, Neu5Ac then Neu5Ac could be potentially "flushed" out of the body by high amounts of Neu5Ac (Samraj et al., 2014). This suggests that ingestion of human sialic acid, Neu5Ac, could help in cancer avoidance if it could prevent the changes in cell glycosylation in favour of Neu5Gc.

Production of sialic acids

It clear that sialic acid is an important metabolite in human health contributing to brain development, protecting against infectious diseases and autoimmune diseases. It may also play a protective role in cancer avoidance by competing with the non-human sialic acid, Neu5Gc in the diet. It has been difficult to thoroughly investigate and test these concepts in the past because sialic acid was not readily available.

Fortunately, in recent years Jennewein Biotechnologie has developed an innovative production process for the efficient and scalable manufacture of a highly pure crystalline form of human sialic acid. The manufacturing process, and the production capacity means that a supply of sialic acid is readily available. Furthermore, sialic acid is now approved for food use in China and EU.

This will allow the development of further applications of sialic acid in the manufacture of food supplements, pharmaceutical products, ingredients in cosmetics and in therapeutic animal feed.

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