

Revolutionising infant nutrition:

Benefits of human milk oligosaccharides

Although it is widely accepted that breast milk provides the best nutrition for new-borns, there is still much we don't know about it. Up until now, one of the most puzzling aspects has been the presence of human milk oligosaccharides (HMOs), components that offer no nutritional value. Nestlé is revolutionising our understanding of these elements. Their research shows that HMOs promote good bacteria in the gut, reduce risks from infection and allergy, and even support brain development and improve cognitive functions. New findings presented by Nestlé at the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Annual Meeting 2019 confirm their position as a world leader in HMO research. This fresh era of infant nutrition brings Nestlé a step closer to their aim of offering formulae for babies that is as close as possible – in composition and benefits – to breast milk. Their new and innovative formula contains two HMOs, providing unique benefits to babies unable to breastfeed.

Breastfeeding a new-born baby has many beneficial effects. High up on the list comes the fact that breast milk is perfectly adapted to the baby's delicate digestive system, with all nutrients available in easily digestible small pieces. With an optimal combination of all essential nutrients, breast milk provides everything a baby needs to grow. Surprisingly, however, in the mix of many different components, the third most common ingredient has virtually no nutritive benefits. This element is a group of sugars called human milk oligosaccharides (HMOs). They provide unique benefits to the baby, including protection against infection at a time when they are most vulnerable.

HMOs are synthesised by the mammary gland and each oligosaccharide contains a basic lactose (milk sugar) backbone to which various other components are added in many different combinations. 200 different HMOs have been identified so far. Curiously, this seems to be a unique feature of human milk; these sugars are almost absent in cow's milk and other farmed animals.

When these fascinating compounds were first described in the early 1930s, their function was a mystery. Eventually, researchers uncovered their importance for the development of the gut microbiota in infants, promoting the establishment of good bacteria, such as *Bifidobacteria* and *Lactobacilli*. But this was just the beginning.

NESTLÉ: LEADING THE CHARGE IN HMO RESEARCH

Nestlé Research, the largest private research organisation working on nutrition, has been at the forefront of innovations in infant nutrition for over 150 years. Over 30 years ago, Nestlé scientists were among the first to identify the potential of HMOs and began further investigations into these wonder molecules.

Since then, scientists working around the world have discovered that HMOs offer many other important functions. A growing body of evidence put forward by Nestlé and others suggests that HMOs are essential to establish beneficial gut microbiota, aid the development of a strong immune system, strengthen the gut barrier, and eliminate infection-causing pathogens.

Today, Nestlé continues to lead the field in exploring the benefits of HMOs and the mechanisms underpinning their beneficial properties. Nestlé's ground-breaking research also highlights the importance of breastfeeding and enables HMOs to be incorporated into formula milk, taking us towards a new era of infant nutrition. At the recent 2019 European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Annual Meeting held in Glasgow, UK, Nestlé presented six different studies on the benefits of HMOs. These also included new data on the two HMOs present in their novel formula, further demonstrating the benefits of these unique components.

A NEW ERA FOR INFANT NUTRITION

Knowing how important all these components are for infant health and encouraged by the results from their research, Nestlé continues their efforts



Breast milk contains HMOs, molecules that provide additional benefits to the baby beyond nutrition.

to improve their formulae by incorporating HMOs to provide the best possible nutrition for babies who cannot be breastfed.

Over 200 different HMOs are present in breast milk. As high levels usually indicate high importance, some of the first studies by the Nestlé team focussed on just two HMOs, known as 2'-fucosyllactose (2'-FL) and tetrasaccharide lacto-N-neotetraose (LNnT). Not only are these two of the most abundant HMOs, making up almost 40% of the total amount of HMOs, they are also readily available for research – an important consideration for the team.

BETTER TOGETHER

Inspired by the positive results of laboratory, animal and human studies obtained with 2'FL and LNnT, Nestlé once again took a pioneering approach and created a unique infant formula: the first to combine two HMOs. These are produced through fermentation and have been recognised as structurally identical to HMOs in breast milk by different regulatory and scientific authorities including the US Food and Drug Administration and the European Food Safety Authority. Nestlé performed the first clinical study in infants on this unique combination of two HMOs which shows promise in terms of stimulating good bacteria in the gut and reducing the risk of certain infections.

In a 2017 paper (Puccio et al) Nestlé researchers confirmed that the new formula was well tolerated and able to support normal growth and development. The Nestlé team also demonstrated that infants receiving this combination of two HMOs had higher levels of *Bifidobacteria* (a group of beneficial bacteria) and a lower propensity to respiratory infections

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and bronchitis. This resulted in a less frequent use of antipyretic and antibiotic medication for the babies which was also noticed by parents. Interestingly, these effects lasted even after the infants stopped feeding on Nestlé's combined HMO formula. These initial results are very promising, suggesting that the formula offers benefits to babies beyond nutrition. If further studies can confirm these protective benefits, this would be of enormous value to those infants who are unable to be breastfed.

DELVING DEEPER

The team at Nestlé were keen to

investigate the link between HMOs and respiratory infections and understand what was going on at a deeper level. They analysed stool samples from infants and found that those who had experienced respiratory infections had less *Bifidobacteria* in their gut. Several studies have shown the importance of gut microbiota in systemic infections, so perhaps the higher levels of beneficial bacteria and the lower levels of respiratory infections in those infants fed the HMO combination formula were linked?

To better understand the mechanism behind the protection conferred by the



Nestlé's research is shedding light on the multiple benefits babies receive from breast milk.



HMOs also play a role to fight respiratory infections.



Breastfeeding provides multiple benefits to babies.

One of the most recently discovered and most fascinating effects of HMOs can be seen in brain development and improved cognitive functions.

particular HMO combination present in the new formula and how it interacts with *Bifidobacteria*, researchers at Nestlé cultured *Bifidobacteria* in a petri dish with 2'FL and LNnT. They demonstrated the ability of the two HMOs to support these beneficial bacteria and enhance the ability of *Bifidobacteria* to target pathogens. Specifically, *Bifidobacteria* support resistance to infection-causing pathogens and improve gut barrier function – the protective wall of the gut that stops harmful items (like pathogens) passing through into the blood. This sheds light on how HMOs may help give protection against respiratory infections.

This connection between HMOs and protection against respiratory diseases was corroborated when looking at 2'FL

levels in breast milk in an association study. The Nestlé team compared mothers able to secrete milk with high 2'FL content – known as secretors – and mothers with lower levels of 2'FL – known as non-secretors. Infants of secretor mothers were less likely to experience a respiratory infection, and it was also observed that this protection only lasted during the breastfeeding period. Once again, it seems that HMOs provide protection to babies against respiratory infections, although further work is required to confirm this.

In addition to the range of studies looking at the links between HMOs and protection against respiratory infections, more and more studies are examining the wider benefits of 2'FL and LNnT. For example, 2'FL could also help reduce the risk of

developing skin conditions for babies whose family history means they may be more likely to develop allergies. In a paper published in 2017, researchers at Nestlé observed a lower incidence of eczema in babies from mothers able to secrete milk with high 2'FL content compared to mothers with lower levels of 2'FL. This effect was particularly visible in babies born by C-section. Typically, these babies are not exposed to the mother's intestinal and vaginal microbiota, but only receive bacteria from the hospital environment and the mother's skin. The authors speculated that breastmilk from secretor mothers helped these babies establish a good microbiota population early, and kept eczema manifestations at bay.

The wider benefits of 2'FL and LNnT are an interesting research area that is generating some exciting new results, like those presented by Nestlé at the recent ESPGHAN Annual Meeting. Using growth-retarded animals, the Nestlé team demonstrated that the combination of 2'FL and LNnT improves pancreatic activity, with effects still visible well past the period when the animals were receiving HMOs. This suggests a long-term impact on pancreatic function and certainly warrants further investigation in infants who are born with low birth weight. Nestlé's unique combination of two HMOs in an infant formula looks set to bring even wider benefits to bottle-fed babies than initially hoped for.

INVESTIGATING NEW HMOs

As the field of HMO research advances, it also brings important technological developments along with it. One of the limiting factors in deciding which HMOs to study has traditionally been the ability



Behind the Research: Nestlé

About Nestlé Research

Nestlé Research is the largest private research organisation working on nutrition. It has been at the forefront of innovations in nutrition for over 150 years. Over 30 years ago, pioneering Nestlé scientists were among the first to identify the potential of HMOs and begin investigations into these wonder molecules. The team's aim is to better understand the benefits of HMOs and to develop formulae that offer those benefits to non-breastfed babies.

Further Information

HMO academy is the first knowledge hub on human milk oligosaccharides. The digital academy provides an excellent source of learning and support to all healthcare professionals interested in HMOs, leveraging state-of-the-art interactive technologies to provide you with the most exciting and user-friendly learning experience. To know more and subscribe to the HMO academy newsletter visit: www.thehmoacademy.com

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to produce the HMOs for use in research. 2'FL and LNnT were two of the first HMOs which could be easily produced and so were obvious candidates for early research. Now, though, as further HMOs become available for research, more clinical studies examining the benefits of a wider range of HMOs are ongoing.

Despite their focus to date on 2'-FL and LNnT, Nestlé continue their work to uncover hidden aspects of HMO functions across the spectrum of these fascinating compounds. True to form, at the ESPGHAN Annual Meeting, the Nestlé team presented work on other HMOs, highlighting their position at the forefront of HMO research.

One of the most recently discovered and most fascinating effects of HMOs can be

seen in brain development and improved cognitive functions. In particular, Nestlé researchers looked at two HMOs – called 3'-SL and 6'-SL – with some interesting effects on cognitive function in mice.

Both 3'-SL and 6'-SL were shown to improve learning and memory in rodents. Curiously, depleting each HMO separately didn't produce the same effects, suggesting that each one may play its own separate role and therefore they cannot replace each other. The exact mechanism is unclear, but it is unlikely that HMOs can enter the brain directly. One hypothesis involves the well-established connection between the gut and the brain, where microbiota may once again prove to have a crucial role. By better understanding the whole range of HMOs, Nestlé's research is shedding

light on the benefits that breastfeeding confers on babies and continuing to push the boundaries of infant formula.

PIONEERS IN INFANT NUTRITION RESEARCH

Building on 150 years at the forefront of research in infant nutrition, Nestlé continue to invest heavily in research. The team's work on HMOs is a good example of how they continue to use the latest research to develop state-of-the-art formulae for those babies unable to breastfeed. The latest results presented at the recent ESPGHAN Annual Meeting are just a glimpse into the valuable research that Nestlé is conducting in the area of infant nutrition. We look forward to following the work of this dynamic team as their work continues to enhance the future of infant nutrition.

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