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THIS ISSUE PAGES

A formula for tolerance: could cow's milk be a novel solution to milk allergy?

Introduction

The last decade has witnessed a significant rise in the prevalence of food allergies worldwide, as well as in the number of food proteins that can trigger an immune response (allergens). A substantial 18% increase in reported food allergies in children, under the age of 18 years, has been observed between 1997 and 2007[1]. Recent studies indicate that up to 10% of the population in the western world now suffer from at least one type of food allergy[2].

Food allergies are most common during infancy. For infants, cow's milk protein allergy (CMPA) is the predominant food allergy, occurring in 2-3% worldwide[3]. Although cow's milk avoidance is the dietary management for infants who suffer with CMPA, accidental exposure is common, which can trigger an allergic response or, in more severe cases, anaphylactic shock.

While it is reassuring that up to 90% of infants outgrow CMPA and develop tolerance by the age of five[3], the small percentage of children who do not develop tolerance have an increased risk of developing conditions associated with atopy, such as asthma, dermatitis, and allergic rhinitis, or additional food allergies in later life[4]. To date, the number of individuals who suffer with respiratory allergic diseases worldwide is almost 700 million[5].

Further research is necessary to acquire a deeper understanding of food allergies in order to develop more effective treatments and to prevent the onset of associated problems in later life. It is well established that the immune system can be easily manipulated during the first months of life, with both positive and negative consequences[6]. Current research suggests that by targeting and priming the immune system of infants in the early stages of life, it could be possible to prevent the sensitisation to allergy and to induce tolerance to harmless food proteins and, subsequently, prevent the onset of other related atopies.

This edition of *DN Forum* will explore the aetiology of CMPA and novel treatment mechanisms, including an innovative research project by Food for Health Ireland (FHI). FHI's early infant development platform has five research areas that aim to narrow the gap between breast and formula milk in terms of composition and functionality. Here, we will focus on their immune-modulatory project, which has identified dairy hydrolysates with the potential to protect against CMPA and gut inflammation. This work shows promising potential for the treatment options available to infants with CMPA.

EDITORIAL

Although breastmilk is indisputably the optimal feed for infants, it is important that research continues to improve the composition of formula feeds available to infants for whom breastmilk is not an option. Researchers at Food for Health Ireland (FHI) are embarking on innovative research to develop specific hydrolysed cow's milk proteins that could help to induce tolerance in allergy-prone infants, thereby reducing the risk of milk allergy and associated atopic conditions in later life. In this edition of *DN Forum*, FHI's Niamh Hunt describes the aetiology of milk allergy, highlighting a novel concept for its treatment and prevention, via early controlled exposure to the potential allergen.

The National Dairy Council has launched a new website (www.ndc.ie), which we invite you to visit. It hosts a wide range of useful resources for both health professionals and consumers, including our new Sports Nutrition booklets, featured on page 4 of this publication.

We hope you enjoy this edition of *DN Forum* and look forward to any feedback or comments you wish to share: nutrition@ndc.ie

Marianne Walsh

Dr Marianne Walsh
Nutrition Manager
The National Dairy Council (NDC)

Novel Irish research paves the way for a reduction in cow's milk protein allergy

Niamh Hunt, Researcher
Food for Health Ireland, Dublin City University.

Niamh Hunt

Protein, a multifunctional nutrient in metabolic and immune processes

Our health and disease risks are heavily influenced by a number of factors. While genetics play a central role, the environment to which we are exposed is also largely responsible, with diet being a leading component. Dietary proteins supply a pool of amino acids that form various protein molecules, which play intricate roles across the body's metabolic pathways. While dietary protein is renowned for its fundamental role in growth and tissue repair[7], it also boasts a plethora of health benefits, with specific peptides playing a major role in the functioning and regulation of the immune system from birth, as well as in protecting against infection by inhibiting microbial growth[8].

Infants have unique dietary needs, particularly in the first few months of life, with exclusive breastfeeding the optimal choice up to six months of age. Breastmilk provides a rich source of protein, which is needed during this time of rapid growth and development, contributing to optimal health in newborns[9,10]. In cases where breastfeeding is not an option, infant formula can provide an alternative source of nutrition and includes key proteins required for development. At weaning, a range of new foods are introduced to the diet, which help to meet the expanding nutritional demands of the growing infant. Therefore, the immature gastrointestinal tract normally undergoes rapid adaption and development during this life stage.

Allergy typically begins during infancy

The gastrointestinal tract plays a critical role in the development of oral tolerance[11,12]. Oral tolerance allows the infant to safely ingest harmless food proteins, such as those found in cow's milk, while retaining the ability to mount an immune response to potential pathogens.

Food allergies are most common during infancy due to the immaturity of the newborn gastrointestinal tract and immune system. This increases the risk of sensitisation to and exposure to allergenic antigens when encountering new foods[13]. As illustrated in Figure 1, infants are often unable to produce all of the enzymes required for complete digestion of dietary protein and this, coupled with their high stomach pH (up to four times higher than that of an adult), can often result in the incomplete digestion of proteins in newborns[14].

The allergic potential of peptides is dependent on the level of exposure and their size, with larger peptides being more allergenic and increasing risk of sensitisation to specific food proteins (Figure 2). As the immature gastrointestinal barrier of vulnerable infants is more permeable, it enables these larger proteins to be absorbed. Once crossed over the gastrointestinal barrier, these larger peptides can activate and overexpress Type 2 helper T-cells (Th2), which act as key drivers of allergy. If the development of the gastrointestinal immune system and oral tolerance can be stimulated in the early stages of life, the likelihood of activating this allergic cell type and, thus, inducing sensitisation is greatly reduced[15].

Proteins can be pre-digested or hydrolysed into smaller protein chains outside of the body, and are known as protein peptides or hydrolysates. Some hydrolysates are known to possess different immunological properties to the whole protein and have been proven to modulate the immune system for benefit. Recent findings indicate that hydrolysed dietary peptides are known to affect major systems such as the cardiovascular, nervous, digestive and immune system[8]. Some cow's milk-protein hydrolysates have been shown to specifically inhibit key cells involved in driving allergy. In addition, studies suggest that cow's milk hydrolysates can stimulate the intestinal epithelial barrier, which may also be useful in preventing food allergy[16].

It is understood that healthy intestinal microbiota display beneficial immunomodulatory activity that leads to the development and maintenance of immune tolerance[17]. Allergy, asthma, eczema and allergic rhinitis have all been associated with the failure to develop the intestinal mucosal defence system. The risk of developing these diseases is reduced in exclusively breastfed infants, as breastmilk is known to induce natural tolerance[17]. Breastmilk contains healthy bacteria, such as *Bifidobacteria*, and a large amount of galacto-oligosaccharides, which influence and support microbial gut colonisation of the infant. *Bifidobacterium* make up the bulk of the gut microbiota (60-70%) in breastfed infants, however, a much lower proportion is observed in formula-fed infants. It has been observed that children with food allergies have a much smaller population of *Bifidobacteria*[17,18]. Formula-fed infants are also statistically more likely to develop CMPA than breastfed infants[5]. It is possible that the gut of formula-fed infants is not as fully developed as those that are breastfed, due to a lower *Bifidobacteria* proportion, resulting in a lower immune tolerance.

Modulation of infant formula to stimulate oral tolerance to cow's milk protein

While breastfeeding is recognised as the most important source of nutrition for newborns, in situations when it is limited or impossible, infant formula is the only alternative that can fulfil the nutritional requirements of infants during the first six months of life. Cow's milk is largely considered the most important and preferred ingredient source for infant formula, as it is made up of many of the constituents found in breastmilk, such as essential

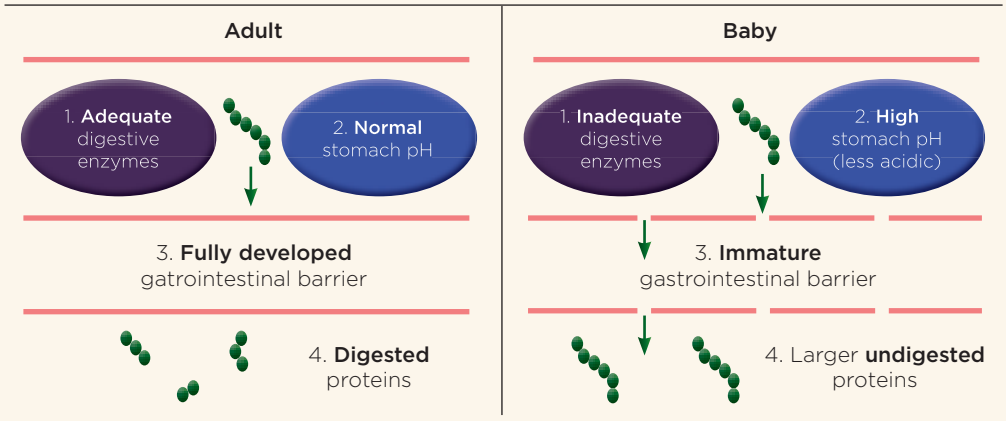

Figure 1: The conditions within the infant gastrointestinal tract that can potentially impact their ability to digest larger proteins and therefore increase susceptibility to allergenicity

amino acids, that are required to support the developmental process of the infant[19].

Current infant milk formulae on the market, suitable for infants with CMPA, are comprised of extensively hydrolysed cow's milk proteins (Figure 2). These milk formulae provide the infant with the high nutritional quality of the proteins, while also reducing their allergenic properties, due to their small size[20,21]. However, while these extensively hydrolysed formulae are more tolerable and prevent allergic symptoms, they cannot induce tolerance to the allergen because extensive protein hydrolysis results in the loss of immunogenicity. This reduces stimulation to the immune system, inhibiting its ability to develop tolerance to these otherwise harmless milk proteins.

Although strict avoidance of cow's milk is advised for the management of CMPA, recent studies suggest that exposure to cow's milk allergens can, in fact, be beneficial for infants that are at risk of developing CMPA through targeting and influencing the immune system from birth[22]. Partially hydrolysed formulae, however, have been shown to reduce the prevalence of atopic dermatitis in infants compared to whole-protein formulae[23,24,25]. Partial hydrolysis of proteins retains the protein's immunogenicity, which provides the infant with an opportunity to develop oral tolerance to the whole protein[11]. Among these hydrolysates, both *in vitro* and *in vivo* studies have identified cow's milk-derived whey and casein hydrolysates that have positive modulatory effects on the immune system[26]. They have been shown to display similar beneficial effects to breastmilk on gut colonisation, through increasing *Bifidobacterium* levels, which are decreased in formula-fed infants and are required to bring about immune balance, thereby promoting oral tolerance[25,26].

Scientists at FHI have identified dairy hydrolysates that demonstrate both a capacity to supress allergenic Th2 cells and to stimulate regulatory T-cells, which play a role in developing oral tolerance. These hydrolysates have been identified through *in vitro* studies and are currently undergoing *in vivo* studies in an animal model to determine their applicability and progression as an ingredient in infant formula.

Conclusion

Although this FHI research is in an exploratory phase, its potential is clearly worthwhile given that approximately 10% of the population suffer with a food allergy. Food allergies impose a significant burden on patients and their families, through dietary restriction, social interactions and they also pose a significant cost on healthcare systems. These costs include medical diagnosis, treatments following accidental ingestion and the purchase of specialised foods[27].

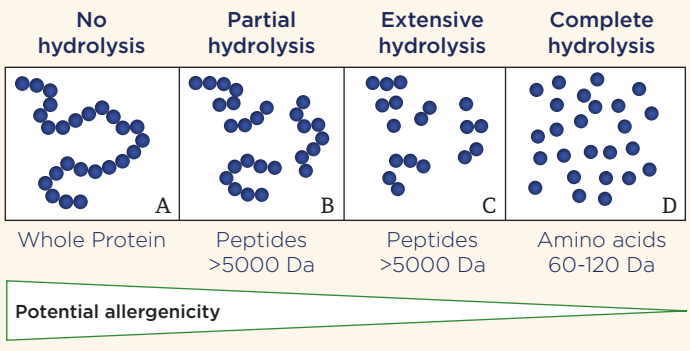

Figure 2: The allergenicity of proteins is dependent on their size.

A Composition of regular infant formula: proteins acceptable in tolerant infants
B Composition of FHI proposed allergy-prevention infant formula: peptides to induce tolerance
C Composition of specialised infant formula: smaller peptides for infants with mild allergy
D Composition of specialised infant formula: amino acids for infants with severe allergy

While scientific studies on cow's milk-protein hydrolysates yield promising results in the area of allergy by targeting the infant immune system, further research is required to determine whether these hydrolysates are capable of inducing long-term tolerance to cow's milk. In addition, the exact mechanisms by which partially hydrolysed proteins could potentially reduce the risk of sensitisation to cow's milk proteins remains unclear and will be investigated as part of the FHI programme. Research to date suggests that they may do so through their role in influencing healthy gut development, specifically by increasing *Bifidobacteria* levels, required for immune balance. If protein hydrolysates can promote healthy microbial gut colonisation in infants who are unable to breastfeed or who are at high risk of developing CMPA, this may subsequently induce tolerance and, thus, prevent sensitisation to cow's milk proteins. Priming the immune system from birth, a most critical time for development, may subsequently prevent or lower the incidence of other atopic conditions associated with food allergies in later life.

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Key points

- Continued research to improve the composition of infant formula is important to ensure the best alternatives are available for infants for whom breastfeeding is not an option. For infants with cow's milk protein allergy (CMPA), the current treatment is strict avoidance of regular cow's milk formula and replacement with extensively hydrolysed or amino acid-based formulae.
- The ability to develop oral tolerance during early infancy is key to preventing or reducing the onset of food allergies and the gastrointestinal immune system plays a major role in this. A combination of low concentrations of digestive enzymes, high stomach pH and an immature gastrointestinal gut barrier makes infants more vulnerable to allergenicity.
- Cow's milk-protein hydrolysates have been shown to stimulate the intestinal epithelial barrier and may promote healthy microbial gut colonisation, which could help to reduce the risk of sensitisation to cow's milk proteins and reduce allergenicity.
- FHI is conducting novel research to explore the potential of specific dairy hydrolysates to stimulate immune function in infant's prone to CMPA. Such hydrolysed formulae offer great potential benefit to reduce the emergence of CMPA in infants and related atopies in later life.

New resources

The NDC has produced two new sports nutrition publications: *Sports Nutrition Handbook – Fuelling Wise for Sport and Exercise* is aimed at consumers, covering topics such as: body weight; carbohydrate; protein; fat; recovery nutrition; hydration; supplements; and the role of milk as part of an active lifestyle. The *Powered By Dairy – the Science* publication outlines the research to date on the role of milk in recovery nutrition; and may be of interest to health professionals, sports instructors and trainers.

Booklets can be downloaded from: www.ndc.ie/health-professionals/our-publications or a limited number of copies can be ordered by contacting hello@ndc.ie

Contact us....

THE NATIONAL DAIRY COUNCIL (NDC)

The National Dairy Council
The Studio, Maple Avenue,
Stillorgan, Co. Dublin, Ireland
Tel: +353 (0)1 290 2451
Email: info@ndc.ie
Web: www.ndc.ie

NDCIreland @NDC_ie

Mission: To deliver real and unique value to Irish dairy farmers by protecting and promoting the image, quality, taste and nutritional credentials of Irish dairy produce to a wide variety of audiences in a clearly defined, focused and effective manner.

FOOD FOR HEALTH IRELAND (FHI)

Food for Health Ireland
Science Centre South
University College Dublin
Tel: + 353 (0)1 716 2391
Email: fhi@ucd.ie
Web: www.fhi.ie

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Mission: To leverage the world-class capabilities of the Irish academic partners, with the market expertise of the industry partners, into a pipeline of innovative, nutritional functional ingredients/products for the global food industry.