Received: 19 March 2019 | Revised: 17 May 2019 | Accepted: 17 June 2019

DOI: 10.1111/apa.14906

A DIFFERENT VIEW

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Glycated proteins in infant formula may cause inflammation that could disturb tolerance induction and lead to autoimmune disease

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Funding information
The study was financed by Dr Per Hakanssons Foundation, by Swedish Medical Research Council and funds from Lund University and Skane University Hospital.

1 | INTRODUCTION

The quality of the food introduced during weaning is important, since this is when the infant develops immunology and tolerance. The general recommendations from leading organisations are to breastfeed for 6 months. After that weaning patterns vary worldwide. In Sweden, for example, it is common for infants to make the transition to infant formulas and eat gruel, which is made from milk and wheat.

Weaning is a physiological pro-inflammatory state, which triggers the growth and maturation of the intestine.[1] The infant's immature intestinal mucosa tends to amplify responses to pro-inflammatory stimuli and this, in turn, increases the risk for inflammatory pathology. This is related to an increased expression of pro-inflammatory genes and suppressed expression of feedback regulation of these genes.[2] Numerous studies in laboratory animals and humans have demonstrated accelerated epithelial cell growth of the intestine during weaning and this more than doubles the intestinal surface that interferes with the nutrients. This interaction triggers the growth of the intestine. At the same time, oral tolerance is developed by an active non-responsiveness to ingested food products that is mediated by the lymphoid tissue of the intestine. This tissue is the largest lymphoid tissue in the body, which provides a protective immune function against any harmful bacteria while, at the same time, accepting nutrients and benign bacteria. Food allergies or inflammation occur when oral tolerance fails and the incidence of allergies is between 0, 1 and 6% in Europe.[3] The incidence of intestinal inflammation is not known. Various guidelines have been issued to avoid allergic symptoms. During weaning, the infant formulas that are mostly used are based on skimmed milk powders. Experimental studies carried out by our team found that infant formulas based on skimmed milk powder, which contains high levels of glycated proteins, triggered an inflammatory condition in rats that may also be relevant for humans.[4]

The production of infant formulas is a complex procedure, which involves mixing and drying at high temperature. This changes the structure of the three macronutrients of fat, protein and carbohydrate in a fundamental way and allows novel interactions with unknown physiological aspects.[5] Fresh milk is initially homogenised at high pressure to prevent the fat separating and to produce a stable milk liquid. During homogenisation, the milk fat globules become smaller and the total surface area of the fat content is increased. As a result, the milk proteins bind to the surface membrane of the fat globules, creating a novel protein-lipid interaction and unfolded protein structures. The pasteurisation process then ensures the microbiological safety and evaporation of the product the shortening of the final spraying time.[6] Pasteurisation changes the secondary structure of the proteins, creating unfolded proteins, while spray drying leads to intensive aggregation of proteins. This affects the tertiary structure of the proteins and creates novel protein to protein interactions. Unlike homogenisation, which causes non-covalent bonds between the macronutrients in milk, pasteurisation and spray drying causes covalent bonds between the milk proteins, fats and carbohydrates. The reaction between lactose and the milk proteins, namely

caseins or whey proteins, is called glycation. In chemical terms, a Schiff's base is formed, which is a reaction between an amino group from the protein, usually from lysine residues, and the carbonyl group of lactose. The reaction starts when the milk is heated above 60°C and ends with the formation of advanced glycation end products. The reaction is pH dependent and is more pronounced during alkaline pH. Whey proteins are more reactive than caseins. The initial rate of reaction determines the overall glycation, which is more prominent in dry mixtures than in liquids. Typical glycation reactions have continuous reactivity, with novel interactions, yielding reactive aldehydes and cross-linking between glycated proteins. We were interested to investigate if elevated amounts of glycated milk proteins could induce an inflammatory reaction.

2 | METHOD

Since weaning is a period when the intestine is hypersensitive to all nutrients, we chose an experimental set-up with weaning rat pups. We weaned 18 rat pups on to a diet based on milk powder with high levels of glycated proteins, namely 577 ± 25 carboxy methyllysine μg per gram of food, while 18 control pups received a milk powder with a low level of 66 ± 6.[4] The higher level was obtained by storing the dry milk powder in hot and humid conditions for 30 days.

3 | RESULTS

After 1 week, the rats fed the highly glycated milk powder had elevated inflammatory cytokines in their blood, namely interleukin-1 beta, interleukin-17 and monocyte chemoattractant protein.[4] This was accompanied by a parallel lower level of body weight gain, despite a similar food intake in both groups. This suggests elevated thermogenesis, which normally occurs during inflammation due to activation of the sympathetic nervous system.[7] An alternative explanation could be decreased absorption of nutrients. They also experienced a decrease in the weight of their thymus and spleen, which could have been mediated by lymphocytes migrating from these organs. The elevated cytokines may have originated from intra-epithelial or lymphoid cells in the gastrointestinal system.

After 4 weeks, the rats in the high-concentration group showed chronic inflammation,[4] namely raised levels of a whole group of cytokines that are expressed during inflammation. Vascular endothelial growth factor was elevated, in line with inflammatory endothelial inflammation in humans. So was the adipose tissue hormone leptin, which is a cytokine that is well known for its role in appetite regulation and energy balance. It has also been documented as a hormone that regulates autoimmunity in a mouse model.

4 | DISCUSSION

The findings of our rat model led us to hypothesise that inflammation may trigger type 1 diabetes in humans, which is characterised by an immune destruction of the insulin-producing beta cells in the pancreas. The cause is currently unknown. In humans, beta cell proliferation starts shortly after birth, including during weaning, and continues during the first year of life to reach critical mass. After that the beta-mass is constant. Ongoing destruction of beta cells during the first year of life may not be evident until puberty, when the demand for insulin is drastically increased.[8] The distribution of ingested glycated proteins is an important issue that needs to be investigated. One study demonstrated that 20% of a given dose of radiolabeled glycated milk proteins were retrieved from three organs—the liver, kidney and the pancreas—as glycated peptides or amino acids.[9] We believe that the presence of reactive glycated products has a negative influence on the highly sensitive beta cells in the pancreas and that there is a risk of disturbed proliferation. There are several target molecules for glycated milk products. It is important to mention micro ribonucleic acid, as this is critically important for the maturation of the beta cells and establishing an appropriate beta cell mass, as demonstrated in another rat study.[10] The possible link between food-induced inflammation and induction of autoimmune disease needs to be further investigated.

5 | CONCLUSION

Weaning is a pro-inflammatory period, when infants have extreme sensitivity to nutrient molecules. We believe that the introduction of novel covalently changed glycated milk proteins, obtained through drying and heating, can lead to inflammation that may disturb tolerance induction and later develop into autoimmune diseases.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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