The influence of dietary nucleotides on humoral and cell immunity in the neonate and lactating infant

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Abstract

The organism constantly requires nucleotides, especially for tissues that present a high rate of turnover, such as the cells of the immune system. In certain circumstances, nucleotides may become semi-essential nutrients required by a particular organ. There is evidence of the potential role of exogenous nucleotides as regulators of the immune function. In experiments carried out with animals, studies have shown that dietary nucleotides stimulate the humoral immune response to T-dependent antigens and raise total antibody levels. The present study reveals an increase in the production of immunoglobulins, an improved response to vaccines, a reduction in morbidity and increased tolerance to dietary antigens. Therefore, the addition of nucleotides to formula appears to favour the immune function. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Dietary nucleotides are considered non-essential nutrients, but under certain conditions they may become semi-essential. Endogenous synthesis of such nucleotides may be insufficient for normal functioning, which would be of particular significance for the growth and development of tissues with a rapid turnover [19], such as cells belonging to the immune system, bone marrow and intestinal mucosa, as these preferentially utilize the nucleotide salvage pathway.

Dietary nucleotides are active in various physiological functions, such as those that control the metabolism of lipoproteins and fatty acids [6,10,25]. They are also involved in
intermediary metabolism, in energy transfer and in the synthesis of carbohydrates [12]. They affect the intestinal ecology of the neonate [9] and stimulate the development of the small intestine [3] and liver [26] as well as their repair if any damage is suffered. They facilitate iron absorption [23] and contribute to maintaining the immune response [12,19,20,23,24,26].

Exogenous nucleotides stimulate lymphoid cell maturation and the lymphoproliferative response to alloantigens and mitogens. They also contribute to the response of T lymphocytes, increase delayed cutaneous hypersensitivity, increase rejection of grafts, counteract malnutrition-induced immunosuppression, increase resistance to certain infections, regulate the quantity of natural killer (NK) cells and macrophages and promote the synthesis of immunoglobulins. The above factors lead us to believe that nucleotides may be of particular benefit during early feeding.

Human milk is the only source of nucleotides for neonates during the first months of life and presents a specific nucleotide profile that markedly differs from that of cow’s milk [8,14,27]. It has been estimated that human milk provides about a third of the neonate’s nucleotide requirements [28]. An exogenous source of nucleotides could be important for the neonate, and particularly for the premature neonate, because of the limited functionality of various metabolic mechanisms. Therefore, the European Union has recognized nucleotides as semi-essential components of initial formula and has drafted norms to regulate nucleotide-supplemented formula [7].

2. Nucleotides and humoral immunity

Pickering et al. [24] studied two groups of term neonates during the first year of life. These were fed formula which differed only in the content (72 mg/l) or otherwise of nucleotides. The object of the study was to determine the immune response to vaccination for *Haemophylus influenzae* type b (Hib), diphtheria, tetanus and oral polio at 6, 7 and 12 months. No differences between the groups were detected at 6 months of age, but the response to both Hib and diphtheria at 7 months and to Hib at 12 months was significantly increased in the nucleotide group. They also compared the response of two groups of neonates, breast fed for less than 6 months and for more than 6 months, respectively. The antibody response of the nucleotide group was similar to that of the >6 months breast-fed group and higher than that of the <6 months breast-fed group.

In a previous paper [20], the present authors described a study carried out during the first 3 months of life of two groups of formula-fed premature neonates, in one case with a nucleotide supplement (20 mg/l) and in the other, with no supplement. We determined the concentration of plasma immunoglobulins at 10 days, 20–30 days and 3 months of life (Table 1).

Maximum IgG levels were found in the samples obtained from the umbilical cord. These levels fell gradually with age and no differences were observed between the two groups at any time, as most of the IgG detected corresponded to the maternal IgG transferred during foetal life. In contrast, low levels of plasma IgM were detected in umbilical cord blood; these increased progressively with age and were significantly
higher at 20–30 days and 3 months of life among the nucleotide-supplemented group. Plasma concentrations of IgA were inappreciable in most cases at 10 days of life, but at 20–30 days 66% of the nucleotide-supplemented neonates and 50% of those fed formula without nucleotides presented quantifiable levels of IgA. At 3 months of life, plasma levels of IgA were significantly higher among the nucleotide-supplemented group.

In the light of the above, dietary nucleotides seem to have a favourable effect on the immune system of neonates and lactating infants, as shown by the greater production of immunoglobulins and the improved vaccine response. This could have a role in defence mechanisms and thus reduce morbidity. It has been reported that nucleotide supplementation of formula reduces the incidence of upper respiratory tract infections (6% vs. 38%) [18], modifies the indices of immunological responsiveness in marasmic infants [16] and reduces the incidence of diarrhoea [2,13].

Brunser et al. [2] studied 392 lactating infants aged less than 6 months enrolled from a low socioeconomic area. They found that the infants given nucleotide-supplemented formula (20 mg/l) for a period of 3 months presented fewer episodes of diarrhoea (109 vs. 140), of less duration (5.6 vs. 6.7 days) and a higher percentage of subjects having no diarrhoea episodes (70.3% vs. 53.2%). Lama and Gil-Alberdi [13] studied 3243 lactating infants aged < 6 months fed formula, with or without nucleotide supplementation. The incidence of diarrhoea was significantly lower among the group fed the nucleotide supplemented formula (11.1% vs. 17.4%), as was the maximum duration of the diarrhoea (1.9 vs. 2.1 days), the intensity (mean number of bowel movements per diarrhoea episode 3.6 vs. 3.9) and the maximum number of bowel movements per diarrhoea episode (4.1 vs. 4.6).

The limited data available on the relationship between nucleotides and allergies suggests that nucleotides may have a tolerizing effect in response to dietary antigens. Pickering et al. [24] consider that nucleotides do not influence the IgE-related immune response. Martínez-Augustí et al. [16,17] found that IgG antibody levels for α-casein and β-lactoglobulin were higher at 7 and 30 days of life among the neonates fed nucleotide-supplemented formula with respect to the control group. Animal studies [18] indicate that the addition of nucleotides to a purified diet upregulates cytokine responses, resulting in decreased total IgG levels and IgG1/IgG2a ratios.

Table 1
Levels of plasma immunoglobulins in preterm lactating infants, fed nucleotide-supplemented formula (FN) and nucleotide-free formula (F)

<table>
<thead>
<tr>
<th>C.U.</th>
<th>10 days</th>
<th>20–30 days</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA</td>
<td>ND</td>
<td>FN</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>ND</td>
<td>F</td>
<td>ND</td>
</tr>
<tr>
<td>IgM</td>
<td>16.6 ± 2.4</td>
<td>FN</td>
<td>62.4 ± 12.1</td>
</tr>
<tr>
<td></td>
<td>16.6 ± 2.4</td>
<td>F</td>
<td>42.2 ± 4.2</td>
</tr>
<tr>
<td>IgG</td>
<td>858.8 ± 51.3</td>
<td>FN</td>
<td>627.2 ± 93.2</td>
</tr>
<tr>
<td></td>
<td>858.8 ± 51.3</td>
<td>F</td>
<td>572.6 ± 75.4</td>
</tr>
</tbody>
</table>

Expressed as mean ± S.E. mg/dl of plasma.
ND: Not detectable; CU: umbilical cord.
* p < 0.05.
3. Nucleotides and cellular immunity

Carver et al. [4] studied the impact of nucleotides on natural killer cell (NK) cytotoxicity and interleukin-2 production in healthy term infants, either breast-fed or given nucleotide-supplemented formula. NK activity was significantly higher in both groups compared to the controls at the age of 2 months; among the formula group, this difference disappeared at 4 months, but persisted among the breast-fed infants. These data, however, have not been corroborated by other authors [12]. The present authors [20] found no differences in the total number of leukocytes, monocytes, granulocytes, total lymphocytes and T, B, T4, T3 and NK cells, although a greater number of T4 cells was observed at 10 days among the infants given nucleotide-supplemented formula (55.8 ± 1.3.2% vs. 44.2 ± 1.6.2%), although not at 20–30 days or at 3 months of life.

4. Discussion

The nucleotides present in human milk are known to affect the composition of intestinal microbiota in lactating infants. Experiments carried out both in vivo and in vitro [9] have shown that the nucleotide supplementation of formula reduces the number of enterobacteria and increases that of bifidobacteria in the faecal flora. This circumstance could be related to the lower incidence of diarrhoea among lactating infants given nucleotide-supplemented formula.

The mechanism by which dietary nucleotides modify the immune system might well be a very complex one. If tissue nucleotides are mainly derived from de novo synthesis [1] and if dietary nucleotides are metabolized by the intestine and liver and present only in very small quantities in peripheral tissues [5], Kuchan et al. [12] believe it is unlikely that dietary nucleotides modify the humoral immune response which determines the clonal expansion of lymphocytes in the peripheral tissues.

Perhaps dietary nucleotides have a more clear-cut influence on the intestinal immune response. Although they have not been found to affect the immune response of the intestinal mucosa to the oral polio vaccine [24], animal studies [3,21,22] have shown that dietary nucleotides contribute to the faster recovery of damaged intestinal mucosa and of its enzymatic activity. Thus, dietary nucleotides favour the maturation of enterocytes, cells which are also involved in the immune response (cytokine production, appearance of antigens). Experimental animal studies have also shown that dietary nucleotides increase the local vaccine response in the peripheral lymph ganglia [11] and affect the maturation of intestinal lymphocytes, and thus the development of the intestinal immune function.

A recent study [15] of male Balb/C mice aged 3–4 weeks shows that the changes of expression of the intraepithelial intestinal lymphocyte populations, of the lamina and of the Peyer patches, mature more quickly among animals fed a nucleotide-supplemented diet. The ontogenic changes to the phenotype that occur during weaning, in each of the intestinal lymphocyte populations, have a positive regulatory effect on cytokine production and speed up the production of secretory IgG in the intestine.

In conclusion, the addition of nucleotides to cow’s milk-based infant formulas seems to produce a favourable effect on the immune function, as shown by the increase in
immunoglobulin production, the improved response to vaccines, the increase in resistance to infections and the greater tolerance to dietary antigens.

References