The role of probiotics in paediatrics

Erika Isolauri*

Department of Paediatrics, University of Turku, 20520 Turku, Finland

Summary The recent demonstration that the gut microbiota, and by the same token probiotics, have a strong impact in priming major maturation processes in the intestine's mucosal barrier has opened up new angles to the science of nutrition. In modulating specific target functions in the gut and the immune system, probiotics in the diet may exert additional beneficial physiological effects beyond the nutritional impact of food. Probiotic bacteria are living microbial food ingredients which have a beneficial effect on human health. These effects are attributed to the normal restoration of increased intestinal permeability and unbalanced gut microbiota, improvement of the intestine's immunological barrier functions and alleviation of the intestinal inflammatory response. The application of probiotics in paediatric practice currently lies in enhancing these barrier functions in the gut and reducing the risk of diseases associated with their dysfunction. The most fully documented probiotic intervention is the treatment and prevention of acute infectious diarrhoea. Recent clinical and nutritional studies and characterisation of the immunomodulatory potential of specific probiotic strains have attracted active research interest also in allergic and inflammatory diseases.

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Practice points

- Probiotic bacteria are living microbial food ingredients which have a beneficial effect on human health
- Modification of intestinal microbiota to increase the predominance of specific non-pathogenic bacteria, thereby altering the intestinal milieu may attain prophylactic or therapeutic effects in intestinal infectious and inflammatory conditions
- An important part of the probiotic effect is associated with their immunomodulatory potential; immune-enhancing as well as anti-inflammatory activity

Research directions

- In view of the current conception of probiotics, specific effects of clearly defined strains and accurate pre-clinical and clinical documentation are required for the selection of probiotics in paediatric practice
- Better characterisation of the role of gut microbiota in the maturation of the host immune defence in health and disease is required for the extended application of probiotics in paediatric practice

Introduction

Probiotics are live microbial food ingredients which are beneficial to health. The prerequisites for
probiotic action include survival in and adhesion to specific areas of the gastrointestinal tract and competitive exclusion of pathogens or harmful antigens. The current emphasis is on survival in the gut and temporary colonisation of the mucosal surfaces in the intestinal tract. The definition of probiotics requires that their efficacy and safety must be verified in clinical studies and thus, assessment of this constitutes an important part of their characterisation for human use. Currently, most probiotics have been selected from members of the normal healthy adult microbiota. The strains with beneficial properties, which are potential sources of probiotics, most frequently belong to the genera *Bifidobacterium* and *Lactobacillus*. Some of these exhibit powerful anti-inflammatory capabilities. Indeed, recent characterisation of the immunomodulatory potential of specific strains of the gut microbiota, beyond their effect on the composition of the microbiota, has led to new criteria for probiotic selection for novel applications in paediatric nutrition.

Modern nutrition for the modern child

The basic foundation of nutrition lies in a healthy, balanced diet to meet the needs for growth and development in children. In addition, a disease state may impose specific requirements for energy and nutrients, a deficiency of these may contribute to a deterioration of nutritional status and growth failure in children. Beyond this function in the prevention of direct diet-related deficiencies, the role of diet has changed as the science of nutrition has evolved. Research interest in paediatric nutrition is currently directed towards improvement of the defined physiologic functions (beyond the nutritional impact of food), including the potential to reduce the risk of disease. This is also the focus for probiotic research.

Modern civilisation is faced with a progressive increase in immune-mediated gut-related health problems such as allergies, autoimmune and inflammatory diseases. Genetic factors are unlikely to explain these rapid increases. The factors responsible relate to the modern lifestyle in western societies: hygiene and nutrition. Children residing in an affluent hygienic environment lack the pressure of microbial stimulation via infectious diseases. This, according to the immunological framework of the hygiene hypothesis, is required for the maturation of the immune system to fight allergic disease. The human diet once contained several thousand times more bacteria than it does today, as changes in food preservation, from drying and natural fermentation to industrial processing, has led to extensive pasteurisation and sterilisation practices. The hygiene hypothesis of allergy may be extended to autoimmune diseases, and possibly to infectious and inflammatory conditions associated with an impaired gut barrier. In probiotic foods, cultures of beneficial live microorganisms characteristic of the healthy human gut microbiota are administered in order to provide a safe microbial stimulus for the maturation of the gut-associated lymphoid tissue, which the modern infant often lacks. The probiotic effects are attributable to the restoration to the normal of increased intestinal permeability and an unbalanced gut microecology. They improve the intestine’s immunological barrier functions, alleviate the intestinal inflammatory response, and reduce generation of pro-inflammatory cytokines characteristic of local and systemic allergic inflammation.

Rationale and targets for probiotic intervention

In addition to its principal physiological function, the digestion and absorption of nutrients, the gastrointestinal tract and the gut-associated immune system have evolved into an integrated barrier between the internal environment and antigens such as food and microorganisms from the external environment. The integrity of the intestine’s mucosal defence depends on a number of factors in both intestinal lumen and mucosa. Nutrition via the gastrointestinal tract is important in maintaining mucosal structure and function; lack of nutrients may result in decreased villous height, increased permeability and decreased immunity. The recent demonstration that the gut microbiota is an active constituent in the intestine’s mucosal barrier has introduced therapeutic strategies for combating enteric infections as well as allergic and inflammatory conditions.

Balanced gut microbiota

Normalisation of the properties in unbalanced indigenous microbiota by specific strains forms the rationale of probiotic therapy. Aberrant gut microbiota may be an important factor in the evolution of allergic disease as well as inflammatory bowel diseases. Importantly, secondary to the inflammatory response in the gut, previously balanced gut microbiota may become immunogenic
and pro-inflammatory, whereby the natural tolerance to the host’s own macrobiota may be abrogated, contributing to the vicious circle in allergic, autoimmune and infectious diseases (Fig. 1).

Enhanced gut barrier

Oral introduction of probiotics has been shown to reinforce the various lines of gut defence: immune exclusion, immune elimination and immune regulation. Probiotics also stimulate non-specific host resistance to microbial pathogens and thereby aid in their eradication. The ability of specific probiotics to increase the expression of mucins may contribute to the barrier effect (Fig. 1).

There are data to suggest that delayed maturation of humoral immune defence mechanisms, particularly of circulating IgA- and IgM-secreting cells, is a consequence of delayed compositional development of the gut microbiota. Significantly, differences in the neonatal gut microecology were recently documented as being associated with the development of atopic diseases.

Furthermore, immaturity of the gut barrier may lead to aberrant antigen transfer, thus explaining the increased likelihood of infants having inflammatory responses to intraluminal antigens (Fig. 1). Notwithstanding the fact that mucosal tolerance is an active immunological process mediated by more than one mechanism, it has become clear that without luminal degradation, unresponsiveness to dietary antigens is not achieved.

Specific strains of the intestinal microbiota contribute to the processing of dietary antigens in the gut and reduce their immunogenicity in vitro and in vivo (Fig. 1). Caseins that have been degraded by probiotic bacteria-derived enzymes have been shown to modulate the cytokine production by anti-CD3 antibody-induced peripheral blood mononuclear cells, in atopic infants with cow milk allergy. Together with the potential to dampen hypersensitivity reactions to these antigens, specific strains of gut microbiota contribute to a T helper cell population that is amenable to oral tolerance induction.

Anti-inflammatory responses

Recent advances in elucidating the interaction between bacteria and mucosal innate and adaptive immune systems provide the basis for understand-
ing the role of gut microbiota in achieving a homeostatic disease-free state of the host. Specific gut microbes may exert an immunosuppressive function by inhibition of the transcription factor NF-κB pathway. In addition, suppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor (TGF)-β produced by regulatory T cells and T helper (h) cells contribute to the anti-inflammatory tone of the gut immune system. Recent experimental and clinical studies demonstrate that specific probiotic strains inhibit proliferation of T cells and reduce secretion of both Th1 and Th2 cytokines, while inducing the development of a population of T cells producing TGF-β and IL-10. Consequently, the gut microbiota may be presumed to provide immunomodulatory activity during a critical age or risk period in life when immunoregulatory aberrancies may induce clinical disease.

Such activity may also be beneficial in established inflammatory conditions. The hallmark of an inflammatory response to dietary and microbial antigens is the generation of proinflammatory cytokines (Fig. 1), with the potential to disrupt the epithelial cells, thus allowing aberrant antigen uptake and immune response, with further impairment of the barrier function. Specific strains of healthy gut microbiota have been shown to balance the generation of pro- and anti-inflammatory cytokines, thereby promoting healthy host-microbe interactions in the gut.

Probiotic intervention strategies in paediatric practice

The potential health effects of normal gut microbiota have to be demonstrated by well controlled clinical and nutritional studies in which lactobacilli or bifidobacteria are used as dietary supplements for the nutritional management of various gastrointestinal infectious and inflammatory diseases, or for reducing the risk of these diseases.

Acute gastroenteritis

A number of studies have approached the efficacy of probiotics in diarrhoea treatment and prevention via a meta-analysis of clinical studies in paediatric patients. Well controlled clinical studies have shown that probiotics such as Lactobacillus rhamnosus GG, L. reuteri, L. casei Shirota and Bifidobacterium lactis Bb12 can safely be applied for the nutritional management of patients with infectious diarrhoea. The consistent effect of probiotic therapy in infectious diarrhoea has been explained by a reduction in the duration of rotavirus shedding, normalisation of gut permeability after rotavirus infection, and by an increase in the expression of mucin and IgA-secreting cells working against rotavirus.

On this basis, it can be concluded that for patients hospitalised for acute rotavirus diarrhoea, probiotic therapy reduces the duration of diarrhoea beyond the beneficial effect of rapid refeeding after oral rehydration. The result has been confirmed in developed as well as developing countries. However, the effect seems to be confined to viral diarrhoea. A multicenter study by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition Working Group demonstrated improved clinical resolution in rotavirus diarrhoea, but not in non-specific or bacterial diarrhoea. Moreover, a recent randomised placebo-controlled study in severely dehydrated male children under 2 years of age showed no clinical benefit to supplementing oral rehydration with probiotics.

Inflammatory bowel diseases

Preliminary reports indicate that there are benefits attained by probiotic intervention in reversing some immunological disturbances, in modification of disease activity and in normalisation of increased intestinal permeability in children with Crohn’s disease. Recent studies in adults provide evidence supporting treatment with probiotics in maintaining remission in ulcerative colitis and in the prevention of relapses of chronic pouchitis. The strains assessed thus far include Lactobacillus GG, a non-pathogenic E. coli, a preparation containing 4 strains of lactobacilli (L. casei, L. plantarum, L. acidophilus and L. delbrückii subsp. bulgaricus) and 3 bifidobacteria strains (B. longum, B. breve and B. infantis) together with Streptococcus salivarius subsp. thermophilus.

Due to the preliminary nature of these prospective data, more research is required to define the effects of specific probiotic strains on distinct forms of inflammatory bowel disease and the attendant complications.

Allergic diseases

Atopic diseases are associated with the generation of Th 2-type cytokines, including interleukin (IL)-4, IL-5 and IL-13, which promote IgE production and eosinophilia. Initial signals to counter IL-4, and thereby IgE and atopy, and IL-5-generated eosinophilic inflammation may stem from compo-
nents of the innate immune system, and structural components of bacteria. The lipopolysaccharide portion of gram-negative bacteria (endotoxin) and a specified CpG motif in bacterial DNA have been shown to elicit an immunosuppressive effect on intestinal epithelial cells by inhibition of the transcription factor NF-kB signalling pathway. In addition, specific probiotic strains have been shown to counter allergy by the generation of IL-10 and TGF-β. The clinical correlate of these activities lies in the suppression in proliferation of Th cells and reduced secretion of pro-inflammatory cytokines, with control of IgE responses and reduced allergic inflammation in the gut.

Further to this, the principal effect of probiotics—control in the balance of the gut microbiota, may be important in allergic disease. Intestinal microbiota from infants at high risk of atopic diseases was analysed at 3 weeks of age by conventional bacterial cultivation and two culture-independent methods. A positive skin prick reaction at 12 months was observed in 29% of subjects. At 3 weeks of age, the bacterial cellular fatty acid profile in faecal samples differed between those infants who later manifested atopic sensitisation and those who did not. Fluorescence in situ hybridisation was used to show that atopic subjects have more Clostridium species and fewer Bifidobacterium species in stools compared with non-atopic subjects. Improvement in the clinical course of atopic eczema and cow’s milk allergy has been achieved in infants given a probiotic-supplemented extensively hydrolysed formula, compared to those given a placebo-supplemented formula. There was a significant reduction in markers of systemic and intestinal allergic inflammation accompanying the clinical improvement. These results have recently been repeated in older children with the same condition.

The preventive potential of probiotics in atopic disease has recently been demonstrated in a double-blind, placebo-controlled study. Probiotics administered pre- and postnatally for 6 months to children at high risk of atopic disease reduced, at the age of 2 years, the prevalence of atopic eczema to half (23%) that in the infants receiving placebo (46%). When probiotic supplementation was given to the lactating mother, the amount of TGF-β in breast milk was promoted. The findings indicate one mechanism by which the risk of infant atopic eczema could be reduced. Probiotic supplementation however, had no preventive potential in the case of cow’s milk allergy. The preventive effect on atopic eczema was not transient, but extended beyond infancy.

The studies listed here corroborate the concept that the burden of allergic diseases has increased in western societies, with one child in four possessing allergies. The prevalence of sensitisation to environmental allergens is up to 40% in unselected young adults, and a secular increase in sensitisation prevalence in children can be expected. Subsequent research has shown an equivalent progression of autoimmune diseases. A unifying theory is sought in the western life-style, nutrition and microbiota. Therefore, rigorous scientific effort is called for to characterise specific probiotic strains which could reduce the risk of developing these debilitating conditions.

References