[総説] Nucleic acids and their components : A requirement for cellular development and immune function

Nucleic acids and their components: A requirement for cellular development and immune function

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(Received on November 22, 1994, accepted on December 20, 1994)

Dietary sources of nucleic acids and their components (nucleosides and nucleotides) have not been considered to be essential for normal growth and development. The liver has an active de novo synthesis of nucleic acid components and supplies them to some tissues such as intestinal epithelium and lymphoid cells which lack the de novo synthesis. However in certain clinical conditions such as infection and surgical stress the requirement of the components increases and the endogenous supply becomes insufficent. In such circumstances, the cells require exogenous sources. The significance of exogenously administered nucleic acids and their components for opitimal function of cellular development and immune response is reviewed. *Ryukyu Med. J., 15(1)13~17, 1995*

Key words: nucleoside, nucleotide, infection, immunity, parenteral formula, enteral formula

Exogenous supply of nucleic acids and their components (nucleosides and nucleotides) have not been considered as essential subtrates, because it was generally assumed that living organisms, including humans, could synthesize adequate amounts of the components de novo. Recently studies have documented some favorable effects of the components when incorporated into parenteral and enteral feeding formulae. For example, total parenteral formula supplemented with nucleic acid components administered after hepatectomy in rats improved the nitrogen balance and protein synthesis[1]. Dietary nucleic acids improved protein synthesis in mammalian tissues[2] and also enhanced the resistance of mice against both bacterial and fungal pathogens[3,4]. These results emphasize that nucleic acids and their components supplied exogenously may be necessary to optimize metabolic and immunologic functions, particularly under conditions of stress. This report reviews current knowledge on the role of nucleic acids and their components in cellular development and the immune response.

EXOGENOUS AND ENDOGENOUS SUUPPLY OF NUCLEIC ACIDS AND THEIR COMPONENTS

The daily requirements of nucleic acids from all sources in the adult is 2 g /day[5]. The daily dietary intake of nucleic acids for Japanese adults is estimated to be 500 - 900mg /day; whereas the intake for Americans is 1000 - 2000mg /day[6]. Beef, chicken, pork, lamb, livers, meat extracts, mackerel, anchovies, and sardines are found to contain high values of purines (150 - 800mg/100 g); whereas fish, seafoods, beans, peas, lentils, and mushrooms contain moderate amounts (50 - 150mg/100 g). Vegetables, cheese, potatoes, eggs, fruits, cereals, and milk are found to contain very low levels of purines (0 - 20mg/100 g). In humans and mammals maintained on normal regular diets, deprivation of nucleic acids (nucleotides) seemed unlikely to occur. However, such deprivation may occur in patients solely on parenteral nutrition, elemental or semi-purified diets, as nucleic acids are not supplemented in these feeding formulae. Although human breast milk contains appreciable amounts of nucleic acids[7], most infant feeding formulae are not fortified with nucleic acids.

Dietary nucleic acids undergo partial hydrolysis in the stomach and then subjected to pancreatic nucleases and phosphoesterases to yield nucleosides and absorbed. The dietary nucleic acds which reach the cell cytoplasm in the form of nucleosides are utilized through the salvage pathway. The liver is the principal site for the formation of nucleic acids and their components to be salvaged and utilized by cells incapable of synthesizing the components de novo. However, in certain clinical conditions such as surgical stress or malnutrition, the endogenous supply may not be adequate for optimal function of the cellular immune response. Under these circumstances the supply of nucleic acids from dietary sources is deemed necessary.

EXOGENOUS SUPPLY OF NUCLEIC ACIDS AND THEIR COMPONENTS IN SURGICAL STRESS

Recent research have shown promising effects of supplementing parenteral and enteral formulae with nucleic acids and components specifically. Supplementation of a nucleoside-nucleotide mixture to the total parenteral nutri-

tion (TPN) solution in rats after hepatectomy resulted in an improvement of the nitrogen balance than in the solution without supplementation. The improved nitrogen balance in the nucleoside-nucleotide mixture group resulted in the acceleration of RNA and DNA synthesis leading to increased protein synthesis[1]. In hepatectomised rats administered with ^{14}C-labeled nucleoside- nucleotide mixture, the radioactivity was rapidly distributed particularly into the liver, lung, kidney, spleen, thymus, bone marrow, and intestinal mucosa[8]. The provision resulted in an increase of the nucleotide pool in the liver, acceleration of protein synthesis in muscle and liver, and improved nitrogen balance. Postoperative enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids improved metabolic, immunologic, and clinical outcomes in patients with upper gastrointesinal malignancies undergoing major elective surgery[9]. Extracellular nucleosides and nucleotides modulate hepatocyte growth and regeneration and play an essential role in the synthesis of glycogen[10, 11]. Enhanced hepatocyte respiration improved survival after infusion of nucleotides[12]. These results suggest that nucleic acids and their components may ameliorate liver damage as well as promote recovery from injury. The results also emphasize that dietary nucleic acids may promote nitrogen retention and enhance protein utilization after surgical stress.

IMMUNOLOGICAL ROLES OF NUCLEIC ACIDS AND THEIR COMPONENTS

Lymphocyte proliferation, differentiation, and function can be activated following stimulation by phytohemagglutinin (PHA) or other mitogens. Splenic lymphocytes from nucleotide-free diet fed mice had diminished blastogenic responses to PHA[13]. Addition of adenosine and uridine to the cultured medium supported proliferative process of rat cervical lymph-node T-lymphocyte after stimulation by concanavalin A (con A) [14]. Similar blastogenic responses of spleen cells were observed in nucleoside-nucleotide treated mice after stimulation with con A and PHA[13, 15]. Dietary nucleotides significantly augmented in vivolymphoproliferative response and expression of interleukin-2 which effected the activation and function of T-helper cells[16]. These results indicate that nucleic acids and their components play a specific regulatory role in the initial phase of antigen processing and lymphocyte proliferation.

The relationship of nucleic acids and their components to cellular immune functions are increasingly becoming evident. The delayed type hypersensitivity (DTH) responses to various antigens has been advocated as reliable means of assessing, predicting, and monitoring nutritional immunomodulation[17, 18]. DTH responses in BALB/c mice fed nucleotide-free 20% casein diet supplemented with RNA, adenine, or uracil were higher than those fed nucleotide-free diet, when they were challenged with purified protein derivative (PPD), dinitrofluorobenzene (DNFB), and sheep red blood cells (SRBC)[19]. Malnutrition or nutritional deficiency have a significant influence on the cell-mediated immunity. Addition of RNA and uracil to protein-free diet caused the improvement of the in vivo immune response in mice[20]. Even though there was a remarkable improvement in body weights, addition of 21% casein protein to the protein-free diet did not cause restoration of the immune response. Nucleic acid-free diet immunosuppression resulted in prolonged cardiac allograft survival in mice with a donor-recipient histoincompatibility. In patients treated by renal allografting and who have been on total parenteral nutrition, the immune responses to allografting were lower as compared to patients on total parenteral nutrition enriched with RNA[21]. Mice fed nucleotide-free 20% casein protein showed a significant prolongation of heart allograft survival as compared to RNA supplemented mice[13].

Recent studies indicate that nucleic acids or nucleotides from dietary sources have a greater impact on the humoral immune system. Addition of RNA to the culture medium increased antibody production in response to SRBC[22]. Elemental diet supplemented with RNA, arginine, and omega-3 fatty acids influenced the humoral immunity (B-cell count, γ-interferon and immunoglobulins particularly IgM)[23]. These results suggest that nucleotides or nucleic acids supplied exogenously from dietary sources may have an impact on the immune system and may be therapeutic in restoring responses to both cellular and humoral immune systems in certain circumstances.

NUCLEIC ACIDS AND THEIR COMPONENTS AND INFECTION

Surgical, trauma, cancer, burn patients, and those on radiotherapy experience a number of physiologic changes; and among these changes are the suppression of the immune response and increased risk of bacteria and fungal infections. Addition of RNA and uracil to nucleotide-free diet improved significantly the survival of mice and enhanced the immune response to both *Staphylococcus aureus* and *Candida albicans*[3, 4]. Methicillin-resistant strains of *Staphylococcus aureus* (MRSA) have emerged as a frequent cause of nosocomial infections world-wide[24]. Most of the strains are virulent and can produce a fatal generalized disease[25]. The morbidity, mortality, and costs associated with treatment and prevention of MRSA infections are substantial[26, 27] and thus any therapy that would prevent infection or enhance the host defense mechanisms would be beneficial.

We have recently demonstrated that mice fed nucleic acid-free 20% casein diet and administered nucleoside-nucleotide mixture intraperitoneally either before[28] or after[29] challenge with MRSA exhibited markedly increased survival in comparison to mice maintained on nucleic acid-free diet. These results suggest the need of nucleic acids in TPN and enteral nutrition formulae to provide more resistance to infection.

NUCLEIC ACIDS AND THEIR COMPONENTS AND GUT FUNCTION

Recent reports have shown that bacterial translocation may represent a significant source of sepsis in the critically ill or immunocompromised patients[30,31]. Bacterial translocation can be stimulated by a disruption in the gastrointestinal microflora due to surgery, antibiotics, radiation, and impaired immune function[32]. Nucleoside-nucleotide mixture averted the intestinal mucosa atrophic changes triggered by TPN, and improved protein, DNA, and RNA contents of the small intestinal mucosa[33]. Nucleoside supplementation increased the rate of maturation and growth in the young rat as determined by mucosal mass, RNA, DNA, and protein concentrations and activity of brush border enzymes[34]. Nucleotide supplementation restored the atrophy of the small intestine at proximal and distal sites, and improved intestinal development after induction of chronic diarrhoea[35,36]. We also observed that intraperitoneal[37] and oral[38] administration of nucleosides and nucleotides inhibited the incidences of endotoxin-induced bacterial translocation, enhanced survival, decreased intestinal injury, and reduced the recovery of colony forming units of both gram-positive and gram-negative enteric and facultative microorganisms in protein-deficient mice.

Nucleotides also modify the type and growth of the intestinal microflora. Young infants fed a nucleotide supplemented formula had higher percentages of fecal bifidobacterial and lactobacilli, and lower percentages of gram-negative enterics as compared to the formula fed infants[39]. These results suggest that current enteral and parenteral formulae result in alteration of intestinal microflora and bacterial translocation from the gut, and that nucleic acids and their components may be necessary to essential gut intergrity and barrier function.

NUCLEIC ACIDS AND THEIR COMPONENTS AND HEMOPOIESIS

Numerous dietary components have been reported to affect the body's immune response. These effects can be beneficial or detrimental. Cells of the body's immune system include those that participate in alloimmune responses, as well as cells that are dedicated to hematopoiesis. It is widely held clinical axiom that patients receiving extensive chemotherapy have an increased susceptibility to infection[40,41]. This altered susceptibility to infectious complications has been attributed to a depression in the function and production of polymorphonulcear leucocytes, particularly neutrophils[42]. We observed that nucleotide-free diet supplemented with nucleosides and nucleotides stimulated the proliferation, differentiation, maturation, and function of peripheral blood neutrophil number in mice challenged with MRSA[43] or treated with cyclophosphamide[44]. The supplemented diet group subsequently led to increased incorporation of bromodeoxyuridine (an analogue of thymidine) into the S phase of the bone marrow cells as compared to the non-supplemented group. Thus, there is evidence that exogenous supply of nucleic acids and components may increase the proliferation of bone marrow cells and peripheral blood neutrophils which are important host defense cells following challenge with bacterial pathogens.

Growth and differentiation of hemopoietic cell precursors in vitro and/or in vivo is regulated by colony-stimulating factors. It has been demonstrated that nucleic acids and components function as a regulatory nutrient for hemopoiesis in mice. When bone marrow cells from control chow fed animals were cultured with supernatant from mitogen activated splenocytes of animals on nucleotide-free diet and nucleotide-free diet supplemented with RNA and uracil, the nucleotide-free diet supernatants significantly decreased bone marrow proliferative response compared with the response observed with RNA and uracil[45]. The absence or presence of nucleic acids and components influenced host immune response and that a diet free of nucleic acids suppresses both in vitro and in vivo cell-mediated immune responses[45]. Rapidly proliferating tissues, particularly lymphoid cells and intestinal epithelium require purine and pyrimidine compounds supplied by dietary sources or the liver[46]. G_1 phase thymocytes and peripheral T-lymphocytes do not have de novo purine biosynthetic activity, whereas S phase enriched large thymocytes do[47]. This suggests that G_1 phase T-cells may depend on circulating sources for nucleotides for the transition to the S phase in these rapidly growing cells. Spleen, thymus, bone marrow from nucleotide-free diet fed mice had a significantly higher number of cells positive for terminal deoxynucleotidyl transferase, a specific marker for immature T-cells as compared with lymphoid cells from RNA diet fed mice, suggesting that there were increased numbers of null or immature T-cells in lymphoid organs of nucleotide-free diet fed mice[48]. These results emphasize that nucleotide-free diet reduces the hemapoietic growth factor production in vivo and in vitro resulting in an immunodeficient state.

CONCLUSION

In conclusion, this report suggests that nucleic acids and their components are "conditionally semi-essential nutrient" and that addition of the components to elemental or chemically defined diets can be beneficial in improving the biological and immunologic functions, particularly during periods of rapid growth and development, and during repair of the injured gut mucosa. This report confirms the growing evidence that provision of elemental or semi-purified diets supplemented or enriched with nucleic acids and their components may be one of such modalities for the enhancement of the immune system of immunocompromised or critically ill patients.

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