Biological Activities of Nucleosides and Their Analogues in Dietary Foods

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Abstract—Nucleosides and their related analogues are a class of low-molecular-weight intracellular compounds that have attracted intense interest in biochemistry, biotechnology and medicine. The present review summarizes the effects of dietary nucleosides and their analogues on various aspects of body function e.g. immune, metabolic, hepatic, cardiovascular, and nervous system, as well as antibacteria, antivirus and other effects. With respect to more practical aspects, further studies are warranted to reveal the potential of nucleotides in maintaining and improving health.

Keywords—Biological activity, dietary, nucleosides and their analogues.

I. INTRODUCTION

NATURAL nucleosides are building blocks of DNA or RNA, the substances that carry the genetic information in the cell and pass it from one generation to the next [1]; while dietary nucleosides may involve in the regulation and modulation of various physiological processes in body, and produce functions through purinergic and/or pyrimidine receptors [2, 3]. Dietary nucleotides and nucleosides, for example in the meat [4], have been demonstrated to have beneficial effects upon the immune system, small intestinal growth and development, lipid metabolism, and hepatic function [5]. In addition, supply of exogenous nucleotides and nucleosides may be particular significance when the endogenous supply of these compounds not be adequate for optimal function under certain clinical conditions, especially in the tissues such as intestinal mucosa, bone marrow hematopoietic cells and brain that have limited capacity for de novo synthesis and depend on the compounds supplied by salvage pathway [6]. Over 90% of the dietary nucleotides are absorbed as nucleosides and subsequently phosphorylated in the enterocyte [7]. Most of the purines are metabolized to uric acid in the enterocytes and only small quantities appear in the hepatic cells; in the contrast, relatively large quantities of dietary pyrimidines are transported from the enterocytes to the hepatic portal vein [7]. Furthermore, nucleoside analogs are first line chemotherapy in various severe diseases: AIDS (acquired immunodeficiency disease syndrome), cytomegalovirus infections, cancer etc [8, 9]. Nucleosides and their analogs are thought to be the active compounds in some tonic mushrooms such as Cordyceps and Ganoderma, and they are also abundant in human breast milk, beer, teas and fish, etc [10]. Besides, there are lots of patents covering nucleoside and nucleotide related functional foods have been issued or published [11-19].

Over all, dietary nucleotides which are deemed conditionally essential in the presence of various physiological stresses should be one of the important factors for the health promotion and diseases prevention. This paper aims to review the biological activities of dietary nucleosides and their analogues, is expected to provide basic information for the future study on the relationship between nucleosides and human health.

II. BIOLOGICAL ACTIVITIES OF DIETARY NUCLEOSIDES AND THEIR ANALOGUES

A. Effects on Immune System

Both in vivo and in vitro studies showed that dietary nucleotides and nucleosides can affect the function of immune system. Dietary nucleotides are reported to play an important role in the modulation of the immune system through influencing lymphocyte maturation, activation and proliferation; enhancing the natural killer cell activity, and macrophage activation and phagocytosis; delaying hypersensitivity as well as allograft and tumor responses; enhancing the production and the genetic expression of interleukin-2 (IL-2), IL-6, IL-8 and IL-2 receptors; increasing the popliteal lymph-node cytokine secretion, peripheral blood total leukocyte counts and neutrophil numbers following infection; and reversal of malnutrition and starvation-induced immunosuppression [6, 20-23]. Currently, purine nucleoside analogues are used in the treatment of lymphoproliferative diseases [24]. Furthermore, infants are at higher risk for morbidity and mortality due in part to immaturity of the infant immune system [25]. Therefore, an increasing number of infant formulas are being marketed with nucleotide supplementation, which is believed to be important for the growth and maturation...
of the gastrointestinal tract and in the development of neonatal immune function of infant [26]. Actually, lots of reports demonstrated that milk and infant formula contained nucleotides have modulation effects on the infant immune system [27-33].

On the other hand, the immunomodulatory effects of several nucleosides such as adenosine [34-39], inosine [40], uridine [41, 42], and guanosine [43], etc. have been demonstrated in previous reports. A nucleoside composition comprises uridine, inosine and guanosine with the designed ratio of 2-34:3-44:1-18 has immune enhancing property [44], while another nucleoside composition comprises uridine, adenosine and guanosine with the designed ratio of 2-22: 1-14: 1-18 has immune suppression property [45]. Therefore, different compositions and ratios of nucleosides may have significant variation on their effects (enhancement or suppression) on immune system, which should be carefully considered and investigated when preparing functional food with nucleoside or their mixture as supplement in the case related to modulation of immune function.

B. Effects on Metabolic System

Nucleosides are precursors of nucleic acid synthesis, which is fundamental to control the growth and metabolism in all living systems. Nucleotides and their analogues, for example, cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP) and adenosine diphosphate (ADP) serve as mediators of many metabolic processes such as ATP energy transfer progress in the cells of biological systems. Furthermore, nucleotide contained coenzymes such as nicotinamide adenine dinucleotide (NAD), flavin adenine dinucleotide (FAD), and coenzyme A (CoA) are organic molecules that assist various biochemical reactions by serving as carriers. In addition, nucleotides serve as carriers of activated intermediates for many reactions. For example, uridine diphosphate glucose (UDP-glucose) is an intermediate in glycogen and glycoprotein synthesis; Guanosine diphosphate mannose (GDP-mannose), guanosine diphosphate fucose (GDP-fucose), UDP-galactose, and Cytidine-5’-monophospho-N-acetylneuraminic acid (CMP-sialic acid) are intermediates in the synthesis of glycoproteins; cytidine diphosphate-choline (CDP-choline) and cytidine diphosphate ethanolamine (CDP-ethanolamine) are involved in phospholipid metabolism; and S-adenosylmethionine serves as a methyl donor [46].

Dietary nucleotides and nucleosides may have important metabolic functions but free adenosine may produce adverse effects [47]. Firstly, dietary nucleotides may be modulators of lipid metabolism. It has been shown that the relative content of omega-6 and omega-3 long-chain polyunsaturated fatty acids (more than 18 carbon atoms), which are structural components of neural membranes and found in high concentrations in the retina and brain, was significantly increased in both term and preterm infants fed with human milk or nucleotide-supplemented infant formula, compared with those fed with regular infant formula without nucleotide supplementation [48, 49]. However, those finding couldn’t be confirm in the later report [50]. Furthermore, nucleotide supplementation also increased serum lipoprotein concentration, mainly due to an increase of apolipoprotein content. Although the cholesterol content of the lipoproteins did not change, the ratio of cholesterol ester to unesterified cholesterol rose [51, 52]. Further study showed that preterm neonates fed from birth by formula supplemented with nucleotides have significantly higher high-density lipoprotein cholesterol (HDL-C) and lower low-density lipoprotein cholesterol (LDL-C) serum levels than neonates fed by nucleotides unsupplemented formula [53]. Secondly, dietary nucleotides can regulate blood glucose and insulin level. It was reported that the serum glucose and insulin concentrations in rats following loading of sucrose or soluble starch were significantly reduced by administration of sucrose or soluble starch that contained inosine, adenosine or cytosine [54, 55]. The results suggested that those nucleosides may be useful for the prevention of lifestyle-related diseases such as obesity and diabetes. Thirdly, dietary nucleotides can influence the food intake. The studies have shown that peripherally administered adenosine and inosine, as well as central administration of adenosine, adenine and AMP can suppress food intake of rats [56, 57]. However, it should be mentioned that high amounts consumption of adenosine can lead to hormone abnormality, weight loss and metabolic anomalies [58]. Besides, consuming large quantities of food (e.g. seafood and beer) high in purines was one of the greatest predictors of developing gout and increasing the blood uric acid level [59].

C. Effects on Nervous System

Adenosine is known to depress the excitability of central nervous system (CNS) neurons and to inhibit release of various neurotransmitters presynaptically [60, 61]. Furthermore, adenosine possesses anticonvulsant activity on animal models of seizure disorder [62]. While inosine, the major biochemical metabolite of adenosine due to oxidative deamination, can stimulate axon growth in vitro and in the adult central nerve system [63]. Guanosine protected against quinolinic acid-induced seizures, but had no effect on picrotoxin-induced seizures, which indicated some degree of specificity towards the glutamatergic system [64]. Furthermore, guanosine could selectively inhibit the locomotor stimulation induced by the N-methyl D-aspartate (NMDA) antagonist dizocilpine [65]. Uridine behaves as an anticonvulsant in a number of seizure models, which can inhibit neuronal activity [66], and competitively inhibit gamma aminobutyric acid (GABA) binding to rat cerebellar membranes, frontal cortex, hippocampus and thalamus [67, 68]. Furthermore, uridine may have potential to aid in the prevention and treatment of epilepsy [69], and some neurodegenerative disorders [70]. Actually, both uridine and its nucleotides have direct actions on and are capable of modulating peripheral nervous system activity [71]. In addition, dietary supplementation with UMP, can significantly increase levels of the phosphatidies throughout the
rodtic brain, increases acetylcholine level and release in stratum of aged rat [72]. While a dietary nucleoside and nucleotide mixture contained inosine, GMP, cytidine, uridine and thymidine are proved to be associated with decreases in the age-induced deterioration of brain morphology and certain memory tasks [73].

It is well known that both the central and peripheral nervous systems are involved in the regulation of food intake with a balance between multiple neurotransmitters carefully regulating the ingestion of food [74]. Therefore, the above mentioned that adenosine, inosine, adenine and AMP suppressed food intake in rats [56, 57], may be resulted from the effect of those compounds on the nervous systems.

D. Effects on Cardiovascular System

Adenosine is an effective anti-arrhythmic agent in the treatment of tachycardia, or for unmasking atrial tachyarrhythmias or ventricular pre-excitation [75-77]. Furthermore, activation of the A1AR (an adenosine receptor subtype) by intravenous infusion of adenosine is used to restore normal heart rhythm in patients with paroxysmal supraventricular tachycardia (PSVT). Actually, A1AR activation can induce a number of effects in the cardiovascular system, including a reduction in heart rate and atrial contractility, and the attenuation of the stimulatory actions of catecholamines on the heart [77, 78]. Besides, adenosine A3 receptors can regulate heart rate, motor activity and body temperature [79]. Also, adenosine is an endogenous antiaggregating substance which can enhance intraplatelet cAMP levels and cause an increase in cGMP concentrations through a mechanism that involves NO synthesis [80].

Inosine, which is selective for the A3-receptor subtype, improves myocardial and endothelial function during early reperfusion after heart transplantation with a persisting beneficial effect against reperfusion induced graft coronary endothelial dysfunction. The effects of inosine are mediated at least partly by modulation of the peroxyxynitrite-poly (ADP-ribose) polymerase pathway [81]. Furthermore, inosine also has inotropic [82] and vasodilatatory [83] effects. On the other hand, UDP possesses the property to activate mitochondrial ATP-dependent potassium channel (mitoKATP), which prevents mainly ischemic injuries and partially rhythm disorders [84]. Therefore, dietary nucleosides and nucleotides may be used as reasonable agents for the prevention of cardiovascular diseases.

E. Effects on Hepatic System

Great portion of the HBV infection will develop chronic hepatitis, which is characterized by chronic liver necroinflammation and may lead to progressive fibrosis [85]. While HCV infection is the leading cause of chronic liver diseases, such as cirrhosis and hepatocellular carcinoma [86]. Nucleosides, nucleotides and their analogues are beneficial for hepatic system for their therapeutic effect on the HBV and HCV infectious hepatic diseases [85, 87-89].

Furthermore, liver and intestine incorporate proportionately greater amounts of dietary nucleotides than other organs. While the liver plays an important role in meeting the requirements of nucleotides in body through active synthesis and release of nucleotides for use by the other tissues [90, 91].The hepatic supply of nucleotides is maintained through de novo synthesis and salvage in addition to sodium-dependent and independent transport of nucleosides into the liver [92, 93]. Furthermore, the nucleotides synthesis and salvage are activated when hepatic injury, and regeneration of new tissue is accomplished by accelerated synthesis of RNA and DNA [94]. In addition, extracellular nucleotides and nucleosides can modulate hepatocyte growth [95] and regeneration [96]. Therefore, it is significant to investigate the effects of dietary supplied nucleosides and nucleotides on the intestinal and hepatic morphology and function. It was reported that the liver function following liver injury [97] and partial hepatectomy [98] was improved by a parenterally administered nucleotides and nucleosides mixture.

F. Antibacterial and Antivirus Effects

Infectious diseases such as human immunodeficiency virus (HIV), hepatitis B and C virus (HBV and HCV) and influenza are serious problems for human being, especially with new viruses such as severe acute respiratory syndrome (SARS) and outbreaks of new strains of influenza virus such as Influenza A virus subtype H3N1. Nucleoside/nucleotide either as sole agents or as a component of combination with other small molecule inhibitors, antibodies or vaccines, have been used for antiviral therapies [85, 87, 99-101]. Furthermore, there is a class of nucleoside derivative from natural products exhibiting antibacterial activity by specific inhibition of bacterial cell wall peptidoglycan biosynthesis [102].

Studies have demonstrated that nucleotides supplemented formula can reduce the incidence of diarrheal diseases in healthy infants [103, 104]. However, recent study showed that nucleotide supplementation of infant formula during episodes of acute diarrhea has no therapeutic advantage compared to conventional infant formula [105]. Furthermore, the gastrointestinal tract plays a primary role in the digestion and absorption of nutrients, but it is also essential as a barrier to prevent host invasion by micro-organisms or bacterial endotoxins [106, 107]. Dietary nucleosides and nucleotides were approved to be essential nutrients for intestinal repair, and mixture of nucleosides and nucleotides or cytidine can provide a better response [108]. Therefore, the effects of dietary nucleotides on reducing the risk of invasive bacterial proliferation of the developing gastrointestinal tract and systemic infection could potentially result from the important role of nucleotides in the differentiation and growth of the immature neonatal gut and enhancement of immune system that has been mentioned above [26].

G. Other Activities

Dietary nucleotides can enhance growth, differentiation, maturation, repair and recovery of intestinal epithelial cells [109, 110] and thus allow optimal catch-up growth due to trophic effects on the intestinal mucosa of infant when their have impairment of intestinal structure and function. However,
those effects did not found in normally grown full-term and preterm infants. This suggests that under normal conditions de novo nucleotide synthesis is sufficient to support normal growth [26, 111].

Inosine, which is involved in oxygen transport by stimulating red blood cell concentrations of 2,3-diphosphoglycerate (2,3-DPG), has been proposed to enhance exercise performance by improving oxygen transport and/or elevating ATP reparation after exercise [112]. Furthermore, inosine, hypoxanthine, and uric acid all significantly increased iron absorption in the rat everted gut [113]. Therefore, human milk-fed infants absorb more than twice as much iron as formula-fed infants, despite breast milk having lower iron levels than infant formula [114]. Besides, nucleosides and nucleotide s are components of human milk that have sleep-promoting characteristics [115].

Nucleosides, nucleotides and their analogue may also have curative effects on the renal diseases such as ischaemic renal injury, acute renal disorders in patients with congestive heart failure and cisplatin-mediated apoptosis of renal proximal tubular epithelial cells by acting on the adenosine receptors [116]. Besides, purines such as adenosine, inosine, and hypoxanthine are known to have potent antiinflammatory effects by serving as endogenous poly (ADP-ribose) polymerase (PARP) inhibitors [117]. In addition, the ribose moiety of the nucleoside and nucleotide has been found to prevent, or alleviate, various secondary complications of diabetes mellitus through inhibiting sorbitol dehydrogenase [118]. Furthermore, nucleosides, nucleotides and their analogue may be used for the treatment of cancer by modulation of immune function, direct act on the tumor cell (for example, Cordycepin (3’-deoxyadenosine), a rich nucleoside in Cordyceps militaris, is known with cytotoxic effects through nucleic acid methylation [119]) or act as A3AR (a subtype of adenosine receptor) agonists [120, 121]. Moreover, a study shows that exogenous plant miRNAs in food can regulate the expression of target genes in mammals [122]; besides, there are reports for plant constituents, which are shown to inhibit e.g. tumor development, both directly as microRNA [123], or indirectly affecting host microRNA [124].

III. CONCLUSIONS

Nucleosides and their analogues are ingredients of importance for human health and involved in many physiological processes, e.g. as units of substances that carry genetic information, in transferring energy, in biosynthetic pathways, as biological regulators and as coenzyme-components. In this review, we described how nucleosides and their related compounds may play a role in many physiological progresses (for example the effect on immune, metabolic, hepatic, nervous, cardiovascular system; anti-virus, anti-bacterial and other effects) and the possible mechanisms may be involved; and more may be demonstrated in the future as our understanding of the relationship between health and dietary nucleosides continues to improve and unfold.

IV. ACKNOWLEDGMENTS

There is no conflict of interest.

References

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