Emergence of Novel Functions of Vitamins for the Prevention of Life-Style Related Diseases

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Summary  Vitamins are a family of micronutrients comprising 13 groups of organic compounds, of which vitamin B1 was identified first, approximately 110 y ago. Deficiency of each vitamin results in specific symptoms, such as neuropathy, dermatitis, diarrhea, dementia, pernicious anemia, scurvy, blindness, rickets, and bleeding. Almost all vitamins can modulate the functions of enzymes and/or other proteins involved in the formation of bone and soft tissues, generation of energy, and regulation of homeostasis via specific vitamin–protein interactions. In addition to the well-known physiological roles of vitamins, novel modes of action of vitamins have been elucidated. These new functions could contribute to extending healthy life expectancy by preventing and curing lifestyle-related diseases. In this mini-review, we introduce the functional properties of three vitamins, vitamin B3 (niacin), biotin, and vitamin K, for the prevention of age-related diseases.

Key Words  vitamin B3, biotin, vitamin K

Vitamins are categorized as micronutrients with recommended daily intake ranging from micrograms to milligrams. Vitamin B1 (thiamine) was the first one identified, approximately 110 y ago, as an anti-beriberi factor. To date, 13 groups of organic compounds have been identified as vitamins (nine water-soluble and four fat-soluble). Insufficient intake of each vitamin results in specific deficient symptoms, such as peripheral neuropathy, dermatitis, blindness, rickets, and bleeding. The physiological function of vitamins is to act as cofactors for functional proteins (enzymes, transcription factors, etc.). and they are involved in various intracellular biological processes that synthesize macromolecules, such as collagens, for the construction of the body, and small molecules that are necessary to maintain homeostasis (serotonin, adrenaline). In addition to the conventionally known actions, novel functions of vitamins have been demonstrated in recent years, which could be involved in the prevention of age-related diseases and extend healthy life expectancy. This review summarizes the preventive effects of vitamins on lifestyle-related diseases. Owing to space limitations, we could not introduce all 13 vitamins and selected three vitamins (vitamin B3, biotin, and vitamin K) and introduced their recently demonstrated functional properties.

Vitamin B3 (niacin)

Vitamin B3 (niacin) was originally discovered as an effective treatment for pellagra, a disease characterized by dermatitis, diarrhea, dementia, and death. Niacin intake has also been associated with a lower liver fat content in humans during lifestyle interventions. Activation of the niacin receptor GPR109A inhibits lipolysis in adipocytes, by lowering the cellular cAMP production and decreasing the hormone-sensitive lipase activity. Further investigation showed that niacin-activated GPR109A inhibited lipogenesis and fatty acid absorption in hepatocytes. Through the same receptor, niacin increases the size and number of mitochondria, along with the thermogenesis of brown adipose tissue. Niacin also inhibits dietary fat absorption by regulating the activity of GPR109A in the intestine (1). Moreover, niacin can regulate lipid metabolism in the intestinal lymphatic system by increasing HDL-ApoA-I synthesis and HDL-associated miR-223 levels while decreasing ApoB48 levels post-transcriptionally, in the lymph chylomicron fraction (2).

At high concentrations, niacin promotes macrophage polarization into anti-inflammatory M2 macrophages and decreases the production of pro-inflammatory cytokines (3). Interestingly, lower concentrations of niacin increased the production of TNF-α, IL-6, and CXCL10 in LPS-stimulated macrophages. Niacin-treated monocytes reduced the growth of brain tumor-initiating cells, possibly by increasing the production of IFN-α14 and regulating its downstream signaling pathway (4). Bioinformatics analysis suggested that niacin might help the prognosis of COVID-19 patients with colorectal cancer, owing to its ability to regulate the BCL2L1, PTGS2, IL-1β, IFNG, and SERPINE1 related pathways (5).

NAD⁺, a coenzyme essential for redox reactions and various functions in the body, is commonly generated from niacin in humans. Low levels of NAD⁺ have been reported in patients with adult-onset mitochondrial myopathy. Niacin supplementation ameliorated NAD⁺ levels, subsequently decreasing the whole-body fat percentage and increasing the muscle mass in these patients. Niacin improved the muscle strength of patients after 10 mo of supplementation, potentially...
due to a decrease in the activation of the mTOR signaling pathway (6).

Nicotinamide can inhibit sirtuin and poly (ADP-ribose) polymerase. Additionally, nicotinamide promotes cell survival in human pluripotent stem cells, by inhibiting the Rho-associated protein kinase and regulating casein kinase 1 and other pluripotency-related pathways (7). As a precursor of NAD⁺, nicotinamide can reduce the incidence of acute kidney injury due to severe metabolic stress caused by systemic inflammation and ischemia (8).

**Biotin**

Biotin functions as a cofactor for four types of carboxylase enzymes that are involved in cytoplasmic fatty acid synthesis, mitochondrial fatty acid oxidation, gluconeogenesis, and the metabolism of several amino acids. These functions are observed at physiological levels of biotin, but high doses of biotin have been reported to have pharmacological effects. For example, a high dose of biotin has been shown to improve hypertension, diabetes, and obesity in animal models.

Biotin treatment reduced blood pressure in stroke-prone spontaneously hypertensive rats (9). Biotin can activate guanylate cyclase in a nitric oxide-independent manner. Thus, a high dose of biotin presumably elevates intracellular cGMP, followed by the relaxation of the vascular smooth muscle and lowering of blood pressure.

Biotin can also alleviate the symptoms of type 1 and type 2 diabetes. Biotin enhanced the mRNA expression and enzyme activity of glucokinase and promoted glucose uptake in the livers of type 1 diabetic rats. In contrast, the mRNA levels of gluconeogenesis genes (PCK1 and G6PC) and the consequent hepatic glucose release were suppressed by biotin treatment. In a study using rats with type 2 diabetes, biotin intake improved insulin resistance in skeletal muscles and increased glucose uptake in peripheral tissues (10). High-dose biotin feeding for the first week after weaning of mice could increase the number and area of islets in the pancreas and increase the proportion of β-cells in the islets (11). These observations may help elucidate the role of biotin and its mechanism of action, in the prevention and treatment of diabetes.

High-dose biotin also has effects on lipid metabolism in the liver and adipose tissue, suggesting a possible role in the improvement of obesity. Dietary supplementation with biotin elevated cGMP levels and phosphorylation of AMP-activated protein kinase (AMPK) in the liver, leading to lower hepatic expression of fatty acid synthase and hepatic and serum triacylglycerol levels. Enhanced cGMP by biotin might activate AMPK, resulting in the phosphorylation (inactivation) of acetyl-CoA carboxylase (ACC)-1. In 3T3-L1 adipocytes, biotin treatment enhanced the activation of AMPK and the inactivation of ACC-1 and -2, reduced fatty acid synthesis, and increased fatty acid oxidation (12).

In addition, biotin supplementation has been reported to affect food intake in mice. Biotin increased the mRNA level of Acc-2 in the mouse hypothalamus, resulting in decreased food intake and suppressed weight gain (13).

Biotin is considered a water-soluble vitamin. However, it is hardly soluble in water at high concentrations. Recently, a novel biotin salt, magnesium biotinate (MgB), was developed, which has higher solubility and showed better bioavailability (1.17–1.57 times) than the natural form biotin (0-biotin) in rats. MgB salt was administered to rats with propionate-induced autism, which improved their behavioral disorders and learning memory in a dose-dependent manner (14). Further, the expression of pro-inflammatory cytokines in the brain was also suppressed by biotin salt. These results suggest that MgB is a suitable biotin derivative for high-dose biotin treatments.

**Vitamin K**

Vitamin K (VK) which is primarily present in the liver, bones, and blood vessels, is a cofactor of γ-glutamyl carboxylase, and is essential for the regulation of blood coagulation and calcification. Analyzing the tissue distribution of VK revealed significant amounts of this vitamin in the pancreas, brain, and testes as well. However, the physiological roles of VK in these tissues have not been fully elucidated. Recently, the function of VK in various cellular events, other than γ-glutamyl carboxylation, has been reported. In this section, we introduce the novel functions of VK.

Menaquinone-4 (MK-4), a form of VK2, directly bound to the pregnane X receptor (PXR) and modulated the gene expression involved in bone formation, and increased cellular collagen levels in osteoblasts (15). We also showed that MK-4 suppressed hepatic mRNA levels of Cyp7a1 and Cyp8b1, which are involved in bile acid synthesis in the liver, in humanized PXR mice but not in wild-type mice (16). VK deficiency is commonly associated with cholestatic liver disease. Thus, VK could participate in bile acid metabolism by regulating gene expression via PXR in humans.

NF-κB is a transcription factor that modulates gene expression in the regulation of inflammation and tumor cell growth. Ozaki et al. showed that the growth inhibition of hepatocarcinoma cells by MK-4 treatment is due to the suppression of NF-κB activation and decreased expression of the downstream factor cyclin D1 (17). The same group also demonstrated that MK-4 suppresses NF-κB activation by inhibiting protein kinase C activity and decreasing the activity of IKK, an upstream kinase of NF-κB. We demonstrated the suppression of NF-κB activation by MK-4 in human monocyte-derived THP-1 cells and mouse microglia-derived MG6 cells (18). In both cell lines, MK-4 suppressed the mRNA expression of pro-inflammatory cytokines induced by lipopolysaccharide. We also found that MK-4 inhibited LPS-induced phosphorylation of IKKα/β in THP-1 cells.

VK1 and MK-4 activated PKA and promoted neurite outgrowth in rat PC12D cells. In addition, MK-4 showed an inhibitory effect on tumor cell growth by activating PKA, followed by the inhibition of Rho GTPase. To clarify the function of MK-4 in the testis, we found that...
treatting mouse testis-derived I-10 cells with MK-4 increased testosterone production, which is regulated by the cAMP–PKA pathway. MK-4 increased the intracellular cAMP levels, followed by the activation of PKA and an increase in testosterone secretion. Similar effects of MK-4 have also been observed in rat pancreas-derived INS-1 cells (19). INS-1 is a pancreatic β-cell-like cell line that can secrete insulin in a glucose-dependent manner. MK-4 increased the intracellular levels of cAMP and enhanced glucose-dependent insulin secretion in these cells. MK-4, which is extremely abundant in the pancreas, exhibits an incretin-like effect and may contribute to the control of postprandial blood glucose levels, to prevent diabetes.

Conclusion
In addition to ones mentioned above, there are many reports regarding the novel functional properties of vitamins, suggesting their role in the prevention of diabetes, osteoporosis, and dementia by activating transcription factors and/or signal transduction pathways. We believe that the emerging roles of vitamins will attract attention to further extend healthy life expectancy and maintain the quality of life in elderly people.

Disclosure of state of COI
No conflicts of interest to be declared.

REFERENCES