Vitamin B6: a heart-protective molecule through a novel mechanism of increasing histidine-related compounds

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It has been reported that a low dietary intake of vitamin B6 is associated with a high risk of mortality from heart disease among Japanese, Americans, and Europeans [1]. Many studies have suggested that vitamin B6 supplementation reduces a risk of heart disease [1–3]. However, the relationship of vitamin B6 intake and risk of heart disease is controversial, and the underlying mechanisms are not fully understood. Since 1969, the role of vitamin B6 in heart disease risk has been mostly addressed through homocysteine hypothesis [4]. However, many recent studies have indicated that the association between vitamin B6 and heart disease risk has been independent of homocysteine, suggesting that vitamin B6 may exert a heart-protective effect through other mechanisms [2,4]. Recently, we found that vitamin B6 supplementation in rats had no effect on homocysteine concentrations in the heart tissue, but markedly increased heart concentrations of histidine-related compounds, such as carnosine, anserine, and histamine [5]. Thus, in the present chapter we propose a novel mechanism underlying heart-protective effect of vitamin B6 and review the currently available knowledge.

Keywords: vitamin B6; histidine-related compounds; carnosine; histamine; heart; cardiovascular disease

1. Introduction

Vitamin B6 is an essential water-soluble vitamin. In humans, our body is lack of an ability to produce this vitamin as well as to store it to long extent due to its water-soluble property. Thus, in order to keep balance of vitamin B6 status, we mainly rely on food consumption. Vitamin B6 can be found in various foods such as fish, beef, poultry, milk products, whole grains, legumes, potatoes, and nuts. There are six isoforms of vitamin B6, which are pyridoxine (PN), pyridoxal (PL), and pyridoxamine (PM), and their phosphorylated forms of pyridoxine 5'-phosphate (PNP), pyridoxal 5'-phosphate (PLP), and pyridoxamine 5'-phosphate (PMP) (Fig. 1). Among those six isoforms, PLP is the most active form that acts as a co-factor or coenzyme in more than 150 enzymatic reactions including amino acid, fatty acid, and carbohydrate metabolisms. For example, PLP is important for enzymes responsible for syntheses of niacin, alanine, histamine, and γ-aminobutyric acid (GABA) from tryptophan, pyruvate, histidine, and glutamic acid, respectively. In fatty acid metabolism, PLP is a co-factor of enzymes responsible for polyunsaturated fatty acid synthesis. In carbohydrate metabolism, PLP is important for generating energy of our body by helping enzymes to breakdown storage carbohydrates to glucose. Being involved in diverse enzymatic reactions, vitamin B6 deficiency has been reported to be associated with an increased risk of many diseases including cardiovascular disease or heart disease [2].

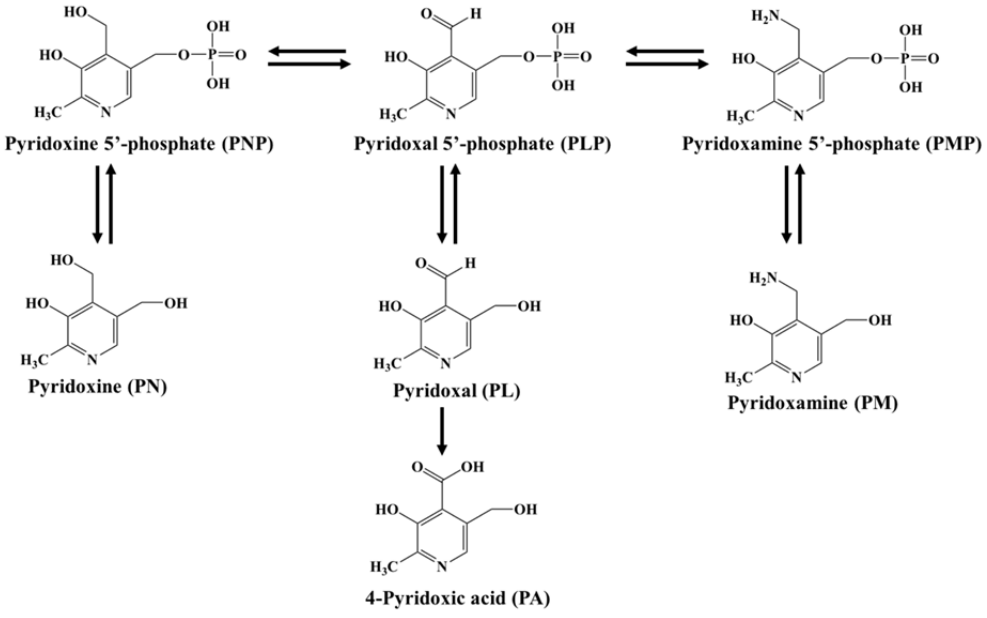

Fig. 1 Vitamin B6 forms. In food, vitamin B6 is existing in PN form. After being absorbed into our body, PN is changed to PLP (the most active form) and/ or PMP, which act as co-factors or co-enzymes.

2. Vitamin B6 and heart disease

After discovery of vitamin B6 in 1934, 15 years later the association of vitamin B6 with heart disease was reported. In 1949, Rinehart and Greenberg [6] demonstrated that monkeys fed a diet with vitamin B6 deficiency had atherosclerosis, a major condition leading to heart disease. Later on, many studies were conducted extensively to address this issue. In 1985, plasma PLP level was proposed to be a risk index for coronary artery disease (CAD), in which low level of PLP in plasma was found to be associated with a high risk of CAD [7]. Both animal and human studies have suggested that vitamin B6 supplementation reduces a risk of various types of heart disease [2,3]. The role of the vitamin in heart disease risk has been mostly addressed through homocysteine and inflammation hypotheses as reviewed below.

2.1 Homocysteine hypothesis

Homocysteine is a sulphur-containing amino acid, which is derived from metabolism of methionine. In general, homocysteine plasma levels increase after meals, especially meals rich in red meat and milk products. Our body maintains homocysteine homeostasis through two main pathways, which are remethylation, in which homocysteine receives a methyl group and is reconverted into methionine, and transulphuration, in which it is degradated to cysteine [4], as shown in Fig. 2. In transulphuration pathway, vitamin B6 plays a crucial role as a coenzyme of cystathionine β-synthetase for the conversion of homocysteine to cystathionine and of cystathionase for the synthesis of cysteine from cystathionine [4]. Thus, vitamin B6 deficiency leads to the accumulation of homocysteine in the body.

Since 1969, homocysteine has been reported to be involved in the pathophysiology of the atherosclerotic process [8]. Since then, many studies have suggested the correlation of elevated homocysteine with cardiovascular risk and established homocysteine as an independent risk factor. Increased homocysteine plasma levels promote blood clots and initiation of endothelial cell damage, which leads to inflammation in the blood vessels [8]. Then, inflammation induces atherogenesis that is an important factor causing blockage of blood flow, which finally contributes to heart disease such as heart attack. Based on the fact that vitamin B6 is a key determinant of total plasma homocysteine concentrations, dietary supplement of vitamin B6 has been proposed for many years to use as a tool for reducing plasma homocysteine levels and incidence of heart disease.

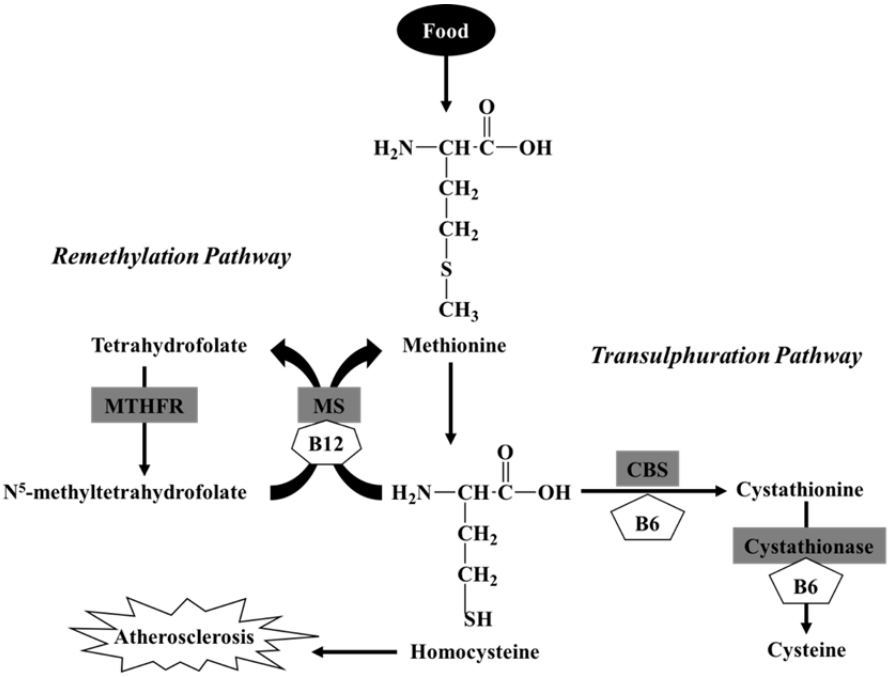

Fig. 2 Homocysteine metabolism. MTHFR: methylene tetrahydrofolate reductase; MS: Methionine Synthase; CBS: Cystathione β-synthase.

2.2 Inflammation hypothesis

Over recent 20 years, vitamin B6 has been proposed to play a role in heart disease through inflammation, which is believed to be a crucial mechanism underlying atherosclerosis and heart disease progression. Many epidemiological studies have demonstrated a strong relationship between vitamin B6 status and inflammation, in which plasma PLP concentrations were inversely correlated with inflammation markers such as C-reactive protein (CRP) [9–13]. A possible mechanism is that vitamin B6 or PLP serves as co-factor in an anti-inflammatory mechanism. When inflammation occurs, vitamin B6 from liver and peripheral tissues is mobilized to the inflammatory sites and acts as a coenzyme in pathways producing metabolites exerting anti-inflammatory or immunomodulatory effects. The use of

vitamin B6 in inflammatory processes results in a decrease in the vitamin concentrations in the body, which could promote and enlarge inflammatory process, thereby leading to chronic inflammatory disease progression. Based on scientific evidences, including human studies, it is unclear whether inflammation induces vitamin B6 deficiency in the body or vitamin B6 deficiency, due to inadequate vitamin B6 intake, induces inflammation. However, it could be said that vitamin B6 deficiency could possibly contribute to impairment of an anti-inflammatory mechanism, consequently leading to chronic inflammation and establishment of heart disease.

Recent research has been focused on clarifying underlying mechanisms in vitamin B6-dependent inflammatory pathways. One of the main pathways is the kynurenine pathway, which involved in tryptophan metabolism [13] as shown in Fig. 3. In this pathway, PLP acts as a co-factor of enzymes that convert kynurenine into a variety of compounds, including kynurenic acid, antranilic acid, xanthurenic acid, and 3-hydroxyanthranilic acid. These kynurenine-related compounds have been reported to have various beneficial effects on anti-inflammatory mechanism.

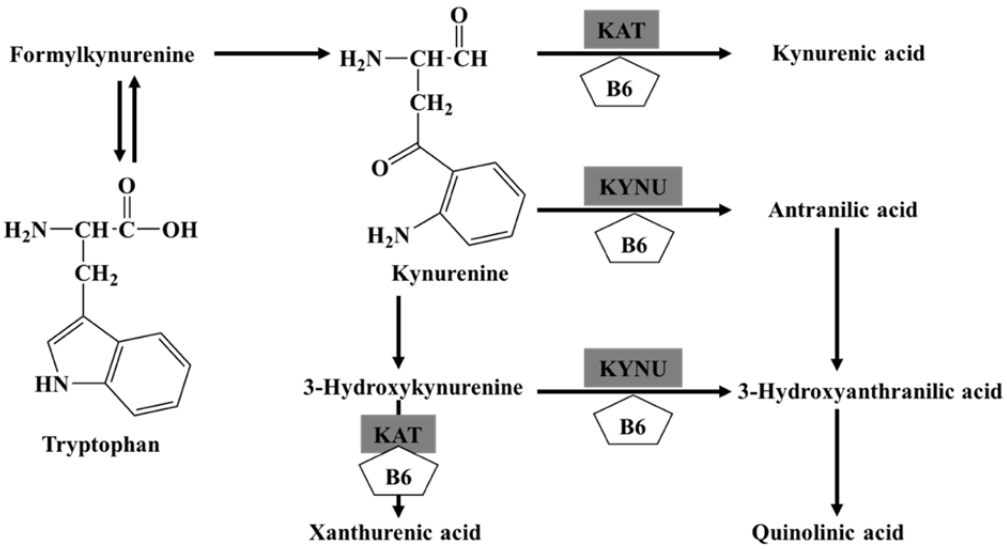

Fig. 3 Kynurenine pathway of tryptophan metabolism and PLP-dependent enzymes involved. KAT: kynurenine aminotransferase; KYNU: kynureninase.

2.3 Controversial in clinical studies

In spite of extensive studies since 1949, the link between vitamin B6 and heart disease is controversial, and the underlying mechanisms are not fully understood. Several large clinical trials have been designed to test the theory of vitamin B6 preventing heart disease, such as the Second Cambridge AntiOxidant Heart Study (CHAOS-2), the Vitamin Intervention for Stroke Prevention (VISP) trial, the Norwegian Vitamin (NORVIT) trial, the Heart Outcome Prevention Evaluation-2 (HOPE-2) trial, the Homocysteinemia in Kidney and End-Stage Renal Disease (HOST) trial, the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS), the Western Norway B-vitamin Intervention Trial (WENBIT), and the Atherosclerosis Risk in Communities (ARIC) study [4]. These studies demonstrated inconsistent results. Many studies have reported that vitamin B6 had no preventive effects on heart disease and there was no inverse association between PLP levels and homocysteine and CRP levels. The controversial results may suggest a potential protective effect of vitamin B6 through mechanisms other than those related to homocysteine metabolism and inflammation.

3. Possible novel mechanism of heart-protective effects of vitamin B6 through histidine-related compounds

Since there are controversial data about heart-protective effects of vitamin B6, in our present study, we directly assessed metabolites in heart tissues of rats fed a normal diet supplemented with low, mild, or high concentration of vitamin B6 (1, 7, or 35 mg pyridoxine (PN) HCl/kg diet, respectively) for 6 weeks. As a result, all vitamin B6 supplementations had no effect on food intake, final body weight, and heart weight (data not shown). PLP concentrations in heart tissues and serum of the 7 and 35 mg PN HCl/kg groups were higher ($P < 0.01$) than those in the 1 mg PN HCl/kg group, while there was no significant difference in PLP concentrations between the 7 and 35 mg PN HCl/kg groups (data not shown). The preliminary study [5] demonstrated that the 7 and 35 mg PN HCl/kg groups had markedly higher concentrations of carnosine (+114 and +162%, respectively, $P < 0.01$, Fig. 4) and anserine (+89 and +101%, respectively, $P < 0.01$, Fig. 4) than those in the 1 mg PN HCl/kg group, while significant differences of those in the 7 and 35 mg PN HCl/kg groups were not observed. These preliminary results led us to apply metabolomics analysis for assessing metabolites in heart

tissues of rats fed a normal diet supplemented with the supplemental level (the 35 mg PN HCl/kg diet) and the marginal deficient level (the 1 mg PN HCl/kg diet). As a result, both vitamin B6 supplementations in rats had no effect on concentrations of homocysteine and kynurenine-related compounds, suggesting that vitamin B6 was not likely to play the role through these two pathways. Over 500 detected compounds, 13 compounds were found to be significantly different between the two groups (Table 1). Serine, alanine, leucine, isoleucine, valine, β-alanine, GABA, histamine, carnosine, 1-methyl histidine, anserine, and homocarnosine levels in the 35 mg PN HCl/kg group were significantly higher than those in the 1 mg PN HCl/kg group. Ornithine was the only compound that its level was lower in the 35 mg PN HCl/kg group than in the 1 mg PN HCl/kg group. Based on these results, we have proposed how vitamin B6 played a role in regulating the levels of those compounds as below.

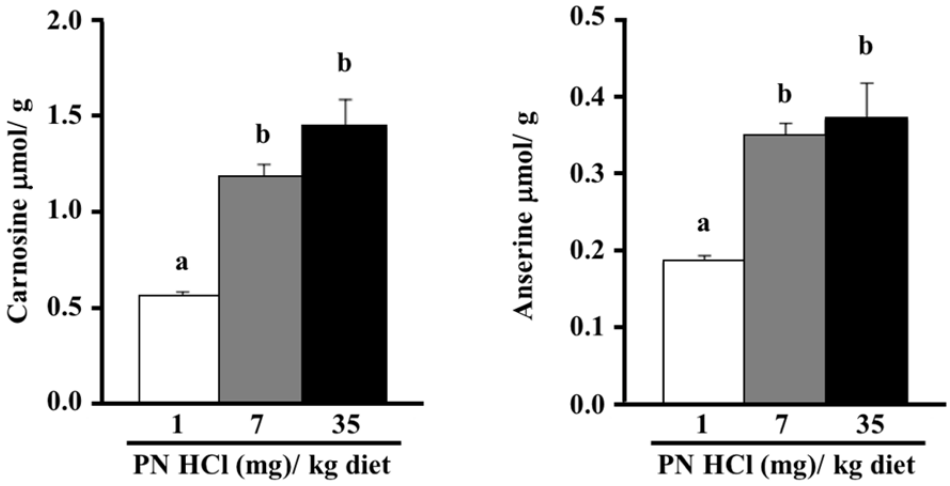

Fig. 4 Effect of dietary levels of vitaminB6 (PN HCl) on concentrations of carnosine and anserine in heart of rats. Mean ± SE (n = 4 for carnosine and anserine). The supernatant samples of each two rats from the same group of eight rats were combined to obtain the pooled four samples. Values with different superscript are significantly different by Tukey's multiple-range test ($P < 0.05$).

Table 1 Compounds with significant different levels detected in heart of rats fed low and high concentrations of vitamin B6 (PN HCl/ kg diet).

Compounds	Comparative Analysis (35 mg PN HCl/kg)/(1mg PN HCl/kg)	
	Ratio	P-value
Serine	1.43	< 0.05
Alanine	1.31	< 0.005
Leucine	1.12	< 0.05
Isoleucine	1.18	< 0.005
Valine	1.14	< 0.05
β-Alanine	1.89	< 0.001
GABA	2.28	< 0.005
Histamine	2.24	< 0.05
Carnosine	2.51	< 0.005
1-Methylhistidine	1.77	< 0.001
Anserine	2.07	< 0.001
Homocarnosine	1.90	< 0.005
Ornithine	0.76	< 0.005

As shown in Fig. 5, it seems likely that vitamin B6 induced the synthesis of histidine-related compounds (HRCs), which were histamine, carnosine, anserine, and homocarnosine. Among these four compounds, histamine is the only compound that its synthesis is directly depended on vitamin B6, since histidine decarboxylase is a PLP-dependent enzyme. For carnosine, anserine, and homocarnosine, these three compounds are the products of carnosine synthase.

Although carnosine synthase is not a PLP-dependent enzyme, it is possible that the vitamin may enhance the enzyme activity by increasing the levels of enzyme substrates, which are β-alanine and GABA. Since β-alanine is rate-limiting for carnosine synthesis [14], it can be speculated that an availability of GABA may be a factor limiting the rate of homocarnosine-synthesis as well. This speculation can be supported by a previous report suggesting that the availability of GABA greatly affected homocarnosine synthesis [15]. It seems reasonable to assume that vitamin B6 upregulates metabolism of amino acids that are reservoirs of β-alanine and GABA (Fig. 5). Vitamin B6 may regulate the levels of serine, alanine, leucine, isoleucine, and valine, which, in turn, play a role in maintaining homeostases of glutamic acid as well as aspartic acid. Then, vitamin B6 is directly involved in the formations of β-alanine and GABA by serving as a coenzyme of aspartate decarboxylase and glutamate decarboxylase, which were reported to be the rate-limiting steps in β-alanine and GABA formations [16,17]. In addition, vitamin B6 might be responsible for the degradation of ornithine to β-alanine and GABA by acting through ornithine decarboxylase and ornithine aminotransferase in polyamines and glutamic acid metabolic pathways. Taken together, we have hypothesized that vitamin B6 may positively influent enzymes involved in the formations of β-alanine and GABA, which are the rate-limiting precursors of histidine-related compounds.

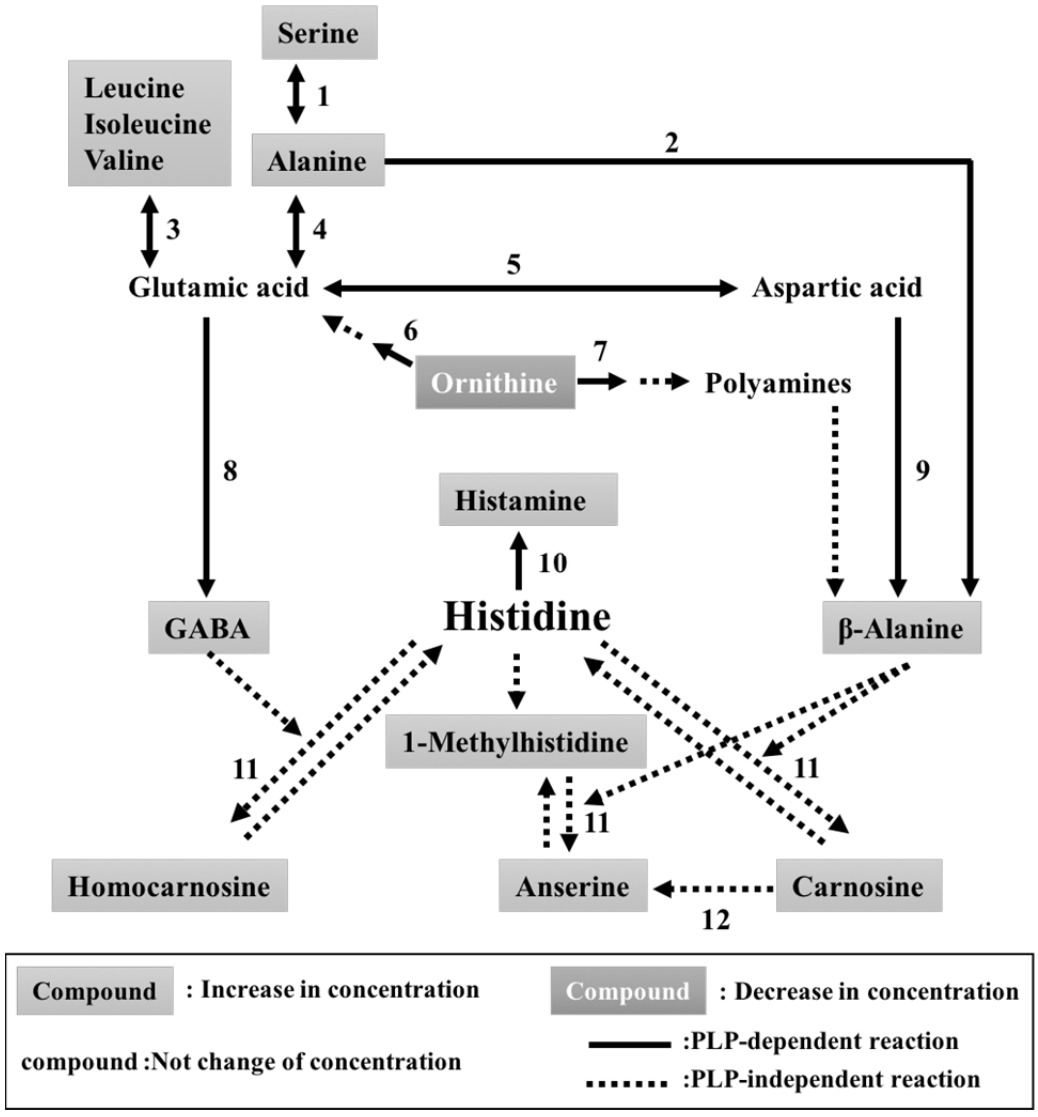

Fig. 5 Putative pathways of compounds affected by vitamin B6 in heat tissues of rats. 1: Serine-pyruvate aminotransferase; 2: β-alanine-pyruvate aminotransferase; 3: Branched-chain-amino acid aminotransferase; 4: Alanine aminotransferase; 5: Aspartate aminotransferase; 6: Ornithine aminotransferase; 7: Ornithine decarboxylase; 8: Glutamate decarboxylase; 9: Aspartate decarboxylase; 10: Histidine decarboxylase; 11: Carnosine synthase; 12: Carnosine N-methyltransferase

There is a large body of evidence showing heart-protective effects of carnosine and related HRCs (anserine and homocarnosine). Recent human study demonstrated that oral administration of carnosine increased exercise tolerance and quality of life in chronic heart failure patients [18]. Many animal studies showed that carnosine and HRCs protected heart tissue from ischaemia-reperfusion damage and cardiomyopathy [19–25], improved contractility of heart in cardiac ischemia [19,26], and decreased cardiotoxicity [24,27]. Carnosine has been reported to have several biochemical functions, including control of pH, antioxidant, metal-ion chelator, carbonyl scavenger, antiglycator, vascular tone

regulator, immunostimulant, and wound healing agent [28,29]. Owning to their imidazole group, HRCs have the crucial physiological function of proton or pH buffering [30]. This crucial function makes HRCs important to skeletal muscle, where there is highly expression of HRCs. Under anaerobic exercise, there is high production of lactic acid, in which its dissociation results in production of protons that brings pH lower than normal levels, which leads to muscle contractile fatigue. Here is where HRCs play a crucial role in proton sequestering to maintain physiological pH. Thus, it can be expected that HRCs also serve this function in heart muscle. In addition to acid-buffering activity, antioxidant activity is another important function of HRCs that have been reported to potentiate preventive effects on cardiac hypertrophy, heart failure, ischemia-reperfusion injury, and myocardial infarction [26,31,32]. Several *in vitro* and animal studies have demonstrated the ability of carnosine and HRCs to deactivate precursors of advanced lipoxidation end-products (ALEs) and advanced glycoxidation end-products (AGEs), leading to the inhibition of AGEs and ALEs formations [33]. Since ALEs and AGEs are associated in the onset and propagation of several oxidative-based diseases such as atherosclerosis, a key factor leading to heart disease, HRCs may exert heart-protective effects through this mechanism. Finally, based on several studies reporting antihypertensive, vasorelaxant, and intracellular calcium-regulating effects of HRCs, it can be expected that HRCs may play a role in modulating contraction/ relaxation of heart muscle [34–41].

Histamine have been reported to be inflammatory mediator and associated with atherosclerosis and myocardial infarction [42]. However, several recent studies have showed beneficial effects on heart. It was found to exert anti-inflammatory effect on human white blood cells [43]. It was also reported to exert a protective role in coronary arteries or heart blood vessels [44]. The study in mice lack of histidine decarboxylase demonstrated that histamine deficiency reduced heart function and enhanced the damage of infarcted heart. The study has suggested a protective role of histamine in the process of myocardial infarction through inhibition of cardiomyocyte apoptosis and promotion of macrophage infiltration that contributes to myocardial healing [45]. It has been proposed that in cardiovascular system, mast cells might not be the predominant source of histamine. Carnosine may serve as a non-mast cell reservoir for histidine as a substrate for histamine synthesis during stress conditions [45–47]. These results may suggest the importance of HRCs in heart.

GABA has been reported to be involved in the regulation of cardiovascular function in mammals, including humans [48]. It was found to exhibit regulatory effects on blood pressure and heart rate [48]. In inducible myocardial ischemia patients, a strikingly decrease in plasma levels of GABA was observed [49]. This compound has been reported to not only be present exclusively in the central nervous system in humans, but also be formed and present in other tissues such as kidney [50]. Based on these results, it is possible to consider that GABA may also play a role in heart protection.

Collectively, among complex metabolic pathways in heart, HRCs such as carnosine, anserine, homocarnosine, and histamine as well as GABA may be the key mediators taking important part in the regulation of heart function and cardiovascular system.

5. Conclusion

Over 60 years past of the discovery of the association of vitamin B6 in heart disease, we still have no complete understanding of its mechanisms. Although its preventive role in heart disease has been mostly addressed through homocysteine and inflammation hypotheses, many recent studies have demonstrated the controversial results and suggested that vitamin B6 may exert a heart-protective effect through other mechanisms. In the present study, we found that the vitamin B6 supplemental level (the 35 mg PN HCl/kg diet) increased the final metabolites in histidine metabolic pathways, which are carnosine, anserine, homocarnosine, and histamine in rat heart tissues, as compared with the marginal deficient level (the 1 mg PN HCl/kg diet). In the present chapter, we propose a novel putative mechanism underlying the heart-protective role of vitamin B6, by which vitamin B6 controls enzymes that are a rate-limiting step in the formation of β-alanine and GABA, which are the rate-limiting precursors of HRCs. Being reported to exert heart-protective effects, those HRCs may, in turn, play important roles in preventing heart disease. Although vitamin B6 is involved in a very large number of physiologic reactions and may affect heart disease in a complex fashion of inter-relationships among several factors and thereby it could be very hard to define the exact mechanism(s), our proposed novel mechanism may add a new piece in the puzzle of how vitamin B6 prevents heart disease.

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