Role of methylglyoxal in essential hypertension

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Altered glucose metabolism due to insulin resistance is a common feature of essential hypertension in humans and in animal models. Elevated endogenous aldehydes in genetic (spontaneously hypertensive rats) and acquired (fructose-induced hypertensive rats) models of essential hypertension may be due to increased production of the reactive aldehyde methylglyoxal, resulting from altered glucose metabolism. Excess methylglyoxal binds sulfhydryl groups of membrane proteins, altering calcium channels and increasing cytosolic free Ca^{2+} and blood pressure. It has been demonstrated that methylglyoxal, when given in drinking water to Wistar-Kyoto rats, leads to an increase in kidney aldehyde conjugates, cytosolic free Ca^{2+} concentration, decreased serum nitric oxide, renal vascular hyperplasia and hypertension. N-acetylcysteine (NAC) in the diet of these animals prevented hypertension and associated biochemical and morphological changes. NAC normalizes blood pressure by directly binding to excess methylglyoxal, thus normalizing Ca^{2+} channels, cytosolic Ca^{2+} and nitric oxide. NAC also leads to increased levels of tissue glutathione, a storage form of cysteine. Glutathione acts as a cofactor in the enzymatic catabolism of methylglyoxal. Cysteine and other antioxidants, such as vitamins B_6, C and E, and lipoic acid, prevented hypertension and associated biochemical and morphological changes in both genetic and acquired rat models of hypertension. The antihypertensive effect of dietary antioxidants may be due to an increase in tissue cysteine and glutathione, which improves glucose metabolism and decreases tissue methylglyoxal. A diet rich in these antioxidants may be effective in preventing and controlling hypertension in humans.

Key Words: *Dietary antioxidants; Hypertension; Methylglyoxal*

More than 600 million people suffer from high blood pressure worldwide. These people are more likely to experience strokes, heart disease and kidney failure. Essential hypertension in humans may develop through a combination of genetic and lifestyle factors. Diet has long been under investigation as an effector of blood pressure. A diet high in sugar or low in antioxidant vitamins can lead to insulin resistance, altered glucose metabolism, low tissue glutathione, hypertension and oxidative stress. Persons with a genetic predisposition for impaired glucose metabolism are particularly vulnerable to the effect of a high-sugar diet. Abnormalities in glucose use are estimated to exist in 25% of the general population and in up to 80% of persons with essential hypertension (1-3). The end result of either genetic sensitivity, a high-sugar diet and/or a diet low in antioxidant vitamins is altered glucose metabolism. Altered glucose metabolism leads to increased levels of the highly reactive ketoaldehyde methylglyoxal (Figure 1).

The purpose of the present review is to discuss the mechanism by which methylglyoxal is formed and its role in causing hypertension. We will discuss the use of dietary antioxidants to lower methylglyoxal and prevent hypertension.

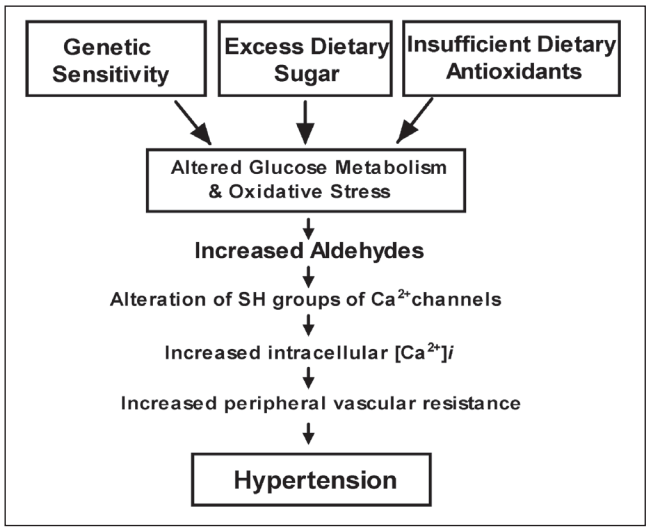

Figure 1) *Role of aldehydes in the development of hypertension. $[Ca^{2+}]_i$ Free Ca^{2+} concentration; SH Sulfhydryl*

ENDOGENOUS FORMATION OF METHYLGLYOXAL

Spontaneously hypertensive rats (SHRs), a genetic model of human essential hypertension, and fructose-treated Wistar-Kyoto (WKY) hypertensive rats show insulin resistance, increased platelet cytosolic free Ca^{2+} and kidney aldehyde conjugates (Figure 2) (4,5). Altered Ca^{2+} handling in platelets is similar to that found in vascular tissue (6). We suggest that the tissue aldehyde conjugates found in these animal models are formed primarily from methylglyoxal produced as a consequence of altered glucose metabolism (Figure 3). Of the two principal pathways of intracellular glucose metabolism, complete oxidation and nonoxidative disposal (glycolytic pathway), only the latter has been shown to be reduced in insulin resistance (2). Under normal physiological conditions, glucose is metabolized to glyceraldehyde-3-phosphate (G3P), which is converted to 1,3-diphosphoglycerate by the enzyme G3P dehydrogenase (GAPDH), with further metabolism to pyruvate via the glycolytic pathway. Insulin has been shown to

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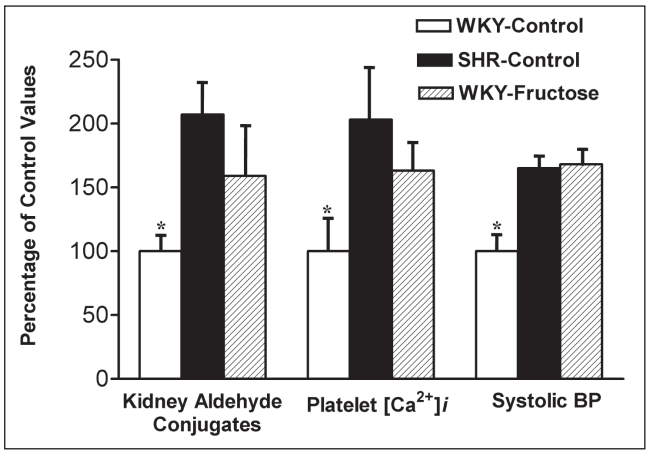

Figure 2) *The bar graph shows kidney aldehyde conjugates, platelet free Ca^{2+} concentration ($[Ca^{2+}]_i$) and systolic blood pressure (BP) in spontaneously hypertensive rats (SHRs) and fructose-induced hypertensive Wistar-Kyoto (WKY) rats. Starting at seven weeks of age, rats were divided into three groups of six animals each. For a period of 14 weeks, animals in the WKY-control and SHR-control groups were given a normal diet and normal drinking water; the WKY-fructose group was given a normal diet and 4% fructose in drinking water. All values (mean ± SD) are expressed as a percentage of the WKY-control group at the completion of the study at 21 weeks of age. *Values are significantly different (P<0.05) from other groups. Data from references 4 and 5*

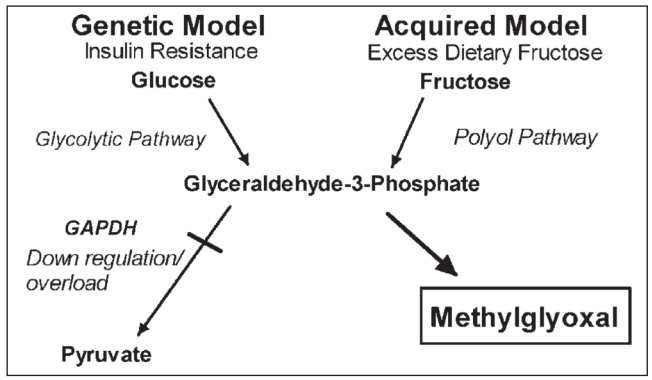

Figure 3) *Formation of excess methylglyoxal due to altered glucose metabolism in genetic and acquired models of hypertension. GAPDH Glyceraldehyde-3-phosphate dehydrogenase*

regulate GAPDH at the messenger RNA level through stimulation of gene expression in adipocytes and hepatoma cell culture (7). In insulin-resistant states, such as type 2 diabetes and essential hypertension, in which GAPDH may be downregulated, there will be a buildup of G3P. Thus, glucose metabolism is slowed through the glycolytic pathway, leading to its conversion to fructose via the polyol pathway. Fructose is further metabolized to D-glyceraldehyde and dihydroxyacetone phosphate. Both D-glyceraldehyde and dihydroxyacetone phosphate are converted to G3P (8,9). This buildup of G3P by both the glycolytic and polyol pathways will result in its conversion to methylglyoxal, especially if further metabolism by GAPDH is impaired (10-13). The effect of GAPDH activity on methylglyoxal levels was demonstrated by Beisswenger et al (14). Koningic acid was used to inhibit GAPDH, resulting in a 79% reduction of GAPDH activity with a sixfold increase in methylglyoxal in human red blood cells in culture (14). SHRs show evidence of insulin resistance before they develop hypertension (15). This inherent insulin resistance may lead to decreased activity of GAPDH and excess methylglyoxal.

Production of excess methylglyoxal can also occur as a consequence of increased dietary sugar. In the course of normal metabolism, fructose bypasses the step in glucose metabolism at phosphofructokinase, where control is exerted on the rate of glucose catabolism. It is rapidly taken up in the liver and converted to intermediate metabolites in the glycolytic pathway. If there is excess dietary sucrose or fructose, this process will deplete cells of inorganic phosphate, leading to inhibition of phosphofructokinase. Inhibition of this enzyme blocks the processing of glucose through the glycolytic pathway. This results in the shunting of glucose through the polyol pathway resulting in the formation of more fructose and, again, a buildup of G3P with further metabolism to methylglyoxal. A diet rich in sucrose or fructose can overload the GAPDH enzyme system, increasing the buildup of G3P and leading to excess methylglyoxal formation.

A recent study (16) reported higher levels of methylglyoxal in vascular smooth muscle cells in SHRs in culture compared with normotensive WKY rats. Methylglyoxal induces aldose reductase in rat aortic vascular smooth muscle cells. This leads to increased flux of glucose through the polyol pathway, with increased formation of methylglyoxal, which may participate in the development of diabetic vascular complications (17-19). Human type 2 diabetic patients have significantly elevated plasma levels of methylglyoxal (20). We have shown elevated levels of plasma methylglyoxal and glyoxal even in young complication-free patients with type 1 diabetes (21). The polyol pathway is especially active in kidney, cardiac muscle, skeletal muscle, vascular smooth muscle, and retinal and neuronal tissue. For this reason, the pathological effects of methylglyoxal would be observed more markedly in these tissues.

ROLE OF METHYLGLYOXAL IN HYPERTENSION

Methylglyoxal and other endogenous aldehydes are compounds of unusually high electrophilic reactivity. They react nonenzymatically with amino (NH_2) and sulfhydryl (SH) groups of membrane proteins, metabolic enzymes and membrane ion channels and inhibit their function. The following reactions of aldehydes are known to occur: reaction with the SH group of a protein (cysteine), leading to formation of hemimercaptals; reaction with a free NH_2 group of a protein (mainly the epsilon-NH_2 group of lysine or arginine), forming a Schiff base or NH_2 compounds; and further stabilization of the hemimercaptals or Schiff base adducts through cross-linking with another free NH_2 group on the protein (Figure 4A). Aldehydes react 100 times faster with SH groups than with NH_2 groups under comparable conditions (22). Methylglyoxal has been shown to bind to thiol groups of epithelial brush border enzymes, causing loss of activity (23).

In diabetes mellitus, aldehyde glyoxal and methylglyoxal modify the free NH_2 groups of lysine and arginine of proteins forming aldehyde conjugates, also called advanced glycation end products (AGEs). Elevated levels of AGEs are implicated in diabetic complications including nephropathy. We have shown that plasma protein AGEs, carboxymethyl cysteine and

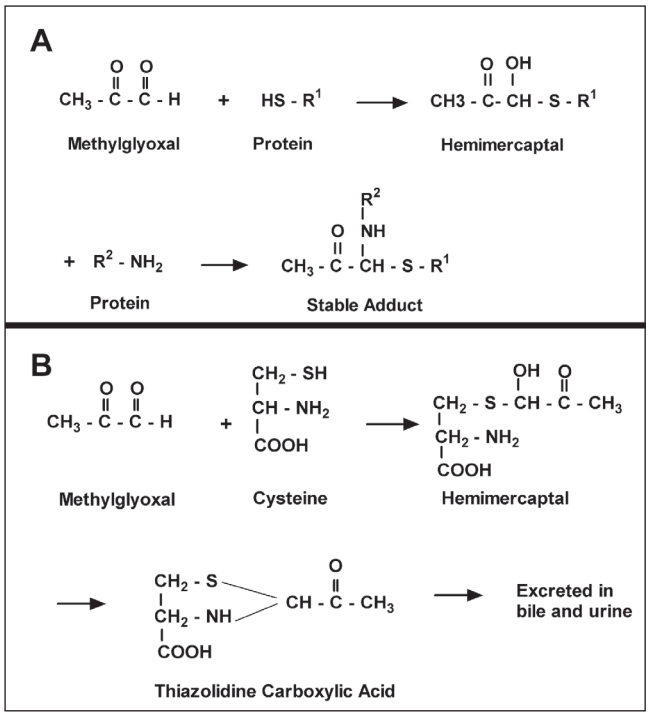

Figure 4) A *Reaction of methylglyoxal with the free sulfhydryl (HS or SH) group of a protein, with a further reaction with a free amino (NH_2) group of protein forming a stable adduct, thus permanently altering its function*. **B** *Protective effect of endogenous cysteine from methylglyoxal by forming a thiazolidine-carboxylic acid derivative, which is excreted in bile and urine*

carboxyethyl cysteine were elevated and related to nephropathy in patients with diabetes (24). Recently, we demonstrated elevated levels of plasma methylglyoxal and methylglyoxal-derived hydroimidazolone AGEs with arginine in type 1 diabetic patients (25). These studies show high reactivity of methylglyoxal with free NH_2 and cysteine groups of tissue proteins.

Under normal physiological conditions, tissue levels of methylglyoxal are maintained at a low level through further catabolism to D-lactate by the glutathione-dependent glyoxalase enzyme system. D-lactate is further converted to pyruvate by 2-hydroxyacid dehydrogenase, thereby rejoining mainstream glycolysis (26). Methylglyoxal will not accumulate as long as the glutathione concentration is adequate to maintain the glyoxalase system. Both SHRs and fructose-induced hypertensive rats show high levels of tissue aldehydes with low levels of glutathione (4,16,27-35). Methylglyoxal also binds to soluble SH compounds, such as reduced glutathione (GSH) and cysteine. Cysteine reacts with methylglyoxal forming a hemimercaptal, which is further converted to a thiazolidine-carboxylic acid, which is excreted in bile and urine (Figure 4B) (22,36,37). Excess methylglyoxal has been shown to lower glutathione in rat vascular smooth muscle cells in culture and in human red blood cells in vitro (16,38).

In essential human hypertension and hypertensive animals, the cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_i$) in vascular smooth muscle cells is elevated. This increase leads to abnormal contractile activity, increased resistance in peripheral vessels and hypertension (39-45). Protein disulphide bonds and SH groups have been shown to be involved in the functioning of L-type Ca^{2+} channels in rabbit cardiac sarcolemmal and skeletal muscle transverse-tubule membranes (46,47). Oxidation of the SH groups of sarcolemmal Ca^{2+} channels and Ca^{2+} release channels of the sarcoplasmic reticulum may increase cytosolic $[Ca^{2+}]_i$, leading to contraction (48). Vascular Ca^{2+} channels could operate in a similar manner. Methylglyoxal has the chemical properties necessary to cause vascular Ca^{2+} channel alterations, leading to increased cytosolic $[Ca^{2+}]_i$, peripheral vascular resistance and hypertension (22,46).

Endogenous nitric oxide (NO) plays an important role in the regulation of blood pressure. NO of endothelial origin normally maintains vascular smooth muscle in a partially relaxed state (49). In human essential hypertensive patients and SHRs, NO production is impaired (50-53). A decrease in NO formation would promote an increase in peripheral vascular resistance and hypertension. Methylglyoxal strongly binds to arginine, which is the precursor to NO synthesis (54,55). Aldehydes may also inhibit NO synthase and guanylate cyclase, both thiol-dependent enzymes (54,56). In in vitro studies, methylglyoxal treatment of rat mesenteric arteries increased intracellular staining of methylglyoxal in endothelial cells and adventitia by fivefold, accompanied by an eightfold increase in the oxidative stress marker nitrotyrosine. This was associated with significantly reduced efficacy of NO-dependent relaxation. Antioxidant pretreatment prevented methylglyoxal-induced impairment of vasoreactivity. This impairment was also not observed in mesenteric arteries of glyoxalase transgenic rats (57).

Increased oxidative stress is present in both human hypertensive patients and SHRs. Methylglyoxal inhibits antioxidant enzymes through binding of SH groups at their active sites and leads to increased oxidative stress (16). The antioxidant enzyme glutathione peroxidase acts on GSH and hydrogen peroxide (H_2O_2) to produce oxidized glutathione (GSSG) and H_2O. This enzyme also scavenges other peroxides. Glutathione reductase plays an important antioxidant defense role by reducing GSSG to GSH. Both these enzymes contain SH groups at their active site (58). In rat vascular smooth muscle cells in culture, these enzymes have been shown to be inhibited by methylglyoxal, leading to oxidative stress, low levels of GSH and increased levels of GSSG (16). Increased oxidative stress can lead to a further increase in reactive aldehydes through lipid peroxidation (22,59-63).

GAPDH, a key glycolytic enzyme, is sensitive to inhibition by agents of oxidative stress such as superoxide radicals and H_2O_2 (64). Of all the glycolytic enzymes, only GAPDH has been shown to be inhibited by H_2O_2 in cardiac muscle (65). Inhibition of GAPDH will lead to increased levels of methylglyoxal. GAPDH consists of four identical polypeptides (monomers) forming a tetramer. Four SH groups are present on each polypeptide, derived from cysteine residues within the polypeptide chain. One of the SH groups is found at the active site (cysteine-149) (66). Cysteine residues of the enzyme are highly reactive and are sensitive to modification by reactive aldehydes such as methylglyoxal. After in vitro incubation with endogenous aldehydes, including methylglyoxal, GAPDH was significantly inhibited (67,68). Incubation of platelets with methylglyoxal also produced significant inhibition of GAPDH (64).

In various in vitro studies, methylglyoxal has been shown to adversely affect metabolic functions at concentrations found in

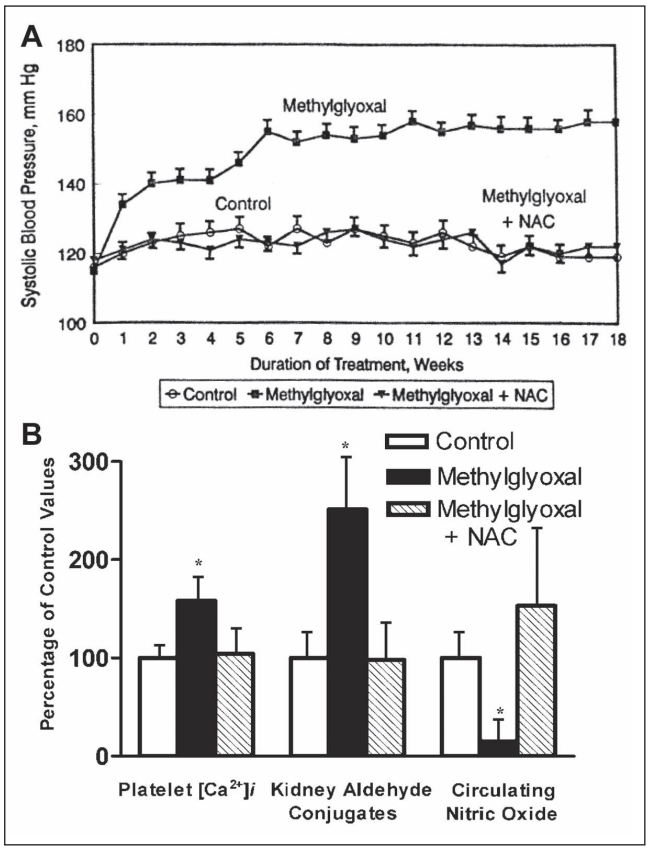

Figure 5) A *The line graph shows the effect of N-acetylcysteine (NAC) on systolic blood pressure in methylglyoxal-treated Wistar-Kyoto (WKY) rats. Starting at seven weeks of age, WKY rats were divided into three groups of six animals each. For the next 18 weeks, animals in the WKY-control group were given a normal diet and normal drinking water; the WKY-methylglyoxal group was given a normal diet and methylglyoxal in drinking water; and the WKY-methylglyoxal + NAC group was given 1.5% NAC in the diet and methylglyoxal in the drinking water. Methylglyoxal was given in the drinking water at a concentration of 0.2% during weeks 0 to 5; 0.4% at weeks 6 to 10; and 0.8% at weeks 11 to 18. Data are presented as mean ± SD of the six animals in each group for each week. Values are significantly different (P<0.05) from one to 18 weeks in the methylglyoxal groups compared with other groups of the same age.* **B** *The bar graph shows the effect of NAC on platelet free Ca^{2+} concentration ($[Ca^{2+}]_i$), kidney aldehyde conjugates and circulating nitric oxide in methylglyoxal-treated WKY rats. The experimental groups and treatment period were the same as in* **A**. *All values (mean ± SD) are expressed as a percentage of the control group values at the completion of the study at 25 weeks of age. *Values are significantly different (P<0.05) from other groups. Data from reference 84*

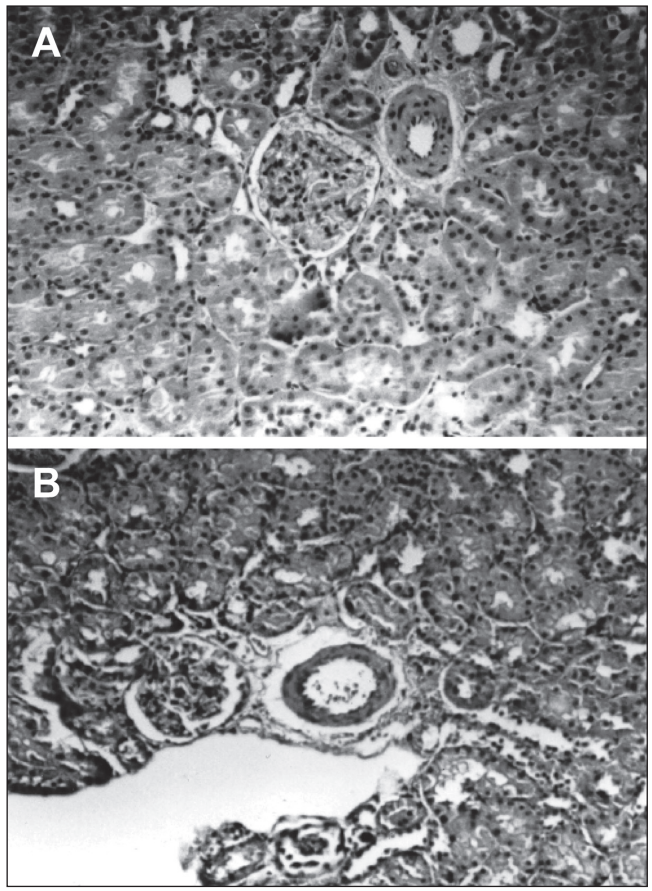

Figure 6) A *Light micrograph of a kidney from a Wistar-Kyoto (WKY) rat given methylglyoxal in drinking water for 18 weeks, showing smooth muscle cell hyperplasia with some narrowing of the lumen in the arteriole (hematoxylin and eosin stain, original magnification ×100).* **B** *Light micrograph of a kidney from a WKY rat given methylglyoxal in drinking water and N-acetylcysteine in the diet for 18 weeks, showing an almost normal-appearing arteriole (hematoxylin and eosin stain, original magnification ×100). Reproduced from reference 84*

diabetic conditions, leading to cell damage and death. In rat renal cortical mitochondria, it inhibited the tricarboxylic acid cycle and electron transport chain (69). Methylglyoxal has been shown to cause apoptosis when incubated with human mesothelial cells and rat mesangial cells (70,71). Chronic oral administration of methylglyoxal leads to increased glomerular basement membrane thickness due to collagen accumulation in the kidneys of mice (72). This may explain the morphological changes we observed in kidney and vascular tissue, in which we have also found higher levels of aldehyde conjugates (Figures 5 to 8).

Thus, methylglyoxal has the potential to elevate cytosolic $[Ca^{2+}]_i$, decrease NO in kidney and vascular tissue, inhibit antioxidant enzymes, deplete glutathione, cause oxidative stress in vascular tissue and produce hypertension (16,39,47,48,73-84). In both genetic (SHRs) and acquired (fructose-, threonine-, ethanol- and salt-induced) rat models of hypertension, we have shown elevated levels of aldehyde conjugates in vascular tissue, elevated cytosolic $[Ca^{2+}]_i$ and adverse renal vascular changes (4,27-33,85-88).

To determine the direct effect of methylglyoxal on blood pressure, it was given in drinking water to WKY rats for 18 weeks (Figure 5A). Methylglyoxal-treated rats displayed a continuous increase in systolic blood pressure, which reached a plateau at six weeks of treatment. Methylglyoxal treatment resulted in significantly higher kidney aldehyde conjugates, platelet cytosolic Ca^{2+} and decreased circulating NO (Figure 5B). Rats treated with methylglyoxal also showed smooth muscle cell hyperplasia, thickening of the wall and narrowing of the lumen in small arteries and arterioles of the kidney (Figure 6) (84).

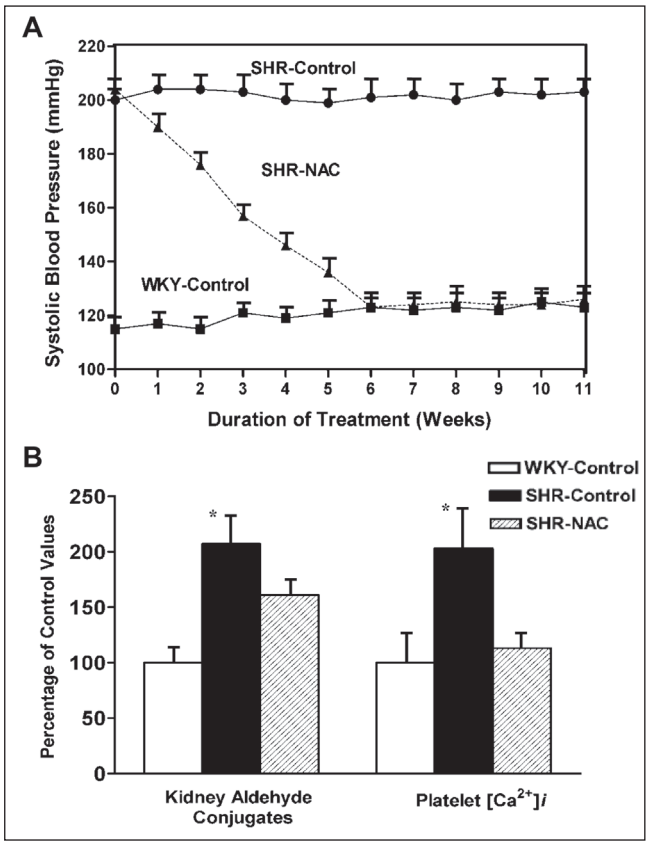

Figure 7) A *The line graph shows the effect of N-acetylcysteine (NAC) on systolic blood pressure in spontaneously hypertensive rats (SHRs). Starting at 12 weeks of age, animals were divided into three groups of six animals each. For the next 11 weeks, the SHR-control and Wistar-Kyoto (WKY)-control groups were given a normal diet and normal drinking water and the SHR-NAC group was given 1.5% NAC in the diet and normal drinking water. Data are presented as mean ± SD of the six animals in each group. Values are significantly different (P<0.05) from one to 11 weeks in the SHR-control group compared with the other groups of the same age.* **B** *The bar graph shows the effect of NAC on kidney aldehyde conjugates and platelet free Ca^{2+} concentration ($[Ca^{2+}]_i$) in SHRs and WKY rats. The experimental groups and treatment period were the same as in* **A**. *All values (mean ± SD) are expressed as a percentage of the WKY-control group at the completion of the study at 23 weeks of age. *Values are significantly different (P<0.05) from other groups. Data from reference 5*

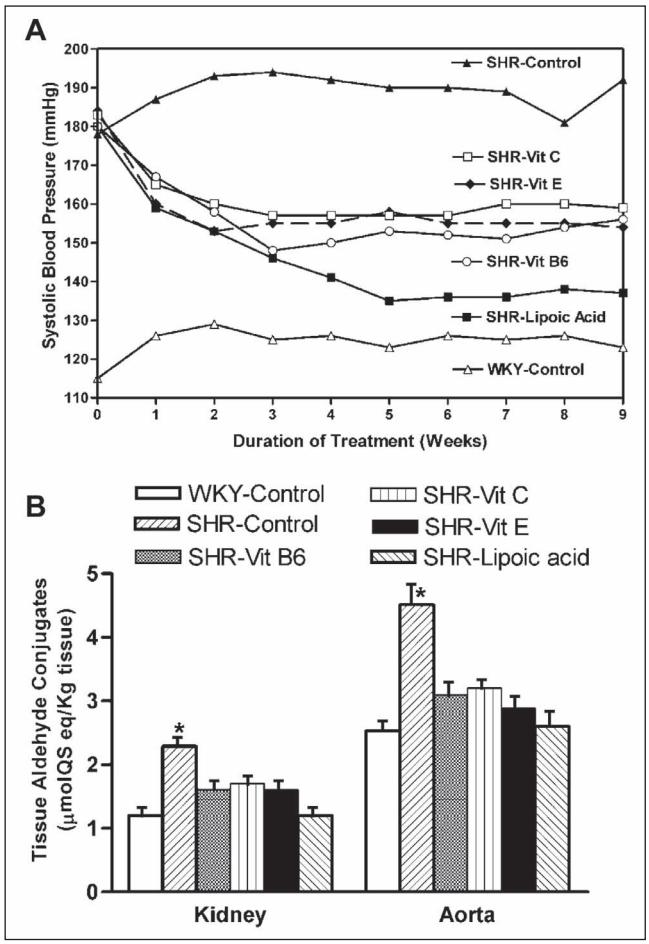

Figure 8) A *The line graph shows the effect of vitamin (Vit) B_6, Vit E, Vit C and lipoic acid supplemented in the diet on systolic blood pressure in spontaneously hypertensive rats (SHRs). Starting at 12 weeks of age, animals were divided into six groups of six animals each. For nine weeks, animals in the Wistar-Kyoto (WKY)-control and SHR-control group were given a normal diet; the SHR-Vit B_6 group was given a diet supplemented with 20 mg Vit B_6; the SHR-Vit C group was given a diet supplemented with 100 mg Vit C; the SHR-Vit E group was given a diet supplemented with 3.4 mg Vit E; and the SHR-lipoic acid group was given a diet supplemented with 50 mg of lipoic acid per 100 g of diet. All animals were given normal drinking water. Values are given as the mean of the six animals in each group. SDs did not vary more than 6 mmHg in each case. Values are significantly different (P<0.05) from one to nine weeks in the SHR-control group compared with other groups of the same age.* **B** *The bar graph shows the effect of an antioxidant-supplemented diet on kidney and aortic aldehyde conjugates in SHRs. The experimental groups and treatment period were the same as in* **A**. *Data are presented as mean ± SD of the six animals in each group at the completion of the study at 21 weeks of age. *Values are significantly different (P<0.05) from other groups. QS Quinine sulphate. Data from references 27 to 30*

ANTIHYPERTENSIVE EFFECTS OF GLUTATHIONE, CYSTEINE, VITAMINS B_6, E AND C, AND LIPOIC ACID VIA MODULATION OF METHYLGLYOXAL

Under normal physiological conditions, tissue levels of methylglyoxal are maintained at a low level. This is accomplished through further catabolism or by binding to soluble SH compounds, such as cysteine, and excretion in bile and urine. Cysteine is also a precursor of glutathione, which is essential as a cofactor in methylglyoxal catabolism. It has antioxidant activity, which acts to reduce oxidative stress and improve insulin-mediated glucose metabolism. In our studies, due to the unstable nature of cysteine, we used N-acetylcysteine (NAC), a commercially available analogue. Oral administration of NAC leads to increased tissue cysteine levels after deacylation, primarily in the kidney. Cysteine is stored in the tissues as glutathione and is released when required. Glutathione represents 90% of the total nonprotein low molecular weight thiol in the body (89).

We investigated the effectiveness of NAC in lowering tissue aldehyde conjugates and blood pressure in methylglyoxal-treated WKY rats. NAC, 1.5% in the diet, prevented the increase in tissue aldehyde conjugates, cytosolic Ca^{2+} and hypertension. It also increased circulating NO and prevented adverse renal vascular changes (Figure 5) (84). We further investigated the antihypertensive effect of dietary cysteine supplementation in SHRs and fructose-induced WKY hypertensive rats. When SHRs were given NAC, their systolic blood pressure decreased significantly at two to 10 weeks. At six to 10 weeks, there was no significant difference in mean blood pressure in SHRs on NAC compared with WKY control rats of similar age. In addition to normalizing blood pressure, NAC also lowered kidney aldehyde conjugates and platelet $[Ca^{2+}]_i$ in SHR rats (Figure 7) (5,88). Our study of fructose-treated WKY rats showed similar results (4).

Because we found NAC to be so effective in lowering aldehydes and preventing hypertension, we decided to look at the possible effects of other antioxidants that normally occur in our diet that are known to increase tissue cysteine and glutathione. We studied the effect of dietary antioxidants on systolic blood pressure in the genetic model of hypertension, the SHR. They were given either vitamins C, E and B_6, or lipoic acid for a period of nine weeks (27-30). We started this study when the rats were 12 weeks of age and already hypertensive. SHRs and normotensive WKY rats on regular chow were used as controls. Supplementation of vitamins B_6, C and E significantly decreased blood pressure, while lipoic acid effectively normalized it. Tissue aldehyde conjugates were elevated in hypertensive animals compared with controls. These antioxidants significantly lowered tissue aldehydes. Treatment with these antioxidants also lowered cytosolic Ca^{2+} and attenuated renal vascular changes (Figure 8). We have also shown that these antioxidants prevent hypertension and normalize tissue aldehyde conjugates and platelet $[Ca^{2+}]_i$ in fructose-treated WKY rats – an acquired model of hypertension (Figure 9) (31-33). The antihypertensive effect of dietary vitamin B_6 in SHRs and fructose-treated rats is probably due to increased synthesis of cysteine from methionine (30,90). The antioxidant vitamins and lipoic acid increase tissue glutathione, improve glucose metabolism and decrease oxidative stress. We suggest that these dietary antioxidants prevent hypertension and associated biochemical and morphological changes by lowering endogenous methylglyoxal.

MODULATION OF METHYLGLYOXAL – A NEW MODALITY TO PREVENT HYPERTENSION

There is an increasing body of evidence demonstrating that essential hypertension, coronary artery disease, diabetes mellitus and hyperlipidemia develop due to the interaction of genetic and environmental factors. Diet and lifestyle factors can strongly influence the progression of hereditable disorders. Persons with a genetic susceptibility toward impaired glucose metabolism will be particularly sensitive to the adverse effects of a high-sucrose or high-fructose diet. A high-sucrose or high-fructose diet in these individuals leads to altered glucose metabolism, insulin resistance, increased levels of tissue methylglyoxal, oxidative stress and hypertension. This can be corrected nutritionally by lowering sucrose or fructose intake, and supplementation with an adequate mix of antioxidants such as vitamins B_6, C and E, cysteine and lipoic acid. In most people, the present

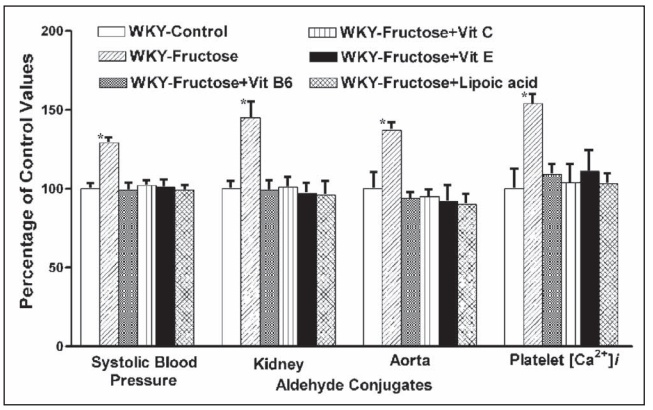

Figure 9) *The bar graph shows the effect of vitamin (Vit) B_6, Vit C, Vit E and lipoic acid supplemented in the diet on systolic blood pressure, kidney and aortic aldehyde conjugates, and platelet free Ca^{2+} concentration ($[Ca^{2+}]_i$) in fructose-induced hypertensive Wistar-Kyoto (WKY) rats. Starting at seven weeks of age, rats were divided into six groups of six animals each. For 14 weeks, animals in the control group were given a normal diet and normal drinking water; fructose group, a normal diet and 4% fructose in drinking water; fructose + Vit B_6 group, a diet supplemented with 20 mg of Vit B_6 and 4% fructose in drinking water; fructose + Vit C group, a diet supplemented with 100 mg of Vit C and 4% fructose in drinking water; fructose + Vit E group, a diet supplemented with 3.4 mg of Vit E and 4% fructose in drinking water; and fructose + lipoic acid group, a diet supplemented with 50 mg of lipoic acid and 4% fructose in drinking water per 100 g of diet. Data (mean ± SD) are expressed as a percentage of the WKY-control group at the completion of the study at 21 weeks of age. *Values are significantly different ($P<0.05$) from other groups. Data from references 31 to 33*

recommended daily allowance of such vitamins may be sufficient to maintain normal glucose metabolism and insulin balance, and additional vitamin supplementation may have no effect on blood pressure. However, for sugar-sensitive persons, particularly those consuming a high-sucrose or high-fructose diet, vitamin supplementation above the recommended daily allowance may be necessary to lower methylglyoxal, preventing insulin resistance, oxidative stress and hypertension. The antihypertensive effect documented in the Dietary Approach to Stop Hypertension (DASH) 1 and DASH 2 studies, which recommend a diet rich in fruit, vegetables, grain products and low-fat dairy goods, and low in total fat and salt intake for the control of mild hypertension, may be due to the antioxidants found in these nutrients.

CONCLUSION

The end result of either a genetic sensitivity, a high-sugar diet and/or a diet low in antioxidant vitamins is altered glucose metabolism. Altered glucose metabolism results in elevated levels of methylglyoxal, leading to hypertension and its associated biochemical and morphological changes. A diet rich in antioxidants such as cysteine, lipoic acid and vitamins B_6, C and E can maintain methylglyoxal at a low level and, thus, prevent hypertension.

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