Original Paper

Comparative Effects of Chromium, Vanadium and Gymnema Sylvestre on Sugar-Induced Blood Pressure Elevations in SHR

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Key words: Hypertension, sucrose-induced; chromium polynicotinate, effects on BP; bis(maltolato)oxovanadium, effects on BP; Gymnema sylvestre, effects on BP; TBARS, chromium effects

Objective: Effects on systolic blood pressure (SBP) of ingesting three agents reported to influence insulin metabolism, i.e., chromium polynicotinate, bis(maltolato)oxovanadium (BMOV), and the herb, *Gymnema sylvestre*, were assessed simultaneously in spontaneously hypertensive rats (SHR).

Methods: In the first study, SHR were fed either a starch, sugar, or sugar diet containing chromium polynicotinate, bis(maltolato)oxovanadium (BMOV), or *G. sylvestre*. Tail SBP was estimated indirectly and various blood chemistries were measured. TBARS formation was determined in hepatic and renal tissue. In a second study, tail SBP was measured in SHR ingesting diets containing different concentrations of BMOV.

Results: Compared to starch, SHR consuming sucrose showed a significant elevation of SBP within days that was maintained for the duration of study. Addition of chromium polynicotinate to the sucrose diet at the beginning of study prevented the sucrose-induced elevation of SBP for 2 weeks, but SBP rose significantly after that. BMOV at high concentrations overcame the sucrose-induced rise in SBP and even decreased SBP below values seen in SHR eating the starch diet, but marked weight loss was noted. A second study examined different concentrations of BMOV. At 0.01% w/w concentration of BMOV, SBP was still significantly decreased, even though SHR did not lose body weight (BW) early on. SHR consuming *G. sylvestre* showed no change or even elevated SBP. Hepatic thiobarbituric acid reacting substances (TBARS) formation, an estimate of lipid peroxidation, was decreased by chromium polynicotinate and BMOV, and renal TBARS by chromium polynicotinate. Circulating cholesterol concentrations were decreased in the SHR consuming *G. sylvestre*.

Conclusions: Chromium decreases the portion of SBP elevated by high sucrose intake as shown previously, but high levels of sucrose ingestion can eventually overcome this. BMOV overcame sucrose-induced elevation of SBP as well as some of the "genetic hypertension." Different from chromium, this decrease was not overcome by high levels of dietary sucrose. The significant lowering of cholesterol with *G. sylvestre* ingestion indicates some effect on metabolism, but *G. sylvestre* did not lower and even raised SBP.

INTRODUCTION

A cause-effect relationship between insulin perturbations (insulin resistance/hyperinsulinemia) and elevated blood pressure (BP) has been suggested [1–4], based largely on findings in diabetics and hypertensives [5]. Fortunately, a good laboratory model exists to examine this possibility: insulin resistance, hyperinsulinemia, and hypertension develop in certain rat strains fed diets containing high concentrations of sugars [6–9]. In support of a cause-effect relationship, a number of agents that favorably influence the insulin system by enhancing insulin sensitivity and/or reducing circulating insulin concentrations have been shown to lower BP in this frequently studied rat model, e.g., somatostatin [10], soluble fibers [11], vanadium

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[12,13], chromium [14], metformin [15], and troglitazone [16]. In the present study, we simultaneously compared effects on BP of three agents with the potential to beneficially influence the insulin system in different ways, i.e., chromium polynicotinate, bis(maltolato)oxovanadium (BMOV), and *Gymnema sylvestre* (*G. sylvestre*), an herb known to affect the glucose/insulin system favorably [17], in spontaneously hypertensive rats (SHR). Chromium and vanadium influence the insulin system at the periphery, perhaps by different mechanisms [12–14], whereas *G. sylvestre* appears to work at the pancreatic level [17]. We found that effects of each agent on BP and other parameters differed.

MATERIAL AND METHODS

The first study was designed to compare the effects of chromium polynicotinate, BMOV, and the herb *G. sylvestre* on various parameters in SHR. The second study examined effects of the vanadium compound in more detail.

Male SHR of the Okamoto strain [18], weighing 150 to 200 g, were obtained from Taconic Farms, Germantown, NY. In the first study, five dietary groups were set up; each contained six SHR. After 2 to 3 weeks of acclimatization to laboratory chow, rats were provided special diets for 1 month. The five special diets were obtained from Teklad, Inc, Madison, WI (Table 1). Attempts were made to keep all diets similar with the exception of the constituent under study. The first diet derived 52% of calories from cornstarch and the last four diets replaced starch with sucrose to provide 52% of calories (Table 1). Minerals and vitamins were added at AIN (American Institute of Nutrition) levels. Additional chromium was added to the third diet as chromium polynicotinate (ChromeMate, Trade Name, InterHealth, Concord, CA) to elevate chromium content to 0.0005% w/w, and vanadium was added to the fourth diet as BMOV, (kind gift of Dr. John McNeill, University of British Columbia, Vancouver, BC, Canada) to elevate vanadium concentrations to 0.12% w/w. In the last diet, *G. sylvestre*, added at a concentration of 1.6% w/w, replaced some cellulose. The *G. sylvestre* was an extract standardized to 25% gymnemic acid content.

Table 1. Basic Diets

Ingredients	% by Weight	% of Calories
Starch or sucrose	57.00	52.1%
Vegetable oil	16.44	36.0%
Casein	13.00	11.9%
Mineral mix, AIN 76A	4.00	
Vitamin mix, AIN 76A	1.20	
Cholesterol	1.10	
NaCl	0.50	
Choline bitartrate	0.50	
dl-Methionine	0.20	
Sodium cholate	0.02	
Ethoxyquin	0.04	
Cellulose	6.00	

In the second study, each of five dietary groups contained eight SHR. The same basic sucrose diet from the first study was used. The control diet contained sucrose at 52% of calories. The next four diets were variants of the basic sucrose diet. To three of the sucrose-containing diets, BMOV was added at different concentrations—0.01, 0.03, and 0.06% w/w, respectively. The last sucrose diet contained vanadyl sulfate at 0.06% w/w.

Systolic BP (SBP)

SBP was estimated by tail plethysmography in unanesthetized rats after a 5-minute warming period [6,19]. Readings were taken 30 to 60 seconds apart. To be accepted, SBP measurements had to be virtually stable for three consecutive readings. Measurements were made 2 to 3 times per week.

Blood Chemistries

Blood was obtained at the end of the experiment (1 month consuming special diets) after the food had been removed for 4 hours. Following blood drawing, rats were sacrificed by inhalation of CO_2. Chemical analyses were performed by routine clinical procedures. Glucose was determined by the hexokinase method (Serono-Baker Diagnostics, Allentown, PA) using a Centrifichem System 600. Immunoreactive insulin was determined by radioimmunoassay (Linco Research Laboratories, St Louis, MO) and glycosylated hemoglobin (HBA1C) by column chromatography (Isolab Inc, Akron, OH). Malondialdehyde (MDA) formed from the breakdown of polyunsaturated fatty acids serves as a convenient index for determining the extent of lipid peroxidation. Lipid peroxidation products are quantified by their reaction with thiobarbituric acid 9 [20]. A 1.0 ml aliquot of hepatic and renal homogenates, precipitated with 0.15 ml of 76% trichloroacetic acid (TCA), is added to 0.35 ml of 1.07% thiobarbituric acid and incubated at 80°C for 30 minutes. A 0.5 ml volume of cold 90% TCA is added and the absorbance read at 532 nm. 1,1,3,3 tetramethoxypropane serves as the standard. Formation of thiobarbituric acid reacting substances (TBARS) estimates the amount of lipid peroxidation products.

Statistical Analyses

Statistics on chemistry values were performed by a one way analysis of variance (ANOVA) using repeated measures. SBP and body weight (BW) were examined by two-way analyses of variance (one factor being diet and the second factor being time of examination). Where a significant effect of diet was detected by ANOVA ($p<0.05$), the Dunnett t-test was used to establish which differences between means reached statistical significance ($p<0.05$) [21].

RESULTS

First Study

BW (Fig. 1). SHR consuming the basic starch (Starch) and basic sucrose (Sucrose) diets, and those consuming diets containing chromium polynicotinate (Chromium) and *G. sylvestre* with sucrose as the sole carbohydrate source showed virtually the same steady increase in BW (Fig. 1). In contrast, SHR consuming vanadium as BMOV (0.12% w/w) showed decreased BW from the beginning of study. Because of this, the BMOV diet was replaced with the basic sucrose diet (no BMOV present) at various intervals. This occurred at days 7 to 10, 14 to 17, and 21 to 27. Changing to the basic sucrose diet resulted in reversal of BW loss during these brief time intervals. SHR had been consuming BMOV for 5 days at termination of study.

SBP (Fig. 2). Although the five arms of the study were examined simultaneously, data in Fig. 2 are divided into three separate graphs for easier discernment, i.e., the chromium, vanadium, and *G. sylvestre* arms are compared individually with the starch and sucrose arms. Compared to the starch diet, SHR consuming the sucrose diet showed a significant elevation of SBP by the fifth day. This significant difference was maintained throughout the entire month of study. Addition of chromium polynicotinate to the basic sucrose diet prevented the sucrose-induced increase in SBP for the initial 2 weeks (Fig. 2 upper). However, SBP eventually increased to that of SHR consuming sucrose alone.

Rats ingesting diets containing vanadium as BMOV with sucrose initially showed the same elevation of SBP above starch control as SHR consuming sucrose alone (Fig. 2 middle). However, after 2 weeks, SBP decreased significantly below that of SHR consuming the basic starch diet. This decreased SBP was maintained at a steady level despite the occasionally brief intervals when the SHR were not consuming BMOV-containing food.

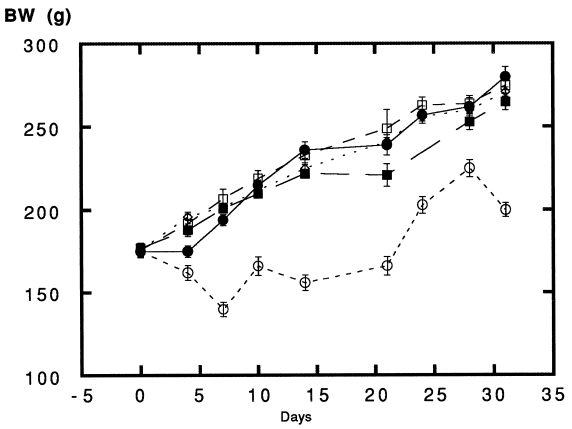

Fig. 1. Study #1. Mean±SEM of BW of 6 SHR in five groups. Symbols for each are as follows: closed circle-Starch, closed squares-Sucrose, open squares-Sucrose+chromium, open circles-Sucrose+BMOV, and open diamonds-Sucrose+*G. sylvestre*. Only values for BMOV are significantly different from other groups.

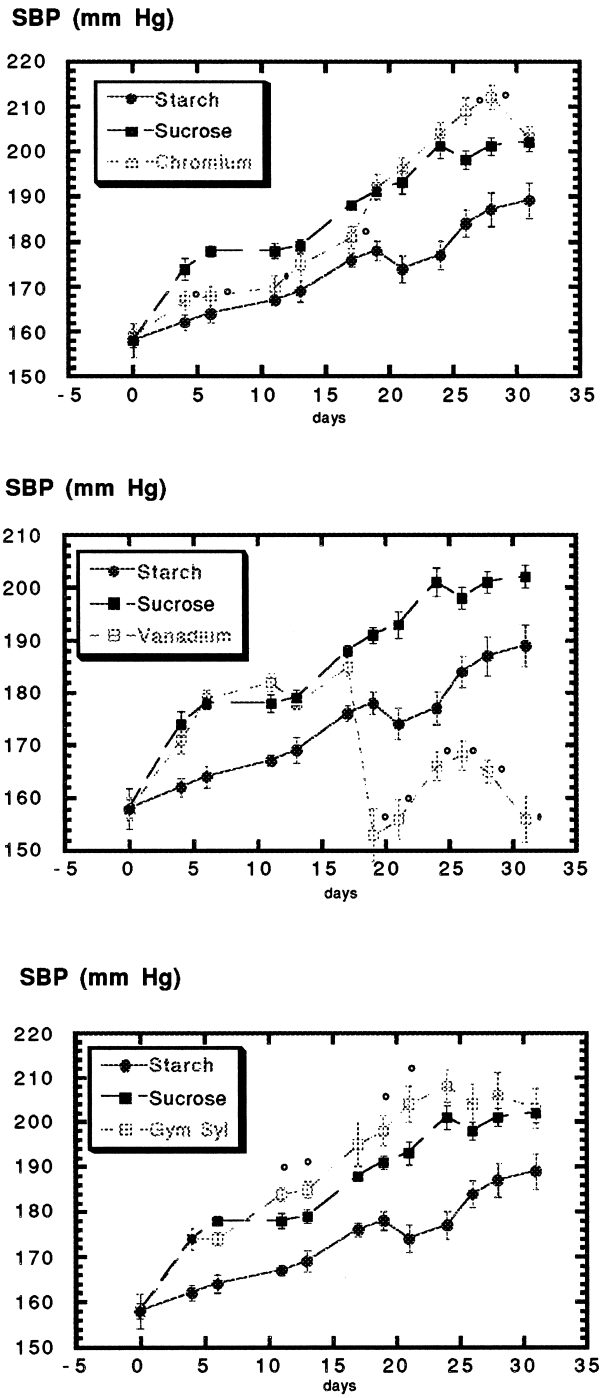

Fig. 2. Study #1. Mean±SEM of SBP of six SHR. Each variation of the sucrose diet is shown individually along with data from SHR consuming the starch and sucrose diets. Chromium data are depicted in upper figure, vanadium data in middle figure, and *G. sylvestre* data in lower figure. Open circles beside points indicate a significant difference from sucrose group.

In SHR consuming *G. sylvestre* (Fig. 2 lower), the tendency was for SBP to be higher than SHR consuming sucrose alone. Blood pressure was significantly higher in the group consuming *G. sylvestre* compared to the Sucrose group at four points indicated in Fig. 2 over the duration of study.

Blood Chemistries (Table 2). Among the five dietary groups, HbA1C was not significantly different. Glucose concentration was highest in the Starch group and lowest in the BMOV group. Compared to the starch and sucrose groups, insulin values were significantly lower in the BMOV and chromium polynicotinate groups. Eating sucrose resulted in a significant increase in cholesterol and triglyceride concentrations. Compared to pure sucrose-eaters, cholesterol was lowered significantly by *G. sylvestre* and triglycerides by BMOV. BUN, creatinine, and uric acid concentrations were significantly elevated in SHR consuming BMOV.

TBARS (Fig. 3). TBARS were measured in hepatic and renal tissues. TBARS were significantly higher in hepatic tissue of SHR consuming the Sucrose diet compared to the Starch diet. The addition of chromium polynicotinate and BMOV prevented this elevation in hepatic TBARS caused by sucrose replacement of starch. Significant differences in mean values did not occur in renal tissue between the sucrose and starch eaters, although addition of chromium polynicotinate caused statistically significantly lower mean values when compared to the basic sucrose group.

Second Study

BW (Fig. 4). The trend was for lower weights in SHR consuming BMOV and vanadyl sulfate. More BMOV present in the diet resulted in a lesser weight gain. For 2 weeks, the young SHR consuming 0.06% w/w BMOV actually lost weight. These SHR were returned to basal sucrose diet and began regaining weight rapidly. The loss of weight at equal concentrations of BMOV and vanadyl sulfate (0.06%) was significantly greater in the former. The BW changes brought on by 0.03% BMOV and 0.06% vanadyl sulfate were similar. Although mean BW was slightly lower in SHR consuming the diet containing 0.01% BMOV compared to the basic sucrose diet, this difference was not statistically significant.

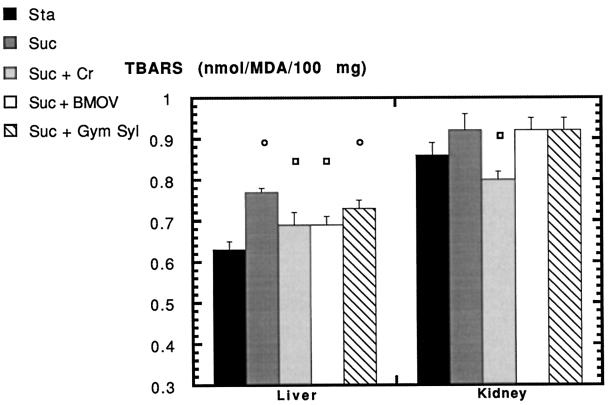

Fig. 3. Study #1. Mean±SEM for TBARS formation in liver and kidney tissue of five different dietary groups. Open circle indicates significant difference from starch group, and open square indicates significant difference from sucrose group.

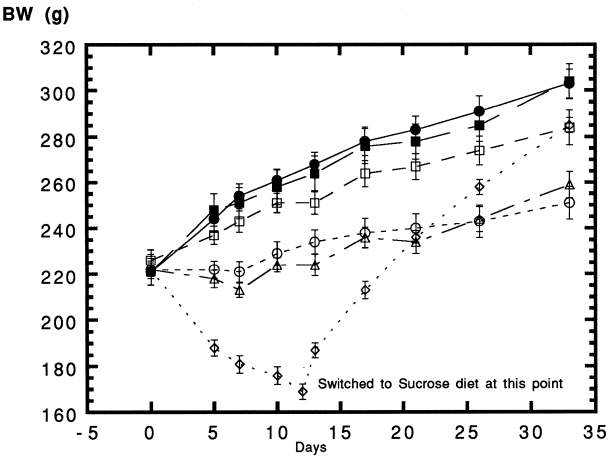

Fig. 4. Study #2. Mean±SEM for BW of eight SHR in six dietary groups is depicted. Symbols representing different dietary groups are as follows: closed circles-Starch, closed squares-Sucrose, open squares-Sucrose+BMOV 0.01, open circles-Sucrose+BMOV 0.03, open diamonds-Sucrose+BMOV 0.06, and open triangles-Sucrose+Vanadyl Sulfate 0.06.

SBP (Fig. 5). Addition of BMOV at various concentrations or vanadyl sulfate resulted in a lowering of SBP in these

Table 2. Blood Chemistries

Parameter	Sta	Suc	CP	BMOV	GS
HbA1C	5.0±.07	4.8±.03	4.8±.08	4.2±.08	5.0±.13
Glu	162±3.4	111±17(1)	136±14.1	56±3.5(1,2,3)	114±9.7(1,4)
Insulin	2.6±0.2	2.7±0.2	1.9±0.2(1,2)	0.7±0.1(1,2,3)	2.4±0.4(4)
Cholesterol	80±3.2	109±5.7(1)	101±2.7(1)	112±3.1(1)	92±4.4(1,2,4)
Triglycerides	63±9.9	139±12.1(1)	223±24	70±7.2(2,3)	165±11.4(1,3)
BUN	17±0.5	18±0.5	20±1.4	26±1.1(1,2,3)	17±0.8(4)
Creatinine	.66±.03	.60±.03	.77±.04(2)	.77±.06(2)	.67±.04
Uric Acid	3.5±0.8	4.0±0.9	3.9±0.3	4.8±0.1(1,2,3)	3.4±0.1(4)

Mean±SEM of six SHR.

Numbers in parentheses indicate significant difference from that column.

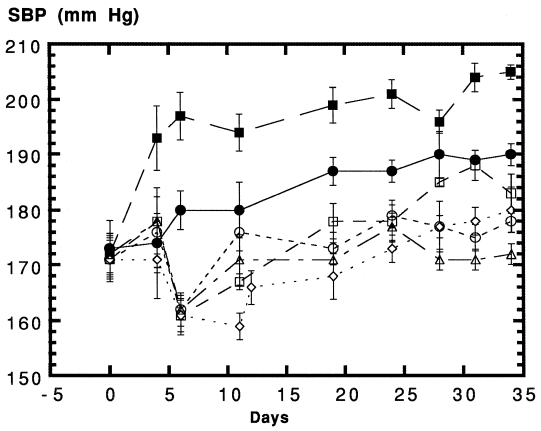

Fig. 5. Study #2. Mean±SEM of SBP of eight SHR is depicted. Symbols representing different dietary groups are as follows: closed circles-Starch, closed squares-Sucrose, open squares-Sucrose+BMOV 0.01, open circles-Sucrose+BMOV 0.03, open diamond-Sucrose+BMOV 0.06, and open triangle-Sucrose+Vanadyl Sulfate 0.06.

sucrose eaters. Despite the switch to a basal sucrose diet after 2 weeks in the group originally consuming the diet containing 0.06% BMOV, SBP remained lower than the starch control group over the duration of study.

Blood Chemistries (Table 3). When consuming BMOV and vanadyl sulfate, circulating insulin and glucose levels tended to be lower. However, differences were statistically significant only in the group receiving the mid range dose of BMOV (0.03) for both. Blood glucose was statistically significantly lower in the group ingesting the lowest dose of BMOV ($p<0.01$). In explaining results, it is important to reemphasize that the BMOV group receiving the highest challenge ($p<0.06$) had consumed regular diet for 2 weeks, i.e., prior to blood drawing. Glucose and insulin levels were not significantly different in the vanadyl sulfate group compared to the basal sucrose eaters.

DISCUSSION

Since the discovery that increasing dietary concentrations of sugars (sucrose, fructose, and glucose) increase SBP of various rat strains significantly, many have studied sugar-induction in an attempt to understand the pathogenesis behind this model [7–9]. Perturbations in catecholamine metabolism [22–24], volume status [23], insulin regulation [6,9,10], a circulating digitalis-like factor [26], magnesium homeostasis [25,27], and the renin-angiotensin system [28] have all been associated with the rise in BP. None of these possibilities is mutually exclusive, because numerous examples exist in the literature to suggest multiple interactions among all these factors.

The role of the insulin system in regulating BP is receiving increased attention [1–5]. In a series of studies, Reaven's group implicated the insulin system in sugar-induced hypertension of rats based upon many accepted methods to evaluate glucose/insulin homeostasis [3,4,6], and the ability of exercise [9] and somatostatin [10] to overcome sugar-induced SBP elevations. More recently, the ability of soluble fiber [11], vanadium [12,13], chromium [14], metformin [15], and troglitazone [16] to overcome or, at least, ameliorate sugar-induced hypertension strengthens the "insulin theory" because each is known to influence the insulin system.

As a first approximation, we simultaneously compared the effects of three nutrients known to influence the insulin system on sugar-induced SBP elevations. Corroborating previous findings, chromium initially overcame the sucrose-induced elevation of SBP induced by dietary sucrose [14]. Although chromium polynicotinate overcame sucrose-induced SBP elevations for only 2 weeks, a previously published study showed that the same compound prevented sucrose induction for the duration of the studies [14]. Data from previous studies were examined to explain these differences (Fig. 6). The reason for the results in the present study most likely resides in the interplay between the negative effects of sucrose and the positive effects of chromium. Up to now, studies examining sucrose at concentrations providing 18% and 52% of calories and chromium at 5 ppm and 25 ppm have been carried out. Fortunately, we have examined all four possible variations as depicted in Fig. 6. Only the combination using the lowest chromium concentration (5 ppm) and the highest sucrose challenge (52% of calories) showed an inability to restrain sugar-induced SBP elevations during the course of study. Accordingly, both intake of sucrose and chromium must both be considered in planning future therapeutic approaches.

Table 3. Blood Chemistries

Parameter	Sta	Suc	BMOV.01	BMOV.03	BMOV.06	VdSO4
HbA1C	3.88±.07	3.63±.14	3.95±.21	4.05±.24	4.08±.16	4.21±.19
Glu	134±8.1	130±4.7	107±5.0*	111±3.8*	134±6.6	119±6.9
Insulin	2.8±.3	2.4±.3	1.9±.4	1.3±.3*	2.9±.2	2.0±.3
Cholesterol	104±3.9*	86±2.5	84±2.0	113±2.5*	59±1.6*	64±2.1*
Triglycerides	184±17*	272±16	358±23*	274±28	155±6*	276±26
Creatinine	.55±.01	.60±.05	.53±.07	.66±.04	.50±.01	.58±.04
Uric Acid	2.1±.12	1.8±.05	1.9±.11	2.1±.18	2.1±.13	1.9±.09

Means±SEM for eight SHR are shown.

* Significant difference from column 2.

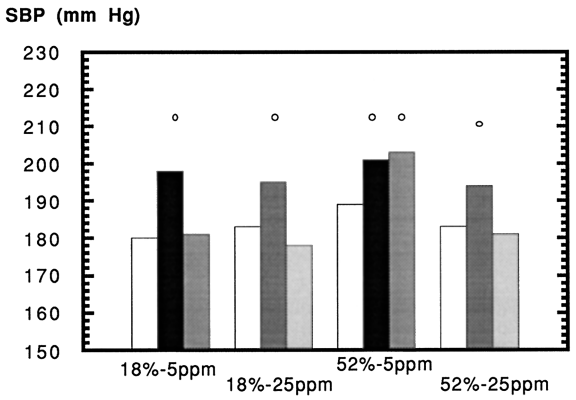

Fig. 6. Data were used from four separate studies performed over 2 to 3 months. The third set of bars depict data from present study. First white bar depicts SBP of rats receiving all carbohydrate calories from starch (52%). Second dark gray bar depicts diets containing either sucrose (52%) or sucrose (18%)—starch (34%). Third light gray bar depicts same second diet plus chromium polynicotinate at the concentration indicated below figure. Percent under bars signifies percent of calories derived from carbohydrate in second and third diets, either 18% from sucrose with rest made up by starch or sucrose 52%. PPM under bars indicates concentration of chromium polynicotinate added to sucrose diets signified by last gray bar. Circle above bar indicates statistical significance vs. first bar (starch) in each set.

The exact mechanisms behind their effects on the insulin system are uncertain; but it is likely that chromium, vanadium, and *G. sylvestre* influence insulin metabolism differently. While the exact mechanism of action for chromium is not known, it has been shown to have an effect on insulin receptor number [29]. Although having multiple effects on electrolyte transport [30], vanadium has been described as an insulin mimic with the ability to bypass the insulin receptor [31]. *G. sylvestre* may rejuvenate beta cells in the pancreas and increase insulin output [17].

How do these three agents influence the glucose/insulin system and/or intermediary metabolism in general in the present study? Examining various blood parameters, circulating insulin decreased with chromium polynicotinate, but glucose concentrations did not. BMOV decreased both glucose and insulin levels, while *G. sylvestre* did not change these levels compared to the basic sugar eaters. Evidence of effect can also be inferred from examination of oxidative metabolism. Insulin resistance is associated with augmented lipid peroxidation and free radical formation which may have some role in elevating BP [32]. We know this through our examination of TBARS. Formation of TBARS is an indirect estimate of lipid peroxidation and free radical formation, and increased formation of TBARS is associated with insulin perturbations [33,34]. Compared to starch eaters, sugar eaters showed increased TBARS formation in hepatic tissue but not renal tissue (Fig. 3). Chromium and BMOV supplementation prevented this increase in the liver, and chromium caused a significantly lower level of renal TBARS formation when compared to sucrose eaters. *G. sylvestre* produced no significant differences in these parameters but did lower cholesterol suggesting some effects on metabolism. Thus, the effects of chromium and vanadium compounds on glucose and insulin values and free radicals is also consistent with an effect of these agents on glucose/insulin metabolism and offers yet another explanation for the lowering of SBP in SHR.

Certain antioxidants appear to decrease blood pressure [32]. Many papers have shown antihypertensive effects with vitamin C [37–40], selenium [41], coenzyme Q10 [42], and nicotineamide adenine dinucleotide (NADH) [43]. Oxygen derived free radical are responsible for faster degradation of nitric oxide, an endothelial derived vasodilator. Accordingly, it has been proposed that and an imbalance in nitric oxide (NO) contributes to the development of arterial hypertension [44]. The antihypertensive effects of antioxidants may occur through protection of NO, a powerful vasodilator [45,46].

BMOV and vanadyl sulfate added to the basic diet at higher concentrations caused a loss of BW. By observation, it was apparent that rats consuming high amounts of BMOV ate less food and drank less water. This state was reversed when the rats were switched to diets devoid of BMOV. Could this decreased weight be responsible for the lowering of BP? We believe that weight loss is not a major factor for many reasons. First, BW changes have never been shown to play a significant role in the sugar-induction model of hypertension [6–11]. Second, when vanadium diets were changed to regular diets, rats on the latter gained weight; but the SBP still remained lower. Third, Bhanot and McNeill [47] noted that vanadium decreased BW while lowering SBP; but pair feeding showed that SBP was reduced by vanadium compared to SHR at the same BW. Finally, the second study was specifically designed to determine if the effects of vanadium on SBP were secondary to weight loss. At the lower concentrations of BMOV (0.1%), the significant decrease in SBP occurred, even though there was no significant loss of BW compared to control, at least in the early phases of study.

Of interest is the finding that *G. sylvestre* actually caused a significant elevation of SBP at certain times. We believe that the different response from chromium polynicotinate and BMOV may relate to mechanism of action, i.e., that *G. sylvestre* stimulates insulin release rather than improving insulin sensitivity [48–50]. Standardized extract of the herb has been reported to have hypoglycemic activity equivalent to tolbutamide.

In summary, the present studies show that some agents affecting the glucose/insulin system can favorably lower BP. Chromium and vanadium have additional benefits on TBARS formation suggesting they may lessen free radical formation. No direct evidence was obtained to indicate that *G. sylvestre* lowers SBP or influences glucose/insulin metabolism. Accordingly, agents that decrease circulating insulin levels, perhaps by augmenting insulin sensitivity, may prove useful in the treatment of high blood pressure.

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