Original Research

Whole Cinnamon and Aqueous Extracts Ameliorate Sucrose-Induced Blood Pressure Elevations in Spontaneously Hypertensive Rats

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Key words: cinnamon, blood pressure, insulin, triglycerides

Objective: Many agents (nutrients, nutraceuticals, and drugs) that enhance insulin sensitivity and/or reduce circulating insulin concentrations lower blood pressure (BP). Recently, it was reported that cinnamon has the potential to favorably influence the glucose/insulin system. Accordingly, the purpose of the present study was to examine the effects of dietary cinnamon on systolic BP (SBP), and various glucose- and insulin-related parameters in spontaneously hypertensive rats (SHR).

Methods: In a series of three experiments, treated SHR eating sucrose and non sucrose containing diets were given various amounts of cinnamon, cinnamon extracts, or chromium. Then various parameters such as: body weight, systolic blood pressure, hematology and blood chemistries were followed for three to four weeks.

Results: Diets high in sucrose content are associated with insulin resistance and the elevation of SBP. Addition to diets of cinnamon (8% w/w) reduced the SBP of rats eating sucrose containing diets to virtually the same levels as SHR consuming non sucrose containing (only starch) diets. The presence of cinnamon in the diet also decreased the SBP of SHR consuming a non sucrose-containing diet, suggesting that cinnamon reduces more than just sucrose-induced SBP elevations—perhaps a genetic component(s) of the elevated BP as well. The effects of cinnamon on SBP tended to be dose-dependent. Cinnamon did not decrease the levels of blood glucose, but did lower circulating insulin concentrations. Aqueous extracts of cinnamon also decreased SBP and lowered the circulating levels of fructosamine.

Conclusions: Cinnamon is used for flavor and taste in food preparation, but cinnamon may have additional roles in glucose metabolism and BP regulation. Therefore, BP regulation may not only be influenced favorably by limiting the amounts of dietary substances that have negative effects on BP and insulin function but also by the addition of beneficial ones, such as cinnamon, that have positive effects.

INTRODUCTION

Hypertension, insulin resistance, and hyperinsulinemia develop in some rat strains fed high concentrations of simple sugars such as sucrose or fructose [1–4]. This model of sugar-induced hypertension and insulin resistance may be clinically relevant, because a cause-effect relationship between insulin perturbations (insulin resistance/hyperinsulinemia) and many hormonal disturbances capable of elevating blood pressure (BP) has been demonstrated [5,6]. Also, many clinical reports closely associate diabetes, insulin resistance, and hypertension [7–11]. In contrast, many agents augmenting insulin sensitivity and/or reducing circulating insulin concentrations have been linked to lower BP in rats consuming high levels of sugars. The enhancing agents include somatostatin [12], soluble fibers [13,14], vanadium [15,16], chromium [17], metformin [18], and troglitazone [19]. Recently, it was reported that cinnamon has the potential to favorably influence the insulin system [20,21] and had beneficial effects on blood glucose, cholesterol and triglycerides of people with type 2 diabetes [22]. The purpose of the present study was to examine the effects of cinnamon on various perturbed parameters noted in Spontaneously Hypertensive Rats (SHR) consuming sucrose, especially focusing on elevated systolic BP (SBP).

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Journal of the American College of Nutrition, Vol. 25, No. 2, 144–150 (2006)
Published by the American College of Nutrition

MATERIAL AND METHODS

One hundred sixteen male Spontaneously Hypertensive Rats (SHR) of the Okamoto strain [23], weighing 150–200 g, were obtained from Taconic Farms, Germantown, NY for three separate studies. Previous investigations have shown that SHR are sensitive to sucrose-induced SBP elevations [1].

Two diets were used (Table 1)—one composed of cornstarch as the sole carbohydrate source (52.1% of calories) and referred to as the Starch Diet; and the second referred to as the Sucrose Diet contained a combination of starch (33.8% of calories) and sucrose (18.3% of calories). Accordingly, 52.1% of all calories were derived from carbohydrates in both basic diets. The remaining constituents with the exception of the ingredients under study were similar in the Starch and Sucrose Diets.

To make the extracts, Cinnamomum burmannii, (McCormick & Company, Inc., Hunt Valley, MD) was suspended in 20 volumes of 0.1 acetic acid and autoclaved for 15 minutes, centrifuged at 1200 g for 25 minutes and freeze-dried. A portion of the sample was treated similarly except it was adjusted to pH 9 with concentrated ammonium hydroxide prior to freeze-drying. For clarity, we refer to the latter as the "treated extract." Extracts were added to the diet at 0.8% w/w. This is roughly the amount of water-soluble material that would be present in a diet containing 4.0% w/w cinnamon.

In the first study, after two of weeks of acclimatization to regular laboratory chow, four groups of six rats were provided four different diets for three to four weeks. The first and second diets derived 52% of calories from cornstarch, and the third and fourth diets replaced some starch with sucrose that provided 18% of calories (Table 1). Minerals and vitamins were included at American Institute of Nutrition (AIN) levels [24]. Cinnamon was added to the second and fourth diets at a concentration of 8.0% w/w. The latter replaced all the cellulose and a small fraction of starch—constituents shown previously to have little influence on SBP in this model [14].

The second study was designed to examine a dose-response of cinnamon on SBP using 40 SHR. After two to three weeks of acclimatization to regular laboratory chow, rats were provided one of the five special diets for four weeks. All the diets in the second study replaced some starch with sucrose to provide 18% of calories (Table 1). Cinnamon was added at 0, 1.0, 2.0, 4.0, and 8.0% w/w. Cinnamon replaced some or all the cellulose, and in the case of 8% w/w cinnamon a small fraction of starch as well.

The third study consisted of seven groups of eight SHR raised on the basic diets depicted in Table 1. The major purpose of this last experiment was to compare the effects of cinnamon extracts against whole cinnamon. The seven groups consisted of a starch control, a sucrose control, and sucrose-eating groups receiving whole cinnamon at 2.0% w/w and 6.0% w/w, a cinnamon extract at 0.8% w/w, a treated cinnamon extract at 0.8% w/w that was adjusted to pH 9 prior to freeze-drying, and finally a chromium group. The concentrations of cinnamon extracts were calculated to fall somewhere between the 2% and 6% concentrations of whole cinnamon powder. The last group received chromium histidinate (2 ppm) for comparative purposes. As in previous studies, body weight and SBP were followed. Circulating glucose, cholesterol, HDL, triglycerides and fructosamine concentrations were measured.

SBP

SBP was estimated by tail plethysmography in unanesthetized rats after a warming period [25]. Readings were taken

Table 1. Two Diets

Basic Diets	Starch Diet		Sucrose-Starch Diet	
Ingredients	% by Weight	% of Calories	% by Weight	% of Calories
Sucrose			20.00	18.3
Cornstarch	57.00	52.1	37.00	33.8
(Common components in each diet)	% by weight		% of Calories	
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*			

* Replace some or all cellulose with 2%, 4%, 6%, and 8% w/w cinnamon.

For the 8%, replace some cornstarch as well.

The diet has been made up under the direction of Dr. Richard Anderson of the USDA at his facility in Beltsville MD.

The food has been maintained at −2° and −4°c.

0.5–1 minute apart. To be accepted, SBP measurements had to be virtually stable for at least 3 consecutive readings. Measurements were made weekly.

Blood Chemistry

Blood was obtained at the end of each experiment following removal of food for 4 hours. Blood was drawn, and rats were sacrificed by inhalation of a high level of CO_2. Fructosamine was measured by using a GlucoProtein™ test strip from the LXN Corporation, San Diego, CA. Immunoreactive insulin was determined by radioimmunoassay (Linco Research Laboratories, St Louis, MO) and glycosylated hemoglobin (HBA1C) by column chromatography (Isolab Inc, Akron, OH). The remaining chemical analyses were performed by routine clinical procedures.

Statistical Analyses

Results are presented as mean ± SEM. Statistics on blood chemistries were performed by a one-way analysis of variance (ANOVA). SBP and body weight (BW) were examined by two-way analysis 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 ($p < 0.05$) [26].

RESULTS

Experiment 1

After three weeks, SHR ingesting the diet deriving 18% of calories from sucrose had gained more body weight than SHR ingesting the pure starch diet, i.e., the absence of sucrose (Fig. 1A). We will refer to the SHR consuming starch as the only carbohydrate (CHO) source as the "starch" group, while SHR consuming starch/sucrose combination will be referred to as the "sucrose" group. Relative to SHR ingesting only starch, SBP of SHR ingesting the sucrose-containing diet showed a significant elevation of SBP after 22 and 25 days (Fig. 1B). Addition of cinnamon to either the starch or sucrose diets caused a significantly lower SBP in their respective dietary group from the first week on. Ingestion of cinnamon resulted in no statistical changes in circulating glucose and HbA1C levels (Table 2), although the sucrose group tended to have a higher average level of HbA1C.

Experiment 2

SHR consuming a diet composed of 8% w/w cinnamon again had decreased body weight compared to control (Fig. 2). Although SHR consuming 1.0, 2.0, and 4.0% w/w cinnamon tended to gain less weight than control, these differences were not statistically different. The studies on SBP are depicted in Fig. 3. At 1 and 2% w/w levels of cinnamon, the SBP were significantly lower than control by the fourth week. At 4 and 8% w/w, the significant changes in SBP occurred by the second week. SHR consuming cinnamon compared to control had the following significant mean differences at the end of study: 1% w/w −9 mm Hg, 2% w/w −10 mm Hg, 4% w/w −10 mm Hg, and −13 mm Hg at 8% w/w. After 4 weeks, the circulating

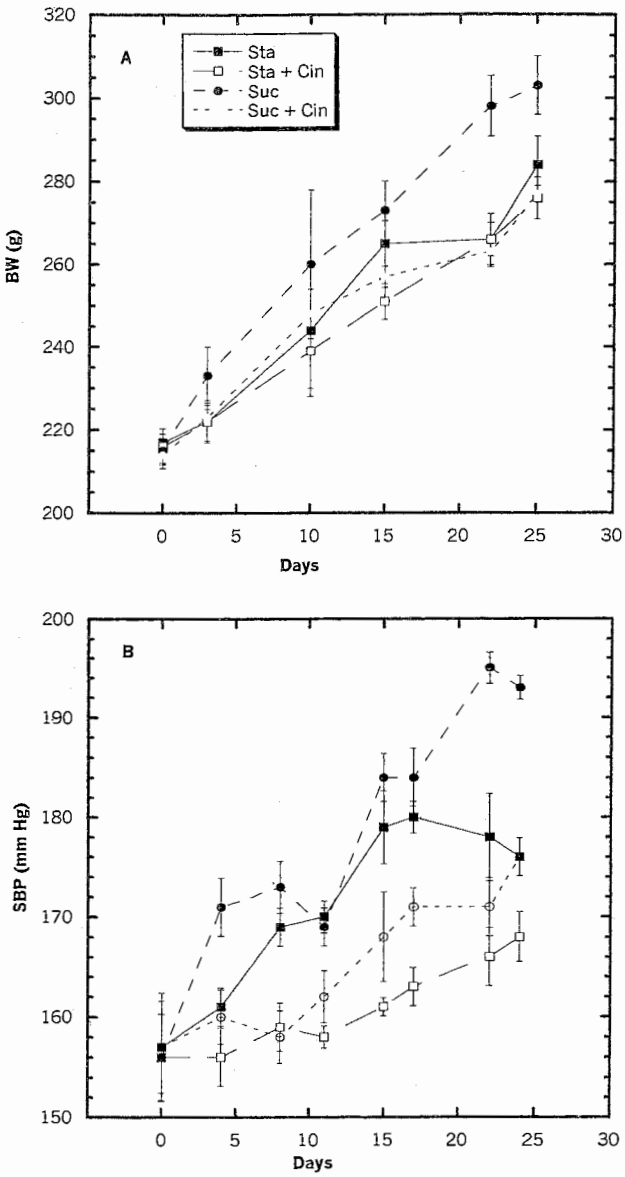

Fig. 1. Body weights and SBP of SHR (Expt 1). See figure insert for group designation. Top figure A depicts body weight (BW) of 4 groups eating sucrose/starch or starch diets with and without the addition of 8% w/w cinnamon. Bottom figure B depicts SBP of 4 groups of six SHR each eating sucrose/starch or starch diets with and without the addition of 8% w/w cinnamon. Means ± SEM are shown. Regarding values for BW and SBP, the average of sugar-eating group is significantly different from other three groups for the last two readings.

Table 2. Blood Chemistries (Expt 1)

Parameter	Sta	Sta-Cin	Suc	Suc + Cin
Glucose	129 ± 4.1	130 ± 2.8	137 ± 4.2	131 ± 3.4
HbA1C	5.9 ± 0.3	5.8 ± 0.2	6.4 ± 0.5	5.6 ± 0.2

Mean ± SEM is shown for 5 rats in each group.
There are no statistically significant differences among the values.
Cin = cinnamon, Sta = starch, Suc = sucrose.

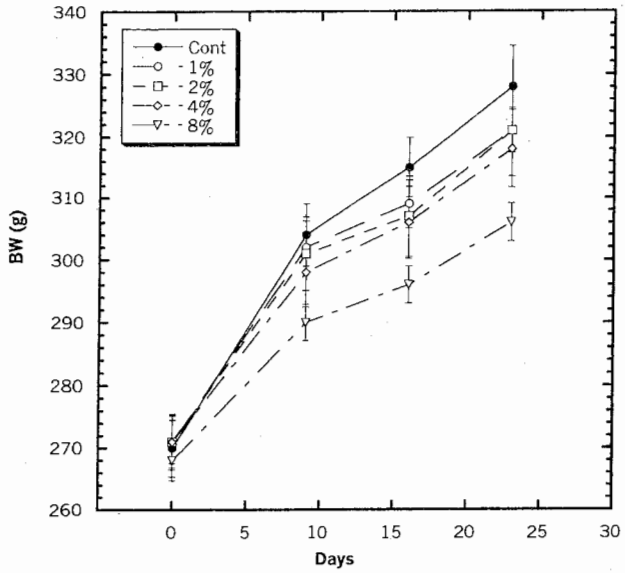

Fig. 2. Body weights of SHR consuming different levels of cinnamon (Expt 2). See figure insert for details. Groups of 8 SHR were examined. Means ± SEM are depicted. Values for the group receiving 8% cinnamon are statistically different from Control.

concentrations of insulin decreased significantly at the 2, 4, and 8% w/w concentrations of cinnamon (Table 3). Although the HbA1C levels were lower compared to control at the 2%, 4% and 8% w/w concentrations of cinnamon, these values did not attain statistical significance.

Experiment 3

At the end of the four-week study, there were no statistically significant differences in the average body weights among the control and test dietary groups (Fig. 4). As in previous studies, the addition of sucrose to replace some starch caused a significant mean elevation in SBP – seven mm Hg (Fig. 5). However, the addition of 2 and 6% w/w cinnamon, the regular extract and the treated extract adjusted to pH 9 prevented this significant elevation of SBP associated with sucrose eating. The treated extract was adjusted to pH 9, since *in vitro* insulin-potentiating activity is higher in these extracts compared to the unadjusted extracts. Those consuming chromium histidinate with the sucrose had lower average SBP than the sucrose control. Among the seven dietary groups, circulating glucose was not statistically different (Table 4). Although the whole

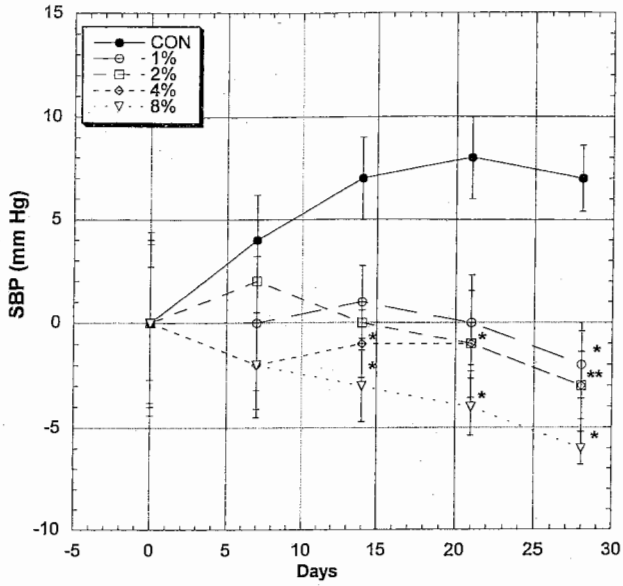

Fig. 3. Change from baseline SBP of SHR consuming different levels of cinnamon (Exp 2). See figure inserts for details. Groups of 8 SHR were examined. Means ± SEM are depicted. Star by each value indicates statistically significant difference from Control.

Table 3. Blood Chemistries (Expt 2)

Group	Circulating Insulin (ng/ml)	HbA1C (%)
0%	2.8 ± 0.3	5.4 ± 0.1
1%	3.1 ± 0.4	5.4 ± 0.1
2%	1.8 ± 0.3*	5.1 ± 0.2
4%	2.2 ± 0.3*	5.2 ± 0.1
8%	2.0 ± 0.2*	5.3 ± 0.1

* Statistically significant.
Groups are distinguished by the amount of cinnamon in the diet (w/w).

cinnamon groups were not different from control in the levels of circulating fructosamine, the two extracts and the chromium compound were associated with significantly lower levels compared to the sucrose-eating control group. HDL and triglyceride concentrations were significantly lower only in the chromium group.

DISCUSSION

Many commonly ingested nutrients or dietary elements known to augment insulin resistance are also associated with elevated BP, e.g., fatty acids [27,28] and sugars [29,30]. In contrast, dietary factors generally accepted to enhance insulin sensitivity such as soluble fibers [13,14,31], chromium [17,32], and vanadium [15,16] are associated with lower BP. In corroboration of the correlation between glucose/insulin metabolism and BP regulation, certain drugs, such as metformin [18] and troglitazone [19], and exercise [4], which all augment insulin sensitivity, are also recognized to lower blood pressure. All this

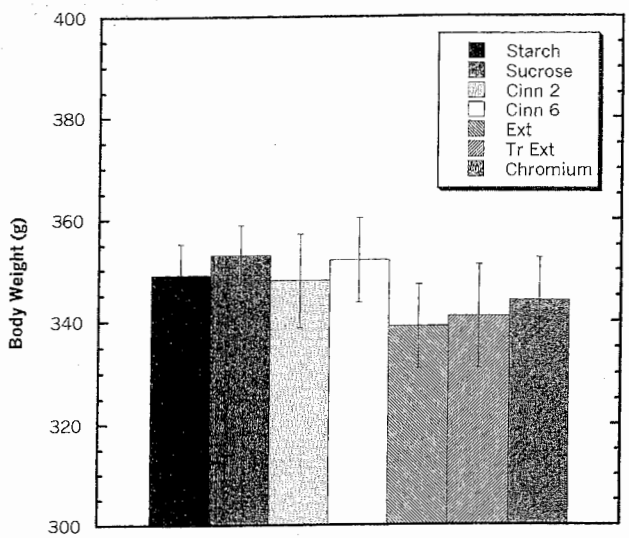

Fig. 4. Body weights of SHR at completion of study (Exp 3). See figure insert for details. Groups of 8 SHR were examined. Means ± SEM are depicted. No values for any group receiving cinnamon are statistically different from other groups.

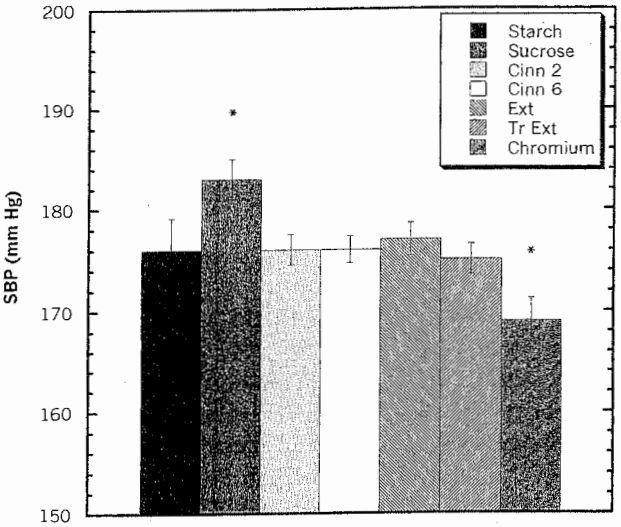

Fig. 5. SBP of SHR at completion of study (Exp 3). See figure insert for details. Groups of 8 SHR were examined. Means ± SEM are depicted. SBP for Sucrose group is statistically higher than the Starch group, however, the mean SBP of the other sucrose-eating groups also consuming cinnamon, extracts, or chromium are not.

suggests that perturbed glucose/insulin metabolism is directly or indirectly involved, at least to some extent, in some forms of hypertension. The studies showing that chromium is associated with decreased BP are especially of interest. Chromium supplementation has few known effects independent of those on insulin metabolism [32].

Cinnamon, cinnamon extracts, and various selected foods and spices are reported to favorably influence the insulin system [20,21,31,33–38]. Based on the correlation between insulin metabolism and BP regulation, we examined the ability of cinnamon to influence SBP of spontaneously hypertensive rats (SHR) with SBP raised even higher by the presence of a moderate amount of sucrose in the diet. Sucrose at 18% of calories resembles the average sugar content in the American diet [39,40]. As expected, this small concentration increased SBP, albeit delayed for approximately three weeks. Had we added more sucrose to the diet, we might have expected a faster onset of the sucrose-induced SBP rise [14]. This sucrose-induced SBP elevation has been associated with development of insulin resistance and/or hyperinsulinemia, based on various means to assess the insulin system [4]. The ability of chromium supplementation to overcome sucrose-induced blood pressure elevations and ameliorate insulin resistance provides more proof of this association [17].

In all three experiments of the present investigation, addition of dietary cinnamon consistently decreased SBP of SHR. However, more than just the reduction in sucrose-induced BP elevations was involved. The reduction in SBP caused by cinnamon consumption took place even in the starch group of the first experiment. Also in the first experiment, sugar-eating rats compared to the other three groups gained more body weight, which could have contributed to discrepancies in BP. Still, body weight changes cannot be fully explanatory, because in the two starch-eating groups a significant decrease in SBP occurred when cinnamon was added to the all starch diet, despite essentially no significant changes in body weight. Since the presence of cinnamon in the diet also decreased SBP of the SHR consuming no sucrose, this suggests that a component(s) of the genetic hypertension was influenced in addition to the sucrose-induced elevations in the other groups. Although rats consuming 8% w/w cinnamon in the second experiment again showed a significantly decreased body weight relative to control, no statistically significant changes in body weight occurred when control was compared to SHR consuming 1%, 2%, and 4% w/w cinnamon in their diets. Suffice it to say, a significant decrease in SBP did take place at these lower concentrations despite little difference in body weight changes from control. Although the trend was for a greater decrease in SBP with increasing dietary content of cinnamon, the differences among the cinnamon groups were not statistically different from one another. As final corroboration, the changes in SBP in the final third experiment were not associated with significant changes in body weight.

In the last study, the two extracts examined were associated with decreased circulating fructosamine levels. In the first two studies, the decreases in HbA1C were not significantly lower, perhaps due to the short duration of use. Using fructosamine, an earlier marker of glycosylation, as a marker instead of HbA1C would overcome this problem, at least to some extent. The lowering of circulating insulin levels in the face of little change in blood glucose concentrations by various doses of cinnamon in the second experiment would support an effect of the spice on insulin sensitivity. Effects of cinnamon on other possible

guar on sugar-induced hypertension in rats. Clin Neph 44:170–177, 1995.
18. Verma S, Bhanot S, McNeill JH: Antihypertensive effects of metformin in fructose-fed hyperinsulinemic, hypertensive rats. JPET 271:1334–1337, 1994.
19. Lee M-K, Miles PDG, Khoursheed M, Gao K-M, Moossa AR, Olefsky JM: Metabolic effects of troglitazone on fructose-induced insulin resistance in the rat. Diabetes 43:1435–1439, 1994.
20. Khan A, Bryden NA, Polansky MM, Anderson RA: Insulin potentiating factor and chromium content of selected foods and spices. Biol Trace Element Res 24:183–188, 1990.
21. Berrio LF, Polansky MM, Anderson RA: Insulin activity: stimulatory effects of cinnamon and Brewer's yeast as influenced by albumin. Horm Res 37:225–229, 1992.
22. Khan A, Safdar M, Ali Khan MM, Khatta KN, Anderson RA: Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care 26:3215–3218, 2003.
23. Okamoto K, Aoki K: Development of a strain of spontaneously hypertensive rat. Jap Circ J: 27:282–293, 1963.
24. Reeves PG, Nielsen FH, Fahey GC Jr: AIN-93 purified diets for laboratory rodents: final report of the American Institute of Nutrition *ad hoc* writing committee on the reformulation of the AIN 76A rodent diet. J Nutr 123:1931–1951, 1993.
25. Bunag RD: Validation in awake rats of a tail-cuff method measuring systolic pressure. J Appl Physiol 34:279–282, 1973.
26. Dunnett C: A multiple comparison procedure for comparing several treatments with control. J Am Statis Assoc 50:1096–1121, 1955.
27. Appel LJ, Miller ER, Seidler AJ, Whelton PK: Does supplementation of diet with "fish oil" reduce blood pressure? A meta-analysis of controlled clinical trials. Arch Intern Med 153:1429–1438, 1993.
28. Kraegen EW, Clark PW, Jenkins AB, Daley EA, Chrisholm DJ, Storlien LH: Development of muscle insulin resistance in high-fat-fed rats. Diabetes 40:1397–1403, 1991.
29. Yudkin J: Sucrose, coronary heart disease, diabetes, and obesity: do hormones provide a link? Am Heart J 115:493–498, 1988.
30. Israel KD, Michaelis OE, Reiser S, Keeney M: Serum uric acid, inorganic phosphorus, and glutamic-oxalacetic transaminase and blood pressure in carbohydrate-sensitive adults consuming three different levels of sucrose. Ann Nutr Metab 27:425–435, 1983.
31. Wright A, Burstyn PG, Gibney MJ: Dietary fibre and blood pressure. Br Med J 2:1541–1543, 1979.
32. Mertz W: Chromium in human nutrition. J Nutr 123:626–633, 1993.
33. Broadhurst CL, Polansky MM, Anderson RA: Insulin-like biological activity of culinary and medicinal plant aqueous extracts in vitro. J Agric Food Chem 48:849–852, 2000.
34. Imparl-Radosevich J, Deas S, Polansky MM, Baedke DA, Ingebritsen TS, Anderson RA, Graves DJ: Regulation of PTP-1 and insulin receptor kinase by fractions from cinnamon: implications for cinnamon regulation of insulin signaling. Horm Res 50:177–182, 1998.
35. Jarvill-Taylor KJ, Anderson RA, Graves DJ: A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. J Am Coll Nutr 20:327–336, 2001.
36. Qin B, Nagasaki M, Ren M, Bajotto G, Oshida Y, Sato Y: Cinnamon extract (traditional herb) potentiates in vivo insulin-regulated glucose utilization via enhancing insulin signaling in rats. Diabetes Res Clin Pract 62:139–148, 2003.
37. Anderson RA, Broadhurst CL, Polansky MM, Schmidt WF, Khan A, Flanagan VP, Schoene NW, Graves DJ: Isolation and characterization of polyphenol type-A polymers from cinnamon with insulin-like biological activity. J Agric Food Chem 52:65–70, 2004.
38. Qin B, Nagasaki M, Ren M, Bajotto G, Oshida Y, Sato Y: Cinnamon extract prevents the insulin resistance induced by a high-fructose diet. Horm Res 36:119–125, 2004.
39. Wotecki CE, Welsh SO, Rapern: Recent trends and levels of dietary sugar and other caloric sweeteners. In Reiser S, (ed): "Metabolic Effects of Utilizable Dietary CHO." New York: Dekkar, 1981.
40. Benson S: Has sugar too many lumps? Health 5:20–22, 1991.
41. Fournier RD, Chiueh CC, Kopin IJ, Knapka JJ, DiPetti D, Preuss HG: The interrelationship between excess CHO ingestion, blood pressure and catecholamine excretion in SHR and WKY. Am J Physiol 250:E381–385, 1986.
42. Balon TW, Jasman A, Scott S, Meehan WP, Rude RK, Nadler JL: Dietary magnesium prevents fructose-induced insulin sensitivity in rats. Hypertension 23 (Part 2), 1036–1039, 1994.
43. Gharib N, Gao CY, Areas J, Zein M, Preuss HG: Correlation of organic anion and cation transport with blood pressure. Clin Nephrol 36:87–92, 1991.
44. Iyer SN, Katovich MJ: Effects of chronic Losartan Potassium treatment on fructose-induced hypertension. Life Sci 55:130–134, 1994.

Received August 15, 2005, revision accepted February 21, 2006.