Somatostatin Inhibition of Fructose-Induced Hypertension

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The role of insulin resistance and hyperinsulinemia in the etiology of fructose-induced hypertension was studied in male Sprague-Dawley rats. Rats consumed a fructose-enriched diet (containing 66% of total calories as fructose) for 11 days and were infused continuously during the last 7 days with either a somatostatin analogue or vehicle. At the end of this period, rats receiving the somatostatin analogue had a lower plasma insulin concentration (52±4 vs. 70±6 μunits/ml, p<0.01) and a lower blood pressure (133±2 vs. 150±2 mm Hg) than did the rats infused with the control solution. In addition, the increase in plasma triglyceride concentration in response to the fructose-enriched diet was significantly attenuated (p<0.001) in the rats infused with somatostatin. These data provide further support that the increase in blood pressure that occurs when normal rats are fed a high fructose diet is dependent on the ability of this intervention to cause insulin resistance and hyperinsulinemia. (Hypertension 1989;14:117-120)

We have recently speculated that resistance to insulin-stimulated glucose uptake and hyperinsulinemia are involved in the etiology of hypertension. To a large extent, this hypothesis was based on observations that patients with hypertension, as a group, are hyperinsulinemic, and the hyperinsulinemia appears to be associated with resistance to insulin-stimulated glucose uptake.

Sprague-Dawley rats become insulin resistant, hyperinsulinemic, and hypertriglyceridemic when fed a fructose-enriched diet, and the fact that this dietary manipulation also leads to an increase in blood pressure lends further support to the possibility that insulin resistance and hyperinsulinemia may play a role in the genesis of high blood pressure. Furthermore, we have shown that exercise training of rats, which enhances insulin sensitivity and reduces fructose-induced hyperinsulinemia, also attenuates the increase in blood pressure seen in fructose-fed rats.

The present experiments were initiated to further study the relation between insulin-resistance, hyperinsulinemia, and hypertension in fructose-fed rats and were based on the use of somatostatin to suppress insulin secretion by β cells in pancreatic islets. We reasoned that the infusion of somatostatin would suppress the hyperinsulinemia that normally results when rats are fed a fructose-enriched diet, and if elevated plasma insulin concentrations play a role in fructose-induced hypertension, this intervention would also ameliorate the rise in blood pressure that occurs when rats eat a high fructose diet. The results indicated that this prediction was borne out, providing further support for the view that insulin plays a role in the regulation of blood pressure in rats with fructose-induced hypertension.

Materials and Methods

General Protocol

Male Sprague-Dawley rats (Simonsen Laboratories, Gilroy, California), initially weighing 160–180 g, were used for all experiments. Before dietary manipulation, all rats were fed standard rat chow (Wayne Lab Blox, Allied Mills, Chicago, Illinois) containing 60% vegetable starch, 11% fat, and 29% protein and were maintained on a 12-hour light/dark (6:00 AM–6:00 PM) cycle. In addition, rats were acclimated to the procedure of blood pressure measurement at 1:00 PM daily for 1 week. After the training period, rats were fed with a diet containing 66% fructose, 12% fat, and 22% protein (Teklad Test Diets, Madison, Wisconsin). Four days later Alza minipumps containing either a somatostatin analogue (dissolved in 0.9% saline) or 0.9% NaCl were placed in all rats. The somatostatin analogue was infused at a rate of 10 μg/kg/hr for 7 days into
14 rats, and an equal volume of NaCl was administered to the 14 control rats. Rats continued to eat the fructose-enriched diet for the entire 11-day experimental period. Although the rate of weight gain during the 11-day experimental period was somewhat lower in somatostatin-infused (235±5 to 261±6 g) as compared with NaCl-infused rats (240±4 to 275±6 g), the difference was not statistically significant.

**Blood Pressure Measurement**

Rats were removed from the animal room and taken to the laboratory at 9:00 AM; they were allowed free access to diet and water and were kept in a quiet area before the blood pressure was measured at 1:00 PM. The tail-cuff method, without external preheating, was used to measure the systolic blood pressure. Ambient temperature was kept at 30°C. The equipment used included magnetic animal holders connected with manual scanner (model 65-12, IITC, Inc., Woodland Hills, California), pulse amplifier (model 59, IITC, Inc.), and dual-channel recorder (model 1202, Linear Instrs. Corp., Reno, Nevada). The systolic blood pressure was measured in the conscious state and is similar to that obtained by direct arterial cannulation. The mean of five consecutive readings was used as the measurement of the systolic blood pressure of each rat for that day, and the average blood pressure was determined 2 days before starting the diet and every other day for the remainder of the experimental period.

**Biochemical Measurements**

Tail blood samples were taken at the beginning of each experiment and at various later times as indicated. The samples were centrifuged, aliquoted, frozen, and later assayed for insulin and triglyceride concentrations. Results are expressed as mean±SEM, and significance of differences between the two groups were estimated by two-way analysis of variance.

**Results**

The effect of the continuous somatostatin analogue infusion on plasma insulin concentrations in fructose-fed rats is illustrated in Figure 1. It is apparent that the expected fructose-induced increase in plasma insulin concentration was attenuated when fructose-fed rats were infused with somatostatin. At the end of the experiment, the plasma insulin concentration was 52±4 µunits/ml in the analogue-infused group versus 70±6 µunits/ml in the rats infused with vehicle (p<0.001).

The changes in blood pressure in the two experimental groups are shown in Figure 2. These data indicate that (mean±SEM) blood pressure increased from 132±2 to 150±2 mm Hg when fructose-fed rats were infused with vehicle (p<0.001). In marked contrast, blood pressure did not change (133±2 vs. 133±2 mm Hg) in response to the fructose-enriched diet when rats were infused with somatostatin.

**Discussion**

The present experiments were done to examine the possibility that the development of high blood pressure in fructose-fed rats is secondary to the insulin resistance and hyperinsulinemia associated with this dietary manipulation. To test this hypothesis, we attempted to suppress the hyperinsulin-
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somatostatin analogue (SMS) or NaCl was started at day 4, indicated by arrow, and continued for 1 week. n=14 rats in each group. Values are mean±SEM.

FIGURE 3. Line graph of plasma triglyceride (TG) concentration during 11-day experimental period. Fructose-enriched diet was started at time zero and was continued throughout entire study. Continuous infusion of either somatostatin analogue (SMS) or NaCl was started at day 150-

emia associated with feeding a fructose-enriched diet by the concomitant infusion of a somatostatin analogue. The results presented indicate that the somatostatin analogue successfully suppressed fructose-induced increased plasma insulin concentrations. In addition, the infusion markedly attenuated the rise in blood pressure ordinarily found in fructose-fed rats.

In view of our previous demonstration that fructose-induced hyperinsulinemia and hypertension was also reduced in exercise-trained rats, the current data provide further evidence that plasma insulin concentration is involved in blood pressure regulation. On the other hand, it is essential to emphasize that the effects of the somatostatin analogue may not be limited to suppression of insulin secretion. Of particular relevance in this regard is that there is some evidence that somatostatin can modify the renin-angiotension system in a manner that could lower blood pressure independent of any effect on the endocrine pancreas. To what extent, if any, the analogue used in our studies modifies the renin-angiotension system or other systems that regulate blood pressure is not known. To evaluate these other possibilities, more information is needed about the effect of a high fructose diet on a variety of issues, including sodium balance, aldosterone secretory status, and the renin-angiotension system. Until these studies are done, it is uncertain if any, the analogue used in our studies modifies the renin-angiotension system or other systems that could lower blood pressure independent of any effect on the endocrine pancreas. To what extent, if any, the analogue used in our studies modifies the renin-angiotension system or other systems that regulate blood pressure is not known. To evaluate these other possibilities, more information is needed about the effect of a high fructose diet on a variety of issues, including sodium balance, aldosterone secretory status, and the renin-angiotension system. Until these studies are done, it is uncertain if any, the analogue used in our studies modifies the renin-angiotension system or other systems that regulate blood pressure is not known. To evaluate these other possibilities, more information is needed about the effect of a high fructose diet on a variety of issues, including sodium balance, aldosterone secretory status, and the renin-angiotension system.

It is apparent that the present results do not prove that plasma insulin concentration plays a role in regulation of blood pressure. However, there are experimental data consistent with this possibility. For example, in human beings an acute increase in plasma insulin concentration leads to significant elevation in plasma catecholamine concentration, and this event is independent of any change in plasma glucose concentration. The potential importance of excessive activity of the sympathetic nervous system in the genesis of experimental hypertension has also been highlighted in sucrose-fed rats with spontaneous hypertension. Sucrose feeding enhances the activity of the sympathetic nervous system. Interestingly, insulin resistance and hyperinsulinemia also develop in sucrose-fed rats. In addition, insulin might act to modify blood pressure at the level of the kidney. Insulin can act on the isolated toad bladder, as well as in intact dog and humans to promote renal-tubular sodium reabsorption. Insulin also seems to act at the level of the proximal tubule to increase volume reabsorption. Thus, the responses of at least two systems to hyperinsulinemia would tend to increase blood pressure.

Finally, attention should also be focused on the ability of somatostatin to inhibit fructose-induced hypertriglyceridemia. We have previously postulated that the ability of either sucrose or fructose to produce an increase in plasma triglyceride concentration in normal, nonobese rats is secondary to the insulin resistance and hyperinsulinemia produced by this dietary intervention. The current results provide additional support for our view that hyperinsulinemia plays a central role in the phenomenon of carbohydrate-induced hypertriglyceridemia.

In conclusion, the hyperinsulinemia and hypertension that occur when rats eat a fructose-enriched diet are attenuated when a somatostatin analogue is also infused. These data provide additional support for the view that ambient plasma insulin concentrations may play a role in regulation of blood pressure in experimental hypertension.

Acknowledgment

The somatostatin analogue was kindly furnished as Sandostatin by Dr. Janos Pless, Pharma Division, Sandoz Pharmaceuticals Corporation, East Hanover, New Jersey.

References


**KEY WORDS** • fructose • somatostatin • hyperinsulinemia • insulin
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Hypertension. 1989;14:117-120
doi: 10.1161/01.HYP.14.2.117

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