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.

We have recently speculated that resistance to insulin-stimulated glucose uptake and hyperinsulinemia are involved in the etiology of hypertension. 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 rate 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 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-
somatostatin analogue (SMS) or NaCl was started at day zero and was continued throughout entire study. Continuous infusion of either 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.

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

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References


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 zero and was continued throughout entire study. Continuous infusion of either 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.

**KEY WORDS**  fructose • somatostatin • hyperinsulinemia • insulin
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