Chronic Intravenous Glucose Infusion Causes Moderate Hypertension in Rats

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We have reported that chronic insulin infusion increases mean arterial pressure (MAP) in rats. In those studies, glucose was coinfused to prevent hypoglycemia, but it is possible that the glucose infusion rate may have exceeded the rate actually required to prevent hypoglycemia. If true, then the glucose infusion alone should have a similar effect, and this study tested that hypothesis. In six rats (insulin group) instrumented with artery and vein catheters, insulin was infused for 7 days intravenously (iv) at 1.5 mU/kg/min together with glucose iv at 18.6 mg/kg/min. Seven other rats (glucose group) received the same glucose infusion for 7 days but without iv insulin. MAP increased significantly in both groups, from 98 ± 3 and 96 ± 2 mm Hg to 107 ± 5 and 104 ± 3 mm Hg in the insulin and glucose groups, respectively, and the renal and hormonal changes were similar to those previously reported during insulin infusion. There were no significant differences between the two groups for any variable measured. These data indicate that the sugar intake provided by the glucose infusion essentially mimics the response to our insulin and glucose infusion protocol, and that similar mechanisms underlie the renal and cardiovascular responses to each protocol. Am J Hypertens 2000;13:99–102 © 2000 American Journal of Hypertension, Ltd.

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We have reported in a series of studies that chronic insulin infusion in rats causes an increase in mean arterial pressure (MAP) that is maintained for at least 7 days.1–7 In those studies, insulin was infused intravenously (iv), and glucose was added to the iv infusion to prevent insulin-mediated hypoglycemia. However, in none of our studies was there evidence of hypoglycemia, and plasma glucose concentration actually tended to increase slightly.3–6 In addition, Koopmans et al.8 using an insulin infusion protocol similar to ours,1–7 required much less glucose than our study over a 24-h period to maintain normoglycemia when adjusting their glucose infusion based on multiple daily glucose measurements. This suggests that the glucose infusion in our protocol1–7 exceeded the amount required to prevent hypoglycemia.

If that is true, then a 7-day iv infusion of glucose at the same rate used during our insulin and glucose infusion protocol1–7 should have the same effects on renal function and blood pressure, and the present study tested that hypothesis by measuring the changes in those variables during 7-day infusions using each protocol.

METHODS

All surgical procedures, housing, infusion procedures, and measurement methods were the same as reported in our previous insulin infusion studies1–7 and are...
described briefly here. All experiments were conducted in male Sprague-Dawley rats (~350 g, Harlan Sprague-Dawley, Madison, WI), and the protocols were approved by the Institutional Animal Care and Use Committee. Under sodium pentobarbital anesthesia (50 mg/kg), a nonocclusive catheter was inserted into the abdominal aorta and a femoral vein catheter was implanted. The catheters were routed subcutaneously (sc) to the scapular region and exteriorized through a Dacron-covered stainless steel button sutured sc over the scapulae.

The rats were housed in individual metabolic cages and were connected to a dual-channel hydraulic swivel (Instech, Plymouth Meeting, PA) via a stainless steel spring. The catheters were passed through the spring and connected to the swivel; the venous channel was connected to a syringe pump (Harvard Apparatus, Millis, MA) that ran continuously throughout the study. The arterial catheter was filled with heparin solution (1000 USP U/mL), and that channel was connected to a pressure transducer (Cobe, Lakewood, CO) mounted on the cage exterior. The amplified pulsatile arterial pressure signals were analyzed each minute, 24 h/day, by computer using customized software.

Sodium intake throughout the experiment was maintained constant at approximately 2.9 mmol/day by continuous iv infusion of 18 mL/day sterile, 0.9% saline, combined with sodium-deficient rat chow (3.04 × 10⁻⁶ mmol sodium/g; Harlan Teklad, Madison, WI). In addition, 19 mL of sterile water was infused as vehicle for the insulin and glucose infusions during the experimental period. This infusion was begun immediately following placement of the rats in the metabolic cages, and 5 to 7 days were allowed for acclimation before control measurements.

**Experimental Protocol**

After a 5-day control period, a 24-h/day iv infusion of insulin (Regular Insulin, pork; Novo Nordisk, Princeton, NJ) at 1.5 mU/kg/min was begun in six rats (insulin group), and the sterile water vehicle from the control infusate was replaced with 50% dextrose solution that provided 18.6 mg glucose per kg/min. In seven other rats (glucose group), the identical glucose infusion was begun, but no insulin was provided in the infusate. These infusions were maintained for 7 days and were followed by a recovery period with a return to the control infusate in both groups.

On the second day of the control, the third day of the experimental, and the end of the recovery periods arterial blood was collected from the fasted rats in chilled sodium EDTA tubes for measurement of plasma insulin and glucose concentrations and for gamma counting. The sample was replaced with an equal volume of 0.9% saline.

**Analytical Methods**

Plasma insulin concentration was measured by radioimmunoassay, and plasma glucose was determined with a Beckman glucose analyzer. Urine electrolyte concentrations were determined using ion-sensitive electrodes (Nova, Waltham, MA). Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured by clearance of $^{125}$I-iothalamate (Glofil) and $^{131}$I-iodohippuran. Data were analyzed using two-factor analysis of variance with repeated measures on one factor (time) and Dunnett’s test for testing within-group effects. Statistical significance was considered to be $P < .05$. Results are presented as means plus or minus standard error.

**RESULTS**

MAP during the control period averaged $98 \pm 3$ and $96 \pm 2$ mm Hg in the insulin group (insulin + glucose infusion) and glucose group (glucose infusion only), respectively, and increased in the respective groups to averages of $107 \pm 5$ and $104 \pm 3$ mm Hg (Fig. 1). Although arterial pressure in two rats in the insulin group continued to increase during the last 2 days of the experimental period, there were no significant differences between the two groups for any study period. Blood pressure returned to levels not different from control levels when restoring the control infusions.

Urinary sodium excretion averaged $2.5 \pm 0.2$ and $2.4 \pm 0.2$ mmol/day during the control period in the insulin and glucose groups, respectively, and decreased in both groups on day 1 of the experimental period. The decrease was not statistically significant, and this response is similar to what we have reported in previous studies, with no significant increase in sodium balance measured in either group during the experimental period.

GFR averaged $3.0 \pm 0.1$ mL/min in the insulin group and $2.7 \pm 0.2$ mL/min in the glucose group during the control period, decreased significantly in both groups on day 3 of the experimental period, and returned to levels not different from control during the recovery period, similar to the response measured previously in this experimental model. No significant changes were measured in renal plasma flow in either group.

Baseline insulin levels tended to be higher in the insulin group, averaging $82 \pm 23$ versus $53 \pm 14$ μU/mL in the glucose group, but there was an approximate 60% increase measured in both groups during the experimental period that was not different between groups. Plasma glucose increased slightly but significantly in the insulin group and glucose group from $135 \pm 4$ and $136 \pm 5$ to $149 \pm 6$ and $144 \pm 1$ mg/dL, respectively. Both variables returned to control during the recovery period. There were no significant between- or within-group differences in plasma...
renin activity, plasma protein concentration, or hematocrit.

Food intake decreased significantly in both groups, similar to the response measured in our previous studies, and there were no differences between groups. This decrease in food intake did not cause total caloric intake to change significantly in either group during the experimental period, however, because of the additional calories derived from the glucose infusion. Interestingly, this “exchange” of glucose for rat chow in terms of caloric balance resulted in a significant increase in the percent of total calories derived from simple sugars. During the control period, sugar (sucrose) accounted for 64.5% of total caloric intake in both groups, but that increased significantly to approximately 81% in both groups during the experimental period. Each variable returned progressively toward control during the recovery period.

**DISCUSSION**

The response to the insulin and glucose infusion in the insulin group in this study was similar to the response in all of our previous studies for every variable measured, and the main finding from this study is that the response in the glucose group, which received only the glucose component of the infusion, was not significantly different for any variable. This suggests that the insulin infusion protocol we have employed previously is not different in terms of its systemic and renal effects from a chronic iv infusion of the glucose alone. The only apparent difference, which we have not evaluated directly, is that the similar increase in plasma insulin is due to infused insulin and endogenous secretion in the former, but due only to endogenous secretion in the latter.

The results from this study also suggest that the mechanisms underlying the increase in blood pressure in the insulin group and glucose group were the same. The changes in sodium excretion were not different between groups, and MAP increased gradually during the experimental period to approximately 9 and 8 mm Hg above control levels in the insulin group and glucose group, respectively. This was associated with a decrease in GFR on day 3 of the experimental period in both groups.

The decrease in GFR and increase in arterial pressure during insulin and glucose infusion have been consistent findings. They are not dependent on the sympathetic nervous system, because neither response was affected by chronic blockade of α- and β-adrenergic receptors, but are almost completely prevented by chronic blockade of thromboxane synthesis or chronic angiotensin-converting enzyme inhibition. We have postulated that these responses together suggest that a complex interaction between insulin, thromboxane, angiotensin II, and tubuloglomerular feedback underlies the decrease in GFR, shift in pressure natriuresis, and increase in arterial pressure. All the variables measured in this study suggest that this same mechanism mediates the response to infusion of glucose alone.

Although there have been no previous reports to our knowledge on the blood pressure effects of chronic iv glucose infusion, previous studies have reported that high sucrose or fructose diets may raise arterial pressure in rats. However, a pressor effect of such diets is not a universal finding, and we also have reported that a high-fructose diet in rats did not increase blood pressure, using 24-h/day measurements. In the present study, however, we report that chronic glucose infusion increased MAP, and one potential explanation for the apparently conflicting responses may be that the response to sugar intake in rats is dose dependent.

Virtually all sugar-feeding studies employ a switch from a low or zero sugar-containing diet to one in which approximately 65% of total calories are derived from simple sugars, typically fructose or sucrose. We followed such a protocol in our fructose-feeding study, however, the rats in our insulin and glucose infusion studies, including the present study, receive a chow throughout the study that derives 64.5% of calories from sucrose. This is a standard sodium-deficient...
test diet from Teklad, and sucrose concentrations in the range of 50% or greater are commonly used in rodent chow provided as pellets. However, with this diet, total calories derived from simple sugars during the experimental infusion in both groups increased to approximately 81%. This was because the rats voluntarily decreased their food intake when given the glucose infusion, thereby substituting glucose-derived calories for the calories derived from protein, fat, and carbohydrate in the chow.

Thus, the typical change from low-sugar chow to a chow with approximately 65% sugar may place rats on a threshold for hyperinsulinemia, increased blood pressure, and changes in other variables measured in many studies,9–12 perhaps explaining why we16 and others13–15 have not measured such responses to that dietary regimen. The present results suggest, in fact, that in our laboratory we can measure such effects with 24-h/day arterial pressure measurements when sugar intake is approximately 80% of total calories.

In conclusion, continuous iv glucose infusion at the rate we have used to prevent hypoglycemia during chronic insulin infusion, previously1–7 and in the present study, caused renal, humoral, and hemodynamic changes that were not different from those measured during the combined infusion of insulin and glucose. This suggests that a sugar intake that is approximately 80% of total caloric intake essentially mimics the response to our insulin and glucose infusion protocol,1–7 which also provides additional evidence that the blood pressure response to high-sugar diets in rats may be dose dependent.

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REFERENCES