Chronic Hyperinsulinemia and Blood Pressure
Interaction With Catecholamines?
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Although hyperinsulinemia and increased adrenergic activity have been postulated to be important factors in obesity-associated hypertension, a cause and effect relation between insulin, catecholamines, and hypertension has not been established. The aim of this study was to determine whether chronic hyperinsulinemia, comparable with that found in obese hypertensive patients, causes hypertension in normal dogs, increases plasma catecholamines, or potentiates the blood pressure effects of norepinephrine. In six normal dogs, insulin infusion (1.0 milliunits/kg/min) for 7 days, with euglycemia maintained, increased fasting insulin fourfold to sixfold. However, mean arterial pressure did not increase, averaging 99±2 mm Hg during the control period and 91±3 mm Hg during the 7 days of insulin infusion. Insulin did not alter plasma norepinephrine or epinephrine, which averaged 171±27 and 71±14 pg/ml, respectively, during the control period and 188±29 and 45±12 pg/ml during the 7 days of insulin infusion. In six dogs, norepinephrine was infused (0.2 μg/kg/min) for 7 days to raise plasma norepinephrine to 2,940±103 pg/ml. Insulin infusion (1.0 milliunits/kg/min) for 7 days during simultaneous infusion of norepinephrine did not further increase mean arterial pressure, which averaged 101±3 during norepinephrine and 98±2 mm Hg during insulin plus norepinephrine infusion. Thus, chronic hyperinsulinemia did not increase mean arterial pressure or plasma catecholamines and did not potentiate the blood pressure actions of norepinephrine. These observations provide no evidence that chronic hyperinsulinemia or interactions between insulin and plasma catecholamines cause hypertension in normal dogs. (Hypertension 1990;15:519–527)

An association between obesity and hypertension has been noted by numerous investigators, and reductions in caloric intake and body weight often lower blood pressure in obese hypertensive patients.1–3 Several lines of indirect evidence suggest that insulin could be an important link between changes in caloric intake, activity of the sympathetic nervous system, and hypertension associated with obesity.4,5 Increased caloric intake because of carbohydrate ingestion elevates insulin levels and appears to activate the sympathetic nervous system, whereas caloric restriction suppresses insulin and sympathetic activity as assessed by various indirect methods.5 Blood pressure, plasma norepinephrine, and insulin levels are increased in obese adolescents compared with nonobese control subjects on similar sodium intakes.6

Experimental hypertension produced by feeding rats sucrose is associated with increased catecholamine secretion and hyperinsulinemia; norepinephrine turnover, an index of sympathetic activity, is increased in heart, pancreas, and liver of overfed rats.4,5 However, it is difficult to determine in these studies whether increased insulin secretion plays a causal role in elevating blood pressure and adrenergic activity or whether these changes occur independently of hyperinsulinemia. There have been only a few studies that have examined the direct effects of insulin on arterial pressure and adrenergic activity. Acute insulin infusion has been reported to elevate plasma norepinephrine even when plasma glucose concentration is maintained constant,6,9 and blockade of adrenergic activity attenuates the rise in blood pressure observed with insulin injections.10 However, the relevance of these observations to the etiology of hypertension is difficult to assess because large,
pharmacological amounts of insulin were used and only the short-term changes in blood pressure were examined.

Although there is a considerable interest in the possibility that insulin may be an important link between increased caloric intake, elevated adrenergic activity, and high blood pressure in obese hypertensive patients, most of the evidence supporting this hypothesis is indirect. There have been no studies, to our knowledge, that have examined the importance of changes in adrenergic activity in modulating the long-term effects of insulin and whether chronic hyperinsulinemia elevates blood pressure in normal animals.

The goals of the present study were to determine whether chronic hyperinsulinemia increases arterial pressure in normal dogs and to examine the changes in renal and endocrine function that occur during sustained hyperinsulinemia. In addition, our studies were designed to determine whether increased adrenergic activity, produced by increased circulating norepinephrine, potentiates the chronic effects of hyperinsulinemia on blood pressure and renal function. And finally, our studies examined whether long-term insulin infusion causes sustained increases in circulating catecholamines.

**Methods**

Experiments were conducted in conscious mongrel dogs weighing 17.7–23.0 kg (average 20.9±0.9 kg). The dogs were anesthetized with sodium pentobarbital (30 mg/kg i.v.), and Tygon catheters (Norton Plastics, Akron, Ohio) were implanted in the femoral arteries and veins under aseptic conditions and advanced into the aorta just below the renal arteries. The catheters were tunneled subcutaneously, exteriorized in the scapular region for protection, and filled with heparin solution (1,000 USP units/ml). The dogs were permitted to recover from surgery, antibiotics were administered daily, and rectal temperatures were monitored to insure that the dogs were afebrile at the time of the studies.

The dogs were allowed a recovery period of approximately 2 weeks and then were placed in individual metabolic cages in a quiet air-conditioned room with a 12-hour light/dark cycle and fitted with harnesses containing a pressure transducer (Statham Medical Instrs., Hato Rey, Puerto Rico) at heart level. Mean arterial pressure signals from a polygraph (model 7D, Grass Instr Co., Quincy, Massachusetts) were sent to an analog-digital converter and analyzed with a digital computer (Turbo X-T, PCs Limited, Austin, Texas). Analog signals from the polygraph were sampled 50 times each minute and digitized to provide an average value for each minute throughout the day. The average pressure for each day was then calculated from pressures recorded each minute over an 18-hour period between 2:00 PM and 8:00 AM.

To infuse the various solutions continuously, one of the femoral venous catheters was connected to a roller pump (model 375A, Sage Instrs., Cambridge, Massachusetts). All solutions were pumped through disposable filters (Cathivex, Millipore Corp., Bedford, Massachusetts) to prevent contaminants and bacteria from passing into the venous infusion catheters. The infusion tubing and cables from the pressure transducers were protected by a flexible vacuum hose attached to a harness that permitted the dogs to move freely in the cage. The dogs were fed two cans (447 g/can) per day of a sodium-deficient diet (H/D Hills Pet Products, Topeka, Kansas) that provided approximately 7 meq sodium and 65 meq potassium/day and were given 5 ml of a vitamin syrup (V.A.L. Syrup, Ft. Dodge Labs., Ft. Dodge, Iowa). Food intake was constant throughout the study. Total sodium intake was maintained constant throughout the study by intravenous infusion of sterile isotonic saline at a rate of approximately 375 ml/day. The infusion, along with the food, provided a total sodium intake of approximately 65 meq/day. In addition, 50 ml/day sterile water was infused intravenously with a syringe pump (Harvard Apparatus, Millis, Massachusetts) and 720–995 ml/day sterile water was infused intravenously with a roller pump to provide the vehicles for the insulin and glucose infusions during the experimental period.

Before control measurements were started, the dogs were trained to lie quietly while blood samples were obtained from the arterial catheters, and studies of renal function were performed beginning at approximately 8:00 AM each day, 18–20 hours after the last feeding.

**Experimental Protocol**

**Insulin infusion in normal dogs.** After 7–10 days of control measurements, an intravenous infusion of insulin was started at a rate of 1.0 milliunits/kg/min and continued for 7 days in six normal dogs. Plasma glucose concentration was held relatively constant using a "glucose clamp" procedure in which a 50% solution of glucose was infused along with the insulin. The rate of glucose infusion needed to maintain plasma concentration constant was calculated with a mathematical model of glucose and insulin kinetics. Quantitative relations for the mathematical model were scaled to the canine and included stimulation of total glucose uptake by insulin, insulin clearance, and the apparent volumes of distribution of insulin and glucose. A glucose infusion rate of 14 mg/kg/min was scheduled for the insulin infusion rate of 1.0 milliunits/kg/min. The total volume of glucose solution infused was the same as the volume of vehicle infused during the control period. No attempt was made to precisely regulate blood glucose after feedings; instead, the rate of glucose infusion selected for each dog was held constant during chronic hyperinsulinemia. After 7 days of insulin and glucose infusions, post-control period measurements were made for 7 days.

**Insulin infusion in dogs with high plasma norepinephrine.** In six dogs, norepinephrine (Levophed, Winthrop-Breon Labs., New York, New York) was...
infused at a rate of 0.2 µg/kg/min i.v. for 7 days while control period measurements were made. Then an intravenous infusion of insulin was started at 1.0 milliunits/kg/min and continued for 7 days while plasma glucose was held constant by intravenous infusion of 50% glucose, as described above, and norepinephrine infusion was continued throughout the experiment at the same rate. After 7 days of insulin and norepinephrine infusion, the insulin and glucose infusions were stopped and post-control period measurements were made for an additional 7 days while norepinephrine infusion was continued.

**Analytical Methods**

Glomerular filtration rate and effective renal plasma flow were estimated from the total clearances of [¹²⁵I]iotothalamate (Giofil, Isotex Diagnostics, Friendwood, Texas) and [¹³¹I]iodohippuritate (Hippuran, Squibb, Princeton, New Jersey), respectively, as previously described.¹⁴ Renal vascular resistance was calculated as mean arterial pressure/effective renal blood flow, where effective renal blood flow is effective renal plasma flow/(1.0–hematocrit). Plasma and urine sodium and potassium concentrations were determined by flame photometry (model IL443, Instrumentation Labs., Lexington, Massachusetts). Plasma and urine chloride concentrations were measured by colorimetric titration (Haake-Buchler Chloridimeter, Saddlebrook, New Jersey), and plasma glucose concentration was determined by refractometry (American Optical, Buffalo, New York), and plasma protein concentration was measured by refractometry (American Optical, Buffalo, New York), and plasma glucose concentration was determined by the hexokinase method (Sigma Diagnostics, St. Louis, Missouri). Plasma concentrations of norepinephrine and epinephrine were measured by high performance liquid chromatography with electrochemical detection. Before assay, the catecholamines were absorbed on alumina.¹⁵ Plasma renin activity was measured by the radioimmunooassay method of Haber et al¹⁶ using [¹²⁵I]angiotensin I (Ang I) from New England Nuclear (Boston, Massachusetts) and antibody from Chemicon (El Segundo, California). Aldosterone was extracted from plasma with 7 volumes dichloromethane, and the dried extract was reconstituted with phosphate gelatin buffer and measured by radioimmunoassay using [¹²⁵I]aldosterone from Amersham (Arlington Heights, Illinois) and liquid phase antibody from Diagnostic Products (Los Angeles, California). Plasma insulin was measured by radioimmunoassay (Cambridge Medical Diagnostics kit, Billerica, Massachusetts).

**Statistical Analyses**

Experimental data were compared with control data by analysis of variance and, when appropriate, with Dunnett's t test for multiple comparisons.¹⁷¹⁸ Statistical significance was considered to be p<0.05. All data are expressed as mean±SEM, unless otherwise indicated.

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**Results**

**Insulin Infusion in Normal Dogs**

Figure 1 shows the effects of 7 days of insulin infusion on mean arterial pressure in normal dogs. Mean arterial pressure decreased from 99±3 to 86±3 mm Hg on the seventh day of insulin infusion. For the entire 7 days of insulin infusion, mean arterial pressure averaged 91±3 mm Hg. When insulin infusion was stopped, arterial pressure gradually increased toward control levels. Urine sodium excretion decreased from a control value of 65.2±2.8 meq/day to 37.3±7.3 and 22.7±5.3 meq/day, respectively, during the first 2 days of insulin infusion and then gradually returned toward control values (Figure 2). For the entire 7 days of insulin infusion, sodium excretion averaged 48.1±3.7 meq/day, resulting in a net retention of approximately 120 meq sodium. Potassium excretion decreased markedly during the first 3 days of insulin infusion and then returned toward control values. For 7 days of insulin infusion, potassium excretion averaged 50.8±6.5 meq/day, compared with a control value of 63.6±5.3 meq/day. Because potassium intake remained constant, there was a net retention of approximately 90 meq potassium during 7 days of insulin infusion. Urine chloride excretion and urine volume paralleled the changes in sodium excretion averaging 98±8 meq/day and 1,308±120 ml/day, respectively, during insulin infusion compared with control values of 108±5 meq/day and 1,612±75 ml/day.

Insulin infusion for 7 days increased glomerular filtration rate (GFR) to an average of 122±7% of control values (Figure 3). Effective renal plasma flow also increased to 117±5% and renal vascular resistance decreased to 80.5±5.1% of control values during 7 days of insulin infusion.

Plasma insulin concentration increased almost fivefold, averaging 8.5±1.0 microunits/ml during the control period and 41.4±9.4 microunits/ml during the 7 days of insulin infusion (Table 1). Plasma glucose increased slightly on days 1 and 3 of insulin and glucose infusion but remained within the normal range. Plasma renin activity increased significantly during insulin infusion, averaging 0.68±0.20 and...
Insulin Infusion in Dogs Infused With Norepinephrine

Baseline values for blood pressure, renal function, and plasma electrolytes did not differ markedly in the norepinephrine-infused and control dogs although plasma norepinephrine levels were elevated 17-fold, from 171±27 pg/ml to 2,940±103 (compare Tables 1 and 2). Plasma renin activity and plasma aldosterone concentration were not significantly different in norepinephrine-infused and control dogs.

Insulin infusion in dogs with elevated plasma norepinephrine did not increase mean arterial pressure further. In fact, there was a small, although statistically insignificant, decrease in mean arterial pressure during insulin infusion (Figure 4); during 7 days of insulin infusion, mean arterial pressure averaged 96±3 mm Hg, compared with a control value of 101±2 mm Hg.

Insulin infusion in dogs with high plasma norepinephrine caused pronounced sodium retention (Figure 5) with sodium excretion decreasing from 59.9±2.7 to 30–40 meq/day during the first 5 days of insulin infusion. For the entire 7 days of insulin infusion, sodium excretion averaged 41.5±2.8 meq/day. Thus, insulin infusion for 7 days caused a net retention of approximately 130 meq sodium. Potassium excretion decreased from 82.7±1.4 to 41–60 meq/day for the first 5 days of insulin infusion; for the entire 7 days of insulin infusion, potassium excretion averaged 55.9±6.1 meq/day, and there was a net potassium retention of approximately 190 meq. Urine volume and chloride excretion paralleled the changes in sodium excretion. Urine volume and chloride excretion averaged 1,480±157 ml/day and 95±11 meq/day, respectively, during 7 days of insulin infusion, compared with control values of 1,672±66 ml/day and 126±2 meq/day.

GFR increased to 119±6 and 117±6% of control values on days 1 and 3 of insulin infusion (Figure 6). On the sixth day of insulin infusion, GFR was still slightly, but not significantly, elevated. Effective renal plasma flow increased slightly, but the changes were not statistically significant during the 7 days of insulin infusion.

Plasma insulin concentration increased over fourfold from a control value of 12.7±2.3 to 51.8±8.6 microunits/ml during insulin infusion (Table 2). Plasma glucose concentration did not change significantly averaging 115±6 mg/100 ml during control and 110±9 mg/ml during the 7 days of insulin infusion. Plasma renin activity increased from 0.43±0.10 to 1.43±0.26 ng/Ang I/ml/hr, and plasma aldosterone concentration increased from 4.8±0.9 to 9.4±1.8 ng/100 ml during insulin infusion. Insulin infusion decreased plasma potassium concentration from 3.91±0.09 to 3.57±0.12 meq/l. There were no significant changes in plasma concentrations of sodium or chloride during insulin infusion, although plasma protein concentration decreased from 7.64±0.38 to 7.08±0.24 g/100 ml. Plasma norepinephrine and epinephrine concentrations were measured in three of the dogs. Plasma norepinephrine concentration, although markedly elevated by the infusion of norepinephrine, did not increase further averaging 2,888±10 pg/ml during insulin infusion compared with a control value of 2,940±103 pg/ml. Insulin infusion also did not alter plasma epinephrine concentration.
concentration. However, heart rate increased markedly from 62±2 to 118±3 beats/min after 7 days of insulin infusion.

Discussion

Hyperinsulinemia and Blood Pressure

An important finding of this study is that sustained hyperinsulinemia did not elevate arterial pressure in normal conscious dogs. In fact, insulin infusion for 7 days, with plasma glucose held relatively constant, caused small but consistent reductions in blood pressure. Our results also provide no evidence that hyperinsulinemia causes sustained increases in plasma catecholamines or elevates blood pressure in dogs with high adrenergic tone due to long-term infusion of norepinephrine.

<p>| TABLE 1. Effects of Insulin Infusion in Normal Dogs |
|---------------------------------|----------------|-------------|-------------|----------------|----------------|-------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>PDIG (units/ml)</th>
<th>PGLU (mg/100 ml)</th>
<th>PRA (ng Ang I/ml/hr)</th>
<th>ALDO (ng/100 ml)</th>
<th>PNOREPI (pg/ml)</th>
<th>PEPI (pg/ml)</th>
<th>PNa (meq/l)</th>
<th>PK (meq/l)</th>
<th>PProt (g/100 ml)</th>
<th>HR (beats/min)</th>
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<tbody>
<tr>
<td>Control</td>
<td>8.5±1.0</td>
<td>90±6</td>
<td>0.68±0.20</td>
<td>3.9±0.9</td>
<td>171±27</td>
<td>71±13</td>
<td>140.1±0.6</td>
<td>3.82±0.11</td>
<td>7.45±0.18</td>
<td>81±7</td>
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<tr>
<td>Insulin (1.0 milliunits/kg/min)</td>
<td>Day 1</td>
<td>49.4±10.3</td>
<td>126±9*</td>
<td>1.35±0.35*</td>
<td>6.0±1.7</td>
<td>219±34</td>
<td>50±12</td>
<td>142.5±1.7</td>
<td>3.38±0.09*</td>
<td>7.29±0.15</td>
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<tr>
<td></td>
<td>Day 3</td>
<td>35.9±2.1*</td>
<td>115±5*</td>
<td>1.07±0.31*</td>
<td>3.9±1.2</td>
<td>152±32</td>
<td>44±8</td>
<td>141.8±0.9</td>
<td>3.45±0.06*</td>
<td>6.76±0.12*</td>
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<tr>
<td></td>
<td>Day 6</td>
<td>38.8±3.1*</td>
<td>112±16</td>
<td>1.19±0.25*</td>
<td>6.8±2.4</td>
<td>193±40</td>
<td>41±17</td>
<td>140.0±1.0</td>
<td>3.63±0.08</td>
<td>6.45±0.12*</td>
</tr>
<tr>
<td>After control</td>
<td>Day 1</td>
<td>9.8±0.4</td>
<td>111±4*</td>
<td>0.86±0.34*</td>
<td>5.3±1.7</td>
<td>152±35</td>
<td>70±8</td>
<td>141.5±0.9</td>
<td>3.99±0.12</td>
<td>6.64±0.13*</td>
</tr>
<tr>
<td></td>
<td>Day 3</td>
<td>9.8±1.0</td>
<td>119±8*</td>
<td>0.59±0.10</td>
<td>3.0±0.8</td>
<td>140.5±0.8</td>
<td>3.95±0.14</td>
<td>7.01±0.16*</td>
<td>79±4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 6</td>
<td>11.0±1.6</td>
<td>120±6*</td>
<td>0.64±0.16</td>
<td>4.1±1.1</td>
<td>234±80</td>
<td>158±111</td>
<td>142.7±1.3</td>
<td>3.94±0.11</td>
<td>7.58±0.18</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Control is the average of days −4 and −1. PDIG, plasma insulin concentration; PGLU, plasma glucose concentration; PRA, plasma renin activity; ALDO, plasma aldosterone concentration; PNOREPI, plasma norepinephrine concentration; PEPI, plasma epinephrine concentration; PNa, plasma sodium concentration; PK, plasma potassium concentration; PProt, plasma protein concentration; HR, heart rate.

*p<0.05 compared with control.
The mechanisms by which insulin infusion lowered blood pressure in these experiments are uncertain as changes in cardiac output and total peripheral resistance were not measured. Although previous short-term experiments suggested that insulin may attenuate the peripheral vasoconstrictor actions of norepinephrine and angiotensin II (Ang II), there have been no reports on whether these acute effects are sustained. It is important to note, however, that reductions in arterial pressure associated with insulin infusion in our study were not as great in dogs with high circulating levels of norepinephrine as in control dogs. This observation suggests that insulin may not have had a powerful effect to blunt norepinephrine-mediated vasoconstriction in these experiments.

In some experiments, mild hyperglycemia was produced by the infusion of glucose and insulin, even though our goal was to maintain plasma glucose constant. It seems unlikely, however, that the small increases in plasma glucose observed in normal dogs can account for the decreased arterial pressure as previous studies in our laboratory have shown that decreased arterial pressure occurs with long-term insulin infusion even when plasma glucose is slightly reduced. Also, obese hypertensive patients have concomitant hyperinsulinemia and increased plasma glucose.

**FIGURE 4.** Bar graph showing effect of insulin infusion (1.0 milliunits/kg/min) for 7 days in dogs infused with norepinephrine (0.2 μg/kg/min). Norepinephrine infusion was started 7 days before beginning insulin infusion and continued throughout the experiment (n=6).

**FIGURE 5.** Bar graphs showing effect of insulin infusion (1.0 milliunits/kg/min) for 7 days on sodium and potassium excretion and urine volume in dogs infused with norepinephrine (0.2 μg/kg/min). Norepinephrine infusion was started 7 days before beginning insulin infusion and continued throughout the experiment (n=6).
FIGURE 6. Bar graphs showing effect of insulin infusion (1.0 milliunits/kg/min) for 7 days on glomerular filtration rate, effective renal plasma flow, and renal vascular resistance in dogs infused with norepinephrine (0.2 µg/kg/min). Norepinephrine infusion was started 7 days before beginning insulin infusion and continued throughout the experiment. C, average control value ± SEM for each variable (n=6).

Hyperinsulinemia has been postulated to increase blood pressure in obese hypertensive patients. Increased plasma insulin is common in obese hypertensive patients, and there is a significant correlation between blood pressure and plasma insulin concentration in these individuals. When caloric intake is restricted in obese subjects, plasma insulin and blood pressure often decrease in parallel even if sodium intake is maintained relatively constant. Furthermore, high insulin may be correlated with high blood pressure even in the absence of obesity as hypertensive men have higher serum insulin levels compared with normotensive control subjects with similar body mass index values. Studies in animal models of hyperinsulinemia also suggest a correlation between blood pressure and insulin. For example, overfeeding rats with sucrose or fructose is associated with hyperinsulinemia and increased arterial pressure. Thus, several studies suggest a significant correlation between elevated insulin and high blood pressure.

There have been only a few acute experiments in which the blood pressure effects of insulin have been examined. In one study, Pereda et al found that injection of large pharmacological amounts of insulin (3,000 milliunits/kg) caused a transient increase in blood pressure that was antagonized by ganglionic or adrenergic blockade. Liang et al also infused insulin at high rates (4 and 8 milliunits/kg/min) for 60 minutes in dogs and reported increases in cardiac output and heart rate, as well as a very slight increase in mean arterial pressure if plasma glucose was held constant. These observations and the correlation observed between insulin and high blood pressure have led to the hypothesis that insulin might be an important pressor agent in hypertension, although a clear cause and effect relation between chronic hyperinsulinemia and hypertension has not been demonstrated.

The results from the present study indicate that elevating plasma insulin levels for 7 days to values similar to those seen in obese hypertensive patients did not significantly increase arterial pressure in normal conscious dogs. This observation suggests that high insulin levels per se may not be a primary cause of increased blood pressure if other factors are normal. This finding, of course, does not rule out the possibility that hyperinsulinemia could contribute in some as yet undefined way to the elevation of blood pressure in obese hypertensive patients. Nor can we
exclude the possibility that insulin levels higher than those achieved in this study might elevate blood pressure.

Another important goal of the present study was to determine whether hyperinsulinemia might cause sustained increases in circulating catecholamines or elevate blood pressure to a greater extent when adrenergic activity was simultaneously increased. Previous studies have suggested that obese hypertensive patients have higher circulating norepinephrine than normotensive control subjects, and it has been suggested that increased sympathetic activity, together with hyperinsulinemia, may be important in the pathogenesis of hypertension.²⁻⁵,²⁶ Rats fed large amounts of sucrose or fructose have increased plasma norepinephrine, hyperinsulinemia, and hypertension.²⁻⁶ Short-term infusion of insulin has been reported to elevate plasma norepinephrine even when euglycemia is maintained.¹ However, no previous studies, to our knowledge, have directly tested whether hyperinsulinemia causes sustained increases in circulating norepinephrine. In the present study, we found no increases in plasma norepinephrine during 7 days of hyperinsulinemia. In addition, long-term insulin infusion did not potentiate the blood pressure effects of norepinephrine. In dogs in which circulating levels of norepinephrine were elevated approximately 17-fold, simultaneous infusion of insulin for 7 days did not elevate blood pressure further. However, it is important to note that hyperinsulinemia did not reduce arterial pressure in dogs with high circulating norepinephrine to as great an extent as in normal control dogs.

Although hyperinsulinemia did not increase circulatory catecholamines, resting heart rate increased significantly during 7 days of hyperinsulinemia. Previous acute studies have also found increased heart rate with hyperinsulinemia,⁹ but this is the first study, to our knowledge, that has reported elevated heart rate during long-term insulin infusion. In the present study, heart rate was measured only under resting conditions; however, in preliminary studies we measured heart rate 24 hours a day and found tachycardia during the 7 days of hyperinsulinemia (personal observations). The exact mechanisms by which insulin raises heart rate are unclear but do not appear to be due to increased circulating catecholamines.

Although the results from the present study provide no evidence that chronic hyperinsulinemia raises blood pressure or potentiates the blood pressure actions of norepinephrine in normal dogs, the close association between hypertension, hyperinsulinemia, and obesity deserves further study. It is possible that some factor associated with obesity other than increased adrenergic activity may interact with insulin to raise blood pressure. What this additional factor might be is still unclear.

**Hyperinsulinemia and Renal Excretion**

Although it is generally accepted that acute insulin administration increases renal sodium reabsorption,²³,²⁸ there have been no previous studies, to our knowledge, that have examined the effects of sustained hyperinsulinemia on control of renal excretion in normal animals. The results of the present study indicate that hyperinsulinemia, comparable with that seen in obese hypertensive patients, causes pronounced reductions in renal excretion of sodium and water without reducing GFR. In fact, GFR was substantially elevated by insulin infusion indicating that insulin increased sodium reabsorption chronically. After several days of hyperinsulinemia, there was an escape from sodium retention and return of excretion toward normal. However, the fact that normal excretion was maintained despite increased GFR indicates a sustained increase in sodium reabsorption.

The mechanisms responsible for renal escape from sodium retention during chronic hyperinsulinemia were not the primary focus of this study but are not secondary to pressure natriuresis as arterial pressure did not increase with insulin infusion. The small reduction of blood pressure that occurred with insulin infusion may have actually contributed to the sodium retention. Decreased formation of Ang II or aldosterone also cannot explain the escape from sodium retention as plasma renin activity and aldosterone concentration were elevated by insulin infusion. Increased Ang II and aldosterone formation may have played a role in stimulating sodium reabsorption, although recent studies from our laboratory indicate that insulin elevates sodium reabsorption chronically in dogs with reduced renal mass even when plasma renin activity and aldosterone concentration are unchanged.²⁰ One mechanism that could play a role in offsetting the effects of insulin on sodium reabsorption is a rise in GFR. GFR and effective renal plasma flow were elevated by 15⁻²⁰% during insulin infusion. Further studies are needed, however, to determine the exact mechanisms by which insulin elevates GFR and the role of other factors in overriding the antinatriuretic action of insulin.

Potassium excretion decreased to less than 50% of control, and this reduction was maintained for at least 3 days of insulin infusion. One potential cause of the antikaliuresis is a decrease in plasma potassium concentration. Acute experiments have suggested that insulin may cause hypokalemia by increasing potassium uptake in extrarenal tissues.³⁰ In the present study, plasma potassium concentration was slightly reduced during long-term insulin infusion. Another possible cause of the decrease in potassium excretion is an increase in sodium reabsorption before the distal nephron, which would tend to reduce distal nephron flow rate and potassium secretion. A reduction in distal nephron flow rate could also activate a macula densa feedback that would increase GFR in an attempt to return distal delivery toward normal,³¹ possibly explaining the increased GFR and renal plasma flow observed with long-term insulin infusion. In support of this possibility, previous acute studies have suggested that
insulin may increase reabsorption in the proximal tubule and loop of Henle.\textsuperscript{12,23} Further studies are needed, however, to fully elucidate the mechanisms by which insulin influences long-term control of sodium and potassium excretion.

In summary, our results indicate that chronic hyperinsulinemia, comparable with that found in obese hypertensive patients, does not elevate blood pressure in normal conscious dogs and does not potentiate the blood pressure effects of norepinephrine. Insulin infusion over a period of 7 days, however, did cause pronounced retention of sodium, potassium, and water. The mechanisms responsible for this decrease in renal excretion appear to be related, in part, to increased tubular reabsorption as GFR and effective renal plasma flow were markedly elevated by insulin infusion. These observations suggest that additional factors besides hyperinsulinemia or interactions between insulin and circulating norepinephrine may play a role in obesity-associated hypertension.

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References

1. Dustan HP: Mechanisms of hypertension associated with obesity. 
2. Sims EAH: Mechanisms of hypertension in the overweight. 
   Hypertension 1982;4(suppl III):III-43–III-49
   Lab Clin Med 1939;25:807–822
4. Landsberg L, Krieger DR: Obesity, metabolism, and the 
5. Young JB, Landsberg L: Diet-induced changes in sympathetic 
   nervous system activity: Possible implications for obesity and hypertension. 
   J Chron Dis 1982;35:879–886
6. Rocchini AP, Key J, Bordie D, Chico R, Moorhead C, Katch V, 
   Martin M: The effect of weight loss on the sensitivity of blood pressure 
7. Fournier RD, Chueh CC, Kopin IJ, Knapka JJ, DiPette D, 
   Preuss HG: Refined carbohydrate increases blood pressure and 
   catecholamine secretion in SHR and WKY. Am J Physiol 1986;250:E381–E385
8. Rowe JW, Young JB, Mimaker KL, Stevens AL, Pallotta J, 
   Landsberg L: Effect of insulin and glucose infusions on 
   sympathetic nervous system activity in normal man. Diabetes 
   1981;30:219–225
9. Liang CS, Doherty JV, Faillace R, Maekawa K, Arnold S, 
   Gavias H, Hood WB Jr: Insulin infusion in conscious dogs: 
   Effects on systemic and coronary hemodynamics, regional 
   69:1321–1336
    responses to insulin in the absence of hypoglycemia. 
    index. Correlation in dogs between values determined from 
    the intravenous glucose tolerance test and the euglycemic 
    glucose clamp. Diabetes 1984;33:362–368
Chronic hyperinsulinemia and blood pressure. Interaction with catecholamines?
J E Hall, M W Brands, S D Kivlighn, H L Mizelle, D A Hildebrandt and C A Gaillard

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