Insulin and Renal Sodium Retention in Hypertension-Prone Men

Tomas Endre, Ingrid Mattiasson, Göran Berglund, U. Lennart Hulthén

Abstract Insulin-stimulated peripheral glucose uptake and insulin-induced renal tubular sodium reabsorption were investigated in normotensive men with a family history of hypertension (relatives, n=35) compared with age- and body mass index-matched normotensive men with no family history of hypertension (controls, n=23). The effect of insulin on the renin-aldosterone system was also studied. The euglycemic hyperinsulinemic clamp technique was used to measure peripheral glucose uptake (insulin sensitivity index). Renal clearance of $^{51}$Cr-labeled EDTA, sodium, and lithium was used to calculate fractional excretion of sodium and fractional proximal and distal tubular reabsorption of sodium before and during insulin infusion. The insulin sensitivity index was lower in relatives than in controls. Fractional excretion of sodium was reduced, and fractional proximal and distal tubular reabsorption of sodium during insulin infusion. Fractional distal tubular reabsorption of sodium was positively correlated to the reduction of serum potassium in all individuals. Plasma renin activity increased to the same extent in both groups, whereas plasma aldosterone was reduced only in controls. In conclusion, the impaired insulin-stimulated glucose uptake in peripheral tissues in normotensive sons of hypertensive families was accompanied by retained insulin-induced tubular sodium reabsorption. The lack of suppression of aldosterone secretion in these individuals may enhance sodium retention. (Hypertension. 1993;23:313-319.)

Key Words • glucose clamp technique • hypertension, genetic • family characteristics • sodium • insulin resistance

Hypertensive individuals are insulin resistant and hyperinsulinemic compared with normotensive control subjects, and it has been proposed that insulin resistance and hyperinsulinemia contribute to the development of hypertension. Recent studies have also shown that normotensive men with a family history of hypertension are insulin resistant and tend to have higher fasting serum insulin levels. A familial predisposition to primary hypertension is associated with a pressor response to high sodium intake. Insulin enhances sodium reabsorption in the renal tubules, and hyperinsulinemia may induce hypertension by its sodium-retaining effect if the effect of insulin in the kidneys is retained despite reduced insulin-induced peripheral glucose uptake.

In the present study the effect of insulin on tubular sodium reabsorption compared with peripheral glucose uptake was investigated in normotensive men with a family history of hypertension and normotensive men with no family history of hypertension. In addition, the effect of insulin on the sympathetic nervous system, the renin-angiotensin-aldosterone system, atrial natriuretic peptide, and parathyroid hormone was studied in these groups.

Methods

Subjects

Two groups of healthy, young volunteers were investigated. The selection procedures have been described in detail.

Received August 18, 1993; accepted in revised form November 30, 1993.

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Briefly, one group included sons of families with a documented family history of essential hypertension in either both parents, one parent and one grandparent on the same side, or one parent and one sibling (relatives). The other group included sons of families without a family history of hypertension (controls). The subjects included were between 25 and 46 years of age and had a supine diastolic blood pressure consistently below 90 mm Hg. They had a normal oral glucose tolerance test and serum y-glutamyl transpeptidase below 0.80 ukat/L to exclude individuals who consumed high amounts of alcohol. None of the subjects had any disease that was judged to influence the results of the experimental study. Of 68 men investigated with the euglycemic hyperinsulinemic clamp technique (39 relatives and 29 controls), renal function studies were successfully performed in 58 (35 relatives and 23 controls).

Study Design

Fig 1 shows the study design. Before the investigation all subjects were instructed to adhere to their ordinary lifestyle and avoid changes in food intake, alcohol consumption, and exercise. The subjects did not smoke and fasted overnight before the study. None of them had been on any regular medication for at least 12 months before the investigation.

The evening before the study the subjects were given two lithium carbonate (600 mg) tablets. On the study day water diuresis was induced by an oral water load of 5 mL of tap water per kilogram of body weight given between 7 and 7:15 AM; urinary losses plus 1 mL·min⁻¹ were replaced with oral tap water every 30 minutes from 8:30 AM until 12:30 PM. Between 10:30 AM and 12:30 PM the water intake was reduced to half because of fluid compensation by glucose and saline infusion (see below). The subjects were supine throughout the study. At 7:15 AM an intravenous catheter was inserted into the right arm for injection of a bolus of $^{125}$labeled hippurate (0.15 MBq) and $^{51}$Cr-labeled EDTA (1.5 MBq) immediately followed by a constant infusion of the two substances in 250 mL saline until 12:30 PM (0.45 and 4.5 MBq, respectively). At 7:45 AM a polyethylene catheter was inserted into the left brachial
glomerular filtration rate (milliliters per minute), respectively. Glomerular filtration rate (GFR) was calculated as clearance divided by effective renal plasma flow/1-hematocrit, and renal vascular resistance (dyne·s·cm⁻²) was calculated as mean blood pressure multiplied by 80,000 and divided by renal blood flow. Filtration fraction was taken as glomerular filtration rate divided by renal blood flow (percent). Fractional excretion (FE) of electrolytes was calculated as clearance divided by renal blood flow.

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Clearances (C) of ¹²³I-hippurate, ⁵¹Cr-EDTA, and electrolytes were calculated according to the formula:

\[ C = \frac{U \cdot V}{P} \]

where U is urine concentration, V is urine flow rate (milliliters per minute), and P is plasma or serum concentration. Clearances for ¹²³I-hippurate and ⁵¹Cr-EDTA were taken to represent effective renal plasma flow (milliliters per minute) and glomerular filtration rate (milliliters per minute), respectively. Renal blood flow (milliliters per minute) was calculated as effective renal plasma flow (1-hematocrit), and renal vascular resistance (dyne·s·cm⁻²) was calculated as mean blood pressure multiplied by 80,000 and divided by renal blood flow. Filtration fraction was taken as glomerular filtration rate divided by renal blood flow (percent). Fractional excretion (FE) of electrolytes was calculated as clearance divided by renal blood flow.

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sium was reduced to a similar extent in the two groups during insulin infusion (−0.40 [−0.28, −0.48] in relatives versus 0.45 [−0.34, −0.51] in controls, P=.30).

Basal values for intra-arterial mean blood pressure, heart rate, renal blood flow, renal vascular resistance, glomerular filtration rate, and filtration fraction did not differ between the groups (Table 2). During insulin infusion mean blood pressure was reduced to a similar extent in both groups, and there was a rise in heart rate only in controls. Renal blood flow did not change in either group, and renal vascular resistance was reduced in relatives. Glomerular filtration rate did not change, but filtration fraction increased during insulin infusion in controls.

During basal conditions FE of sodium, lithium, calcium, magnesium, chloride, and phosphate did not differ between the groups, whereas FE of potassium was lower in relatives than controls (P=.02) (Table 3). During insulin infusion FE of sodium, lithium, potassium, chloride, and phosphate was reduced, whereas FE of calcium and magnesium increased in both groups (Table 3). The decrease in FE of sodium, lithium, chloride, and phosphate and the increase in FE of calcium also were the same in the two groups when corrected for the prevailing insulin concentration (see Fig 2b for sodium). The decrease in FE of potassium and the increase in FE of magnesium were greater in controls compared with relatives. Basal values for FPRN,+ and FDRN,+ were similar in the two groups (Fig 3), and during insulin infusion FPRN,+ and FDRN,+ increased to the same extent in both groups. The reduction of serum potassium was closely correlated to the change in FDRN,+ (P=.52, P=.0001) but not to the change in FPRN,+ (P=.52) when calculated for all subjects (controls plus relatives).

Basal plasma levels of norepinephrine, epinephrine, PRA, aldosterone, ANP, and PTH did not differ between the groups (Table 4). During insulin infusion norepinephrine increased to a greater extent in controls than relatives, and PRA was equally elevated in controls and relatives. The increases in norepinephrine and PRA were not related to the increase in either FPRN,+ or FDRN,+. Epinephrine was unaltered in both groups. Aldosterone was reduced only in controls. ANP decreased in both groups. PTH was reduced when calculated for all subjects (controls plus relatives), and this reduction was positively related to the increase in FE of calcium (ρ=.30, P=.027) but not the changes in FE of magnesium and phosphate. There were no correlations between the change in FE of the ions measured and the change in insulin, norepinephrine, PRA, or ANP in either group.

Discussion

In the present study men with a family history of hypertension were shown to have a lower insulin sensitivity index than men with no family history of hypertension (Fig 2a). This is most likely because of reduced insulin-stimulated peripheral glucose uptake, as endogenous glucose release from the liver has been shown to be completely blocked in normotensive and hypertensive individuals at an insulin level of 100 mU/L. The reduction of insulin-stimulated peripheral glucose uptake was coupled with retained insulin-mediated renal tubular sodium reabsorption in men with a family history of hypertension (Fig 2b). Rocchini et al24 have reported retained insulin-induced sodium retention in young, obese individuals showing fasting hyperinsulinemia, markedly reduced peripheral glucose disposal.

**Table 2. Hemodynamic and Renal Effects of Insulin in Men Without and With a Family History of Hypertension**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=23)</th>
<th>relatives (n=35)</th>
<th>Control vs Relatives, P(Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Δ</td>
<td>P(Δ)</td>
</tr>
<tr>
<td></td>
<td>(79.2, 98.0)</td>
<td>(−0.4, −4.8)</td>
<td>.0005</td>
</tr>
<tr>
<td></td>
<td>85.3</td>
<td>−2.0</td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>(47.57)</td>
<td>+2.1</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>+0.2, +3.4</td>
<td>.45</td>
</tr>
<tr>
<td>Renal blood flow, ml/min</td>
<td>(793, 1128)</td>
<td>(−170, +81)</td>
<td>.97</td>
</tr>
<tr>
<td></td>
<td>912</td>
<td>+4</td>
<td></td>
</tr>
<tr>
<td>Renal vascular resistance, dyne·cm⁻²</td>
<td>(5924, 8535)</td>
<td>(−797, +1046)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7030</td>
<td>−231</td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate, ml/min</td>
<td>(87, 119)</td>
<td>(−11, +16)</td>
<td>.08</td>
</tr>
<tr>
<td></td>
<td>104</td>
<td>+5.5</td>
<td></td>
</tr>
<tr>
<td>Filtration fraction, %</td>
<td>(17.9, 20.0)</td>
<td>(0.2, +1.9)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>19.2</td>
<td>+1.2</td>
<td></td>
</tr>
</tbody>
</table>

Δ indicates change during euglycemic hyperinsulinemic clamp; bpm, beats per minute. Values are presented as medians and quartiles (Q₁, Q₃).
TABLE 3. Insulin-Induced Change in Fractional Excretion of Electrolytes During Euglycemic Hyperinsulinemic Clamp in Men Without and With a Family History of Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=23)</th>
<th>P</th>
<th>Relatives (n=35)</th>
<th>P</th>
<th>Controls vs Relatives, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔFE\text{Na}^-</td>
<td>-0.56</td>
<td>.0001</td>
<td>-0.64</td>
<td>.0001</td>
<td>.40</td>
</tr>
<tr>
<td></td>
<td>(-0.38, -0.91)</td>
<td></td>
<td>(-0.48, -0.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔFE_{K}^-</td>
<td>-10.7</td>
<td>.0001</td>
<td>-6.49</td>
<td>.0001</td>
<td>.011</td>
</tr>
<tr>
<td></td>
<td>(-7.16, -13.5)</td>
<td></td>
<td>(-4.88, -8.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔFE_{\text{Na}^+}^-</td>
<td>+0.32</td>
<td>.026</td>
<td>+0.12</td>
<td>.38</td>
<td>.24</td>
</tr>
<tr>
<td></td>
<td>(+0.02, +0.46)</td>
<td></td>
<td>(-0.10, +0.39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔFE_{\text{HCO}_3^-}^-</td>
<td>+2.35</td>
<td>.0005</td>
<td>+1.45</td>
<td>.0001</td>
<td>.020</td>
</tr>
<tr>
<td></td>
<td>(+1.29, +3.13)</td>
<td></td>
<td>(+0.88, +2.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔFE_{\text{Cl}^-}^-</td>
<td>-0.39</td>
<td>.0003</td>
<td>-0.29</td>
<td>.0001</td>
<td>.61</td>
</tr>
<tr>
<td></td>
<td>(-0.12, -0.75)</td>
<td></td>
<td>(-0.08, -0.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔFE_{\text{HPO}_4^-}^-</td>
<td>-1.84</td>
<td>.0006</td>
<td>-1.62</td>
<td>.0002</td>
<td>.40</td>
</tr>
<tr>
<td></td>
<td>(-0.53, -3.93)</td>
<td></td>
<td>(-0.26, -2.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔFE_{\text{U}^-}^-</td>
<td>-2.37</td>
<td>.0026</td>
<td>-3.87</td>
<td>.0001</td>
<td>.39</td>
</tr>
<tr>
<td></td>
<td>(-0.22, -6.04)</td>
<td></td>
<td>(-0.43, -7.38)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ΔFE indicates change in fractional excretion. Values are presented as medians and quartiles (Q₁, Q₃).

and increased blood pressure compared with nonobese control subjects.

In the present study relatives had a higher steady-state insulin concentration during the euglycemic hyperinsulinemic clamp. This was also shown in the obese individuals studied by Rocchini et al.24 The difference in insulin concentration between the groups in this study was probably due to the lower MCR\text{ins} shown in relatives. However, it cannot be elucidated whether this was due to a reduced clearance of insulin in muscles and kidney as shown in spontaneously hypertensive rats23,26 or a diminished hepatic insulin extraction as has been reported in some obese subjects.27 However, it cannot be due to higher fasting insulin levels as suggested by Rocchini et al24 because in the present study both groups had similar basal insulin concentrations. Because of the difference in serum insulin concentration between the groups, glucose disposal rate corrected for steady-state insulin concentration during glucose clamp (M/I) has consequently been used as the most appropriate measure of insulin sensitivity. Accordingly, a linear correlation between insulin concentration and peripheral glucose disposal at the insulin concentration achieved in this study has been demonstrated.16,28–29

The reduction of blood pressure in both groups during insulin infusion is in accordance with the finding of Anderson et al in normotensive30 and borderline hypertensive31 subjects. On the other hand, blood pressure was unchanged in the study by Gans et al32 in normotensive subjects as well as in both groups studied by Rocchini et al.24 During long-term insulin infusion in normotensive rats, blood pressure increased,33 but this was not dependent on sodium retention.34 The same investigators found a decrease in blood pressure during 7 days of insulin infusion but unchanged blood pressure after 28 days of insulin infusion in normotensive dogs.35,36 These variable effects of insulin on blood pressure with respect to species and duration of infusion may reflect different physiological mechanisms for the regulation of blood pressure.

As in the study by Anderson et al,30 plasma norepinephrine and heart rate increased during insulin infusion in the control group. These changes were less marked in the relatives, which may be consistent with attenuated insulin-induced sympathetic neural activation in this group. On the other hand, Anderson et al31 did not find any changes in the response of muscle sympathetic nerve activity or heart rate during insulin infusion in borderline hypertensive humans.

The sodium-retaining effect of insulin has been known for a long time,11 but there is no consensus as to the exact mechanism of its action.14 Experimental studies support an antinatriuretic effect of insulin predominantly in the postproximal tubules,37,38 and earlier studies in humans indicate that insulin increases sodium reabsorption in the distal tubules.12 In the present study, reabsorption of potassium was enhanced in both proximal and distal tubules, as judged from lithium clearance (Fig 3). Changes in FE of potassium has been shown to well reflect changes in proximal tubular sodium reabsorption of sodium-replete humans.40 Using
lithium clearance Skett et al. found that infusion of insulin in healthy subjects in lower doses than given in the present study increased sodium reabsorption only in the postproximal tubules. An increase in proximal tubular sodium reabsorption at higher serum insulin levels may be due to a decrease in mean blood pressure, increase in filtration fraction, and/or stimulation of the sympathetic and renin-angiotensin systems, as observed in the present and earlier studies. However, no correlation was found between the increase in norepinephrine or PRA and the increase in fractional proximal reabsorption of sodium.

Reduction of serum potassium, as demonstrated in both groups, might also induce enhanced sodium reabsorption. The reduction of serum potassium was positively correlated to the increase in fractional distal tubular sodium reabsorption.

In normotensive subjects with hypertensive parents, van Hooft et al. reported lower PRA and aldosterone levels as well as lower renal blood flow and higher renal vascular resistance than in normotensive control subjects. Baseline values for PRA, aldosterone, renal blood flow, and renal vascular resistance did not differ between the groups in the present study. The reason for these discrepant findings is not clear.

The decrease in aldosterone in controls is in accordance with the finding by Trovati et al., who achieved serum insulin levels during insulin infusion similar to those in the present study. This decrease in aldosterone level may be explained by the reduction of serum potassium. The unchanged aldosterone level during insulin infusion in relatives, despite a reduction of serum potassium similar to that in controls, suggests abnormal regulation of aldosterone secretion. In borderline hypertensive individuals, increased plasma aldosterone levels have been reported, and the aldosterone response to angiotensin II is enhanced in established hypertension. On the other hand, Widgren et al. found that the fall in serum aldosterone levels during an acute saline load was similar in normotensive men with a positive family history of hypertension and control subjects. The unaltered aldosterone level in relatives may explain the lower reduction of FE of potassium during insulin infusion in this group. It may also add to other mechanisms for sodium retention during hyperinsulinemia, which may lead to the development of hypertension.

The effect of insulin on ANP secretion has not been clarified by earlier studies. The reduction of serum ANP in both groups during 2 hours of insulin infusion could not be explained by the modest retention of sodium (approximately 12 mmol). It may reflect a natural circadian rhythm of ANP secretion, with a decrease during morning hours. This decrease in ANP may to a minor extent explain the reduction of sodium excretion during insulin infusion.

The increase in FE of calcium and decrease in FE of phosphate in both groups during insulin infusion is in accordance with earlier findings. To our knowledge, an increased FE of magnesium during insulin infusion has not been reported earlier. A decrease in FE of phosphate in combination with an increase in FE of calcium and magnesium suggest diminished renal action of PTH. Insulin has been reported to suppress PTH-dependent cyclic AMP production in the renal cortex. When calculated for all individuals, PTH levels decreased, and this reduction in PTH was positively correlated to the increase in FE of calcium.

In conclusion, the impaired insulin-induced glucose disposal in peripheral tissues in normotensive sons of hypertensive families was accompanied by retarded insulin-stimulated tubular sodium reabsorption. The lack of suppression of aldosterone secretion in these subjects may enhance sodium retention.

The enhancement of sodium reabsorption at a serum insulin concentration around 100 mU/L was due to an increased reabsorption in the proximal and distal renal tubules in both relatives and controls, and the increase of distal tubular sodium reabsorption was closely related to the reduction of serum potassium levels.
Acknowledgments

Supported by grants from the Swedish Heart and Lung Foundation, the Nordic Insulin Fund, the Ehrnhold Lundströms Research Foundation, the Swedish Hoochst Diabetes Fund, the Albert Påhlsson Research Foundation, Malmö Diabetes Association, the Research Funds of Malmö General Hospital, and the Medical Faculty of Lund University.

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Hypertension. 1994;23:313-319
doi: 10.1161/01.HYP.23.3.313

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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