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 were increased to the same extent in both groups 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.

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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or radial artery. Intravenous systolic, diastolic, and mean blood pressures were measured using the DTS 150 uniflow pressure set model (Baxter) and monitored on a model OEC-6105K Life Scope 6 (Nihon Kohden) together with an electrocardiogram. Blood pressure and heart rate were registered on a paper chart every 15 minutes throughout the investigation. The intra-arterial basal blood pressures presented are the average blood pressures during the second hour before insulin administration.

When steady-state serum concentrations were reached for \(^{131}\)I-hippurate and \(^{31}\)Cr-EDTA, a basal period of 2 hours was started at 8:30 AM. Arterial blood samples were drawn every hour from 8:30 AM for measurement of \(^{131}I\), \(^{31}Cr\), sodium, potassium, calcium, magnesium, chloride, phosphate, lithium, and norepinephrine, and epinephrine. At 8:30 and 10:30 AM and 12:30 PM, samples for plasma renin activity (PRA), aldosterone, atrial natriuretic peptide (ANP), and parathyroid hormone (PTH) were collected. The subjects were allowed to stand to void, and urine samples were collected from 8:30 to 10:30 AM and 10:30 AM to 12:30 PM for measurement of \(^{131}I\), \(^{31}Cr\), sodium, potassium, calcium, magnesium, chloride, phosphate, and lithium.

From 10:30 AM to 12:30 PM a euglycemic hyperinsulinemic clamp was performed. The steady-state serum insulin concentration was approximately 100 mU/L, and the target level of plasma glucose was 5.0 mmol/L. The total amount of glucose infused during the last hour is a measure of insulin sensitivity to the prevailing insulin concentration. Glucose disposal (M) was calculated as the amount of glucose infused and is expressed per kilogram of body weight (mg·kg body wt\(^{-1}\)·min\(^{-1}\)); the insulin sensitivity index was calculated as the amount of glucose metabolized per unit of plasma insulin multiplied by 100 (M/I, where I is the mean of insulin concentrations at 60 and 120 minutes). The metabolic clearance rate for insulin (MCR\(_I\)) was calculated as insulin infusion rate (47 mU/m\(^2\) body surface area per minute) divided by the increase in plasma insulin concentration above baseline.

The study protocol was approved by the Ethics Committee of the Medical Faculty at the Lund University, and informed consent was obtained from all subjects.

### Analytical Procedures

Clearances (C) of \(^{131}\)I-hippurate, \(^{31}Cr\)-EDTA, and electrolytes were calculated according to the formula C = U ⋅ V/P, where U is urine concentration, V is urine flow rate (milliliters per minute), and P is plasma or serum concentration. Clearances for \(^{131}\)I-hippurate and \(^{31}Cr\)-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 (l/hematocrit), and renal vascular resistance (dyne·s·cm\(^{-5}\)) 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 glomerular filtration rate. Fractional proximal tubular reabsorption of sodium, potassium, and creatinine did not differ between the groups (7.74 [10.6, 15.2] versus 10.6 [9.8, 14.4], P=.66), whereas insulin sensitivity index was lower in relatives than controls (6.08 [4.24, 9.00] versus 7.0 [5.5, 11.2], P=.66).

### Statistical Analyses

Nonparametric methods were used for statistical evaluation. The Wilcoxon signed rank test was used for paired data, Mann-Whitney U test for unpaired data, and Spearman's rank correlation test to calculate correlation coefficients (r). Values are presented as medians and quartiles (Q1, Q3); the level of significance was taken at a value of P<.05.

### Results

The two groups were well matched for age and body mass index (Table 1). They had similar waist-to-hip ratios, basal blood pressures, heart rates, and serum insulin concentrations. Twenty-four-hour urinary excretions of sodium, potassium, and creatinine did not differ significantly.

During the hyperinsulinemic euglycemic clamp, mean serum insulin levels were higher in relatives than controls (112.0 [102.2, 126.2] versus 100.5 [87.1, 105.8], P=.003). Glucose disposal rate was not significantly different between the groups (7.74 [4.90, 10.2] versus 5.5 [5.0, 11.2], P=.20). However, insulin sensitivity index was lower in relatives than controls (6.08 [4.24, 8.42] versus 7.00 [5.99, 11.28], P=.026, Fig 2a). MCR\(_I\) was reduced in relatives compared with controls (452 [404, 484] and 508 [473, 575], P=.0006).

### Table 1. Basal Characteristics of Study Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=23)</th>
<th>Relatives (n=35)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>39</td>
<td>38</td>
<td>.25</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>24.1</td>
<td>25.0</td>
<td>.96</td>
</tr>
<tr>
<td>(22.8, 25.9)</td>
<td>(22.8, 26.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.92</td>
<td>0.92</td>
<td>.79</td>
</tr>
<tr>
<td>(0.86, 0.97)</td>
<td>(0.84, 0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>54</td>
<td>56</td>
<td>.11</td>
</tr>
<tr>
<td>(47, 57)</td>
<td>(51, 62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-arterial systolic blood pressure, mm Hg</td>
<td>121 (115, 127)</td>
<td>124 (117, 129)</td>
<td>.38</td>
</tr>
<tr>
<td>Intra-arterial diastolic blood pressure, mm Hg</td>
<td>64 (62, 89)</td>
<td>68 (64, 72)</td>
<td>.09</td>
</tr>
<tr>
<td>Serum basal insulin, mU/L</td>
<td>7.5</td>
<td>7.0</td>
<td>.66</td>
</tr>
<tr>
<td>(4.8, 10.2)</td>
<td>(5.5, 11.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-Hour urinary sodium, mmol/d</td>
<td>128 (111, 156)</td>
<td>150 (120, 170)</td>
<td>.17</td>
</tr>
<tr>
<td>24-Hour urinary potassium, mmol/d</td>
<td>51 (40, 89)</td>
<td>56 (38, 76)</td>
<td>.51</td>
</tr>
<tr>
<td>24-Hour urinary creatinine, mmol/d</td>
<td>12.8 (9.8, 14.4)</td>
<td>13.3 (10.6, 15.2)</td>
<td>.54</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute. Values are presented as medians and quartiles (Q1, Q3).
and the increase in FE of magnesium were greater in controls compared with relatives. Basal values for FPRNa+ and FDRNa+ were similar in the two groups (Fig 3), and during insulin infusion FPRNa+ and FDRNa+ increased to the same extent in both groups. The reduction of serum potassium was closely correlated to the change in FDRNa+ (P=.52, P=.0001) but not to the change in FPRNa+ (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 FPRNa+ or FDRNa+. 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.2 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). Rocchiini et al34 have reported retained insulin-induced sodium retention in young, obese individuals showing fasting hyperinsulinemia, markedly reduced peripheral glucose disposal.

<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>85.3 (79.2, 88.0)</td>
<td>87.2 (82.4, 91.9)</td>
<td>.0005</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>54 (47, 57)</td>
<td>58 (53, 62)</td>
<td>.002</td>
</tr>
<tr>
<td>Renal blood flow, ml/min</td>
<td>912 (793, 1128)</td>
<td>871 (796, 1035)</td>
<td>.45</td>
</tr>
<tr>
<td>Renal vascular resistance, dyne · s · cm⁻²</td>
<td>7030 (5924, 8535)</td>
<td>7781 (6373, 9753)</td>
<td>.97</td>
</tr>
<tr>
<td>Glomerular filtration rate, ml/min</td>
<td>104 (87, 119)</td>
<td>106 (97, 115)</td>
<td>.08</td>
</tr>
<tr>
<td>Filtration fraction, %</td>
<td>19.2 (17.9, 20.0)</td>
<td>20.1 (17.2, 21.6)</td>
<td>.002</td>
</tr>
</tbody>
</table>

Δ indicates change during euglycemic hyperinsulinemic clamp; bpm, beats per minute. 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* 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 al 24 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 normotensive subjects and borderline hypertensive subjects.31 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.33,35 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,16,38 and earlier studies in humans indicate that insulin increases sodium reabsorption in the distal tubules.12,39 In the present study, reabsorption of sodium was enhanced in both proximal and distal tubules, as judged from lithium clearance (Fig 3). Changes in FE of lithium has been shown to well reflect changes in proximal tubular sodium reabsorption of sodium-replete humans.40 Using

### 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>ΔFEK+</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>ΔFEK−</td>
<td>−10.7</td>
<td>.0001</td>
<td>−8.49</td>
<td>.0001</td>
<td>.011</td>
</tr>
<tr>
<td></td>
<td>(−7.16, −13.5)</td>
<td></td>
<td>(−8.88, −8.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔFEK±</td>
<td>+0.32</td>
<td>.026</td>
<td>+0.12</td>
<td>.383</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>ΔFAEN</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>ΔFAEw</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>ΔFAEw−</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>ΔFAEw+</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).
lithium clearance Skøt et al\textsuperscript{30} 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.\textsuperscript{30,41,44} 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 in normotensive subjects with hypertensive parents, might also induce enhanced sodium reabsorption.\textsuperscript{45} The reduction of serum potassium was positively correlated to the increase in fractional distal reabsorption of sodium in the present study, suggesting a mechanism of action for serum potassium on distal tubular sodium handling. In normotensive subjects with hypertensive parents, van Hooft et al\textsuperscript{46} reported lower PRA and aldosterone levels, and aldosterone levels have been reported,\textsuperscript{30} and the aldosterone response to angiotensin II is enhanced in established hypertension.\textsuperscript{51} On the other hand, Widgren et al\textsuperscript{52} 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.\textsuperscript{9} 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.\textsuperscript{53} This decrease in ANP may to a minor extent explain the reduction of sodium excretion during insulin infusion.\textsuperscript{54,55}

The increase in FE of calcium and decrease in FE of phosphate in both groups during insulin infusion is in accordance with earlier findings.\textsuperscript{12,29} 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.\textsuperscript{56} 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 tissue in normotensive sons of hypertensive families was accompanied by retained 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 Ehrnold Lundströms Research Foundation, the Swedish Hordervist Diabetes Foundation, the Albert Påhlsson Research Foundation, Malmö Diabetes Association, the Research Funds of Malmö General Hospital, and the Medical Faculty of Lund University.

References


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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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