Renal handling of urate and sodium during acute physiological hyperinsulinaemia in healthy subjects

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1. The renal effects of insulin may play a central role in the association between insulin resistance, hypertension and hyperuricaemia. After a 2-h baseline period, we investigated the effects of exogenous insulin for 4 h (50 m-units h⁻¹ kg⁻¹) on fractional renal sodium and urate excretion in 13 healthy subjects, using the euglycaemic clamp and lithium clearance technique, and performed a control experiment in eight of the subjects.

2. Insulin caused a decline in both fractional renal sodium excretion, from 1.13 ± 0.41% to 0.88 ± 0.58% (control study: 0.81 ± 0.35 to 1.35 ± 0.49%; \( P < 0.001 \), insulin versus control), and fractional renal urate excretion, from 6.72 ± 1.87% to 5.71 ± 2.02% (control study: 7.03 ± 2.06 to 7.05 ± 1.94%; \( P = 0.085 \), insulin versus control). The changes in fractional renal sodium and urate excretion were positively correlated \( (r = 0.71, P < 0.01) \). Estimated fractional distal sodium reabsorption increased during insulin infusion from 93.7 ± 2.8% to 96.7 ± 1.9% (control study: 95.7 ± 1.5% to 93.6 ± 1.1%; \( P < 0.001 \), insulin versus control). Estimated fractional proximal tubular sodium reabsorption fell from 81.0 ± 0.5% to 73.7 ± 4.7% during insulin infusion, but less in the control study (81.5 ± 4.3% to 79.3 ± 4.8%; \( P = 0.056 \), insulin versus control). The changes in fractional proximal tubular sodium reabsorption and fractional distal sodium reabsorption during insulin infusion were inversely correlated \( (r = -0.59, P = 0.03) \).

3. During the course of the insulin infusion experiment an inverse correlation between the changes in fractional sodium and urate excretion, and the insulin-mediated glucose disposal, became gradually evident \( (r = -0.73, P < 0.01, \text{ and } r = -0.71, P < 0.01, \text{ respectively; fourth hour of the insulin infusion period}) \).

4. We conclude that exogenous insulin acutely decreases renal sodium and urate excretion, and that this effect is probably exerted at a site beyond the proximal tubule.

Key words: insulin, insulin resistance, lithium, renal sodium excretion, urate.

Abbreviations: ANOVA, analysis of variance; FE, fractional excretion; NIDDM, non-insulin-dependent diabetes mellitus.

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INTRODUCTION

Insulin resistance is associated with hypertension and hyperuricaemia [1–5]. It has been proposed that the attendant compensatory hyperinsulinaemia may contribute to the pathogenesis of elevated blood pressure and hyperuricaemia through its renal effects [6, 7]. This hypothesis is supported by several observations. Exogenous administration of insulin reduces sodium and urate excretion in acute experiments [8–13]. In addition, the sodium-retaining action of insulin has been shown to be preserved in insulin-resistant states such as essential hypertension, obesity, and non-insulin-dependent diabetes mellitus (NIDDM) [14–17]. Notably, both the severity of hypertension and the elevation in serum uric acid levels are related to the degree of insulin resistance [2, 7]. Furthermore, hypertension associated with NIDDM and obesity often displays salt sensitivity, as does essential hypertension [18–21].

It is not clear where in the nephron insulin exerts its action on sodium and urate excretion. Insulin's antinatriuretic effect has been localized in the distal tubule in most studies [9–12, 17, 22, 23]. However, an increased proximal tubular sodium reabsorption during insulin administration has also been reported [24]. On the other hand, the renal handling of urate occurs almost exclusively in the proximal tubule [25]. Indeed, the results of a recent population-based study showed that elevated serum urate levels are independently associated with increased proximal tubular sodium reabsorption as denoted by decreased fractional lithium excretion [26]. The notion that insulin affects sodium in the distal tubule while urate is handled in the proximal tubule is difficult to reconcile with the recent observation that acute, physiological hyperinsulinaemia decreases sodium and urate excretion in a coupled fashion [13]. Moreover, an increase in fractional lithium excretion, indicating a decreased proximal sodium reabsorption, has been demonstrated to accompany insulin-induced sodium retention in several studies of similar design [11, 12, 17, 22, 23].
As the relationship between the effects of insulin on renal urate handling and segmental tubular sodium reabsorption has not been studied, we assessed the effect of acute, physiological hyperinsulinaemia on renal sodium, lithium and urate handling in healthy subjects.

METHODS

Subjects

Thirteen healthy male Caucasian subjects, mean age 21 (range 18–23) years, were studied. All were normotensive (blood pressure less than 140/90 mmHg) with a mean weight of 74.2 (range 64.3–88.0) kg, a body mass index (mean ± SD) of 21.8 ± 1.7 kg/m² and a waist–hip ratio (mean ± SD) of 0.84 ± 0.04, and none was taking medication. Three subjects had a first-degree relative and four others a second-degree relative with hypertension, and two subjects had a second-degree relative with NIDDM. Normal glucose tolerance according to World Health Organization criteria was confirmed by an oral glucose tolerance test. Informed consent was obtained from all subjects. The protocol had been approved by the local ethics committee, and the study was carried out in accordance with the Declaration of Helsinki.

In the week before the insulin infusion study and the control study all subjects adhered to a diet containing 200 mmol of sodium; the extra amount of sodium, necessary in all but one subject, was supplied by capsules containing 8.5 mmol of sodium chloride. Compliance with the diet was confirmed by measurement of 24-h urinary sodium excretion during the last 2 days before each study.

Insulin infusion experiment

The subjects received 300 mg of lithium carbonate orally at 22.00 hours the evening before the insulin infusion and control study. For practical reasons the experiments were performed in the afternoon. Therefore, subjects were allowed to eat one slice of bread and to drink one cup of tea without sugar at 08.00 hours. No food or drinks except water were allowed thereafter. This intake will not perturb the fasting state to a significant extent. All subjects refrained from smoking. The subjects came to the outpatient clinic at noon. Studies were conducted in a room with a constant temperature of 22°C. Polytetrafluoroethylene cannulae (Venflon; Viggo, Helsinborg, Sweden) were inserted for intermittent blood pressure-measuring device (Nippon Colin BP 103 N Sphygmomanometer, Hayashi, Komaki-City, Japan).

Control experiment

Only eight of the subjects were willing and available for the control experiment. This experiment was carried out in an identical fashion as the insulin infusion study with infusion of the same amount of insulin solvent and with blood sampling at the same time intervals, including blood sampling for glucose measurements. Control experiments had to be performed after the insulin clamp experiments because we could not determine beforehand the amount of 20% glucose to be infused each hour to maintain euglycaemia. To correct for any (non-specific) change in sodium excretion or change in blood pressure, heart rate or both, due to volume expansion as the result of 20% glucose infusion to maintain euglycaemia during the insulin infusion experiment, a corresponding amount of water was given orally each hour. Absorption of water from the gastrointestinal tract is rapid and complete, so that no relevant lag in volume expansion was to be expected when compared with intravenous administration of 20% glucose. Control experiments enabled us to correct for any circadian variation in the variables under evaluation.

Blood samples for measurements of the various substances were drawn halfway through each clearance period. Urine and serum concentrations of sodium, potassium, urate and creatinine were determined by standard laboratory techniques. Serum and urinary concentrations of lithium were measured by atomic absorption (Atomic Absorption Spectrophotometer, Perkin Elmer, Norwalk, CT, U.S.A.). Blood samples for measurement of plasma insulin were drawn four times during the second and fourth hour of the insulin infusion period. Plasma insulin concentrations were measured by radio-
immunoassay (Immunoradiometric Assay, Medgenix Diagnostics, Fleurus, Belgium). A quantitative estimate of insulin sensitivity was provided by the mean glucose infusion rate in the second, third, and fourth hour of the euglycaemic clamp (M value (mg min\(^{-1}\) kg\(^{-1}\)) [28] and expressed per unit of plasma insulin concentration (M/I value), thereby correcting for differences in steady-state plasma insulin levels [29]. For convenience, the M/I ratio was multiplied by 100. To calculate the M/I value during the second and fourth hour of the hyperinsulinaemic clamp, we used the average value of the four plasma insulin concentrations obtained during each of these periods. The average of the plasma insulin concentrations during the second and fourth hour was used to calculate the M/I value during the third hour of the clamp.

Calculations

Sodium, potassium urate, lithium and creatinine clearances were calculated according to standard formulas. Fractional clearances were preferred to absolute clearances, because they correct for changes in glomerular filtration rate as well as for dead space or incomplete voiding. Hence, fractional proximal tubular sodium reabsorption was calculated as \(1 - (C_{\text{Lithium}}/C_{\text{Creatinine}}) \times 100\%\), and the fractional distal tubular sodium reabsorption as \(1 - (C_{\text{Sodium}}/C_{\text{Lithium}}) \times 100\%\).

Statistical analysis

Data are expressed as means of the measurements obtained during each clearance period. All variables were analysed by the method of analysis of variance (ANOVA) for repeated measurements to detect differences over time, and differences between the control and study days. Correlation and linear regression analysis and Fisher’s test for the comparison of correlations were applied when appropriate. Correlation between the fractional excretion rates of solutes was performed using the average of the values obtained in all clearance periods after data point distributions in each clearance period had been shown not to differ. Correlation between changes in the fractional excretion rates was performed using the average of the values obtained during the second, third and fourth clearance periods versus the baseline values. A P-value of <0.05 was considered significant. Data are expressed as means ± SD, unless stated otherwise. All analyses were performed on a personal computer using the statistical software package SPSS version 6.0 (SPSS, Chicago, IL, U.S.A.).

RESULTS

The subjects showed a good compliance with the diet. The average urinary sodium excretion per day amounted to 244 ± 52 mmol before the insulin infusion study \((n = 13)\) and 210 ± 42 mmol before the control experiment \((n = 8)\). Clamp characteristics and insulin sensitivity variables are shown in Table 1. The M-value increased from the second to the fourth hour of the clamp. The M/I value did not change because plasma insulin levels demonstrated a small, albeit insignificant \((P = 0.10;\) two-sample t-test), increase over the infusion period. Mean blood glucose levels during the control experiment \((n = 8)\) were not different from those during the insulin clamp experiment \((n = 13)\).

Measurements of plasma concentrations of solutes during the experiments are listed in Table 2. Plasma potassium declined significantly during insulin infusion. Plasma urate showed a similar decline during both studies. The clearance data are shown in Tables 3 and 4. No changes in creatinine clearance were observed during both experiments \((P = 0.29)\). Fractional excretion rate of sodium \((\text{FENa})\) decreased by 22\% during the clamp \((P < 0.001)\), whereas an increase of 66\% \((P = 0.002)\) was noted during the control experiment as compared with baseline. Fractional excretion of lithium \((\text{FEli})\) increased during the clamp, indicating that proximal tubular sodium reabsorption decreased. \(\text{FEli}\) also tended to increase over time during the control study. Estimated fractional distal tubular sodium reabsorption increased during the clamp but decreased during the control experiment. The changes in estimated distal and proximal

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>2 h</th>
<th>3 h</th>
<th>4 h</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Insulin infusion study</strong></td>
<td></td>
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<tr>
<td>Mean glucose concentration (mmol/l)</td>
<td>4.1 ± 0.4</td>
<td>4.1 ± 0.5</td>
<td>4.0 ± 0.3</td>
<td>4.1 ± 0.4</td>
<td>0.23</td>
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<tr>
<td>coefficient of variation (%)</td>
<td>9.8 ± 2.1</td>
<td>9.1 ± 2.3</td>
<td>9.7 ± 1.8</td>
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<tr>
<td>Insulin concentration (pmol/l)</td>
<td>32.0 ± 7.9</td>
<td>270.2 ± 59.2</td>
<td>293.9 ± 48.5</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M-value (mg min(^{-1}) kg(^{-1}))</td>
<td>10.4 ± 4.4</td>
<td>11.3 ± 3.7</td>
<td>12.4 ± 3.1</td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>M/I value (mg min(^{-1}) kg(^{-1}) per pmol/l × 100)</td>
<td>3.94 ± 1.79</td>
<td>4.09 ± 1.53</td>
<td>4.29 ± 1.18</td>
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<td>0.45</td>
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<td><strong>Control experiment</strong></td>
<td></td>
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<tr>
<td>Mean glucose concentration (mmol/l)</td>
<td>4.2 ± 0.3</td>
<td>4.1 ± 0.2</td>
<td>4.2 ± 0.4</td>
<td>4.2 ± 0.5</td>
<td>0.73</td>
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</table>

Table 1. Clamp characteristics and insulin sensitivity variables. Values are means ± SD and analysed to detect differences over time (ANOVA).
sodium reabsorption during the insulin infusion study were inversely correlated (r = -0.59, P = 0.03; Fig. 1).

As expected, changes in the fractional excretion of urate (FEUr) paralleled changes in fractional excretion of sodium (FENa) throughout the clamp (r = 0.71, P < 0.01; Fig. 2). In addition, FEUr and FE Li were positively correlated during the insulin infusion experiment (r = 0.70, P < 0.01; Fig. 3). However, in contrast to the increase in FE Li, FEUr decreased during the hyperinsulinemic clamp. Compared with the control experiment, the decline in FEUr approached statistical significance (P = 0.085). Notably, the changes in FEUr were not related to changes in FE Li.

During the course of the study, an inverse correlation between the changes in FENa and FEUr, and the M/I value became apparent. The correlations with the M/I value reached significance during the third hour of the clamp for the changes in both FENa (second hour: r = -0.31, P = 0.30; third hour: r = -0.56, P = 0.048; fourth hour: r = -0.73, P < 0.01) and FEUr (second hour: r = -0.44, P = 0.13; third hour: r = -0.56, P = 0.049; fourth hour: r = -0.71, P < 0.01). Thus, the higher the insulin-mediated glucose disposal, the more sodium and urate was retained (Figs 4 and 5).

Both systolic and diastolic blood pressure increased more during the insulin infusion study (from 120.5 ± 6.8 to 129.1 ± 8.6 mmHg and from 67.7 ± 6.0 to 68.9 ± 7.4 mmHg respectively) than during the control experiment (from 127.0 ± 7.5 to 131.2 ± 10.4 mmHg and from 67.9 ± 6.0 to 69.8 ± 3.8 mmHg respectively; P = 0.04 and P = 0.03, insulin

| Table 2. Plasma concentrations of solutes at baseline and during hyperinsulinaemic euglycaemic clamp (n = 13) and time-control studies (n = 8). Values are means ± SD. Column A denotes significant changes over time during the separate studies, and column B denotes significant differences over time between the insulin and control studies. |

| Table 3. Clearance data of solutes at baseline and during hyperinsulinaemic euglycaemic clamp (n = 13) and time-control studies (n = 8). Values are means ± SD. Abbreviations: C, clearance; FE, fractional excretion; 1—FE Li, fractional proximal tubular sodium reabsorption; 1—(CNa/Cr), fractional distal tubular sodium reabsorption. Column A denotes significant changes over time during the separate studies, and column B denotes significant differences over time between the insulin and control studies. |
Table 4. Clearance data of markers of segmental tubular solute reabsorption at baseline and during hyperinsulinaemic euglycaemic clamp (n = 13) and time-control studies (n = 8). Values are means ± SD. Abbreviations: C, clearance; FE, fractional excretion; I−FEU, fractional proximal tubular sodium reabsorption; I−(CNJCu), fractional distal tubular sodium reabsorption. Column A denotes significant changes over time during the separate studies, and column B denotes significant differences over time between the insulin and control studies.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>4 h</th>
<th>A</th>
<th>B</th>
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<tbody>
<tr>
<td>FEU (%) Insulin</td>
<td>19.0 ± 5.9</td>
<td>22.1 ± 4.9</td>
<td>24.3 ± 6.5</td>
<td>26.6 ± 5.3</td>
<td>26.3 ± 4.7</td>
<td>&lt;0.001</td>
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<tr>
<td>FEU (%) Control</td>
<td>18.5 ± 4.3</td>
<td>19.6 ± 3.8</td>
<td>17.5 ± 4.0</td>
<td>21.4 ± 5.6</td>
<td>20.7 ± 4.8</td>
<td>0.09</td>
<td>0.056</td>
</tr>
<tr>
<td>I−FEU (%) Insulin</td>
<td>81.0 ± 5.9</td>
<td>77.9 ± 4.9</td>
<td>75.7 ± 6.5</td>
<td>75.4 ± 5.3</td>
<td>73.7 ± 4.7</td>
<td>&lt;0.001</td>
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<tr>
<td>I−FEU (%) Control</td>
<td>81.5 ± 4.3</td>
<td>80.4 ± 3.8</td>
<td>82.5 ± 4.0</td>
<td>78.6 ± 5.6</td>
<td>79.3 ± 4.8</td>
<td>0.09</td>
<td>0.056</td>
</tr>
<tr>
<td>I−(CNJCu) (%) Insulin</td>
<td>93.7 ± 2.8</td>
<td>95.1 ± 1.4</td>
<td>96.7 ± 1.9</td>
<td>96.8 ± 1.5</td>
<td>96.7 ± 1.9</td>
<td>&lt;0.001</td>
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<tr>
<td>I−(CNJCu) (%) Control</td>
<td>95.7 ± 1.5</td>
<td>95.3 ± 1.4</td>
<td>94.0 ± 1.4</td>
<td>94.2 ± 1.8</td>
<td>93.6 ± 1.1</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEU (%) Insulin</td>
<td>6.72 ± 1.87</td>
<td>6.37 ± 1.35</td>
<td>5.54 ± 1.56</td>
<td>5.43 ± 1.78</td>
<td>5.71 ± 2.02</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>FEU (%) Control</td>
<td>7.03 ± 2.06</td>
<td>6.66 ± 1.52</td>
<td>6.54 ± 1.59</td>
<td>7.06 ± 1.98</td>
<td>7.05 ± 1.94</td>
<td>0.73</td>
<td>0.085</td>
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versus control). We found a weak correlation between mean arterial pressure at baseline and the M/I value (r = 0.48, P = 0.10). Notably, no relations were observed between the changes in blood pressure and the changes in FENa and changes in segmental tubular sodium reabsorption during the clamp studies. After correction for changes in mean arterial blood pressure, the inverse correlation between the M/I value and changes in FENa and FeU persisted.

**DISCUSSION**

Recently, it has been shown that acute, physiological hyperinsulinaemia induces a joint reduction in sodium and urate excretion [13]. In that study, however, the conclusions regarding both sodium and urate handling were hampered by the absence of a time-control experiment and an analysis of segmental tubular sodium reabsorption [13]. The results of the present study demonstrate that insulin increases both sodium and urate reabsorption at a
site beyond the proximal tubule, with a concomitant decrease in estimated fractional proximal tubular sodium reabsorption.

It is well known that the kidney regulates sodium and urate reabsorption in a parallel fashion under several (patho)physiological conditions [30] and that filtered urate is almost totally absorbed in the proximal tubule [25]. This has been confirmed by the observation of a clear (positive) correlation between the fractional excretion rates of lithium and urate in a population study [26]. We also observed a similar correlation between FE\(_{Li}\) and FE\(_{Ur}\) (Fig. 3). However, during acute insulin administration the fractional excretion of lithium and urate changed in opposite directions (Table 4).

The cause of this discrepancy most likely resides in the acute nature of our experiments as compared with the observational character of the previous studies. It might be that under chronic conditions renal urate handling is in some way correlated with the degree of insulin resistance and not with hyperinsulinaemia per se. Preliminary evidence suggests that, although the sodium-retaining effect of insulin is preserved, the decreased proximal tubular sodium reabsorption, as denoted by the increased lithium clearance during acute insulin administration, is absent in insulin-resistant conditions [17, 23]. The absence of an increase in atrial natriuretic peptide and/or renal plasma flow has been implicated as possible mechanisms. This notion gains some support from an earlier study among essential hypertensive patients, which showed that renal blood flow was lower and renal vascular resistance increased in patients with high uric acid levels [31].

The renal handling of urate is a complex process, consisting of glomerular filtration, tubular reabsorption, tubular secretion and post-secretory reabsorption [32, 33]. It has been proposed that the final rate of urate excretion is determined by the last two

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Fig. 3. Scatterplot showing correlation between the fractional excretion rates of urate (FE\(_{Ur}\)) and lithium (FE\(_{Li}\)). Each value represents the averages of the values obtained in all timed periods before and during hyperinsulinaemic euglycaemic clamp studies. \(r = 0.70, P < 0.01\).

Fig. 4. Scatterplot showing correlation between rates of insulin-mediated glucose uptake and changes in the fractional excretion rates of sodium (FE\(_{Na}\)) during the fourth hour of hyperinsulinaemic euglycaemic clamp studies. Insulin-mediated glucose uptake is expressed as the MI value (mg min\(^{-1}\) kg\(^{-1}\) per pmol/l \(\times 100\)). Changes in FE\(_{Na}\) represent the values during the fourth hour of the clamp studies compared with baseline values. \(r = -0.71, P < 0.01\).

Fig. 5. Scatterplot showing correlation between rates of insulin-mediated glucose uptake and changes in the fractional excretion rates of urate (FE\(_{Ur}\)) during the fourth hour of hyperinsulinaemic euglycaemic clamp studies. Insulin-mediated glucose uptake is expressed as the MI value (mg min\(^{-1}\) kg\(^{-1}\) per pmol/l \(\times 100\)). Changes in FE\(_{Ur}\) represent the values during the fourth hour of the clamp studies compared with baseline values. \(r = -0.73, P < 0.02\).
processes, which may take place both in the late part of the proximal tubule and in the distal tubule [32, 33]. As no appreciable changes in glomerular filtration rate occurred in our study, the finding of a correlation between the changes in sodium and urate excretion, together with the observation that insulin increased distal tubular sodium reabsorption with a concomitant decrease in proximal sodium reabsorption, suggests that insulin modifies urate handling by enhancing the post-secretory reabsorption of urate beyond the proximal tubule. It is less likely that insulin decreased urate excretion by a decrease in filtration or tubular secretion as the glomerular filtration rate did not change and a similar decrease in plasma urate levels was observed during the insulin and control experiment. It is also unlikely that some, possibly hypokalemia-related, distal lithium secretion contributed to the increments in the fractional excretion of lithium in the course of the insulin infusion study [34]. In insulin-resistant states, e.g. NIDDM and the nephrotic syndrome, the absence of a decreased proximal sodium reabsorption (or increased lithium excretion) has been shown despite the preservation of the insulin-lowering effect on potassium [17, 23].

Evidence for direct and coupled renal tubular handling of sodium and urate is lacking. It has been proposed that the tubular transport of sodium and urate transport is indirectly coupled by anion exchange mechanisms [35]. Possibly, insulin promotes a parallel increase in anion reabsorption, including urate, by activation of the sodium–hydrogen exchanger [36, 37]. One may argue that lithium is less than an optimum marker for proximal tubular sodium reabsorption [38]. It is important to remember that lithium clearance gives an estimate of end-proximal sodium delivery and not a precise quantitative measurement [39]. However, we applied appropriate precautions to improve the usefulness of the method [39], such as the provision of a relatively small amount of lithium and performance of the experiments in the sodium-replete state.

A surprising result of our study is the inverse correlation between insulin-mediated glucose disposal and the changes in sodium and urate excretion. In previous studies, comparing groups, similar antinatriuretic effects have been found in insulin-resistant and insulin-sensitive subjects [14, 15, 17, 22, 23, 36, 40]. The discrepant observation in the present study may be related to the longer duration of the clamp experiment, as the correlation between insulin's renal effects and the insulin-mediated glucose disposal did not reach significance until the third hour of the clamp. Time-dependent changes in the renal handling of sodium during insulin infusion have been documented before [12]. Also, it has been shown that changes in muscle blood flow do not reach a steady state until the third hour of an insulin infusion experiment [41]. It is possible that the attenuated antinatriuretic response in the subjects with the lowest insulin-mediated glucose disposal in our study is related to pre-existing (insulin induced or insulin resistance related) sodium retention and volume expansion. Alternatively, our results might imply that resistance to the glucose-lowering effects of insulin is coupled with resistance to its antinatriuretic and antiuricosuric effects. This view is supported by the results of a recent experiment which showed that the response of the tubular cation transport to insulin in rats is abolished by fructose-induced hypertension [42].

We observed a rise in blood pressure during the clamp, contrary to previous studies during acute, physiological hyperinsulinaemia. It is unlikely that the change in blood pressure confounded our results as changes in sodium excretion were not related to changes in blood pressure, and because the inverse relation between the insulin-mediated glucose disposal and changes in sodium and urate excretion was still present after correction for the changes in blood pressure.

In conclusion, insulin acutely decreases both urate and sodium excretion by an effect beyond the proximal tubule. The exact localization in the nephron and the mechanisms involved are not clear. However, the significance of insulin's antinatriuretic and antiuricosuric effects for the pathogenesis of hypertension and hyperuricaemia in insulin-resistant states remains to be demonstrated.

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