Effect of insulin on uric acid excretion in humans

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Quinones Galvan, Alfredo, Andrea Natali, Simona Baldi, Silvia Frascerra, Giovanna Sanna, Demetrio Ciociaro, and Ele Ferrannini. Effect of insulin on uric acid excretion in humans. Am. J. Physiol. 268 (Endocrinol. Metab. 31): E1–E5, 1995.—Although hyperuricemia is a frequent finding in insulin-resistant states, insulin’s effect on renal uric acid (UA) handling is not known. In 20 healthy volunteers, diastolic blood pressure, body weight, and fasting plasma insulin were positively (and age was negatively) related to fasting plasma UA concentrations, together accounting for 53% of their variability. During an insulin clamp, urine flow was lower than during fasting conditions (1.01 ± 0.12 vs. 1.56 ± 0.32 ml/min, P = 0.04), whereas creatinine clearance was unchanged (129 ± 7 and 131 ± 9 ml/min, P = not significant). Hyperinsulinemia did not alter serum UA concentrations (303 ± 3 vs. 304 ± 12 μM) but caused a significant decrease in urinary UA excretion (whether expressed as absolute excretion rate [1.66 ± 0.21 vs. 2.12 ± 0.23 pmol/min, P = 0.03], clearance rate [5.6 ± 0.8 vs. 7.3 ± 0.8 ml/min, P = 0.03], or fractional excretion [4.48 ± 0.80 ml/min vs. 6.06 ± 0.64%, P < 0.03]). Hyperinsulinemia was also associated with a 30% (P < 0.001) fall in urine Na excretion. Fractional UA excretion was related to Na fractional excretion under basal conditions (r = 0.59, P < 0.01) and during the insulin period (r = 0.63, P < 0.02). Furthermore, the insulin-induced changes in fractional UA and Na excretion correlated with one another (r = 0.66, P < 0.001). Physiological hyperinsulinemia acutely reduces urinary UA and Na excretion in a coupled fashion.

hyperuricemia; insulin action; renal urate handling; insulin clamp

THE ASSOCIATION OF hyperuricemia with obesity (14), diabetes mellitus (32), hypertension (6), and dyslipidemia (1, 2) is a common clinical observation. Obese people present hyperuricemia three times more often than nonobese people. In patients with diabetes mellitus or impaired glucose tolerance, hyperuricemia has been reported in 250% of the cases (16, 17). In essential hypertension, the prevalence of hyperuricemia is higher than that expected in an unselected population (27), and a similar trend has been reported in patients with hypertriglyceridemia (33). The nature of these complex associations remains largely unexplained.

During the last decade, a number of investigations have shown that a defect in insulin sensitivity is present in non-insulin-dependent diabetes mellitus, hypertriglyceridemia, essential hypertension, and obesity (11, 10). Thus hyperuricemia is often present in the same clinical conditions that are associated with insulin resistance with the attendant hyperinsulinemia. This aspect, however, has received little attention. A large epidemiological survey in Israel (23) reported a positive association between hyperinsulinemia and elevated serum uric acid in the general population, this association remained significant after accounting for known correlates of serum uric acid, such as body mass, degree of glucose tolerance, blood pressure, and serum triglycerides (23).

A recent study (9) has shown an association between fasting serum uric acid concentrations and insulin resistance (as measured by the insulin suppression test) in nondiabetic individuals. Moreover, in that study, urinary uric acid clearance was found to be lower in insulin-resistant than in insulin-sensitive subjects (9). These observations raise the possibility that insulin influences uric acid metabolism and that insulin resistance/hyperinsulinemia may play a role in the pathogenesis of hyperuricemia.

We have studied the renal handling of uric acid in response to physiological hyperinsulinemia in healthy individuals under euglycemic and isovolemic conditions.

MATERIALS AND METHODS

Study population. Twenty healthy volunteers were studied. Their anthropometrical and clinical characteristics are given in Table 1. Inclusion criteria were as follows: age, between 30 and 60 yr; body mass index, <30 kg/m²; fasting plasma glucose levels, <6.67 mM; normal glucose tolerance (by National Diabetes Data Group criteria [25]); systolic blood pressure, <150 mmHg; diastolic blood pressure, <95 mmHg; and plasma triglyceride levels, <3 mM. All subjects were free from intercurrent illness and were taking no medications. Subjects were asked to refrain from strenuous exercise on the day before the study. The protocol was reviewed and approved by the Ethics Committee of the National Research Council Institute of Clinical Physiology. The purpose, nature, and risks involved in the study were explained to all of the subjects before obtaining their consent to participate.

Experimental design and methods. Subjects were admitted to the clinical research center at 7:00 A.M. after an overnight (10- to 12-h) fast. They were instructed to void the bladder before leaving home. At 7:30 A.M., subjects drank a glass of water (150 ml). A polyethylene 18-gauge catheter was then inserted into an antecubital vein for the infusion of test substances. Another catheter was threaded into a wrist vein retrogradely, and the hand was placed in a heated box (60°C) for the sampling of arterialized venous blood (20). After a basal period of 2 h in the supine position, subjects voided, urine volume was recorded, and a urine sample was stored for biochemical determinations. Blood pressure was measured by mercury sphygmomanometry.

Insulin sensitivity was assessed by the euglycemic insulin clamp technique (8) at an insulin infusion rate of 6 pmol·ml⁻¹·kg⁻¹. Before the start of the study and at timed intervals during the clamp, arterialized venous blood samples were obtained for the measurement of plasma glucose (by the glucose oxidase method on a Beckman glucose analyzer; Beckman Instruments, Fullerton, CA), insulin (by radioimmunoassay), and creatinine (Jaffé method). In an attempt to maintain urine flow approximately constant throughout the experiment, water was given (with the aqueous glucose solution) during the clamp study at a rate of ~90 ml every 20 min,
whereas blood loss was replaced with saline. To avoid additional NaCl administration, the patency of the sampling catheter was maintained by injecting 1 ml saline via the catheter after each blood sample. At the end of the clamp, subjects voided, urine volume was recorded, and a urine sample was taken for subsequent analysis.

Plasma and urinary K and Na were determined by a specific electrode on a Microlyte Analyzer (Kone, Finland).

Data analysis. Whole body glucose utilization (in pmol min\(^{-1}\) kg\(^{-1}\)) was calculated from the infusion rate of exogenous glucose during the 2nd h of the insulin clamp period, after correction for changes in glucose levels in a distribution volume of 250 ml/kg (12). Endogenous glucose production was assumed to be fully suppressed during euglycemic hyperinsulinemia, as previously demonstrated with the dose of insulin used in the present studies (11). Standard formulas were used to calculate the urinary excretion and clearance rate of creatinine, Na, K, and uric acid. Solute fractional excretion rates were calculated by dividing the solute clearance by the creatinine clearance.

All data are given as means ± SE. The statistical significance of differences between basal and insulinized conditions was tested with the use of the paired Student’s t-test. Simple and multiple linear regression analysis was carried out by standard methods.

RESULTS

After exogenous insulin infusion, plasma insulin concentrations reached a plateau of 312 ± 18 pmol/l during the 2nd h of the euglycemic clamp. Euglycemia was maintained during insulin infusion (steady-state plasma glucose 5.1 ± 0.6 mM vs. a fasting value of 5.2 ± 0.1, P = not significant). Glucose disposal rate in the whole group averaged 33.1 ± 2.2 pmol min\(^{-1}\) kg\(^{-1}\).

Basal urine output averaged 261 ± 7 ml collected in 163 ± 29 min. The corresponding collection after the clamp was 152 ± 15 ml in 148 ± 1 min. Plasma and urine concentrations and urinary excretion of electrolytes under basal conditions and during euglycemic hyperinsulinemia are given in Table 2. During the clamp, urine flow was significantly (P = 0.04) lower (1.01 ± 0.12 vs. 1.56 ± 0.32 ml/min) than during fasting conditions. Mean creatinine clearance rate was virtually superimposable under insulin and basal conditions (129 ± 7 and 131 ± 9 ml/min, respectively, P = 0.63).

Under steady-state conditions of plasma glucose, plasma insulin, and creatinine clearance, the following results were obtained (Table 2): plasma K levels fell by 17% during the clamp, whereas plasma Na rose by ~ 1.5 mmol/l, and serum uric acid remained unchanged. Urine concentrations of K, but not Na or uric acid, were significantly lower during insulin than at baseline.

During the clamp, urine excretion of K, Na, and uric acid decreased by 39, 29, and 22%, respectively, compared with baseline. The respective clearance rates were reduced to a similar extent. When solute urinary excretion was corrected for creatinine clearance, the fractional excretion rates of K, Na, and uric acid all fell by ~ 30% during 2 h of euglycemic hyperinsulinemia (Fig. 1).

To eliminate the possible influence of urine output on the solute excretion rates, the urinary concentration ratios between uric acid, Na, or K and creatinine were calculated. This ratio (in mmol/mmol) decreased from 0.24 ± 0.03 to 0.18 ± 0.02 for uric acid (P < 0.03), from 1.46 ± 0.13 to 1.01 ± 0.08 for Na (P < 0.002), and from 8.12 ± 0.76 to 4.82 ± 0.43 for K (P < 0.0001). Percentagewise, these changes (~ 25, ~ 31, and ~ 41%, respectively) are similar to those obtained from the fractional excretion rates.

In the basal state, diastolic blood pressure, body weight, and fasting plasma insulin were positively (and age was negatively) related to fasting plasma uric acid concentrations (Fig. 2), together accounting for 53% of their variability, whereas a weak inverse relationship was found between uric acid clearance and fasting serum uric acid (r = 0.40, P = 0.06). In the fasting state, fractional urate excretion was significantly related to both K (r = 0.62, P < 0.004) and Na (r = 0.59, P < 0.007) fractional excretion. During the insulin period, these relationships remained essentially unaltered. As a consequence, the change (between insulinized and basal conditions) in fractional urate excretion was directly related to the respective changes in the fractional excretion rates.

Table 2. Plasma concentrations and urinary excretion and clearance rate of solutes at baseline and during euglycemic hyperinsulinemia

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Clamp</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum uric acid, µmol/l</td>
<td>304 ± 12</td>
<td>303 ± 13</td>
<td>0.57</td>
</tr>
<tr>
<td>Plasma creatinine, µmol/l</td>
<td>76 ± 2</td>
<td>77 ± 2</td>
<td>0.26</td>
</tr>
<tr>
<td>Plasma K, µmol/l</td>
<td>4.52 ± 0.09</td>
<td>3.77 ± 0.08</td>
<td>0.0001</td>
</tr>
<tr>
<td>Plasma Na, µmol/l</td>
<td>138.7 ± 0.9</td>
<td>140.2 ± 1.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Urine uric acid, µmol/l</td>
<td>1.74 ± 0.24</td>
<td>1.80 ± 0.26</td>
<td>0.75</td>
</tr>
<tr>
<td>Urine creatinine, µmol/l</td>
<td>9.1 ± 1.3</td>
<td>12.1 ± 1.2</td>
<td>0.08</td>
</tr>
<tr>
<td>Urine K, µmol/l</td>
<td>64 ± 7</td>
<td>54 ± 6</td>
<td>0.02</td>
</tr>
<tr>
<td>Urine Na, µmol/l</td>
<td>129 ± 12</td>
<td>123 ± 11</td>
<td>0.42</td>
</tr>
<tr>
<td>Urine flux, ml/min</td>
<td>1.6 ± 0.3</td>
<td>1.0 ± 0.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Uric acid excretion, µmol/min</td>
<td>2.12 ± 0.23</td>
<td>1.66 ± 0.21</td>
<td>0.03</td>
</tr>
<tr>
<td>K excretion, µmol/min</td>
<td>74 ± 6</td>
<td>45 ± 3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Na excretion, µmol/min</td>
<td>155 ± 13</td>
<td>110 ± 9</td>
<td>0.0005</td>
</tr>
<tr>
<td>Creatinine clearance, ml/min</td>
<td>131 ± 9</td>
<td>129 ± 7</td>
<td>0.63</td>
</tr>
<tr>
<td>Uric acid clearance, ml/min</td>
<td>7.3 ± 0.8</td>
<td>5.6 ± 0.8</td>
<td>0.03</td>
</tr>
<tr>
<td>K clearance, ml/min</td>
<td>16.4 ± 1.2</td>
<td>11.8 ± 0.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Na clearance, ml/min</td>
<td>12.1 ± 0.10</td>
<td>7.6 ± 0.07</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Values are means ± SE. P values refer to comparison of mean group values by paired Student’s t-test.
tion of K and Na (Fig. 3). This latter correlation persisted ($r = 0.56, P = 0.01$) when the insulin-induced change in the urine-to-plasma uric acid ratio was regressed against the corresponding ratio for Na, thereby eliminating any common terms (i.e., urine and plasma creatinine levels) in the correlation.

**DISCUSSION**

Our results confirm the association between plasma uric acid and insulin levels (23), which has led to postulate a role of insulin in the pathogenesis of the hyperuricemia associated with insulin-resistant states. In experiments using the insulin suppression test to measure insulin sensitivity, Facchini et al. (9) also found a direct relationship between insulin-mediated glucose disposal and 24-h uric acid clearance, such that the most insulin-resistant individuals exhibited the lowest uric acid clearance values. In the current studies, although uric acid clearance was inversely related to serum uric acid levels and the latter were positively associated with fasting insulin concentrations, the relationship between uric acid clearance and the whole body glucose utilization...
value was not statistically significant, possibly because of the smaller number of subjects studied.

Hyperuricemia can result from elevated production or reduced net renal excretion of uric acid (4). The aim of the present study was to test the possibility that insulin affects renal urate excretion. Net renal uric acid excretion is regulated by a three-component system (glomerular filtration, tubular reabsorption, and tubular secretion; see Ref. 19). It is usually assumed that virtually all of the urate in plasma is freely filterable at the glomerulus. Filtered uric acid is almost totally absorbed in the proximal tubule (19). Thus renal uric acid clearance depends mainly on tubular secretion and postsecretory reabsorption. Numerous studies have shown that the fractional excretion of uric acid in healthy humans is \(~7\)%, indicating that only a small amount of uric acid escapes tubular reabsorption. Accordingly, in our subjects, fractional uric acid excretion at baseline averaged \(6.1 \pm 0.8\)%.

Acute euglycemic hyperinsulinemia of a 2-h duration reduced fractional uric acid excretion by \(26\)% (to \(4.5 \pm 0.6\)%). This occurred in the absence of detectable changes in glomerular filtration rate (as estimated by the creatinine clearance), indicating that insulin inhibits uric acid secretion or enhances uric acid reabsorption at the tubular level. The effect of insulin was evident also when the data were calculated as the urine urate-to-creatinine ratio, thereby eliminating any bias introduced by urine flow measurements. The exact tubular site (distal and/or proximal) of this insulin action cannot be established from our experiments.

In agreement with previous results (29), we found that acute hyperinsulinemia decreases the excretion (absolute and fractional) and clearance rate of both Na and K. Insulin antikaliuresis is a direct consequence of insulin-induced hypokalemia. In the present studies, urinary K excretion rates were strongly related to plasma K levels \((r = 0.61, P < 0.0001)\) on the pooled basal and insulin data. In previous studies, when insulin-induced hypokalemia was prevented by an exogenous K infusion, the antikaliuretic effect of insulin was abolished (24). In contrast, insulin antinatriuresis is not accompanied by major changes in plasma Na levels (Table 2) and is not markedly influenced by changes in plasma K levels (24). Likewise, the antiuricosuric effect of insulin reported here occurred in the absence of changes in plasma uric acid levels. These findings, and the existence of a correlation between insulin-induced antinatriuresis and antiiuricosuria (Fig. 3), support the concept of a joint influence of insulin per se on the renal handling of Na and uric acid.

The pioneer studies of Holmes et al. (19) have shown that the kidney handles Na and uric acid in a parallel fashion under many physiological conditions. Thus salt restriction (31), diuretic therapy without salt replacement (3), diabetes insipidus (15), hypertension (5), angiotensin, and norepinephrine infusion (13) all are associated with increased Na reabsorption and decreased uric acid clearance. Conversely, salt loading (6), inappropriate anti-diuretic hormone secretion (21), and diuretic therapy with salt replacement (31) lead to a decrease in tubular Na reabsorption associated with increased uric acid clearance. Also in agreement with our results are the findings of a recent population study in which serum uric acid levels were found to be independently associated with increased proximal tubular Na reabsorption (7). In that study, a direct relationship between the fractional excretion of Na and serum uric acid was also found.

The mechanisms underlying the joint renal handling of Na and uric acid are not fully understood. A “physiologic” factor (changes in extracellular fluid volume and hydrostatic or oncotic pressure in peritubular capillarities) could be implicated in the genesis of this phenomenon (22). The consensual changes in the urinary excretion of Na and uric acid observed in our study could be explained also by changes in renal plasma flow and filtration fraction. However, this hemodynamic effect of insulin has been shown to attenuate the antinatriuresis observed during insulin infusion by reducing proximal tubular reabsorption of Na (30). It seems plausible that the joint effect of insulin on net Na and uric acid excretion is exerted at a distal tubular site independently of changes in renal hemodynamics.

The finding that Na and uric acid excretion are both inhibited by physiological hyperinsulinemia is relevant to the yet unexplained association between hypertension and hyperuricemia. Hypertensive individuals develop hyperuricemia more often than normotensive individuals, and, according to recent findings, high uric acid concentrations are a risk factor for the development of essential hypertension (28). Because essential hypertension is an insulin-resistant state (11), insulin resistance/hyperinsulinemia could well represent the link between high blood pressure and hyperuricemia. In fact, hyperuricemia might exert a constant antinatriuretic pressure, thereby leading or predisposing to raised blood pressure, and chronically restrain uric acid excretion, eventually leading or contributing to hyperuricemia. Alternatively, the presence of insulin resistance could mark for the presence of a renal defect in Na and uric acid handling in individuals predisposed to hypertension. These pathophysiological connections would apply to other insulin-resistant states (diabetes, obesity, and dyslipidemia) that share altered serum uric acid levels. In addition, they would provide a background for some therapeutic effects. Thus thiazide administration gives rise to both insulin resistance (26) and hyperuricemia (18), whereas weight reduction improves insulin sensitivity (and reduces plasma insulin concentrations) and reduces blood pressure and serum uric acid concentrations (18).

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3. Bryant J. M., T. F. Yu, L. Berger, N. Schwartz, S. Torsdags, L. Fletcher, H. Fertig, M. S. Schwartz, and R. B. F. Quan. (US), whereas weight reduction improves insulin sensitivity (and reduces plasma insulin concentrations) and reduces blood pressure and serum uric acid concentrations (18).

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EFFECT OF INSULIN ON URIC ACID


