The Generalized Aminoaciduria Seen in Patients With Hepatocyte Nuclear Factor-1α Mutations Is a Feature of All Patients With Diabetes and Is Associated With Glucosuria

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Hepatocyte nuclear factor-1α (HNF-1α) mutations are the most common cause of maturity-onset diabetes of the young. HNF-1α homozygous knockout mice exhibit a renal Fanconi syndrome with glucosuria and generalized aminoaciduria in addition to diabetes. We investigated glucosuria and aminoaciduria in patients with HNF-1α mutations. Sixteen amino acids were measured in urine samples from patients with HNF-1α mutations, age-matched nondiabetic control subjects, and age-matched type 1 diabetic patients, type 2 diabetic patients, and patients with diabetes and chronic renal failure. The HNF-1α patients had glucosuria at lower glycemic control (as shown by HbA1c) than type 1 and type 2 diabetic patients, consistent with a lower renal glucose threshold. The HNF-1α patients had a generalized aminoaciduria with elevated levels of 14 of 16 amino acids and an increased mean Z score for all amino acids compared with control subjects (0.66 vs. 0.00; P < 0.0005). Generalized aminoaciduria was also present in type 1 diabetic (Z score, 0.80; P < 0.0001), type 2 diabetic (Z score, 0.71; P < 0.0002), and chronic renal failure (Z score, 0.65; P < 0.01) patients. Aminoaciduria was not associated with microalbuminuria or proteinuria but was associated with glucosuria (1.00 glucosuria vs. 0.19 no glucosuria; P = 0.002). In type 1 diabetic patients, urine samples taken on the same day showed significantly more aminoaciduria when glucosuria was present compared with when it was absent (P < 0.01). In conclusion, HNF-1α mutation carriers have a mutation-specific defect of proximal tubular glucose transport, resulting in increased glucosuria. In contrast, the generalized aminoaciduria seen in patients with HNF-1α mutations is a general feature of patients with diabetes and glucosuria. Glucose may depolarize and dissipate the electrical gradient of the sodium-dependent amino acid transporters in the proximal renal tubule, causing a reduction in amino acid resorption.

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Received for publication 12 January 2001 and accepted in revised form 21 May 2001.

Hepatocyte nuclear factor-1α (HNF-1α) is a member of the homeodomain-containing superfamily of transcription factors (1–4). These factors have a role in the tissue-specific regulation of gene expression in a number of tissues, including liver, kidney, intestine, and pancreatic islets (5). Heterozygous mutations in the gene encoding HNF-1α are the most common cause of maturity-onset diabetes of the young (MODY) (6). MODY is a subgroup of type 2 diabetes characterized by autosomal dominant inheritance and a young age of onset (7).

The HNF-1α gene is expressed in the kidney. In situ hybridization experiments in developing rat kidney have shown that HNF-1α is first expressed at 15–16 days post coitum, the postinductive phase, in the s-shaped structure in cells committed to tubular differentiation (5). In the newborn rat kidney, HNF-1α is present in the proximal convoluted tubule, distal convoluted tubule, and loop of Henle but not in the collecting ducts (5).

The HNF-1α knockout mouse has a severe renal Fanconi syndrome with polyuria (85% body wt/day), glucosuria, increased renal fractional excretion of 24 amino acids, and phosphaturia caused by renal proximal tubular dysfunction (8). The defect in renal proximal tubular glucose resorption in the HNF-1α knockout mouse is caused by a significant reduction in expression of the high-capacity/low-affinity sodium-glucose transporter-2 (SGLT-2) (9).

In humans, there is evidence to support a specific alteration in renal glucose handling. In the early descriptions of MODY, a reduced renal glucose threshold was noticed to be a phenotypic marker in some families (10). Some of these families have been subsequently found to have mutations in the HNF-1α gene (11). A low renal threshold for glucose has been found in small studies of individuals with HNF-1α mutations (9,12). There has been no comprehensive study of aminoaciduria in individuals with HNF-1α mutations, although in a preliminary study, increased excretion of two amino acids, glycine and alanine, was recorded in three individuals with HNF-1α mutations (13).

Diabetic renal complications have been described in patients with HNF-1α mutations (14,15). As a feature of diabetic nephropathy, microalbuminuria has been report-
ed in 19% of HNF-1α patients (15). As in type 1 and type 2 diabetes, glycemic control is the best predictor of the development of microalbuminuria in individuals with HNF-1α mutations, as this is a microvascular complication of hyperglycemia rather than a direct result of the mutation (15).

We hypothesized that aminoaciduria is a specific phenotypic feature of individuals with HNF-1α mutations as a result of a direct mutational effect that alters amino acid transport. We aimed to test this hypothesis and to study whether aminoaciduria is a more generalized feature of type 1 and type 2 diabetes. If aminoaciduria is specific to individuals with HNF-1α mutations, then it could be used as a phenotypic marker before confirmatory genetic testing.

RESEARCH DESIGN AND METHODS

Participants. A total of 50 people with HNF-1α mutations were recruited from the U.K. MODY collection, and 50 age-matched normal (nonmutation carriers) control subjects were recruited from MODY families. Further control were recruited from diabetes hospital subjects and renal clinics: 25 participants with type 1 diabetes (age and diabetes duration matched to the HNF-1α patients), 25 participants with type 2 diabetes, and 10 participants with diabetes and non–dialysis-dependent chronic renal failure. The clinical characteristics of the participants are shown in Table 1.

Laboratory assays. Early morning urine samples were taken from all participants except for the renal failure patients, who gave random samples. The urine pH and glucose level was tested using BM-Test-7 strips (Boehringer Mannheim). Glucosuria was detected using these strips at a concentration of ≥2.8 mmol/l. Urine albumin and creatinine concentrations were measured using a Bayer Technicon opeRA analyzer, and albumin/creatinine ratios were calculated. Urine samples were then frozen before being analyzed for amino acids. This analysis was conducted with the laboratory blinded to the patient status. All of the urine samples were assayed for the levels of 16 amino acids—aspartate, threonine, serine, glycine, alanine, valine, cystine, methionine, isoleucine, leucine, tyrosine, phenylalanine, ornithine, lysine, histidine, and arginine—with a Beckman autoanalyzer using high-performance liquid chromatography method (normal range 4.0–5.5).

Statistical analysis. Z scores were calculated for all individual amino acids as the number of standard deviations from the mean using values measured in the control group. Results are expressed as means ± SE. The results between groups were compared using unpaired Student’s t Tests were two-tailed except when glucosuria was analyzed, for which, in view of previous studies that showed a low renal threshold for glucose in individuals with HNF-1α mutations, a single-tailed test was used. P ≤ 0.05 was considered significant, except in tests that used a correction for multiple analysis.

RESULTS

Glucosuria was more likely in participants with HNF-1α mutations compared with type 1 and type 2 diabetic patients for a given level of HbA1c. The distribution of percentage of participants with glucosuria for a given level of HbA1c in HNF-1α mutation carriers or in the combined type 1 and type 2 diabetic group is shown in Fig. 1. Glucosuria was more likely in the HNF-1α participants at almost all levels of glycemia. In patients with an HbA1c below 6.9%, 63% of the 30 HNF-1α participants and 36% of the 14 type 1 and type 2 diabetic participants had glucosuria (P = 0.043, one-tailed χ2 test). These results indirectly support that the glucose renal threshold is lower in HNF-1α mutation carriers compared with type 1 and type 2 diabetic patients.

Urine amino acid concentrations were elevated in participants with HNF-1α mutations compared with control subjects. The results of the individual amino acid concentrations in participants with HNF-1α and non–diabetic control subjects are shown in Table 2. For 14 of the 16 amino acids, concentrations were higher in the HNF-1α participants compared with the nondiabetic control subjects; for 6 amino acids, statistical significance was reached after Bonferroni correction for performing 16 analyses. An elevation of urinary amino acid concentration in the HNF-1α participants was seen in all of the basic (n = 4) and neutral (n = 11) amino acids except for valine, which was significantly lower. The only acidic amino acid measured, aspartate, showed a significantly lower level in the HNF-1α participants than in the control subjects (P < 0.0001). The mean combined Z score for a given level of HbA1c in HNF-1α mutation carriers or in the combined type 1 and type 2 diabetic group is shown in Fig. 1.
for all of the amino acids in the HNF-1α participants was 0.66 compared with 0.0 in the control subjects ($P < 0.0005$). This is consistent with a generalized aminoaciduria in the HNF-1α participants.

**Urine amino acid concentrations were elevated in HNF-1α, type 1 diabetic, type 2 diabetic, and diabetic chronic renal failure participants.** The mean combined $Z$ score for all amino acids in all four groups of diabetic participants is shown in Table 3. A similar degree of aminoaciduria seen in the HNF-1α participants (0.66) was seen in type 1 diabetic participants (0.80, $P < 0.0001$ vs. control subjects), in type 2 diabetic participants (0.71; $P < 0.0002$), and in the diabetic chronic renal failure participants (0.65; $P < 0.01$). This is consistent with aminoaciduria being a generalized feature of diabetes.

**Aminoaciduria was not associated with microalbuminuria and proteinuria.** To assess whether generalized aminoaciduria is an early marker of diabetic nephropathy, we compared the mean amino acid $Z$ scores in patients with and without microalbuminuria and with proteinuria for the three different etiological subgroups of diabetic participants. The results are shown in Table 4. When the results from the HNF-1α, type 1, and type 2 groups of diabetic participants were combined, there was no significant difference between the mean combined amino acid $Z$ score in the presence of microalbuminuria (0.70) and proteinuria (0.82) compared with the absence of microalbuminuria (0.68, $P = 0.81$). In no etiological subgroup was there a significant increase in aminoaciduria in the patients with microalbuminuria or proteinuria. In type 1 diabetes, aminoaciduria was significantly lower in patients with microalbuminuria or nephropathy. These results do not support generalized aminoaciduria as an early marker of diabetic nephropathy.

**Aminoaciduria was associated with glucosuria.** We went on to determine whether aminoaciduria was associated with glucosuria. In the HNF-1α participants, the mean amino acid $Z$ score was 0.88 in the presence of glucosuria and 0.28 in the absence of glucosuria ($P = 0.12$). In type 1 diabetic participants, the mean amino acid $Z$ score was 1.19 in the presence and $-0.047$ in the absence of glucosuria ($P = 0.02$); in type 2 diabetic participants, the mean amino acid $Z$ score was 1.07 in the presence and 0.21 in the absence of glucosuria ($P = 0.13$). When all groups were combined, the mean amino acid $Z$ score was 1.00 in the presence of glucosuria and 0.19 in the absence of glucosuria ($P = 0.002$).

The degree of aminoaciduria was related to the degree of glucosuria; in the combined HNF-1α and type 1 and type 2 diabetic participant group, the mean amino acid $Z$ score in those participants with glucosuria of $\geq 16.7$ mmol/l ($n = 42$) was 1.27; the mean $Z$ score in participants with glucosuria of 2.8–16.7 mmol/l was 0.46 ($n = 21$; $P = 0.01$).

The individual amino acid $Z$ scores show the same general trend of increased levels in the presence of glucosuria (data not shown). There was no evidence that any amino acid was specifically elevated in HNF-1α participants independent of the effects of glucosuria. The acidic amino acid aspartate was reduced in all samples from

### Table 2

Comparison of the mean levels (μmol/mmol creatinine) of each amino acid measured in the HNF-1α participants with those in the control subjects

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Charge</th>
<th>HNF-1α participants ($n = 50$)</th>
<th>Control subjects ($n = 50$)</th>
<th>$P$ (HNF-1α vs. control subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystine</td>
<td>Basic</td>
<td>9.6 ± 1.0</td>
<td>5.8 ± 0.4</td>
<td>0.0004</td>
</tr>
<tr>
<td>Lysine</td>
<td>Basic</td>
<td>26.6 ± 5.1</td>
<td>17.9 ± 1.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Arginine</td>
<td>Basic</td>
<td>2.0 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Ornithine</td>
<td>Basic</td>
<td>3.5 ± 0.4</td>
<td>2.0 ± 0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Aspartate</td>
<td>Acidic</td>
<td>4.0 ± 0.4</td>
<td>8.1 ± 0.4</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Threonine</td>
<td>Neutral</td>
<td>17.3 ± 2.3</td>
<td>10.9 ± 0.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Serine</td>
<td>Neutral</td>
<td>30.8 ± 3.0</td>
<td>23.0 ± 2.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Glycine</td>
<td>Neutral</td>
<td>214.9 ± 55.8</td>
<td>121.4 ± 11.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Alanine</td>
<td>Neutral</td>
<td>43.0 ± 3.9</td>
<td>22.6 ± 1.6</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Valine</td>
<td>Neutral</td>
<td>5.4 ± 0.6</td>
<td>8.6 ± 0.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Methionine</td>
<td>Neutral</td>
<td>5.9 ± 0.5</td>
<td>5.1 ± 0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Neutral</td>
<td>3.2 ± 0.2</td>
<td>2.7 ± 0.2</td>
<td>0.08</td>
</tr>
<tr>
<td>Leucine</td>
<td>Neutral</td>
<td>3.4 ± 0.3</td>
<td>2.1 ± 0.1</td>
<td>0.0007</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>Neutral</td>
<td>12.3 ± 0.9</td>
<td>9.1 ± 0.7</td>
<td>0.006</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>Neutral</td>
<td>9.1 ± 0.9</td>
<td>3.6 ± 0.5</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Histidine</td>
<td>Neutral</td>
<td>75.2 ± 7.0</td>
<td>60.6 ± 5.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Data are means ± SE. $P$ values are calculated by unpaired Student’s $t$ tests comparing HNF-1α participants with control subjects. For individual values to be significant after a Bonferroni correction for analyzing 16 amino acids, $P < 0.0031$.

### Table 3

Comparison of the mean combined amino acid $Z$ scores for the three groups of diabetic participants and the participants with renal failure and diabetes

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean $Z$ score</th>
<th>$P$ vs. control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF-1α ($n = 50$)</td>
<td>0.66 ± 0.17</td>
<td>0.0005</td>
</tr>
<tr>
<td>Type 1 ($n = 25$)</td>
<td>0.80 ± 0.22</td>
<td>0.0001</td>
</tr>
<tr>
<td>Type 2 ($n = 25$)</td>
<td>0.71 ± 0.22</td>
<td>0.0002</td>
</tr>
<tr>
<td>CRF and diabetes ($n = 10$)</td>
<td>0.65 ± 0.41</td>
<td>0.01</td>
</tr>
<tr>
<td>Control group ($n = 50$)</td>
<td>0.00 ± 0.13</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are means ± SE. Combined $Z$ scores for all 16 amino acids measured in the HNF-1α and type 1 and type 2 diabetic groups and the participants with chronic renal failure (CRF) and diabetes. $P$ values based on unpaired Student’s $t$ tests compared with the control group.
diabetic participants and was not altered by the presence or absence of glucosuria.

Levels of aminoaciduria at different times of day in individual participants depended on the presence or absence of glucosuria. In a further study, 14 of the type 1 diabetic participants provided 3–5 urine samples collected at different times of a single 24-h period. Samples with and without glucosuria were available from 10 of the 14 participants. A total of 49 urine samples were collected from these 10 participants, and these samples were analyzed for 16 amino acids, and Z scores were calculated as described previously.

In 8 of these 10 participants, the mean combined Z score was higher in the samples with glucosuria than in those without glucosuria. The overall mean combined Z score in the samples in the presence of glucosuria was 0.76 higher in the presence of glucosuria compared with when glucosuria was absent (0.43 vs. −0.32; P = 0.01, single-tailed paired Student’s t test; P = 0.02, two-tailed paired Student’s t test). A discordant pair analysis was also used to compare all paired urine samples from the same individual that were discordant for the presence of glucosuria. With the use of this approach, 44 discordant urine sample pairs were identified. The overall mean combined Z score was 0.81 higher in these paired samples in the presence of glucosuria (0.56 vs. −0.25; P < 0.0001, single-tailed paired Student’s t test; P < 0.0001, two-tailed paired Student’s t test). These results in the same patient further established the close association of generalized aminoaciduria with glucosuria.

DISCUSSION
We found that humans with HNF-1α mutations, like the homozygous HNF-1α knockout mouse, have both glucosuria and a generalized aminoaciduria. Our observations support a mutation-specific effect on glucose handling in the proximal renal tubule but do not support our hypothesis that the aminoaciduria was a phenotype specific to HNF-1α mutation carriers. We showed that the aminoaciduria seen in individuals with HNF-1α mutations is likely to represent a manifestation of their glucosuria, as a generalized aminoaciduria is associated with glucosuria in all types of diabetes.

In mice with a homozygous inactivation of the HNF-1α gene, glucosuria results in the animals having marked polyuria with up to 85% of the animals’ body weight being passed in urine each day (8). This is seen, to a lesser extent, in humans. A reduced renal threshold for glucose was described as a specific feature of two of the three families described in Tattersall’s early description of MODY (10). One of these families has been shown to have a mutation in HNF-1α (11). A low renal threshold for glucose has been demonstrated in five members of one family with the HNF-1α missense mutation R272H (12) and in a small group of French mutation carriers (9). We found individuals with a wide range of HNF-1α mutations showed more glucosuria at a similar level of HbA1c than type 1 and type 2 diabetic patients. This provides indirect evidence of a lower renal threshold in patients with a large number of different HNF-1α mutations. Direct measurement of the renal threshold, preferably using clamp methodology, would be needed to confirm this.

The handling of glucose in the kidney is not completely understood. The luminal transport of glucose in the proximal convoluted tubule involves two sodium coupled transport proteins. SGLT-2 is kidney specific and of high capacity for bulk resorption of glucose in the S1 and S2 segments of the proximal tubule. SGLT-1 is of high affinity and is present in the S3 segment of the proximal tubule and the small intestine. In normal subjects, SGLT-1 resorbs all of the remaining glucose in the proximal tubule fluid. The basolateral glucose transporters (GLUT-1 and -2) are not sodium coupled (16). The HNF-1α knockout mouse has been shown to have a significant reduction in the expression of SGLT-2, which causes the defect in glucose resorption in the proximal renal tubule (9). HNF-1α probably has a direct role in the regulation of transcription of the SGLT-2 gene mediated through the HNF-1α binding sites (9).

We found evidence of a generalized aminoaciduria in HNF-1α mutation carriers who showed increased urinary concentrations in the urine of 14 of 16 amino acids when compared with age-matched, family control subjects. This was similar to the generalized aminoaciduria found in mice with homozygous inactivation of HNF-1α. However, the subsequent studies in type 1 and type 2 diabetic participants showed that the generalized aminoaciduria was a feature of all subtypes of diabetes and not specific to HNF-1α mutation carriers. The generalized aminoaciduria is not related to preexisting renal damage, as diabetic participants with chronic renal failure had a similar level of aminoaciduria as participants without nephropathy, and there was no significant difference in the mean amino acid Z score in diabetic participants with microalbuminuria and proteinuria compared with those without microalbuminuria.

### Table 4
Comparison of the mean combined amino acid Z scores in the presence and absence of microalbuminuria and proteinuria in the three groups of diabetic participants

<table>
<thead>
<tr>
<th>Group</th>
<th>No microalbuminuria</th>
<th>Microalbuminuria present</th>
<th>Proteinuria present</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF-1α</td>
<td>0.60 ± 0.17 (43)</td>
<td>1.01 ± 0.68 (7)</td>
<td>n = 0</td>
<td>0.41</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>1.23 ± 0.33 (14)</td>
<td>0.36 ± 0.21 (8)</td>
<td>0.24 ± 0.32 (8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>0.37 ± 0.18 (13)</td>
<td>0.74 ± 0.22 (11)</td>
<td>1.59 ± 0.87 (6)</td>
<td>0.12</td>
</tr>
<tr>
<td>HNF-1α + type 1 + type 2 diabetes</td>
<td>0.68 ± 0.13 (70)</td>
<td>0.70 ± 0.21 (26)</td>
<td>0.82 ± 0.44 (14)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Data are means ± SE (n). Mean combined Z scores for all 16 amino acids measured in participants with no microalbuminuria and with microalbuminuria and proteinuria for the HNF-1α and the type 1 and type 2 diabetic groups. Microalbuminuria is defined by a urinary albumin of >20 mg/l and <200 mg/l, with a urine albumin/creatinine ratio of >2.5 mg/mmol. Proteinuria is defined by a urinary albumin of >200 mg/l. P values are calculated using unpaired Student’s t tests comparing the results in the presence of microalbuminuria and proteinuria with those in the absence of microalbuminuria for each group.
Aminoaciduria was very strongly associated with the presence of glucosuria. In all patient groups, aminoaciduria was increased in the presence of glucosuria. To our knowledge, this is the first description of the generalized aminoaciduria seen in all subtypes of diabetes. Considerable evidence supports that the aminoaciduria was a direct result of the glucosuria: the individual amino acids showed a generalized trend of increased urinary excretion in the presence of glucosuria; there was increasing aminoaciduria with increasing degrees of glucosuria; and in type 1 diabetic patients, within a 24-h period, the degree of aminoaciduria varied with the presence or absence of glucosuria.

If glucosuria is associated with generalized aminoaciduria in all types of diabetes, then aminoaciduria also should be seen in other conditions in which there is glucosuria without diabetes. Aminoaciduria together with glucosuria has been reported in a number of conditions. Aminoaciduria (aspartate, glutamic acid, citrulline, and alanine) was reported in two individuals with renal glucosuria (16). Renal glucosuria is a familial condition associated with a defect in the SGLT-2, resulting in glucosuria despite a normal 24-h blood glucose level and a normal glucose tolerance test. Acute lead poisoning produces renal manifestations of the renal Fanconi syndrome, including glucosuria, aminoaciduria, and phosphaturia. Lead has an effect on mitochondrial respiration and phosphorylation and also a direct inhibitory effect on the rBAT amino acid transporter. Persistent glucosuria and aminoaciduria (as measured by the urinary a-amino nitrogen/creatinine ratio), in the presence of normal renal function, has been reported up to 13 years after childhood lead poisoning (17). Glucosuria and aminoaciduria are general features of the renal Fanconi syndrome that may be primary or secondary to other causes, including inborn errors of metabolism, myeloma, or exposure to cisplatin or ifosfamide in addition to lead (18). In addition to these pathological examples, infusion of a 10% glucose solution in non-diabetic humans has been shown to produce glucosuria and generalized aminoaciduria, as measured by the increased excretion of 16 amino acids in four subjects (19).

The mechanism for the generalized aminoaciduria seen in the presence of glucosuria is not known. Amino acids, like glucose, are nearly totally resorbed in the proximal tubule in normal subjects (20). A number of different amino acid transport systems have been identified, and it is likely that there are others as yet unidentified. There are three categories of transporter for acidic, basic, and neutral amino acids. These transporters include EAAC1 for transport of the acidic amino acids glutamate and aspartate; D2H/rBAT for the basic amino acids lysine, arginine, ornithine, and cystine; and mCAT for lysine, arginine, and ornithine (20–23). Neutral amino acid transporters include system A, which is a member of the SGLT family of proteins, and system ASC (24, 25). Our work suggests that generalized aminoaciduria, seen in all studies of patients with diabetes, is a direct effect of glucose on amino acid resorption and not a specific alteration of transporter transcription. The most likely explanation is that the presence of glucose in the proximal renal tubule depolarizes and dissipates the electrical gradient of the sodium-dependent amino acid transporters, causing a reduction in amino acid resorption. Further animal studies are required to examine this in greater detail.

In conclusion, HNF-1α mutation carriers have a specific defect of proximal tubular glucose transport, resulting in increased glucosuria. This is probably mediated through a direct effect of reduced HNF-1α activity, leading to reduced transcription of the SGLT-2 glucose transporter. In contrast, the generalized aminoaciduria seen in individuals with HNF-1α mutations is a general feature of all patients with diabetes and glucosuria, possibly reflecting reduced amino acid resorption as a result of glucose depolarizing and dissipating the electrical gradient of the sodium-dependent amino acid transporters in the proximal renal tubule.

ACKNOWLEDGMENTS

We thank Eli Lilly, the National Kidney Research Fund (grant reference no. TF13/2000), Diabetes U.K., and the Exeter Kidney Unit Development Fund for support of this work.

The technical assistance of Catherine Murdoch-Davis and Lisa Allen is appreciated.

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