Kidney plays a major role in ammonia homeostasis after portasystemic shunting in patients with cirrhosis

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1Department of Surgery, Maastricht University, Maastricht, The Netherlands; 2Liver Unit, 3Department of Surgery and 4Radiology, Royal Infirmary of Edinburgh, Edinburgh, Scotland, United Kingdom; and 5Liver Failure Group, Institute of Hepatology, Royal Free and University College Medical School, University College London, London, United Kingdom

Submitted 11 April 2005; accepted in final form 22 January 2006

Kidney plays a major role in ammonia homeostasis after portasystemic shunting in patients with cirrhosis. Am J Physiol Gastrointest Liver Physiol 291: G189–G194, 2006. First published February 2, 2006; doi:10.1152/ajpgi.00165.2005.—The kidney plays an important role in ammonia metabolism. In this study the hypothesis was tested that the kidney can acutely diminish ammonia release after portacaval shunting. Thirteen patients with cirrhosis (6 female/7 male, age 54.4 ± 3.3 yr) were studied. Blood was sampled prior to and 1 h after transjugular intrahepatic stent-shunt (TIPSS) insertion from the portal vein, a hepatic vein, the right renal vein, and the femoral vein, and renal and liver plasma flow were measured. Prior to TIPSS, renal ammonia release was significantly higher than ammonia release from the splanchnic region, which was not significantly different from zero. TIPSS insertion did not change arterial ammonia concentration or ammonia release from the splanchnic region but reduced renal ammonia release into the circulation (P < 0.05) to values that were not different from zero. TIPSS resulted in a tendency toward increased venous-arterial ammonia concentration differences across leg muscle. Post-TIPSS ammonia efflux via portasystemic shunts was estimated to be seven times higher than renal efflux. Kidneys have the ability to acutely diminish systemic ammonia release after portacaval shunting. Diminished renal ammonia release and enhanced muscle ammonia uptake are important mechanisms by which the cirrhotic patient maintains ammonia homeostasis after portasystemic shunting.

ABOUT 15–20% OF PATIENTS with cirrhosis of the liver develop hepatic encephalopathy after insertion of a transjugular intrahepatic portosystemic stent-shunt (TIPSS). This has been attributed to the induction of hyperammonemia by an acute increase of portasystemic shunting of portal-drained viscera-generated ammonia (15). Occasionally, TIPSS insertion results in fatal increases in intracranial pressure in cirrhotic patients (14), which may be induced by hyperammonemia (4). Present ammonia-lowering therapies are predominantly directed at intestinal ammonia production, but therapeutic results are modest. We have recently shown that the kidney plays a major role in the hyperammonemia that follows upper gastrointestinal hemorrhage (22). Interventions such as altering the intravascular volume status or acid-base balance can alter renal ammonia metabolism acutely (17), making the kidney a potential target organ for therapy. In experimental animals it has been shown that the kidney is able to switch from net ammonia production in to net ammonia removal from the body following hyperammonemia induced by portacaval shunting (10). The present study was performed to evaluate whether this metabolic adaptation to portacaval shunting was present in patients with cirrhosis of the liver.

MATERIALS AND METHODS

Studies were undertaken with the approval of the Lothian Research Ethics Committee and after obtaining written informed consent from each patient or next of kin. Patients were eligible to participate in the study if they had cirrhosis of the liver and needed treatment with TIPSS for the management of variceal bleeding. Patients were excluded if they had diabetes, clinically evident cardiovascular disease, malignancy, or pregnancy. None of the patients were taking angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

Patients. Thirteen patients were studied, following admission to the Royal Infirmary of Edinburgh, with an acute variceal bleed that was initially controlled with endoscopic variceal band ligation (Table 1). Patients were studied after an overnight fast.

TIPSS procedure and catheter placement. Before the TIPSS procedure was started, the femoral artery was cannulated. A single interventional radiologist (D. N. Redhead) performed all the TIPSS procedures. Procedures were performed in an angiography laboratory under sedation. For TIPSS insertion, the right internal jugular vein was punctured, and a 10-French sheath (William-Cook, Bjaeverskov, Denmark) was introduced over a guide wire into the inferior vena cava. The right or middle hepatic vein was selected using a stiff hydrophilic guide wire (Terumo; Tokyo, Japan). Hereafter, a 16-gauge curved transjugular needle (William-Cook) was introduced over the guide wire into the hepatic vein and used to guide a fine styllet anteromedially towards a branch of the portal vein. Aspiration of blood followed by delineation of the portal system by injection of contrast medium. Hereafter, the stent (10-mm Wallstent; Schneider, Bulach, Switzerland) was inserted. Pressure measurements and photography were performed at the time of portal vein catheterization and after shunt creation to ensure adequate shunting (portal pressure gradient below 12 mmHg).

Sampling. Directly prior to and 1 h after TIPSS insertion, a 5-French catheter (femoral-venous angiographic catheter; Terumo, Leuven, Belgium) was introduced through the sheath in the right internal jugular vein to enable blood sampling in the right renal vein, a hepatic vein, and the portal vein. The portal vein sample was taken directly after puncturing the portal vein, before the TIPSS was inserted (pre-TIPSS), and 1 h after the TIPSS was inserted (post-TIPSS). Blood was collected from the middle or right hepatic vein that did not contain the TIPSS to prevent mixing of hepatic and portal venous blood. In the last four patients additional measurements were made to obtain preliminary information on muscle ammonia handling.

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and measurements of ammonia excretion by the kidney were obtained in the last three patients. In these patients blood samples were also collected from the right femoral vein, urine samples were collected from an indwelling urine catheter, and urine output was measured.

**Blood flow measurements.** To enable determination of renal and liver plasma flow, patients received a primed (0.56 ml/kg body wt), continuous infusion (50 ml/h) of p-aminohippuric acid (PAH, aminohippurate sodium 20% solution; Merck Sharp and Dohme, Haarlem, The Netherlands) and a primed (12 mg), continuous infusion (1 mg/min) of indocyanine green (FCG; Cardiogreen; Becton Dickinson Microbiology Systems, Cockeysville, MD) into a dorsal hand vein. PAH infusion was started at least 3 h and indocyanine green at least 1 h before TIPSS insertion to ensure steady state (23, 24). Renal and liver plasma flow measurements were made pre-TIPSS and post-TIPSS by simultaneous sampling of arterial, renal, and hepatic venous blood for determination of PAH and ICG.

**Sampling and analytical procedures.** Blood samples were collected on ice for the measurement of ammonia, amino acids, and acid-base status at the times of measurement of blood flow. Urine samples were collected on ice and acid (6 N HCl) to prevent evaporation of ammonia (10). Blood electrolyte concentrations were directly measured using a CO oximeter (model IL 282; Instrumentation Laboratories, Boston, MA). Blood and urine samples were processed as described previously (8) and stored at −80°C. Plasma and urine ammonia, plasma urea, PAH, and indocyanine green were determined spectrophotometrically as detailed previously (8, 13); plasma amino acids were determined using HPLC (11).

**Calculations.** Renal and liver plasma flow were calculated according to the Fick principle, using standard equations (8). Renal ammonia release or uptake was calculated as the venous minus arterial concentration difference times plasma flow. The hepatic venous minus arterial concentration difference multiplied by the liver blood flow reflects the substrate release or uptake across the nonshunted splanchnic region. Positive values reflect substrate release, and negative values reflect substrate uptake. In the present study we were unable to measure the degree of portosystemic shunting, and therefore we were unable to determine the amount of ammonia that was released from the splanchnic region via portosystemic shunts (like the TIPSS), thereby escaping clearance by the liver. This “shunted” splanchnic region release was estimated using portosystemic flow data from the literature and the measured portal venous-arterial ammonia differences of the present study (detailed in the DISCUSSION).

Total renal ammonia production could only be calculated in those three patients in whom urinary ammonia excretion was calculated. Hepatic extraction of ICG was calculated as the arterial minus hepatic venous concentration divided by the arterial concentration.

**BCAA represents the sum of the branched chain amino acids (leucine, valine, and isoleucine), TEAA represents the sum of the essential amino acids, TNEAA represents the sum of the nonessential amino acids, and TAA represents the sum of all amino acids measured.**

**Statistics.** Values are means ± SE. Nonparametric statistics were used. The Wilcoxon signed rank test was used for differences between pre-TIPSS and post-TIPSS values and to test for differences from zero. The Mann-Whitney U-test was used to test for differences between renal and nonshunted splanchnic region ammonia handling. Significance was considered at P < 0.05.

**RESULTS**

**Patients.** All patients included in the study underwent successful TIPSS insertion. The mean portal pressure gradient before TIPSS was 17.8 ± 1.5 mmHg, and this was successfully reduced to 8.9 ± 0.8 mmHg. At the time of TIPSS insertion the patients were hemodynamically stable (see Table 1).

**Plasma flow.** Hepatic and renal plasma flow did not change significantly following TIPSS insertion (liver, 8.0 ± 2.0 vs. 6.5 ± 1.0 ml·kg body wt⁻¹·min⁻¹; renal, 11.5 ± 0.9 vs. 12.1 ± 2.3 ml·kg body wt⁻¹·min⁻¹). The mean hepatic extraction of ICG did not change after the TIPSS placement.
(0.26 ± 0.05 pre-TIPSS and 0.25 ± 0.04 post-TIPSS) and was sufficiently high to allow a valid determination of plasma liver flow (3).

Arterial data. Table 2 shows the concentrations of ammonia, urea, and amino acids in arterial plasma; and the venous-arterial concentration differences across the liver, kidney, and portal bed during the TIPSS procedure. Interestingly, TIPSS insertion did not change arterial ammonia concentrations but resulted in a significant increase in arterial alanine, TNEAA, and TAA concentrations.

Renal metabolism. Ammonia, urea, and amino acid release or uptake across the kidney and the nonshunted splanchnic region are shown in Table 3. Prior to TIPSS, the kidney produced significant amounts of ammonia, but TIPSS insertion reduced renal ammonia release into the circulation significantly (P < 0.05) to values that were not significantly different from zero (see also Fig. 1). Interestingly, the uptake of the amino-niagenic amino acids glutamine and glycine was not influenced by TIPSS insertion. Furthermore, there was a significant uptake of urea by the kidney that was not altered by TIPSS. Renal urea extraction was not significantly altered by the TIPSS procedure (3.4 ± 1.3% vs. 4.1 ± 1.1%). After TIPSS, the net efflux of BCAA, TEAA, TNEAA, and TAA became significant.

Table 4 shows the total renal ammonia production of the three patients in whom urine samples were collected and the amount of ammonia released into the systemic circulation and excreted into the urine. Total renal ammonia production decreased markedly in all patients, whereas the percentage of total ammonia production that was excreted into the urine increased in all patients after TIPSS insertion. Urinary ammonia excretion exceeded renal release of ammonia to the circulation in only one patient. Interestingly, this was the patient with the highest arterial ammonia concentration pre-TIPSS. After TIPSS insertion, arterial ammonia concentration decreased slightly in this patient, which was associated with a reduction in total renal ammonia production and renal glutamine uptake.

Portal-drained viscera metabolism. Ammonia concentration in the portal vein was significantly higher than the arterial concentration, and the resulting venous-arterial concentration difference did not change significantly after the TIPSS insertion. There was a significant negative net balance of glutamine across the portal-drained viscera, which did not change significantly following TIPSS.

Splanchnic metabolism. There was no significant release or uptake of ammonia by the nonshunted splanchnic region before and after the TIPSS insertion. Apart from a net release of urea, all other substrates were taken up by the nonshunted splanchnic region. Ammonia release into the systemic circulation by the kidney was significantly greater than that by the nonshunted splanchnic region prior to TIPSS. After TIPSS insertion, systemic ammonia release by the kidney was reduced to values that were not significantly different from zero and similar to that in the nonshunted splanchnic region.

Muscle metabolism. Prior to TIPSS, ammonia was taken up by leg muscle in all the four patients studied. The femoral venous-arterial ammonia concentration difference increased after TIPSS insertion in all four patients. Glutamine was released by skeletal muscle in all four patients before TIPSS and did not change after TIPSS insertion.

Acid-base balance. Insertion of TIPSS did not change hydrogen ion concentration in the artery (39 ± 2 vs. 38 ± 2 nM), which were all within the normal physiological range.
The present study confirms our recent observation (22) that the kidney plays a major role in the hyperammonemia that is observed in patients with cirrhosis of the liver. As we have shown previously, systemic ammonia release from the kidneys exceeded that from the nonshunted splanchnic region. We also confirm that the main ammonia-removing organs in this situation are the liver and muscle. The most important observation of our study was the demonstration that renal ammonia release into the circulation was acutely diminished after TIPSS insertion, despite the marked increase in shunting of portal-drained viscera produced ammonia after TIPSS. Our findings also suggest increased uptake of ammonia by the leg (muscle) after TIPSS, whereas the nonshunted splanchnic region uptake of ammonia did not change. Our data suggest that the reduced renal ammonia production and increased muscle ammonia uptake are responsible for the observed maintenance of arterial ammonia concentration after TIPSS insertion in patients with cirrhosis. These results again underline the important role of the kidney in ammonia metabolism.

TIPSS insertion reduced renal ammonia release into the circulation to values that were not significantly different from zero. Recently, we showed that renal ammonia production is negligible in metabolically stable patients with cirrhosis of the liver who had a TIPSS inserted on average 25 mo previously (21). This suggests that the observed instantaneous adaptation of the kidney to TIPSS-induced alterations in ammonia metabolism is not a transient phenomenon and is probably still active 2 years after TIPSS insertion. The hyperammonemia observed in patients with a previously inserted TIPSS was slightly less than that observed in the present study (95 vs. 45 μM for healthy controls; Ref. 5) and was also related to the shunting of ammonia production in the portal-drained viscera (21).

Creation of a portacaval shunt in rats resulted in a reduction in renal ammonia production despite markedly elevated arterial ammonia concentrations (9, 10). Renal glutamine consumption was reduced concomitantly. In addition, 70% of total ammonia produced in the kidney was excreted into urine and 30% was released into the renal vein, resulting in a negative renal venous-arterial ammonia concentration (10), making the kidney an organ of net ammonia removal during hyperammonemia. In the present study, a mechanistic interpretation of the cause of the diminished systemic ammonia release was prevented by our inability to determine urinary ammonia excretion in all patients. In the three patients in whom we measured urinary ammonia excretion, total renal ammonia production decreased, and percentage of renal ammonia production that was excreted via the urine increased in all patients, in one patient to even 86% of total renal ammonia production excreted via the urine. Net renal ammonia flux remained positive in all three. In the whole group, TIPSS insertion reduced renal ammonia release into the circulation to values that were not significantly different from zero.

TIPSS insertion was not associated with significant differences in the uptake or release of the ammoniagenic amino acids glutamine and glycine (12) by the kidney, despite a reduction in systemic ammonia release. This observation suggests unaltered renal ammoniagenesis. This issue needs further confirmation in future studies. In the present study, the changes in renal ammonia metabolism did not appear to be related to changes in acid-base homeostasis. Acidosis induces enhanced renal glutamine extraction and increases ammonia release into the urine at the expense of urea excretion, whereas total urinary nitrogen excretion remains constant (25, 26). During acidosis the fraction of ammonia excreted in the urine rises to 70%, but the exact underlying mechanism is unknown.

### Table 4. Renal ammonia metabolism

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tipps</th>
<th>Arterial Creatinine, μM</th>
<th>Urine Production, ml/h</th>
<th>Arterial Ammonia, μM</th>
<th>Renal Glutamine Flux, mmol/kg body wt⁻¹min⁻¹</th>
<th>Renal Ammonia Flux, mmol/kg body wt⁻¹min⁻¹</th>
<th>Renal Ammonia Production, mmol/kg body wt⁻¹min⁻¹</th>
<th>Percentage Urinary Ammonia Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Pre</td>
<td>66</td>
<td>114</td>
<td>89</td>
<td>−429</td>
<td>411</td>
<td>104</td>
<td>515</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>105</td>
<td>100</td>
<td>−457</td>
<td>183</td>
<td>159</td>
<td>342</td>
<td>46</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Pre</td>
<td>50</td>
<td>270</td>
<td>74</td>
<td>−1,005</td>
<td>440</td>
<td>60</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>286</td>
<td>79</td>
<td>−1,132</td>
<td>290</td>
<td>122</td>
<td>422</td>
<td>29</td>
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<tr>
<td>Patient 3</td>
<td>Pre</td>
<td>290</td>
<td>160</td>
<td>181</td>
<td>−1,353</td>
<td>894</td>
<td>458</td>
<td>1,352</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>200</td>
<td>166</td>
<td>−203</td>
<td>70</td>
<td>415</td>
<td>485</td>
<td>86</td>
</tr>
</tbody>
</table>
Renal ammonia excretion into the urine cannot be explained simply as pH dependent (the “diffusion-trapping” system), but several other mechanisms (e.g., tubular urine flow, several ion exchangers, and the ammonia countercurrent system) appear to be more important than pH in the complex regulation of urinary ammonia excretion (12, 20). To be excreted in urine, ammonia must be synthesized by proximal tubular cells, secreted into the proximal tubular fluid, reabsorbed by the medullary thick ascending limb (MTAL), accumulated in the medullary interstitium, and finally secreted in medullary collecting ducts. Each step of this renal pathway is highly regulated and, in addition to acute events, mediated by peptide hormones like angiotensin II (see Ref. 18 for review). As we have shown recently, acute changes in the volume status of patients with cirrhosis produced an increase in urinary excretion of ammonia with a simultaneous decrease in plasma ammonia levels (17), which was closely related to changes in plasma angiotensin II concentrations. Angiotensin II is known to enhance renal ammoniagenesis in a dose-dependent manner independent of changes in pH via its ability to directly influence absorption of ammonia from the MTAL, the pivotal step in urinary ammonia excretion (1). Absorption of ammonia by the MTAL can be influenced via both the apical and basolateral carriers. On the apical site, the \( \text{Na}^+/\text{K}^+\text{-NH}_4^+\text{-Cl}^- \) cotransporter (which ensures ~50–65% of MTAL active luminal ammonia uptake under basal conditions) is influenced by angiotensin II, bumetanide, and furosemide, whereas the \( \text{K}^+/\text{NH}_4^+ \) antiport is sensitive to verapamil and barium. On the basolateral site the \( \text{Na}^+/\text{K}^+\text{-NH}_4^+\text{-ATPase} \) is sensitive to ouabain, whereas the \( \text{NH}_4^+\text{-Cl}^- \) cotransport is sensitive to furosemide, bumetanide, and barium (see Ref. 1 for review).

There are no data available on the angiotensin II levels in patients undergoing acute TIPSS insertion. Patients with advanced cirrhosis depict classic haemodynamic characteristics of splanchnic vasodilation and consequent activation of the renin-aldosterone-angiotensin axis. The creation of a portasystemic shunt increases preload acutely, resulting in hemodynamic and neurohumoral changes that may be similar to those observed following acute volume expansion described above (2). This hypothesis needs further study.

In the present study we were unable to measure the degree of portasystemic shunting and have therefore presented substrate handling across the nonshunted splanchnic region. However, ammonia release via the portasystemic shunts can be estimated using flow data from the literature and the measured portal venous-arterial ammonia differences of the present study. Azygos venous blood flow is an accepted measure of extrahepatic shunt flow and is reduced immediately after TIPSS insertion (from 450 ml/min pre-TIPSS to 300 ml/min post-TIPSS; Ref. 7, 19). In a study by Lotterer et al. (19), shunting of portal blood via the TIPSS was shown to be ~1,400 ml/min immediately after TIPSS insertion. The measured liver plasma flow in their study was similar to our findings (6 ml·kg body wt\(^{-1}\)·min\(^{-1}\)). In Fig. 1 we display a pre-TIPSS and post-TIPSS model of estimated portasystemic ammonia production vs. a wide range of shunt flows. Using the pre-TIPSS portasystemic shunting estimate of 450 ml/min, we calculated the portasystemic ammonia production would be ~300 nmol·kg body wt\(^{-1}\)·min\(^{-1}\), which is lower than the observed pre-TIPSS renal ammonia release (500 nmol·kg body wt\(^{-1}\)·min\(^{-1}\)). These data are similar to the data that we published recently (22). After TIPSS insertion, the estimated portasystemic ammonia production would increase to ~1,100 nmol·kg body wt\(^{-1}\)·min\(^{-1}\) (using an estimated azygos flow of 300 ml/min and an estimated TIPSS flow of 1,400 ml/min). Interestingly, TIPSS insertion did not change arterial ammonia levels in the present study. This observation could be due to the short duration of the present study or reflect the fact that hyperammonemia, following the increased release of ammonia into the circulation through enhanced shunting of portal-drained blood after TIPSS, is effectively prevented by enhanced ammonia removal from the circulation. Our data suggest that diminished renal ammonia release into the circulation and probably increased muscle ammonia uptake may be the important mechanisms to control arterial ammonia concentration. Although not measured, uptake of ammonia can also occur in astrocytes in the brain (6). Increased cerebral ammonia uptake following TIPSS in patients with cirrhosis of the liver could be the cause of the observed acute increase in intracranial pressure in these patients, which can be sometimes fatal (14). Recently, we showed in a case report that TIPSS insertion in a patient with cirrhosis and variceal bleeding of the esophagus resulted in a slight reduction in arterial ammonia but doubled ammonia uptake by the brain (16). The quantitative contribution of the brain in whole body ammonia removal during TIPSS insertion needs further study.

In conclusion, the present study shows that the kidney plays a very important role in the instantaneous adaptation to portasystemic shunting in patients with cirrhosis by reducing ammonia efflux into the circulation. In view of the fact that this adaptation appears to be long lasting (22), attention to the role of the kidney in ammonia homeostasis may provide new treatment options for hyperammonemia.

ACKNOWLEDGMENTS

We gratefully acknowledge Stuart McLennan, Alistair Lee, and the nursing staff of the Liver Unit and the Department of Radiology for support and help. We thank Hans M. H. van Eijk, Jean L. J. M. Scheyen, and Gabrie A. M. ten Have for analytical help.

GRANTS

S. W. M. Olde Damink is supported by grants from the Netherlands Organisation for Scientific Research (NWO-AGIKO, nr 920-03-036), the Wellcome Trust (195MED R34543), and the De Drie Lichten Foundation.

C. H. C. Dejong acknowledges financial support by the Niels Stensen Foundation and the Dutch Organization for Scientific Research (Zon-MW/NOW, Grant 907-00-033).

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