THE EFFECT OF INDUCED HYPERAMMONEMIA ON RENAL AMMONIA METABOLISM * †

By EDWARD E. OWEN, JAMES H. JOHNSON and MALCOLM P. TYOR

(From the Department of Medicine, Duke University Medical Center and the Veterans Administration Hospital, Durham, N. C.)

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Although the excretion of ammonia into urine has been extensively studied, there is little information in animals or man concerning the quantitative and regulatory aspects of the ammonia released into the renal veins. Previous observations in this laboratory and in others have demonstrated that the kidney consistently releases ammonia into the systemic circulation of normal subjects and patients with liver disease whose arterial ammonia concentrations are normal (1–5). Patients with liver disease and moderate to marked hyperammonemia, however, usually release minimal quantities of ammonia into their renal veins and occasionally exhibit renal uptake of ammonia from the circulation (2). In order to further define the possible role of the blood ammonia concentration on renal ammonia release, acute hyperammonemia has been induced in normal subjects and the subsequent changes in renal vein ammonia release and urine ammonia excretion determined.

METHODS

Nine patients without hepatic or renal disease were studied. All were hospitalized ambulatory males ranging in age from 28 to 49 years.

Subjects were studied in the recumbent position after an overnight fast. In order to initiate a water diuresis, 1,000 to 1,500 ml of water was ingested 30 minutes to 1 hour before each procedure. A constant intravenous infusion (Bowman pump) which delivered 14 to 18 mg of para-aminohippurate (PAH) per minute was maintained throughout the study period and was preceded by a priming dose calculated to provide plasma levels of approximately 2 mg per 100 ml. The water diuresis was maintained throughout the procedure by the intravenous infusion of 5 per cent dextrose and water at a rate of 15 to 20 ml per minute. Arterial samples were obtained from a brachial artery and renal venous samples from the right renal vein by way of a no. 8 catheter. Control voided urine specimens were collected during and after equilibration of the PAH infusion. Baseline arterial and renal venous samples were begun 45 to 60 minutes after the PAH infusion was started. Each patient received an intravenous infusion of 0.155 M ammonium lactate at a rate of 0.50 mEq of ammonia per minute for 30 minutes and 0.75 mEq of ammonia per minute for the subsequent 15 minutes. Serial arterial-renal venous ammonia differences were obtained at 15-minute intervals during the infusion and at the 15 minute post-infusion period. Voided urine samples collected in an oil-toluene mixture were obtained at 15- to 30-minute intervals during the infusion and in 4 subjects for 30 to 60 minutes after the infusion was terminated.

Blood and urine ammonia was measured by a modification (6) of the microdiffusion method of Brown, Duda, Korkes and Handler (7). PAH concentration in blood and infusion media was determined by the method of Selkurt (8), with the N-napthyl ethylenediamine dihydrochloride recrystallized with hydrochloric acid as described by Bratton and Marshall (9). The pH of whole blood and urine was measured with a Cambridge model R pH meter equipped with an enclosed glass electrode. Measurements were made at room temperature usually at 25° to 26° C and the results corrected to 37° C by Rosenthal's factor (10). The CO_2 content of whole blood was determined by the method of Van Slyke and Neill (11). The CO_2 tension was calculated from this value, the pH and the hemoglobin concentration by the line chart of Van Slyke and Sendroy (12), using a pK of 6.11. Oxygen content and saturation were determined by the spectrophotometric method of Hickam and Frayser (13). Hematocrits were determined in duplicate from arterial blood in Wintrobe tubes centrifuged at 3,000 rpm for 30 minutes. Renal plasma flow (RPF) was calculated by a modification (14) of the Fick principle using the formula $RPF = IR/(A\text{-}R)$, where IR represents the infusion rate of PAH in milligrams per minute and A-R represents the PAH concentration in arterial and renal venous blood. The PAH concentration in arterial blood remained essentially constant throughout each study period. Renal blood flow was obtained using RPF and hematocrit. Details of this method and its comparison with standard clearance techniques have been described previously (3). Release or uptake of ammonia by the kidney was calculated from the arterial-renal venous ammonia differences and renal blood flow. Renal oxygen consumption was determined using arterial-renal venous oxygen differences.

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TABLE I

The effect of induced hyperammonemia on release of ammonia by the kidney

Patient	Time	Arterial NH_3	Renal NH_3 A-V	Renal O_2 A-V	Renal blood flow	Release of NH_3 into renal veins	Removal of NH_3 from circulation	Renal O_2 consumption	Arterial pH	Arterial Serum CO_2	Arterial pCO_2
	min	*μg/100 ml*		*vol %*	*ml/min**	*μEq/min*		*ml/min*		*vol %*	*mm Hg*
	Rest †	88	−36	1.18	2,220	47		26.2	7.37	48.6	38.1
W.H.	15	292	+67		2,240		88				
	30‡	283	+24	1.13	2,443		35	27.6	7.34	49.6	41.5
	45	425	+29		2,426		72				
	60§	108	−25	1.07	2,445	36		26.2	7.35	49.5	40.2
	Rest †	73	−37	0.92	1,023	23		9.4	7.34	53.0	43.8
J.H.	15	249	+22		1,144		15				
	30‡	281	+39	1.02	1,223		28	12.5	7.34	53.5	44.7
	45	428	+50		1,191		35				
	60§	124	−20	1.01	1,310	16		13.2	7.33	53.9	45.2
	Rest †	97	−19	1.08	1,622	18		16.3	7.38	47.1	35.6
E.Q.	15	319	+72		2,002		85				
	30‡	311	+80	0.72	1,743		82	12.5	7.37	47.6	36.7
	45	540	+132								
	Rest †	95	−48	0.59	2,727	77		14.1	7.35	63.5	51.1
R.L.	15	206	−24		2,500	36					
	30‡	223	−28	0.69	2,345	39		16.2	7.36	62.7	49.5
	45	348	+ 4		2,400		6				
	60§	125	−65	0.98	2,500	91		24.5	7.36	63.9	51.1
	Rest †	55	−67	0.05					7.32	54.8	47.8
C.L.	15	235	−39								
	30‡	213	−58	0.18					7.34	53.6	45.1
	45	540	−34								
	60§	98	−64	0.28					7.34	53.4	44.9
	Rest †	88	−35	0.78	1,641	34		12.8	7.33	53.2	45.5
I.W.	15	238	+28		1,995		35				
	30‡	290	+53	0.68	2,219		69	15.1	7.34	51.9	43.5
	45	346	+87								
	60§	100	− 9	0.94					7.38	51.9	39.5
	Rest †	79	−21	0.71	930	12		6.8	7.38	57.0	43.0
E.H.	15	212	+12		1,066		8				
	30‡	249	+ 5	0.91	1,070		3	7.7	7.36	57.0	45.0
	45	397	+53		1,085		34				
	60§	102	−24	1.13	1,141	15		12.8	7.38	56.4	42.9
	Rest †	70	−54	1.18					7.37	54.4	41.6
R.S.	15	250	+34								
	30‡	236	+45	1.68					7.36	55.1	41.8
	45	459	+111								
	60§	94	−36	1.69					7.38	56.1	43.8
	Rest †	79	−35	0.86	1,204	25		10.4	7.34	53.2	44.5
E.G.	15	332	+62		1,124		41				
	30‡	234	−35	1.04	1,181	25		12.3	7.30	54.6	49.3
	45	330	+27		1,015		16				
	60§	92	−26	0.79	1,358	21		10.5	7.31	54.7	48.2

* Instantaneous values obtained at indicated time periods.
† Ammonium lactate infused at 0.5 mEq of NH_3 per minute from 0 to 30 minutes.
‡ Ammonium lactate infused at 0.75 mEq of NH_3 per minute from 30 minutes to 45 minutes.
§ 15 minute post-ammonium lactate infusion.

RESULTS

The data obtained from blood analyses in each subject as well as mean values before, during and after intravenous ammonium lactate are presented in Tables I and II. An abrupt increase in arterial ammonia concentration occurred in each subject. Mean levels were 179, 180 and 344 μg per 100 ml higher than baseline values at the 15, 30 and 45 minute infusion periods, respectively. Fifteen minutes after the infusion was terminated, the mean arterial concentration was 105 μg per 100 ml (mean control arterial ammonia concentration, 80 μg per 100 ml). No mental or neurologic abnormalities were observed during the hyperammonemic period, nor were there significant changes observed in arterial pH or calculated pCO_2.

Negative baseline arterial-renal venous ammonia differences, indicating ammonia release and averaging 39 μg per 100 ml, were promptly altered by the ammonium lactate infusion. In seven subjects these alterations were quantitated using renal blood flows. During the control period, a mean of 34 μEq of ammonia per minute was released into the renal venous circulation. At the 15 minute period of infusion, an average of 34 μEq of ammonia per minute was removed from the circulation by the kidneys. Removal tended to decrease somewhat at the 30 minute period but increased again during the peak arterial ammonia concentration. Fifteen minutes after the infusion was discontinued, release of ammonia into the renal veins was again evident and approximated values obtained during the control periods.

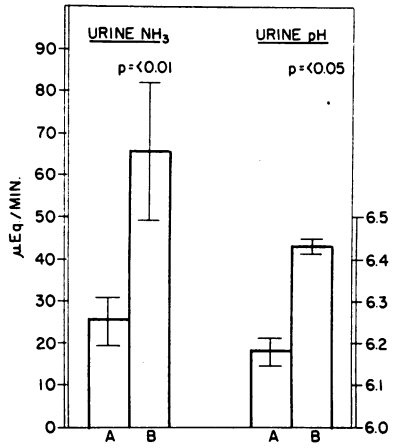

FIG. 1. URINE AMMONIA EXCRETION AND pH DURING AMMONIUM LACTATE-INDUCED HYPERAMMONEMIA (MEAN VALUES OF EIGHT SUBJECTS ± 1 SD). **A** represents control values and **B** represents hyperammonemic values.

Mean urine ammonia excretion and pH in four catheterized subjects and in four additional individuals infused with similar quantities of ammonium lactate are shown in Figure 1. Urine ammonia excretion increased significantly from a control of 25 to 65 μEq per minute ($p < 0.01$) during the hyperammonemic period. This augmented urine ammonia excretion occurred during the first 15 to 20 minutes of hyperammonemia and remained two to three times higher than baseline for 20 to 40 minutes after the infusion was dis-

TABLE II

Comparison of mean values for renal ammonia release after intravenous infusion of ammonium lactate

Time	Arterial NH_3	Renal NH_3 A-V	Renal O_2 A-V	Renal blood flow	Release of NH_3 into renal veins	Removal of NH_3 from circulation	Renal O_2 consumption	Arterial pH	Arterial Serum CO_2	Arterial pCO_2
min	*μg/100 ml*		*vol %*	*ml/min*	*μEq/min*		*ml/min*		*vol %*	*mm Hg*
Rest †	$\bar{d}$* 80.4	−39	0.82	1,623	34		13.7	7.35	53.9	43.4
15	$\bar{d}$ 259	+26		1,724		34				
	p‡ <0.01	<0.01		<0.01		<0.01				
30§	$\bar{d}$ 258	+14	0.89	1,746		22	14.8	7.35	54.0	44.1
	p <0.01	<0.01	>0.1	>0.1		<0.01	>0.1	>0.1	>0.1	>0.1
45	$\bar{d}$ 424	+51		1,623		33				
	p <0.01	<0.01		>0.1		<0.01				
60‖	$\bar{d}$ 105	−34	0.86	1,751	37		17.4	7.35	55.0	44.5
	p <0.01	>0.1	>0.1	<0.01	>0.1		>0.1	>0.1	>0.1	>0.1

* Mean values at the time periods indicated.
† Ammonium lactate infused at 0.5 mEq of NH_3 per minute from 0 to 30 minutes.
‡ Significance as compared with control values.
§ Ammonium lactate infused at 0.75 mEq of NH_3 per minute from 30 to 45 minutes.
‖ 15 minute post-ammonium lactate infusion.

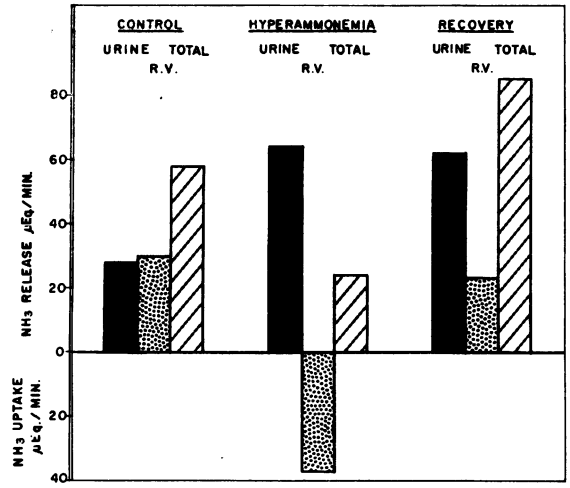

FIG. 2. RENAL AMMONIA BALANCE BEFORE, DURING, AND AFTER AMMONIUM LACTATE-INDUCED HYPERAMMONEMIA (MEAN VALUES OF FOUR SUBJECTS). R.V. represents net ammonia balance across the renal circulation.

continued in the four subjects who had continuous collections. Accompanying this increased urine ammonia excretion was a slight but significant increase in mean urine pH, 6.18 to 6.43. Urine flow decreased slightly in six of the eight subjects during the study (mean control urine flow = 10.8 ml per minute, mean infusion urine flow = 7.1 ml per minute).

Simultaneous observations obtained in four subjects permit calculations of net renal ammonia balance. Mean values are presented in Figure 2. During the control period, total bidirectional ammonia release was 56 μEq per minute. The quantity released into the renal veins averaged 52 per cent of the total. Although urine ammonia excretion increased significantly in this group ($p < 0.02$) during the hyperammonemic period, this was partially balanced by the renal uptake of ammonia from the circulation (mean uptake = 37 μEq per minute). During the recovery period, release of ammonia into the renal veins was again observed. Urine ammonia excretion remained at levels similar to those of the infusion period and mean total release was slightly but not significantly greater than that during the control period.

DISCUSSION

The concentration of ammonia in arterial blood is the resultant of a number of factors, including the rate of production and utilization by various tissues and the rate of diffusion into and out of cells. In normal subjects and patients with liver disease without hyperammonemia, the blood ammonia appears to be largely of renal origin (1, 2). Liver (2, 4), muscle (15, 16), and brain (15, 17), as measured by A-V differences, primarily serve to remove ammonia from the circulation under basal conditions. The present study provides quantitative data on the amount of ammonia normally released into the renal venous circulation and also indicates that the kidney's role as a donor of ammonia to the circulation can be abruptly altered by acutely increasing the blood ammonia concentration.

Recent quantitative studies in cirrhotics with chronic hyperammonemia have shown a marked decrease in renal vein ammonia release when compared to subjects with normal blood ammonia concentrations (18). Indeed, net removal of ammonia from the circulation has occasionally been observed (2). The notion that the level of the arterial ammonia concentration may be a factor governing the release of ammonia into the renal veins is supported by the results presented in the present acute experiments. In each subject, hyperammonemia induced by intravenous ammonium lactate was associated with a prompt decrease in renal vein ammonia release, with net uptake of ammonia from the circulation by the kidney being observed in eight of nine studies. Further evidence to support the role of the arterial ammonia concentration may be obtained from the prompt return to resting release within 15 minutes after ammonium lactate was discontinued, a time when the arterial ammonia concentrations were normal to slightly elevated. The precise level of arterial ammonia concentration at which uptake occurs is not evident from these data. It is apparent, however, that this level is significantly above normal and that there is considerable individual variation. Subject C.L., for example, continued to release ammonia despite an arterial concentration of 540 μg per 100 ml, whereas J.H. exhibited uptake at an arterial concentration of 240 μg per 100 ml.

The precise mechanism involved in the movement of ammonia from tubular cell to tubular urine and peritubular fluid has not been clearly elucidated. Currently available evidence based primarily on urine studies suggests that ammonia

escapes from the renal tubular cells as molecular NH_3 by a process of passive diffusion (19–21). The relative amounts appearing in each fluid, i.e., tubular urine and peritubular fluid, appear to depend on intracellular ammonia concentration, the pH of each surrounding fluid, and the fluid flows past the cell membranes. Under normal conditions, the escaping NH_3 rapidly traps protons forming ammonium ion (NH_4^+). Since cell membranes in general are relatively impermeable to NH_4^+, back diffusion into the tubular cells is minimized. Ammonia in blood even during extreme hyperammonemia exists primarily in the NH_4^+ form. The concentration of NH_3 represents only a minute fraction of the total blood ammonia concentration (22), and in the present study is obviously of insufficient magnitude to explain the alterations in renal ammonia balance across the renal circulation during ammonium lactate infusion. It would seem likely, therefore, that the renal tubular cells removed significant quantities of NH_4^+ from the blood during these experiments. Liver, muscle and brain also appear to remove NH_4^+ under similar conditions of induced hyperammonemia (17, 18).

The level of circulating ammonia also appears to affect the quantity of ammonia excreted into urine. A significant increase in mean urine ammonia excretion occurred in association with mean net removal of ammonia from the circulation. An increase in tubular ammonia secretion probably occurred during this period since only 40 to 50 per cent of the observed increment can be explained by filtration, even assuming no reabsorption during tubular passage. The augmented urine ammonia excretion occurred in association with a slight but significant increase in mean urine pH. Under most conditions, acute increases in ammonia excretion are associated with decreases in urine pH since increased H^+ ion concentrations facilitate the escape of ammonia from the tubular cells. The observed increase in urine pH could result from an increased exchange of cellular NH_4^+ for urinary sodium (23), or from increased diffusion of NH_3 from cell to urine, thereby trapping H^+ ions and thus allowing further H^+ ions for sodium exchange. A similar pattern of augmented urine ammonia excretion in association with an increase in urine pH has been observed following amino acid loads (24, 25). Presumably the common factor in each of these situations is an increase in renal tubular cell ammonia concentration.

Although there are relatively few observations on the relationship of resting urine pH to the release of ammonia into the renal veins, studies previously reported (3) suggest that there is little correlation within a range of urine pH of 4.99 to 7.15. It has been clearly shown, however, that acute increases in urine pH following carbonic anhydrase inhibition (3, 26) or metabolic alkalosis (18) are associated with rapid increases in ammonia released into renal veins, a rapid decrease in urine ammonia excretion, and an essentially unchanged total bidirectional release. These changes appear to occur irrespective of the level of control arterial ammonia concentration.

Quantitatively, the increase in urine ammonia excretion in these experiments was partially balanced by the renal uptake of ammonia from the circulation. Indeed, the magnitude of this uptake was such that it more than made up for the increase in urine ammonia excretion and resulted in a significant decrease in net release of ammonia by the kidney in the four patients who had simultaneous measurements. These observations suggest that net renal ammonia production was decreased during the ammonium lactate infusion.

The origin of urine and renal vein ammonia and the mechanisms of its escape from or entry into renal tubular cells are not answered by these experiments. Regardless of the mechanisms involved, it is clear that the kidney serves to lower the blood ammonia concentration during hyperammonemia by decreasing its release and by increasing urine ammonia excretion. These alterations would appear to be of clinical importance in patients with liver disease by aiding in the regulation of blood ammonia concentration. Since moderate amounts of oral ammonium chloride result in significant and often marked elevations of arterial ammonia concentration (27), the present observations may also be of importance in partially explaining the augmented urine ammonia excretion seen during chronic ammonium chloride loads (19, 28). The increased urine ammonia excretion which attends amino acid loads is also associated with striking elevations of the blood ammonia concentration (29). During intravenous glycine infusions, renal ammonia production ap-

pears to increase, and presumably the increased ammonia appearing in the renal veins partially accounts for the increased blood ammonia concentration (30). Whether the increase in urine ammonia excretion seen following oral or intravenous loading with other amino acids is related to augmented production or hyperammonemia must await more definitive studies.

SUMMARY

The release of ammonia into the renal veins was determined in nine normal subjects before, during and after the intravenous administration of isotonic ammonium lactate. Concomitant measurements of urine ammonia excretion were obtained in four catheterized subjects and in four additional individuals infused with similar quantities of ammonium lactate.

Hyperammonemia was associated with a prompt decrease in the amount of ammonia normally released into the renal veins with uptake of ammonia from the blood by the kidneys being observed in eight of nine subjects. Release reappeared and approximated control values 15 minutes after the infusion was terminated, a time when the blood ammonia concentrations were normal to slightly elevated.

Urine ammonia excretion increased two- to threefold during the infusion in association with a slight increase in urine pH, suggesting augmented tubular secretion. The resultant of these two processes, however, indicates an over-all decrease in bidirectional release and presumably in total ammonia production.

These observations provide additional evidence of the kidney's role in the regulation of the blood ammonia concentration and, in addition, demonstrate that the arterial ammonia concentration significantly influences urine ammonia excretion.

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