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Mechanisms of lysine-induced acute renal failure in rats

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Mechanisms of lysine-induced acute renal failure in rats. We have previously found that lysine produces acute renal failure in rats. To define the acute effects of lysine, rats given lysine at 8.9 mg/kg/min, i.v. for 4.5 hr were compared with control rats receiving equiosmolar dextrose. Systemic blood pressure was stable in both groups. Mean intratubular pressure, inulin clearance (C_{In}), and renal blood flow were determined at 45-min intervals. Intratubular pressures measured with a servonulling micropressure device were elevated by 90 min in lysine-treated animals, with tubular heterogeneity, while pressures in dextrose-treated rats were normal and homogeneous. By 135 min C_{In} in lysine-treated rats was 45% of C_{In} in dextrose rats. Urine output fell in lysine-treated rats. Renal blood flow determined by flow probe remained normal in lysine-treated rats through 135 min and did not decline significantly until 180 min. Significant dilatation of surface tubules was documented by intravital microscopy beginning at 90 min in lysine-treated rats. The sequence of elevated intratubular pressure and tubular dilatation, followed by decreased C_{In}, and then by decreased renal blood flow suggests that lysine produces acute renal failure primarily through tubular obstruction. The tubular obstruction is followed later by an increase in renal vascular resistance.

Mécanismes de l'insuffisance rénale aiguë induite par la lysine chez des rats. Nous préalablement trouvâmes que la lysine entraîne une insuffisance rénale aiguë chez les rats. Afin de définir les effets aigus de la lysine, des rats ayant recu de la lysine à 8,9 mg/kg/min i.v. pendant 4.5 hr ont été comparés à des rats contrôles recevant du glucose équimolaire. La pression artérielle systémique était stable dans les deux groupes. La pression intratubulaire moyenne, la clearance de l'inuline (C_{In}) et le flux sanguin rénal ont été déterminés à des intervalles de 45 min. Les pressions intratubulaires mesurées avec un appareil à micropression asservi étaient élevées dés 90 min chez les animaux traités avec la lysine, avec une hétérogénéité tubulaire, tandis que les pressions des rats traités au glucose étaient normales et homogènes. Au bout de 135 min, C_{In} des rats traités par la lysine était de 45% de C_{In} des rats glucose. Le débit urinaire a chuté chez les rats traités par la lysine. Le débit sanguin rénal déterminé par une sonde de flux est resté normal chez les rats traités par la lysine pendant 135 min, et n'a pas décliné significativement jusqu'à 180 min. Une dilatation significative des tubules superficiels a été documentée par microscopie intravitale, comencant à 90 min chez les rats traités par la lysine. La séquence de pression intratubulaire élevée et de dilatation tubulaire, suivie par une C_{In} diminuée, puis par une diminution du flux sanguin rénal suggère que la lysine entraine une insuffisance rénale aiguë essentiellement par obstruction tubulaire. L'obstruction tubulaire est suivie plus tard d'une élévation de la résistance vasculaire rénale.

Amino acid therapy has been advocated for patients with acute renal failure [1, 2], and there is experimental evidence in rats that amino acid administration speeds tubular regeneration following acute tubular necrosis [3, 4]. However, it now appears that some amino acids or amino acid mixtures can depress renal function, especially if given in combination with other nephrotoxins [5, 6] or in the setting of renal ischemia [7]. For example, we have previously reported that a 4-hr infusion of the dibasic amino acid lysine in rats reduced glomerular filtration rate (GFR) by approximately 50% [6]. An acute decrease in GFR following large doses of acidic, basic, and neutral amino acids has also been reported [8]. The mechanism of this renal dysfunction, however, remains unclear.

To further define the nephrotoxic properties of amino acid solutions, clearance and micropuncture studies were performed in conjunction with morphologic studies during the evolution of lysine-induced acute renal failure. The renal insufficiency developed gradually over several hours, making it possible to perform sequential measurements of inulin clearance, intratubular pressures and renal blood flow, and sequential intravital microscopy to further delineate the pathogenesis of lysine-induced acute renal failure. The data from the micropuncture studies in the present study indicate that lysine-induced acute renal failure is characterized by an initial tubular obstruction, followed by a significant decrease in GFR and urine output, with the later development of increased renal vascular resistance and reduced renal blood flow.

Methods

All studies were performed in nonfasted male Munich-Wistar rats weighing 210 to 290 g and obtained from Simonsen Labs, Gilroy, California, USA.

Inulin clearance, micropuncture, and renal blood flow studies. Following induction of pentobarbital anesthesia, rats were placed on a temperature-regulated table which maintained body temperature at 36 to 38°C. A tracheostomy was performed and the right external jugular vein was cannulated with PE 50 through which saline (0.9% NaCl) was infused at 3.3 cc/hr. The right femoral artery was canulated with PE 50 for continuous arterial blood pressure determinations. Abdominal and left subcostal incisions were made to expose the left kidney which was stabilized using a diaphragm retractor and body wall clamp. The kidney was packed in cotton soaked in saline warmed to 37°C, with care to avoid manipulation of the adrenal gland or traction on the renal pedicle. Ureters were cannulated bilaterally. Animals received approximately 3 to 4 cc of saline during preparative surgery.

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Table 1. Results of micropuncture studies during lysine infusion

		45 min	90 min	135 min	180 min	225 min	270 min
BP, *mm Hg*	DEX	128 ± 5	129 ± 5	137 ± 4	131 ± 6	132 ± 4	127 ± 4
	LYS	127 ± 4	123 ± 4	124 ± 4[a]	129 ± 3	128 ± 4	127 ± 3
Hct, %	DEX	51 ± 1	50 ± 1	49 ± 1	49 ± 1	49 ± 1	51 ± 1
	LYS	52 ± 1	51 ± 1	50 ± 1	50 ± 1	50 ± 1	53 ± 1
Urine flow, *μl/min*	DEX	5.7 ± 2.4	4.7 ± 1.4	6.9 ± 2.3	9.2 ± 3.3	13.9 ± 4.0	13.0 ± 3.3
	LYS	11.8 ± 1.8	7.9 ± 1.7	3.5 ± 1.0	2.9 ± 0.6[b]	3.8 ± 0.9[b]	3.7 ± 0.7[b]
ITP, *mm Hg*	DEX	11.3 ± 0.7	12.1 ± 0.7	12.2 ± 0.6	13.2 ± 1.1	13.3 ± 1.1	14.4 ± 1.3
	LYS	10.7 ± 1.3	18.8 ± 2.0[b]	24.7 ± 4.1[b]	26.5 ± 4.1[b]	31.5 ± 3.3[a]	28.1 ± 4.2[b]
C_{In}, *ml/min*	DEX	0.87 ± 0.07	0.82 ± 0.15	0.91 ± 0.12	0.91 ± 0.12	1.10 ± 0.15	1.01 ± 0.19
	LYS	0.90 ± 0.08	0.67 ± 0.12	0.33 ± 0.11[b]	0.18 ± 0.04[a]	0.23 ± 0.07[a]	0.16 ± 0.03[a]
RBF, *ml/min*[c]	DEX	6.58 ± 0.71	6.66 ± 0.50	6.90 ± 0.58	7.27 ± 0.65	7.31 ± 0.71	7.36 ± 0.83
	LYS	6.43 ± 0.52	6.49 ± 0.45	6.36 ± 0.45	5.32 ± 0.50[b]	4.71 ± 0.26[b]	3.92 ± 0.43[b]
RVR, *dyn·sec/cm*^{5}	DEX	16.9 ± 1.8	15.1 ± 1.8	16.6 ± 1.9	14.7 ± 2.5	14.3 ± 1.5	14.0 ± 1.8
	LYS	16.9 ± 2.0	15.7 ± 2.0	15.5 ± 1.8	21.4 ± 2.1	21.9 ± 1.9[b]	29.3 ± 4.5[b]

Abbreviations: BP, blood pressure; Hct, hematocrit; ITP, intratubular pressure; C_{In}, clearance of inulin; RBF, renal blood flow; RVR, renal vascular resistance; DEX, dextrose; LYS, lysine.

[a] $P < 0.001$ vs. dextrose controls by analysis of variance.

[b] $P < 0.05$ vs. dextrose controls by analysis of variance.

[c] If the later LYS values are compared with 45-min LYS values, significant differences do not appear until 225 min for RBF and 270 min for RVR. For other parameters, when the LYS and DEX groups are different, the LYS group is also different from its own 45-min value.

The animals were divided into two groups: Control animals were infused with a dextrose solution (220 mM, pH 9.3, 238 mOsm) containing 2% inulin at 4.3 cc/hr. Lysine-treated animals received a solution of lysine-free base (220 mM, pH 9.3, 238 mOsm, total 4.40 mmoles) containing 2% inulin infused at a rate of 4.3 cc/hr (61 μmoles/kg/min). At 45-min intervals (100 mg increments of lysine) a 10-min urine collection was performed; blood samples were collected in all rats for inulin clearance determinations.

In six lysine-treated rats and six dextrose-treated rats, five to nine random proximal intratubular pressures were determined at the time of each clearance period using sharpened glass micropipettes (4 to 6 μ O.D.) filled with 2 M NaCl and connected to a servonulling pressure device (Eutechtic Electronics, Raleigh, North Carolina, USA). When dilated tubules were present, punctures were made in tubules that did not appear dilated as well as in dilated tubules in proportion to their relative numbers on the cortical surface in view. Renal blood flow was monitored constantly in ten lysine rats and five dextrose rats using a noncanulating electromagnetic flow transducer (2 mm, internal circumference) connected to a square-wave flow meter (Carolina Medical Electronics, King, North Carolina, USA). Calibration was confirmed using a segment of femoral artery according to a technique described by Arendshorst, Finn, and Gottschalk [9]. The servonulling apparatus, flow meter, and systemic blood pressure transducer were attached to a polygraph recorder (Grass 78D, Grass Instrument Co., Quincy, Massachusetts, USA) for continuous monitoring. The left kidney was harvested from each animal and prepared for microscopy using standard techniques.

Intravital microscopy. In six other rats, following surgical preparation, the kidney surface was bathed with warm saline and covered with a layer of flexible transparent cellophane. Following stabilization, lysine ($N = 3$) or dextrose ($N = 3$) solutions were then infused as described for micropuncture studies. At 45-min intervals, sequential photographs of three adjacent fields on the kidney surface were taken, using an incident light microscope (Leitz Ultropak, Ernst Leitz Wetzlar, Germany) and camera with a 22× microscope objective and 3M 1000 ASA color transparency film. Fields were selected for a uniform plane of focus and generally contained a reference characteristic such as a prominent vessel. When possible, a superficial glomerulus was included in at least one photographic field in each animal. Three to six photographs were taken of each field at each time point, and the photograph best focused was used for subsequent analysis.

Color slides of each field at each time point were projected, and all topographical details traced on white tracing paper with special attention to the tubular lumen and brush border. One to two proximal tubular luminal diameters were measured at random orientation in each proximal tubular profile in each field; the number of measurements in each field at each time point varied from 14 to 20. When possible, measurements were generally made adjacent to obvious tissue landmarks so that identical measurement points could be used in sequential photographs over the 4-hr observation period. Results were expressed as luminal diameters (in microns) and absolute changes in luminal diameter of each tubule from the 45-min value.

Analytical and statistical techniques. Inulin concentrations were measured by a standard acid anthrone chemical assay. Statistical comparisons were performed using the analysis of variance and Student *t* test [10]. Results are reported as mean ± SE. A P value less than 0.05 was considered statistically significant.

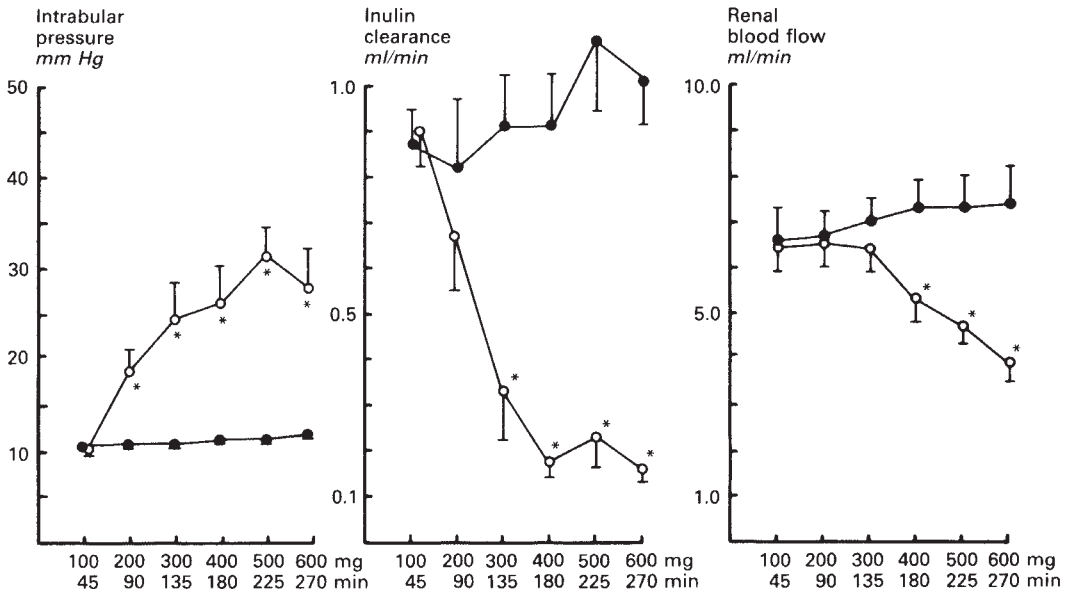

Fig. 1. *Intratubular pressure, inulin clearance, and renal blood flow (mean* ± SEM) in lysine and dextrose-treated animals. Significant alterations are seen in these parameters beginning at 90, 135, and 180 min, respectively. Symbols are: ●—●, dextrose; ○—○, lysine; * $P < 0.05$ compared to dextrose values.

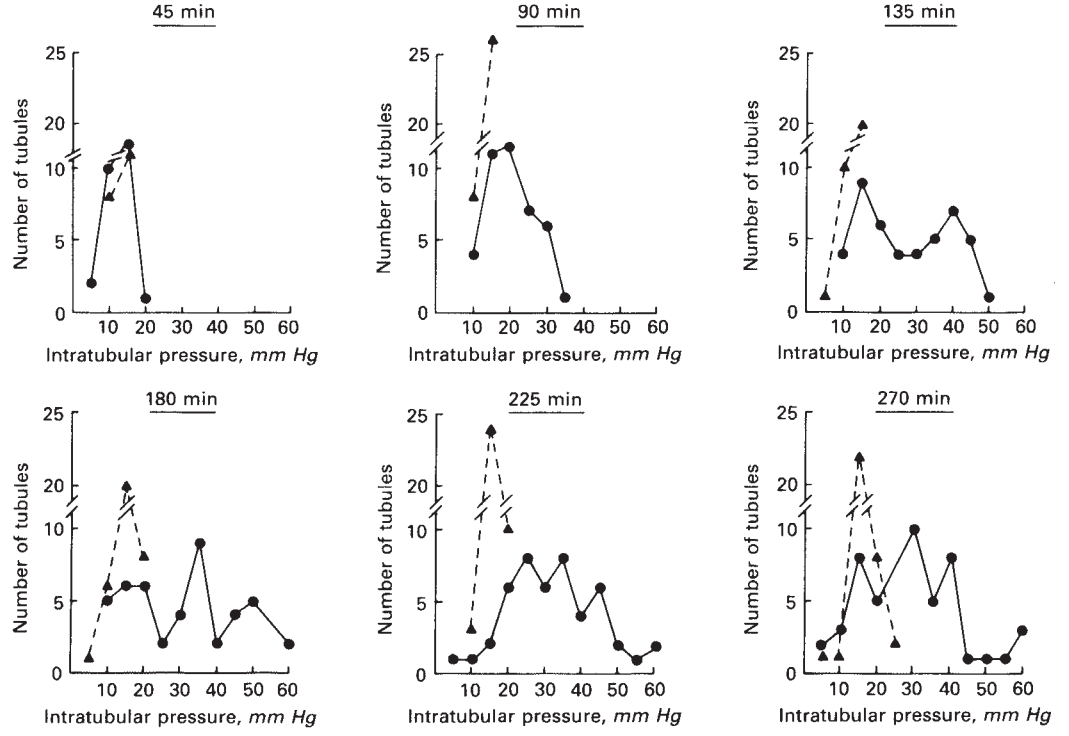

Fig. 2. *Distribution of intratubular pressures at various times after beginning lysine or dextrose infusions.* Symbols are: ▲---▲, dextrose; ●—●, lysine.

Results

Inulin clearance, micropuncture, and renal blood flow studies in rats treated with lysine. At the time of the first clearance period, 45 min after the lysine or dextrose infusions were begun, mean values for arterial blood pressure, hematocrit, urine flow rates, proximal intratubular hydrostatic pressure, inulin clearance, and renal blood flow were not different in dextrose control and lysine experimental groups (see Table 1 and Fig. 1). No significant changes in arterial blood pressure and hematocrit were observed in either group throughout the studies. At 45 min, proximal intratubular pressure averaged 11.3 ± 0.7 mm Hg in dextrose control animals and 10.7 ± 1.3 mm Hg in lysine-treated animals. At 90 min, however, lysine-

Table 2. Tubular diameter and changes in tubular diameter at 45-min intervals during infusion of dextrose or lysine

		Minutes of infusion					
		45	90	135	180	225	270
Tubular diameter, *microns*	DEX (N = 3)	15.9 ± 0.8	16.1 ± 0.7	16.5 ± 1.0	17.0 ± 1.0	16.4 ± 1.1	18.5[b]
	LYS (N = 3)	17.1 ± 0.8	21.3 ± 1.2	21.6 ± 1.1	22.1 ± 1.7	21.9 ± 1.2	20.4 ± 0.6
	LYS vs. DEX[c]	$P > 0.3$	$P < 0.02$	$P < 0.05$	$P < 0.06$	$P < 0.05$	NS
Change in diameter, *microns*	DEX (N = 3)		+0.1 ± 0.1	+0.7 ± 0.3	+0.8 ± 0.4	+0.4 ± 0.1	+1.5[b]
	LYS (N = 3)		+4.2 ± 0.7	+4.9 ± 0.6	+4.8 ± 0.8	+4.4 ± 0.6	+2.8 ± 1.2
	LYS vs. DEX[c]		$P < 0.01$	$P < 0.01$	$P < 0.02$	$P < 0.01$	NS

[a] The change in diameter was compared to the 45-min measurement.
[b] N = 2.
[c] Student t test values were confirmed by analysis of variance.

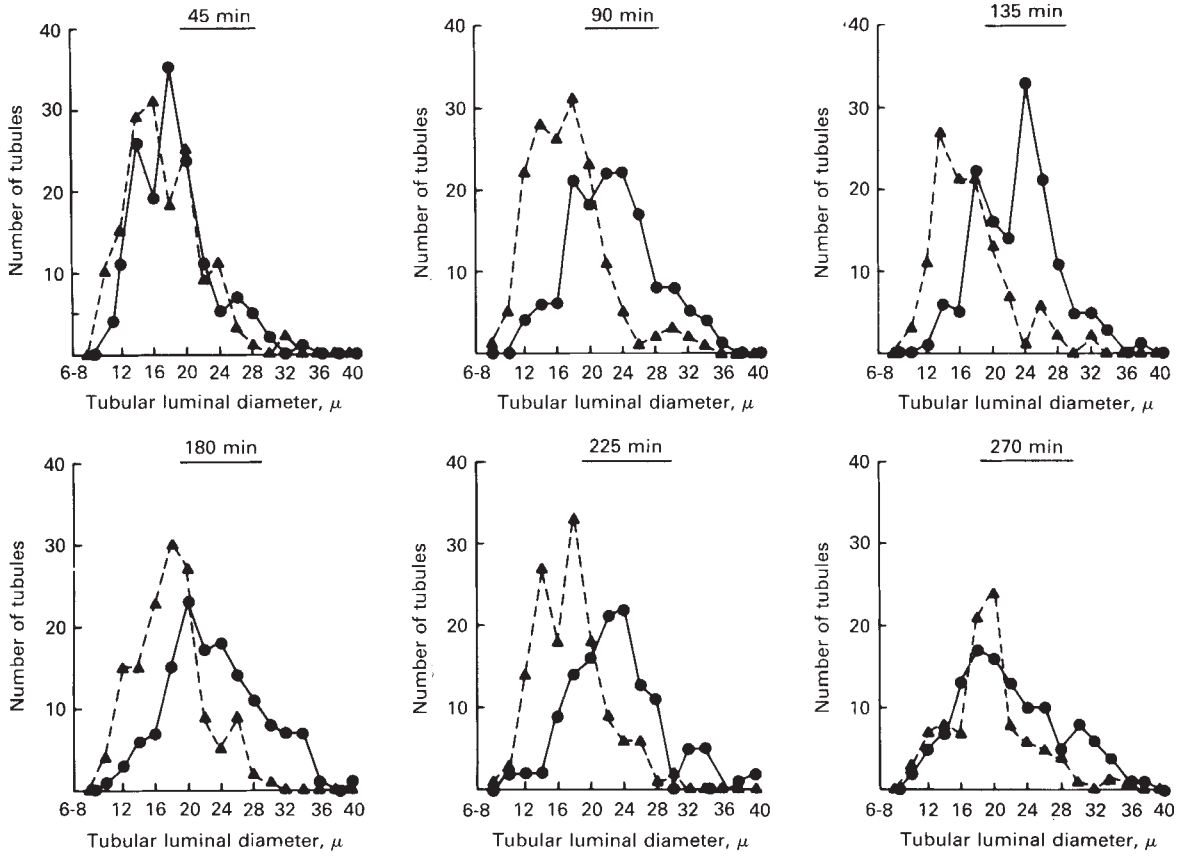

Fig. 3. *Distribution of tubular luminal diameters at various times after beginning of lysine or dextrose infusions.* Symbols are: ▲---▲, dextrose; ●—●, lysine.

treated animals had a significant elevation in mean proximal intratubular pressure (18.8 ± 2.0 mm Hg) compared to the 45-min value in these animals ($P < 0.01$) and to values for dextrose-infused controls at 90 min (12.1 ± 0.7 mm Hg, $P < 0.01$). There was tubular heterogeneity in lysine-treated animals with some tubules having normal pressure and others elevated pressures (see Fig. 2). Urine output was well maintained at this time. By the third clearance period (135 min), while all parameters remained normal in control animals, intratubular pressure continued to rise (to 24.7 mm Hg, $P = 0.01$), inulin clearance fell significantly ($P = 0.002$) to 36% of values in control animals, and urine output tended to decrease in lysine-treated animals. Renal blood flow in lysine-treated rats was unchanged until the fourth clearance period, when it began to fall. In contrast, renal blood flow in dextrose-treated animals tended to rise, perhaps due to volume expansion. Renal blood flow and inulin clearance remained significantly decreased and intratubular pressures remained elevated in lysine-treated animals for the remainder of the 4.5-hr infusion period (see Fig. 1).

By paraffin section light microscopy, tubular morphology was

normal in animals infused with dextrose, with only occasional apical blebs, and very focal accumulations of intratubular debris. In contrast, as in previous studies [6] lysine infusion produced tubular cell swelling and vacuolization, especially at the cortico-medullary junction, with proximal tubular dilatation, loss of brush border, and accumulation of intratubular debris in the pars recta.

Intravital microscopy. At 45 min, tubular-luminal diameters averaged 15.9 μ in dextrose-infused and 17.1 μ in lysine-infused animals, but they were not significantly different. By 90 min, tubular dilatation was evident in all lysine animals, with an average increase of 4.2 μ (see Table 2 and Fig. 3). By 135 min, there was a striking and uniform increase in tubular diameter, which persisted through 225 min. By 270 min, however, there was heterogeneity, similar to the pattern seen with intratubular pressures (see Fig. 2), with some tubules remaining dilated and others decreasing in diameter. The brightly refractile tubular brush border became somewhat less apparent as infusion of lysine progressed, but this was quite variable from field to field among animals and among fields from the same animal, and may not have reflected true brushborder loss. By paraffin section light microscopy, brushborder loss was seen at the cortico-medullary junction, but not in the superficial cortex (see above).

Even in the most optimal intravital microscopic pictures, the glomerular images were indistinct and individual glomerular capillaries could not be seen. Therefore, although no changes in glomerular diameter were observed, this does not exclude a change in glomerular capillary caliber.

Discussion

These studies extend the observation that high doses of the dibasic cationic amino acid lysine in the rat produce a rapid and sustained decrease in renal function [6]. Tubular obstruction appears to be the primary event in the pathogenesis of this type of acute renal failure, with a later decrease in renal blood flow. Lysine is the *only essential* amino acid which has been shown to depress renal function.

The micropuncture studies performed during lysine infusion provide considerable insight into the mechanism of the renal dysfunction produced by the amino acid. The early elevation in intratubular pressure and the proximal tubular dilatation seen at 90 min by intravital microscopy are highly significant and consistent with tubular obstruction. It is important to note that at this time whole kidney inulin clearance is not significantly decreased and renal vascular resistance and renal blood flow are unchanged. As the infusion continues, mean intratubular pressures and tubular diameters continue to increase, urine flow rates decrease in most animals, and inulin clearance falls to approximately one third of control levels. This condition persists to the end of the infusion period, and in addition, renal blood flow eventually begins to fall and renal vascular resistance increases.

The kinetics of the functional changes in this animal model are unusual and make lysine-induced acute renal failure particularly suitable for physiologic study. While in other models renal failure develops either very rapidly, as in ischemia, or quite gradually, as in ureteral obstruction or following administration of nephrotoxins such as aminoglycosides, lysine-induced acute renal failure develops over a period of a few hours, allowing continuous monitoring of functional parameters as renal dysfunction develops. At early time periods in the lysine model the micropuncture data and the results of intravital microscopy are consistent with a somewhat heterogeneous population of proximal tubules, with some obstructed and some not. Subsequently, intratubular pressures become more uniformly elevated, consistent with widespread tubular obstruction. At 270 min, heterogeneity reappears perhaps as a consequence of decreased renal blood flow or decompression of some tubules.

It is likely that the apparent heterogeneity of tubular pressures and diameters is real and not just the consequence of making observations proximal to and distal to points of obstruction. There is no morphologic evidence of obstructing material in the superficial proximal convoluted tubules accessible to micropuncture. Tubular debris and cell swelling are seen in the medullary straight segments of the proximal tubule at 4 hr, and hyaline casts are seen in the thin limbs of the loops of Henle and more distal segments at 20 and 48 hr [6] (Racusen, Whelton, and Solez, unpublished).

The impairment of renal function seen with high dose lysine infusion is associated with morphologic evidence of tubular dilatation. Intravital microscopy enabled quantitation of dilitation of surface proximal tubules. The changes in luminal diameter detected by our morphometric methods reflect significant tubular volume changes. If a segment of tubule is considered a perfect cylinder, with the volume calculated by the formula $\pi r^2 \times h$ where r is tubular radius and h is tubular length, at a theoretical length of 1 μ, a change in diameter from 16 to 20 μ would produce an increase in tubular volume from 201 to 314 μ^3, representing a greater than 50% increase in volume. This tubular expansion and the elevated intratubular pressures strongly suggest tubular obstruction.

The initial cause of this functional tubular obstruction is somewhat difficult to pinpoint, but it is probably related to plugging the tubule by sloughed brush border and tubular cell debris, and by loosely aggregated cast material incorporating filtered protein [11] combined with tubular cell vacuolization and swelling, which is most striking in the outer stripe of the outer medulla, well beyond the proximal tubular segments accessible to micropuncture. A focal obstruction at any point in the nephron would potentially be sufficient to obstruct free flow of tubular fluid [12] resulting in obstruction in the absence of extensive tubular damage or cast formation. The histologic alterations seen in these studies at 4.5 hr are sufficient to produce obstruction. At later time periods large numbers of typical hyaline casts are seen, especially in the thin limbs of the loop of Henle. These probably form from propogation and condensation of the loosely aggregated luminal material seen at the end of the 4.5 hr infusion period. Interestingly, although Tamm-Horsfall protein is thought to be produced only by cells of the ascending thick limb [13], these more proximal casts contain Tamm-Horsfall protein (Racusen, Whelton, and Solez, unpublished) suggesting either that Tamm-Horsfall protein is produced proximal to the thick ascending limbs, or that these casts form at least in part by retrograde propagation of casts which form initially in more distal regions.

The decrease in renal blood flow which is observed late in the infusion period is probably a consequence of tubular obstruction. Obstruction may lead to decreased renal blood flow through compression of peritubular capillaries by distended

tubules and increased tissue pressure [14, 15] or through delayed afferent arteriolar constriction due perhaps to a feedback mechanism [16–18]. Tubular obstruction with reflex arteriolar vasoconstriction has been postulated to contribute to the renal dysfunction seen in postischemic [19–21] and gentamicin-induced acute renal failure [22].

Since changes in renal blood flow are a relatively late phenomenon in lysine-induced acute renal failure, the tubular degeneration effects and resulting obstruction are most likely due to a direct toxic effect of the amino acid. Lysine blocks tubular protein reabsorption [23, 24] and has been used in diuresing human volunteers in an attempt to totally suppress albumin reabsorption and thereby determine GFR for albumin [24]. It seems possible that the elevated protein concentration in tubular fluid in a lysine-treated animal might increase the propensity for obstructive cast formation [13]. Possible metabolic effects of producing significant elevations in plasma and presumably tissue lysine concentrations might be involved in the pathogenesis of lysine-induced renal dysfunction and require further investigation.

Although urine concentrations of lysine were not determined, it is likely that the dose of lysine administered exceeded the K_m for tubular reabsorption [25], especially if the more proximal tubular segments are damaged by the amino acid. Lysine, therefore, would be reaching the pars recta and more distal portions of the nephron at relatively high concentrations, and it is these segments, especially as they pass through the outer stripe of the outer medulla, which show evidence of histologic damage following infusion of the amino acid.

Of the amino acids present in hyperalimentation solutions, lysine is the only one which has been shown to cause persistent acute renal failure. It is possible that lysine is the component of hyperalimentation solutions responsible for their adverse effects in experimental animals [5, 7] and that similar effects occur in humans. However, although doses of lysine comparable to those given in the present study have been administered to human volunteers [24], the amounts of lysine received by a patient on standard essential amino acid therapy would be at least 30-fold less. Further clinical studies are necessary to establish whether hyperalimentation solutions do increase the risk of acute renal failure in humans, and if so, whether lysine is responsible for this effect.

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