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Renal cyst epithelial transport in non-uremic polycystic kidney disease

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Renal cyst epithelial transport in non-uremic polycystic kidney disease. Renal cyst epithelial transport of organic molecules was investigated during three separate cyst drainage procedures in a non-uremic patient with polycystic kidney disease (PCKD). Following constant intravenous inulin infusion, four of eight sampled cysts achieved concentrations exceeding those expected by glomerular filtration alone. Likewise, cyst concentrations of the filtered radionuclide Tc DTPA were up to 3.7 times simultaneous plasma levels. Both PAH and I-131 hippuran accumulated in all cysts suggesting intact tubular secretory mechanisms. Quantitative amino acid levels in two proximal nephron cysts were identical to serum. Since concentrations of inulin, DTPA, and amino acids exceed levels expected if cystic nephrons had normal glomerular filtration and tubular reabsorptive properties, other mechanisms are likely. Simple diffusion across altered epithelial surfaces could partially account for the observed cyst concentrations of each organic molecule and, by ion trapping, contribute to progressive cyst growth in PCKD.

Transport épithélial kystique rénal dans la maladie polykystique rénale non-urémique. Le transport épithélial kystique rénal de molécules organiques a été étudié pendant trois drainages kystiques séparés chez un malade non urémique atteint de maladie polykystique (PCKD). Après une perfusion constante intraveineuse d'inuline, les recueils de quartre sur huit kystes indiquaient des concentrations dépassant celles attendues par la seule filtration glomérulaire. De même, les concentrations kystiques du radionuclide Tc DTPA filtré atteignaient jusqu'à 3,7 fois les valeurs plasmatiques au même moment. Le PAH et le I-131 hippuran s'accumulaient dans tous les kystes, suggérant des mécanismes sécrétoires tubulaires intacts. Les niveaux quantitatifs d'aminoacides dans deux kystes néphroniques proximaux étaient identiques au sérum. Puisque les concentrations d'inuline, de DTPA et d'aminoacides dépassent les niveaux attendus si les néphrons kystiques avaient une filtration glomérulaire normale et des propriétés de réabsorption tubulaire, d'autres mécanismes sont probables. La simple diffusion à travers des surfaces épithéliales altérées pourrait partiellement rendre compte des concentrations kystiques observées pour chaque molécule organique, et, par capture ionique, contribuer à la croissance progressive des kystes dans la PCKD.

Polycystic kidney disease (PCKD) is responsible for 5 to 10% of endstage renal disease in the United States [1]. Although the clinical consequences of progressive cyst enlargement and renal failure are well known aspects of PCKD, the precise pathogenesis of cyst growth is not well understood.

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Histologically, cysts may arise from any nephron segment, but they are in continuity with a single glomerular and tubular unit. Intratubular obstruction [2, 3] or an inherent basement membrane defect [4] may lead to initial cyst development. Lambert [5] and Bricker and Patton [6] demonstrated penetration of inulin and PAH into cysts and suggested that subsequent cyst growth is largely due to fluid produced by glomerular filtration. Other authors, however, have failed to demonstrate measurable cyst concentrations of inulin despite prolonged intravenous infusions [7]. It is difficult to explain the presence of measurable inulin in cysts by filtration alone since the single nephron GFR in normal man is only 10^{-8} liter/min. This suggests that additional cyst cell transport mechanisms could be present. Gardner [8] and Huseman et al [9] have presented strong evidence that cyst epithelium continues to function in a manner similar to cells lining the nephron segment of origin. Individual cyst fluid turnover rates may approach 100 ml/24 hr [10].

Kidney cysts appear to be focal dilations of functioning nephrons with complex transport mechanisms. Observations of the following patient with polycystic kidney disease and well preserved renal function may help to elucidate cyst transport processes.

Case report. The patient is a 28-year-old white female with autosomal dominant, adult polycystic kidney disease (PCKD). Her history dates to an episode of pyelonephritis at age 12. An intravenous pyelogram performed in 1974 during evaluation of chronic flank pain was characteristic of PCKD. The creatinine clearance at that time was 126 ml/min. In 1976, a motorcycle accident precipitated hematuria and an increase in right flank pain; she underwent aspiration of three cysts in the mid-region and inferior pole of the right kidney with partial pain relief. Over the ensuing 5 years, she noted progressive flank pain (right greater than left) requiring daily narcotics to assure adequate analgesia. Early satiety and anorexia were associated with a 15-pound weight loss during the year prior to her admission to The Oregon Health Sciences University (OHSU). An ultrasound examination in January 1981 revealed a large right inferior pole cyst. Creatinine clearance was 75 ml/min. She had not had any recent urinary tract infections, hematuria, or hypertension. Both the patient's father and aunt had endstage PCKD.

On January 29, 1981, percutaneous cyst puncture of a large right lower pole cyst was performed with ultrasound localization. The procedure was preceded by a 7-hr para-aminohippur-

Table 1. Cyst fluid chemistries[a]

Cyst no.	Procedure	Na^+ *mEq/liter*	K^+ *mEq/liter*	Cl^- *mEq/liter*	Urea *mg/dl*	Creatinine *mg/dl*	Glucose *mg/dl*	Protein *g/dl*	Osmolality *mOsm*	pH	PO_2	PCO_2
1A	Percutaneous puncture of right-sided cyst	144	3.0	113	0.5	1.25	—	1.0	248	7.38	90	38
1B	Right kidney cyst marsupialization	140	4.1	111	20	1.65	76	2.3	286			
2	Right kidney cyst marsupialization	145	4.1	112	27	1.73	—	2.3	290	7.41	93	25
3	Right kidney cyst marsupialization	146	4.2	115	20	—	91	—	289			
4	Right kidney cyst marsupialization	143	4.1	111	19	1.99	94	—	290			
5	Left kidney cyst marsupialization	146	4.1	120	23	1.26	91	—	294			
6	Left kidney cyst marsupialization	146	4.1	119	30	1.25	94	3.3	296			
7	Left kidney cyst marsupialization	145	4.2	117	25	1.49	93	—	293			
8	Left kidney cyst marsupialization	152	4.2	124	21	1.20	90	—	304			

[a] Expressed as concentration/volume cyst fluid.

ate (PAH) and inulin infusion (see below). The patient received a moderate amount of pain relief.

She was readmitted 1 month later for right renal cyst marsupialization. Through a dorsal lumbotomy incision, three large cysts and multiple small cysts were marsupialized. A radioisotope renogram was performed 18 hr prior to surgery to verify symmetrical renal function. PAH and inulin infusions to measure inulin clearance and PAH transport maximum (TmPAH) were completed on the morning of surgery.

Dramatic unilateral relief of pain followed the first marsupialization, and in July 1981, she underwent a similar procedure on the left with marsupialization of six medium-sized cysts. PAH and inulin infusions, as well as a repeat radioisotopic renogram, were repeated prior to surgery. She has noted marked bilateral relief of flank pain during a 7-month follow-up. Serum creatinine remains stable at 1.2 mg/dl (creatinine clearance = 76 cc/min).

Methods

Cyst fluid was obtained for analysis at the first percutaneous cyst puncture and at two subsequent cyst marsupialization procedures. Cyst fluid and serum were analyzed for sodium, potassium, chloride, urea nitrogen, creatinine, and glucose (Autolyzer Technicon™ Technicon Instruments Corporation, Tarrytown, New York). Cyst fluid osmolalities were determined by osmometer. Quantitative amino acid levels were determined by spectrophotometric techniques. Cyst fluid gases (PO_2, PCO_2) and pH were determined by electrode.

Eighteen hours prior to each surgical marsupialization, a standard renal nucleotide scan utilizing 10 mCi of technecium-labelled diethylenetriaminepentaacetic acid (DTPA) and 0.3 mCi of I-131 labelled hippurate was completed. At surgery, simultaneous samples of blood, urine, and cyst fluid were obtained and counted for radioactive label.

Seven hours prior to the initial percutaneous cyst puncture, PAH and inulin clearances were determined. After an oral water load, loading doses of 10% inulin (0.5 mg/kg) and 20% PAH (0.03 ml/kg) were given intravenously and followed by a continuous infusion (75 ml of 10% inulin, 15 ml of 20% inulin, 450 ml of 5% dextrose with 0.45% saline at 150 ml/hr). Four 20-min clearance periods followed a 45-min equilibration period. The infusion was continued for 7 hr until cyst aspiration was completed. Cyst fluid and simultaneous samples of blood and urine were analyzed for inulin and PAH. Inulin and PAH were not detected in cyst fluid blanks.

On the morning of each marsupialization, PAH and inulin were infused to determine inulin clearance and PAH transport maximum (TmPAH) of proximal tubular cells. After a 750-cc intravenous fluid load (D5/0.45 NS), loading doses of 10% inulin (0.5 ml/kg) and PAH (10 g) were given and followed by a constant infusion (40 ml of 10% inulin and 125 ml of 20% PAH in 435 ml of 5% dextrose at 300 ml/hr). Four 20-min clearance periods followed a 45-min equilibration period. Cyst fluid obtained at surgery was analyzed for PAH and inulin levels.

The cyst transport studies are part of an ongoing clinical research center study approved by the Oregon Health Sciences Center Human Use Committee. Informed consent was obtained.

Results

A total of nine cysts were sampled with volumes ranging from 4 to 250 ml. Based on cyst fluid electrolyte evaluation described by Huseman et al [9], all sampled cysts were characterized as proximal nephron cysts (cyst fluid:serum sodium ratios > 0.9). Cyst chemistry data and simultaneous serum values are listed in Tables 1 and 2. Cyst 1B was considered to be the same cyst sampled percutaneously 1 month earlier (cyst 1A).

Cyst fluid electrolyte, urea, creatinine, and glucose levels were all similar to serum concentrations. Cyst fluid protein, determined in four cysts, ranged from 1.0 to 3.3 g/dl, and cyst fluid was isosmolar with serum. Cyst fluid gas and pH determinations in two cysts revealed levels similar to arterial blood with pH of 7.38 to 7.41, PO_2 of 90 to 93 mm Hg and PCO_2 of 25 to 38 mm Hg. Quantitative amino acid levels were very similar to human plasma levels in two cysts. Protein electrophoresis of fluid from a single cyst revealed large amounts of albumin and small amounts of alpha and beta globulins.

Whole kidney inulin and PAH clearances prior to the first cyst puncture were 71.8 ml/min and 408.5 ml/min, respectively. The PAH secretory maximum (TmPAH) determined prior to the two marsupialization procedures was 70.8 and 52.8 mg/min, respectively. Table 3 summarizes the inulin and PAH concentrations of cyst fluid and serum. PAH reached significant concentrations (1.1 to 12.6% of average serum levels) in all cysts sampled after high-dose infusion. Inulin, in contrast, reached detectable cyst concentrations only after the last infusion. Although the cyst inulin concentrations are low, they are within the assay range (> 0.005 mg%) and are 2.0 to 22.2% of average serum values.

Table 2. Serum chemistries

Procedure	Na^+ *mEq/liter*	K^+ *mEq/liter*	Cl^- *mEq/liter*	Urea *mg/dl*	Creatinine *mg/dl*	Glucose *mg/dl*	Protein *g/dl*
Percutaneous cyst puncture	140	4.2	105	16	1.0	76	7.6
Right kidney cyst marsupialization	141	4.6	104	21	1.1	71	7.4
Left kidney cyst marsupialization	141	4.5	103	20	1.1	70	7.6

Table 3. PAH and inulin cyst penetrance

Cyst no.	Cyst vol. *ml*	PAH *dose*	Cyst [PAH] *mg%*	Avg. serum [PAH] *mg%*	Cyst [Inulin] *mg%*	Avg. serum [Inulin] *mg%*	Infusion *duration*	Infusion *to sampling*
1A	250	Low dose for PAH clearance	0	3.14	0	0.53	7 hr	0
1B	55	High dose for Tmax PAH	1.94 (3.0)[a]	65.5	0	0.39	2 hr	1.5 hr
2	120	Tmax	0.72 (1.1)	65.5	0	0.39	2 hr	1.5 hr
4	22	Tmax	4.25 (6.5)	65.5	0	0.39	2 hr	1.5 hr
5	10	Tmax	6.85 (7.1)	97.3	0.09[b] (19.6)	0.46	2 hr	2 hr
6	21	Tmax	2.30 (2.4)	97.3	0.013 (2.8)	0.46	2 hr	2 hr
7	27	Tmax	4.90 (5.1)	97.3	0.009 (1.96)	0.46	2 hr	2 hr
8	8	Tmax	12.21 (12.6)	97.3	0.102 (22.2)	0.46	2 hr	2 hr

[a] Numbers in parentheses represent % cyst concentration/peak serum concentration.
[b] Lower limits of inulin assay = 0.005 mg%.

DTPA and hippuran were detected in cyst fluid 18 hr after each of the two renal scans (Table 4). DTPA levels were 0.4 to 3.7 times simultaneous plasma concentrations, and hippuran reached concentrations of 0.29 to 2.4 times plasma levels. At the time of cyst sampling, urinary excretion of both DTPA and hippuran persisted with urinary technecium activity of 29,000 cpm/ml and I-131 activity of 3,500 cpm/ml.

Discussion

Renal cysts are focal dilations of functioning nephrons [5, 8]. The mechanisms of cyst fluid transport and cyst growth reportedly depend on intact glomerular filtration and tubular transport processes. Cyst penetration by DTPA, inulin, and gentamicin in concentrations exceeding glomerular filtration suggests that other epithelial transport processes contribute to cyst growth.

Inulin is used to study glomerular filtration because it is filtered by the glomerulus but not secreted or reabsorbed by normal tubular epithelium. Measurable inulin was detected in four of eight cysts sampled after a 2-hr infusion. If inulin gained access to cysts exclusively by filtration in a single nephron, chemically measurable cyst concentrations of inulin should not be achievable during a standard infusion. Let us assume that inulin gains access to a 25 ml proximal tubular cyst by glomerular filtration in a nephron with a SNGFR of 65×10^{-6} ml/min [11]. If the serum inulin concentration is maintained at 0.45 mg/dl during a 120-min infusion, and molecules entering the cyst are not reabsorbed or drained, the expected cyst inulin concentration could be calculated as follows:

$$\frac{65 \times 10^{-6}\ \text{ml}}{\text{min}} \times \frac{0.45\ \text{mg inulin}}{10^{2}\ \text{ml}} \times \frac{120\ \text{min}}{25\ \text{ml cyst fluid}} = \frac{1.4 \times 10^{-6}\ \text{mg inulin}}{\text{ml fluid}}.$$

It is obvious, then, that cyst inulin concentrations reached by glomerular filtration alone are well below the sensitivity of standard chemical assay techniques (which detect inulin concentrations > 0.005 mg%).

Alternatively, the SNGFR required to deliver the quantity of inulin to the cysts could be calculated as:

$$\frac{\text{Cyst [inulin]} \times \text{volume}}{\text{Plasma [inulin]} \times 120\ \text{min}}.$$

Ignoring the underestimation of cyst volume (and therefore filtration) inherent in the surgical procedure, and assuming inulin penetrates cysts by filtration alone, the calculated SNGFR varies from 4.4×10^{-3} to 16.3×10^{-3} ml/min. Inulin penetration into cysts by filtration alone would require 68 to 250 times the accepted SNGFR of 65×10^{-6} ml/min.

The detection of inulin in 50% of the sampled cysts is consistent with other reports in the literature. Perhaps the variable penetrance of inulin reflects passive diffusion across cyst epithelium which has been altered by mechanical distention, inflammation, or other processes. Alternatively, differing serum inulin concentrations in different studies could have produced varying gradient drives for diffusion. Bricker and Patton [6] demonstrated penetrance of inulin into cysts by infusing inulin to maintain plasma concentrations of 41 to 77 mg%, 100-fold greater than in this study. Likewise, Lambert [5] injected large premorbid intraperitoneal doses of inulin (41 g) and noted cyst penetrance. Interestingly, inulin reached measurable cyst concentrations in the reported patient only after the third infusion, which produced the highest serum concentration and gradient for diffusion. Alternatively, inulin may have accumulated during each infusion reaching measurable levels only after the third infusion. In the face of well preserved renal function, plasma inulin should have been rapidly cleared with

Table 4. DPTA and hippuran concentrations in cyst fluid and blood after intravenous infusion

Cyst no.	T_c DTPA, *cpm*				I_{131} Hippurate, *cpm*			
	Cyst	Whole blood[a]	Cyst/blood	Cyst/plasma	Cyst	Whole blood	Cyst/blood	Cyst/plasma
1B	9,031	2,223	4.1	2.4	309	316	0.9	0.5
2	2,286	2,223	1.02	0.6	160	316	0.5	0.3
4	13,946	2,223	6.3	3.7	549	316	1.74	1.0
5	16,160	7,348	2.2	1.3	805	249	3.2	1.9
6	5,257	7,348	0.7	0.4	1,052	249	4.2	2.4
7	11,848	7,348	1.6	0.9	634	249	2.5	1.5

Abbreviation: cpm, counts/min/cc fluid above background.
[a] Blood specimens were obtained simultaneously with cyst sampling.

each infusion. Cyst inulin accumulation by filtration alone would not have reached measurable concentrations, even after three infusions.

DTPA is another substance felt to be filtered by the nephron but not secreted or reabsorbed by the tubule. Although DTPA is 1.8 to 5.9% protein bound after a single injection, its clearance correlates closely with that of inulin and is not altered by probenecid. The radiolabel is 96 to 98% bound in vitro at 8 hr without further in vivo breakdown after a 3-hr infusion [12, 13]. Like inulin, the penetration of DTPA in measurable concentrations into all cysts sampled is consistent with solute transport mechanisms other than, or in addition to, filtration. Although these data do not preclude a major role for glomerular filtration in cyst growth, other transport processes must exist to explain cyst penetrance by inulin and DTPA in the concentrations noted in the reported patient.

Based on cyst fluid electrolyte analysis, Gardner suggested that cyst walls continue to function as either proximal or distal nephrons [8]. Additionally, Cuppage et al [14] demonstrated ultrastructural differences in cyst epithelium which correspond to the nephron segment of origin, as defined by fluid chemistries. The accumulation of PAH and hippuran (substances handled by tubular secretion) in cysts also suggests intact tubular secretory mechanisms in cyst epithelium. While simple diffusion cannot be excluded, the relatively high concentrations of hippuran in cyst fluid favors an active secretory process. Alternatively, relatively low cyst epithelial permeability may allow organic anion trapping within cysts after penetrance by simple diffusion, while plasma hippuran would be cleared more rapidly by normal renal tubules.

If the plasma PAH concentration is adjusted for protein binding [15], the relative clearances of PAH and inulin by cystic nephrons can be compared:

$$\frac{\text{(Cyst/plasma PAH) (0.83)}}{\text{Cyst/plasma inulin}}.$$

Since cyst fluid protein concentration does not alter the measurement of PAH nor the mechanism of PAH cyst penetrance, cyst fluid PAH concentrations were not adjusted for protein binding. Using this analysis, three of four cysts in which inulin could be measured accurately had PAH clearances less than or identical to inulin. If inulin is assumed to reach cyst fluid by filtration alone, secretion of PAH must not occur. Inulin, however, most likely penetrates cyst fluid by mechanisms other than filtration (see above), and no conclusions can be reached about the relative secretion, filtration, or diffusion of PAH.

Amino acids are filtered freely at the glomerulus and virtually completely reabsorbed in the proximal tubule [16]. Furthermore, in rat isolated perfused proximal convoluted tubules, when the flow of tubule fluid is stopped, a low steady state concentration of amino acids and other organic solutes is achieved [17]. If one views kidney cyst epithelium as functionally identical to normal tubular epithelium, proximal nephron cysts should contain amino acids in low concentrations. Two proximal cysts evaluated in this patient, however, had quantitative amino acid levels identical to serum. The apparent equilibration of serum and cyst amino acid concentrations suggests that simple diffusion from peritubular blood may overwhelm any concurrent active reabsorptive process, or that amino acid reabsorption by cyst wall epithelium is less efficient than by normal tubular cells. The cyst albumin concentrations further suggest a leaky cyst epithelial barrier.

Muther and Bennett [7] have recently reported the appearance of gentamicin in proximal cysts after 36 to 48 hr of intravenous therapy. The appearance in cysts of this aminoglycoside, which depends primarily on glomerular filtration for excretion, suggests that gentamicin could gain access to cysts by a transtubular route. Collier, Lietman, and Mitch [18] have shown that only 75% of renal gentamicin uptake could be eliminated by rendering an isolated perfused rat kidney nonfiltering. Furthermore, basolateral aminoglycoside transport, although perhaps not as quantitatively important as luminal uptake, can be inferred from renal cortical slice studies in animals and man [19–21]. Perhaps active basolateral transport of endogenous anions such as hippurates, with sequestration inside cysts precluding efflux, plays a role in the process of cyst growth. Diffusion across an altered epithelial barrier, as hypothesized for inulin, is an alternative possibility.

The measurable concentration of erythromycin in three cysts of a patient with PCKD on oral antibiotic (unpublished data) further supports the diffusion hypothesis. Although erythromycin penetrates body fluids well, it is not excreted by the kidney. Its appearance in kidney cyst fluid again raises the possibility that cyst epithelium differs from intact tubular epithelium.

Cysts from patients with PCKD are thought to be dilations of functioning nephrons with retained epithelial transport mechanisms. The demonstration of DTPA, inulin, and aminoglycosides in relatively high concentrations is inconsistent with cyst growth by the accumulation of glomerular filtrate alone. Simple

diffusion across altered epithelial surfaces could account for the cyst penetrance of each of the above agents as well as erythromycin. The apparent amino acid equilibration across cyst walls lends further support to this theory. Although this study represents relatively few observations in a single patient, the data refute the commonly held assumption that cyst growth is due to glomerular filtration alone. Further study of organic molecules and their movement into cyst fluid might help clarify complex transport mechanisms and elucidate the processes involved in progressive cyst growth.

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