JCI The Journal of Clinical Investigation

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F Y Liu, M G Cogan

J Clin Invest. 1986;78(6):1547-1557. https://doi.org/10.1172/JCI112747.

Research Article

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Axial Heterogeneity of Bicarbonate, Chloride, and Water Transport in the Rat Proximal Convoluted Tubule

Effects of Change in Luminal Flow Rate and of Alkalemia

Fu-Ying Liu and Martin G. Cogan

Cardiovascular Research Institute and Department of Medicine, University of California, San Francisco, California 94143

Abstract

These studies examined regulation of superficial proximal convoluted tubule (PCT) transport as a function of length. When single nephron glomerular filtration rate (SNGFR) increased from 28.7±0.7 nl/min in hydropenia to 41.5±0.4 nl/min in euvolemia, bicarbonate, chloride, and water reabsorption in the early (1st mm) PCT increased proportionally: from 354±21 peq/ mm · min, 206±55 peq/mm · min, and 5.9±0.4 nl/mm · min to 520 ± 12 peq/mm · min, 585 ± 21 peq/mm · min, and 10.1 ± 0.4 nl/ mm · min, respectively. These high transport rates did not increase further, however, when SNGFR went to 51.2±0.7 or 50.7±0.6 nl/min after atrial natriuretic factor or glucagon administration. Anion and water transport rates in the late PCT were lower and exhibited less flow dependence. During chronic metabolic alkalosis, acidification was inhibited in the late but not early PCT. In conclusion, the early PCT is distinguished from the late PCT by having high-capacity, flow-responsive but saturable, anion- and water-reabsorptive processes relatively unaffected by alkalemia.

Introduction

The rat proximal convoluted tubule $(PCT)^1$ exhibits structural and functional differences along its length (1–3). The early PCT is distinguished by having cells (S₁ subtype) with greater membrane surface area and more mitochondria (1) and by having greater avidity for reabsorption of several solutes, including glucose, amino acids, and phosphate, than cells (S₂) resident in the late PCT (2, 3).

We recently extended this description of axial heterogeneity by examining free-flow anion reabsorption along the length of the superficial PCT in hydropenic rats. The early PCT reabsorbed bicarbonate at a greater rate than has been observed in the late PCT (4), even when the latter has been presented with similar bicarbonate loads by means of microperfusion (5, 6). The high rate of acidification in the early PCT has been confirmed (7, 8). In addition, we demonstrated that the early PCT was capable of reabsorbing chloride at a substantial rate (4), a surprising finding inasmuch as minimal chloride transport in this nephron

Portions of this work were presented at the Western Section and National Meetings of the American Federation for Clinical Research and have been published as abstracts (1986. *Clin. Res.* 34:109A and 698A).

Received for publication 21 March 1986.

J. Clin. Invest. © The American Society for Clinical Investigation, Inc. 0021-9738/86/12/1547/11 \$1.00 Volume 78, December 1986, 1547–1557 segment was expected based on previous theoretical considerations (9).

However, the reabsorptive kinetics of these robust anion transport processes in the early PCT in response to change in luminal flow and substrate delivery rate have not been clearly defined. Conflicting conclusions have been advanced recently regarding the saturability of early PCT bicarbonate reabsorption under physiological conditions as load is increased (8, 10). Although microperfusion studies have demonstrated saturability of acidification in the late PCT in vivo (5, 6), the early PCT has not been examined. Another issue that has not yet been addressed is whether chloride transport in the early PCT can increase when flow rises (11). Flow dependence of chloride transport has been found to occur in some (12–14), but not other (14–16), microperfusion studies of the late PCT in vivo.

In addition to the quantitative and possible kinetic differences with regard to luminal determinants of anion transport in the early versus late PCT, there may also be axial differences in control of transport by peritubular factors. It has been proposed, for instance, that alkalemia suppresses late, but not early, acidification (17, 18). Such differential regulation has been posited because of the findings that bicarbonate absorption in the late PCT determined by in vivo microperfusion was markedly inhibited during metabolic alkalosis (19), whereas total bicarbonate reabsorption over the entire length of the PCT determined by free-flow micropuncture was not substantially altered by alkalemia (20).

The first purpose of the present studies was to compare the flow dependency of bicarbonate, chloride, and water reabsorption in the early versus late superficial PCT. Anion and water transport was examined over the entire length of the tubule by the retrograde, sequential free-flow micropuncture technique (developed in this laboratory) as single nephron glomerular filtration rate (SNGFR) was systematically altered in increments of ~ 10 nl/min. Axial PCT transport during the volume-contracted, low-SNGFR condition of hydropenia was compared with proximal transport during the normal-SNGFR condition of euvolemia and finally with the high-SNGFR condition induced by administration of either atrial natriuretic hormone (ANF) or glucagon. The use of vasoactive hormones, ANF and glucagon, for this purpose is predicated on the assumption that they raise SNGFR but do not independently alter proximal transport. The lack of direct effect by ANF on the proximal tubule is supported by several lines of evidence: (a) there are no extraglomerular cortical ANF receptors (21, 22); (b) the second messenger for ANF, cyclic GMP, is not produced by the PCT either in vivo (23) or in vitro (21, 24, 25), and the PCT has no particulate guanylate cyclase (21, 25); and (c) all micropuncture and microperfusion studies to date both in vivo (26-29) and in vitro (30) have failed to show any direct effect by ANF on solute or volume transport in the PCT independent of flow rate. Similarly, glucagon causes no increase in its second messenger, cyclic AMP, in the proximal tubule (24, 31) and does not affect proximal sodium transport (32).

^{1.} Abbreviations used in this paper: ANF, atrial natriuretic factor; GFR, glomerular filtration rate; PCT, proximal convoluted tubule; SNGFR, single-nephron glomerular filtration rate.

Our second purpose was to test the prediction that acidification in the late, but not early, PCT is suppressed by alkalemia (17, 18). For this purpose, bicarbonate reabsorption in the early and late PCT was compared during normal and alkalotic conditions at comparable filtered bicarbonate loads.

Methods

Free-flow micropuncture studies were performed in 27 Munich–Wistar rats. We employed the technique previously developed in this laboratory by which multiple punctures are made sequentially along the entire length of the superficial PCT in a retrograde fashion, from the end-proximal tubule to Bowman's space (4). This technique permits assessment of the axial profiles of bicarbonate, chloride, and volume transport.

Protocols

The first four protocols were designed to systematically alter SNGFR from subnormal to normal to supernormal levels to assess the effect of changes in luminal flow rate on segmental anion and water reabsorption. The last protocol, in which chronic metabolic alkalosis was induced, was performed to permit comparison of segmental bicarbonate reabsorption in alkalotic and normal animals with similar filtered bicarbonate loads.

Group 1: hydropenia. The results of studies in 10 hydropenic rats on a normal diet have been reported previously (4) and are repeated here for comparison with the other groups. Surgically induced plasma volume loss was not replaced so that SNGFR was subnormal (33).

Group 2: euvolemia. Six rats were studied in which the plasma volume contraction incurred by the micropuncture preparatory surgery was corrected by isoncotic plasma infusion, as previously described (8, 33). Isoncotic plasma obtained from donor sibling rats maintained identically to the rat under study was given as an infusion of 1.3% body weight over 45 min and then as a sustaining infusion of 5 μ l/min to maintain a normal plasma volume and SNGFR.

Group 3: ANF. After the achievement of the euvolemic state in five rats, an intravenous infusion was begun of synthetic, rat ANF (Auriculin B, 25 amino acids: arg^{126} to tyr^{150} residues, generously provided by Dr. J. Lewicki, California Biotechnology, Inc., Palo Alto, CA). ANF was given as a bolus of 5 μ g/kg followed by a sustaining rate of 0.5 μ g/ kg \cdot min in a bicarbonate Ringer's solution at a rate (30 μ l/min) sufficient to replace urinary solute and volume losses (23, 26, 29). ANF used in this manner causes a stable state of glomerular hyperfiltration (23, 26, 29).

Group 4: glucagon. The same protocol as for group 3 was followed except that glucagon was given as a bolus of 10 μ g/kg followed by a sustaining rate of 1.0 μ g/kg \cdot min at 50 μ l/min.

Group 5: chronic metabolic alkalosis. As previously described (20), six rats were maintained for 2 wk on a standard liquid electrolyte-deficient diet (40 ml/day) supplemented with Na₂SO₄ (2.6 meq/d) and injected with 0.5 mg/d deoxycorticosterone acetate i.m. Surgically induced plasma volume losses were replenished prior to micropuncture. Rats prepared in this way have hyperbicarbonatemia with reduction in SNGFR.

Micropuncture technique

The rats were prepared for micropuncture as previously described (4, 20, 23, 26, 33, 34). Briefly, the animals were anesthetized with Inactin (100 mg/kg, i.p.) and placed on a thermostatically controlled (37°C) micropuncture table. Catheters (PE-50) were inserted into the femoral artery for blood sampling and into a jugular vein for inulin infusion. A tracheostomy was performed. The abdomen was opened by a midline incision, the kidney was stabilized and bathed in warmed saline (37°C), and the ureter was cannulated. A 20-min equilibration was allowed to elapse.

A surface glomerulus was then located. A small pipette $(3-5 \mu m OD)$ was inserted into Bowman's space and a small droplet of oil stained with Sudan black was injected. The course of the injected oil droplet was carefully observed and mapped. Only glomeruli followed by at least six to seven surface proximal convolutions were used. The localization pipette was withdrawn and 1 h was allowed to elapse, which we have previously

shown is sufficient time for the hole in Bowman's space to seal (4). The plasma volume in groups 2-4 was then replenished as described above and a [³H]methoxyinulin infusion commenced (25-50 μ Ci bolus, then 50-100 μ Ci/h in bicarbonate Ringer's solution at 0.8-1.6 ml/h).

After an equilibration time of at least 1 h, sequential, timed 3-8min collections were begun using 7-9- μ m OD glass pipettes. They started at the end-proximal convolution and worked in a retrograde fashion to Bowman's space. Because of the special interest in these studies in early PCT transport, care was taken to obtain at least one sample within the estimated initial mm of the tubule.

After 5 h, to allow the tubule puncture sites to seal, Microfil (Canton Biomedical Products, Boulder, CO) was injected into Bowman's space to fill the entire tubule. At a later time, the kidney was incubated for 30-40 min in 6 N HCl. The cast of the tubule was dissected, with the multiple puncture sites identified using the initial localization map, and it then was photographed. The entire accessible proximal tubule length (glomerulus to the last puncture site) and the length to each puncture site were measured and recorded.

Analysis

The volume of collected tubule fluid samples was determined by injecting them into constant-bore capillary glass tubing with a known volume per length and measuring the length occupied. Aliquots of the fluid were used to measure inulin by scintillation counting, total CO_2 by micro-calorimetry (35), and chloride by the microtitrimetric method of Ramsay et al. (36), as previously described (4, 20, 23, 26, 33, 34). For ease of presentation, bicarbonate is used to represent total CO_2 content of tubular fluids and urine under physiologic conditions.

Calculations

The SNGFR was estimated as the product of the flow rate at a given point multiplied by the corresponding inulin concentration ratio (tubular fluid/plasma water). SNGFR values in the text refer to mean determinations, but there were no systematic changes in SNGFR as a function of length of time, as previously documented (4). Water reabsorption at a given point was the flow rate at that point subtracted from the SNGFR. Bicarbonate and chloride reabsorption were the filtered load (anion concentration in Bowman's space multiplied by the SNGFR) minus the anion delivery at that point (anion concentration multiplied by the flow rate). Reabsorption at a given length (e.g., 1 mm) was estimated by interpolation between the two closest measured data points to that length for each tubule. The fractional reabsorption for a given nephron millimeter segment was calculated as the anion or volume reabsorption of that millimeter segment divided by the delivery of anion or volume to that segment. All data are expressed as mean±SEM. Statistical comparisions between groups were made using the unpaired t test.

Results

General. As shown in Table I, all groups had similar values for animal weight and for total length of the accessible superficial PCT (~ 5 mm). Mean values for SNGFR in groups 1–4 differed from each other by increments of ~ 10 nl/min whereas plasma anion concentrations were stable. In group 5 with chronic met-

Table I. General Characteristics

Group	Animal weight	Tubule length	SNGFR	Plasma [HCO3]	Plasma [Cl⁻]	
	g	mm	nl/min	meq/liter	meq/liter	
1. Hydropenia	216±3	4.83±0.07	28.7±0.7*	24.1±0.5	105±1*	
2. Euvolemia	217±6	4.98±0.10	41.5±0.4	24.1±0.5	109±1	
3. ANF	213±3	5.18±0.06	51.2±0.7*	24.5±0.5	104±1*	
4. Glucagon	210±5	5.10±0.07	50.7±0.6*	24.7±0.1	104±1*	
5. Alkalosis	207±5	4.88±0.07	30.9±0.6*	41.3±0.9*	93±1*	

* P < 0.001 group 2 compared with Groups 1, 3, 4, and 5.

abolic alkalosis, hyperbicarbonatemia and glomerular hypofiltration were present. No differences in plasma protein concentration or hematocrit were found between groups. Blood pressure was stable during the observation period in each group, though \sim 5–10 mmHg less in groups 3 and 4 than in groups 1 and 2.

In the following description of results, data will be presented by millimeter increments. To be concise, transport rates in the 3rd to 5th mm of the late PCT have been consolidated in the figures inasmuch as results for these segments were relatively homogeneous. The impact of altering luminal flow rate or peritubular anion composition on segmental bicarbonate, chloride, or water transport will be displayed in three ways: (a) absolute transport as a function of length, (b) absolute transport as a function of delivered load, and (c) fraction of the delivered load reabsorbed as a function of the delivered load. There were no statistical differences in any of the transport data between the hyperfiltration groups 3 and 4.

Flow dependence of bicarbonate transport. As shown in Table II and Fig. 1 A and B, a progressive increase in luminal flow rate in groups 1–4 resulted in lesser depression in the luminal bicarbonate concentration and tubular fluid/glomerular ultra-filtrate (TF/UF) concentration ratio as a function of length.

In the transition from hydropenia to euvolemia (groups 1 and 2), the rise in filtered bicarbonate load $(740\pm31 \text{ to } 1,135\pm9$

$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	Group		Millimeter segment					
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$		Bowman's space	lst	2nd	3rd	4th	5th	
Anion concentrations HCO5 i. Hydropenia 25.7±0.7 16.9±0.8 10.4±0.6* 8.6±0.6* 6.8±0.7 5.7±0.3 2. Euvolemia 27.3±0.2 19.6±0.4 13.9±0.4 10.8±0.5 8.6±0.3 6.4±0.4 3. ANF 27.8±0.5 21.5±0.5* 17.1±0.4‡ 14.3±0.3‡ 11.5±0.2‡ 9.1±0.3‡ 4. Glucagon 28.2±0.6 21.3±0.7 16.7±0.7‡ 14.4±0.7* 11.7±0.3‡ 9.3±0.4* 5. Alkalosis 46.6±1.5‡" 36.1±1.4‡" 28.5±1.2‡" 27.0±1.1‡" 25.5±1.0‡" 23.9±0.8‡ CF 1. Hydropenia 118.6±0.6‡ 138.9±1.8* 140.7±2.4* 139.4±1.8* 140.1±1.9 138.5±2.5 3. ANF 107.6±1.2‡ 121.1±0.7‡ 123.2±1.2* 132.2±2.1 134.1±2.1 135.5±2.5 3. ANF 107.6±1.2‡ 121.1±0.7‡ 123.2±1.2* 124.2±1.0* 125.1±0.7* 125.6±1.2* 4. Glucagon 107.4±0.9‡ 117.5±0.3‡ 120.5±0.9* 123.5±1.2* 125.1±1.1* 124.9±1.5* 5. Alkalosis 96.8±0.6‡ 138.9±1.8* 129.9±0.7* 127.2±1.3 129.7±2.8 133.1±5.1 peg/min peg/min peg/min peg/min peg/min peg/min peg/min peg/min Ped/min peg/min peg/min peg/min peg/min peg/min peg/min peg/min CF 1. Hydropenia 74.0±31 385±2.4‡ 199±1.6‡ 151±1.5‡ 110±1.5* 86±1.5* 3. ANF 1.424±24‡ 882±14‡ 628±17‡ 484±9‡ 359±6‡ 266±13‡ 4. Glucagon 1.430±3.6‡ 883±2.5‡ 622±3.4‡ 485±3.0\$ 358±1.3* 263±1.2‡ 2. Euvolemia 1.135±9 615±18 382±15 272±15 196±10 133±10 3. ANF 1.424±24‡ 882±14‡ 628±17‡ 484±9‡ 359±6‡ 266±13‡ 4. Glucagon 1.430±3.6‡ 883±2.5‡ 622±3.4‡ 485±3.0\$ 358±1.3* 263±1.2‡ 2. Euvolemia 3.363±88‡ 3.157±118‡ 5.6±2.1‡ 483±1.9‡ 339±6‡ 266±13‡ 4. Glucagon 1.430±3.6‡ 831±2.5‡ 622±3.4‡ 485±3.0\$ 358±1.3* 263±1.2‡ 2. Euvolemia 4.37±2.8‡ 671±2.8‡ 5.62±2.1‡ 485±3.0\$ 358±1.3* 263±1.2‡ 2. Euvolemia 4.37±2.8‡ 671±2.8‡ 5.2±2.1‡ 485±3.0\$ 358±1.3* 263±1.2‡ 3. ANF 5.503±5.6‡ 4.966±4.8‡ 4.524±4.2‡ 4.209±3.8‡ 3.907±4.8‡ 3.56±1.4\$ 3. ANF 5.503±5.6‡ 4.966±4.8‡ 4.524±4.2‡ 4.209±3.8‡ 3.907±4.8‡ 3.56±1.4\$ 4. Glucagon 5.443±6.6‡ 4.886±4.4‡ 4.489±5.2‡ 4.157±5.0\$ 3.839±8.0\$ 3.547±112] 3. ANE 5.503±5.6‡ 4.966±4.8‡ 4.524±4.2‡ 4.209±3.8‡ 3.907±4.8‡ 3.56±1.4\$ 4. Glucagon 5.443±6.6‡ 4.846±4.4‡ 4.489±5.2‡ 4.157±5.0\$ 3.839±8.0\$ 3.547±112] 3. ANF 5.503±5.6‡ 4.966±4.8‡ 4.524±4.2‡ 4.209±3.8‡ 3.907±4.8‡ 3.56±1.4\$ 4±6.6‡ 4. Euvolemia 4.15±0.4\$ 31.4±0.5\$ 27.4±0.4\$ 2		meq/liter	meq/liter	meq/liter	meq/liter	meq/liter	meq/liter	
$\begin{array}{l} \text{HCO5} \\ \text{I. Hydropenia} & 25.7\pm0.7 & 16.9\pm0.8 & 10.4\pm0.6^{*} & 8.6\pm0.6^{*} & 6.8\pm0.7 & 5.7\pm0.3 \\ \text{2. Euvolemia} & 27.3\pm0.2 & 19.6\pm0.4 & 13.9\pm0.4 & 10.8\pm0.5 & 8.6\pm0.3 & 6.4\pm0.4 \\ \text{3. ANF} & 27.8\pm0.5 & 21.5\pm0.5^{*} & 17.1\pm0.4 \ddagger & 14.3\pm0.3 \ddagger & 11.5\pm0.2 \ddagger & 9.1\pm0.3 \ddagger \\ \text{4. Glucagon} & 28.2\pm0.6 & 21.3\pm0.7 & 16.7\pm0.7 \ddagger & 14.4\pm0.7^{*} & 11.7\pm0.3 \ddagger & 9.3\pm0.4^{*} \\ \text{5. Alkalosis} & 4.6\pm1.5 \ddagger & 36.1\pm1.4 \ddagger & 28.5\pm1.2 \ddagger & 7.0\pm1.1 \ddagger & 25.5\pm1.0 \ddagger & 9.3\pm0.4 \ddagger \\ \text{5. Alkalosis} & 4.6\pm1.5 \ddagger & 36.9\pm1.8^{*} & 140.7\pm2.4^{*} & 139.4\pm1.8^{*} & 140.1\pm1.9 & 138.5\pm2.5 \\ \text{5. Alkalosis} & 118.6\pm0.6 \ddagger & 138.9\pm1.8^{*} & 140.7\pm2.4^{*} & 139.4\pm1.8^{*} & 140.1\pm1.9 & 138.5\pm2.5 \\ \text{3. ANF} & 107.6\pm1.2 \ddagger & 121.1\pm0.7 \ddagger & 123.2\pm1.2^{*} & 124.2\pm1.0^{*} & 125.1\pm0.7^{*} & 125.6\pm1.2^{*} \\ \text{4. Glucagon} & 107.4\pm0.9 \ddagger & 17.5\pm0.3 \ddagger & 120.5\pm0.9^{*} & 123.5\pm1.2^{*} & 125.1\pm1.8^{*} & 124.9\pm1.5^{*} \\ \text{5. Alkalosis} & 96.8\pm0.64^{*} & 115.4\pm1.4 \ddagger & 125.9\pm0.7^{*} & 127.2\pm1.3 & 129.7\pm2.8 & 133.1\pm5.1 \\ p.64/min & p.64/min & p.64/min & p.64/min & p.64/min & p.64/min & p.64/min \\ P.64/min & p.64/min & p.64/min & p.64/min & p.64/min & p.64/min & p.64/min \\ P.64/min & p.64/min \\ P.64/min & p.64/min$	Anion concentrations							
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$\begin{array}{c c c c c c c c c c c c c c c c c c c $	1. Hydropenia	25.7±0.7	16.9±0.8	10.4±0.6*	8.6±0.6*	6.8±0.7	5.7±0.3	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	2. Euvolemia	27.3±0.2	19.6±0.4	13.9±0.4	10.8±0.5	8.6±0.3	6.4±0.4	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	3. ANF	27.8±0.5	21.5±0.5*	17.1±0.4‡	14.3±0.3‡	11.5±0.2‡	9.1±0.3‡	
5. Alkalosis $46.6\pm 1.54^{\text{in}}$ $36.1\pm 1.44^{\text{in}}$ $28.5\pm 1.24^{\text{in}}$ $27.0\pm 1.14^{\text{in}}$ $25.5\pm 1.04^{\text{in}}$ $23.9\pm 0.84^{\text{in}}$ CI 1. Hydropenia $118.6\pm 0.64^{\text{in}}$ $138.9\pm 1.8^{\text{in}}$ $140.7\pm 2.4^{\text{in}}$ $139.4\pm 1.8^{\text{in}}$ 140.1 ± 1.9 138.5 ± 2.5 2. Euvolemia 113.4 ± 0.4 131.8 ± 1.3 132.9 ± 2.2 132.2 ± 2.1 134.1 ± 2.1 135.5 ± 2.5 3. ANF $107.6\pm 1.24^{\text{in}}$ $121.1\pm 0.74^{\text{in}}$ $123.2\pm 1.2^{\text{in}}$ $124.2\pm 1.0^{\text{in}}$ $125.1\pm 0.7^{\text{in}}$ $125.5\pm 1.2^{\text{in}}$ 4. Glucagon $107.4\pm 0.94^{\text{in}}$ $117.5\pm 0.34^{\text{in}}$ $120.5\pm 0.9^{\text{in}}$ $123.5\pm 1.2^{\text{in}}$ $125.1\pm 0.7^{\text{in}}$ $125.1\pm 1.1^{\text{in}}$ $124.9\pm 1.5^{\text{in}}$ 5. Alkalosis $96.8\pm 0.64^{\text{in}}$ $115.4\pm 1.44^{\text{in}}$ $125.9\pm 0.7^{\text{in}}$ 127.2 ± 1.3 129.7 ± 2.8 133.1 ± 5.1 peq/min peq/min peq/min peq/min peq/min peq/min peq/min $peq/minDelivery ratesHCO51. Hydropenia 740\pm 314^{\text{in}} 385\pm 244^{\text{in}} 199\pm 164^{\text{in}} 151\pm 154^{\text{in}} 110\pm 15^{\text{in}} 86\pm 15^{\text{in}}2. Euvolemia 1,135\pm 9 615\pm 18 382\pm 15 272\pm 15 196\pm 10 133\pm 103. ANF 1.424\pm 244^{\text{in}} 883\pm 254^{\text{in}} 622\pm 174^{\text{in}} 484\pm 94^{\text{in}} 359\pm 64^{\text{in}} 266-134^{\text{in}}4. Glucagon 1.430\pm 364^{\text{in}} 883\pm 255^{\text{in}} 622\pm 344^{\text{in}} 485\pm 304^{\text{in}} 358\pm 13^{\text{in}} 263\pm 124^{\text{in}}5. Alkalosis 1.437\pm 284^{\text{in}} 871\pm 284^{\text{in}} 569\pm 214^{\text{in}} 481\pm 194^{\text{in}} 3056\pm 164^{\text{in}} 2323\pm 174^{\text{in}}peq/min$ peq/min ped/min pe	4. Glucagon	28.2±0.6	21.3±0.7	16.7±0.7‡	14.4±0.7*	11.7±0.3‡	9.3±0.4*	
CF 1. Hydropenia 118.6±0.6‡ 138.9±1.8* 140.7±2.4* 139.4±1.8* 140.1±1.9 138.5±2.5 2. Euvolemia 113.4±0.4 131.8±1.3 132.9±2.2 132.2±2.1 134.1±2.1 135.5±2.5 3. ANF 107.6±1.2‡ 121.1±0.7‡ 123.2±1.2* 124.2±1.0* 125.1±0.7* 125.6±1.2* 4. Glucagon 107.4±0.9‡ 117.5±0.3‡ 120.5±0.9* 123.5±1.2* 125.1±1.1* 124.9±1.5* 5. Alkalosis 96.8±0.6‡ ^{il} 115.4±1.4‡§ 125.9±0.7* 127.2±1.3 129.7±2.8 133.1±5.1 peg/min peg/min peg/min peg/min peg/min peg/min peg/min Delivery rates HCO ₅ 1. Hydropenia 740±31‡ 385±24‡ 199±16‡ 151±15‡ 110±15* 86±15* 2. Euvolemia 1,135±9 615±18 382±15 272±15 196±10 133±10 3. ANF 1.424±24‡ 882±14‡ 628±17‡ 484±9‡ 359±6‡ 266±13‡ 4. Glucagon 1.430±36‡ 883±25‡ 622±34‡ 485±30‡ 358±13* 265±12‡ 5. Alkalosis 1.437±28‡ 871±28‡ 569±21‡ 481±19‡ 396±18‡ 323±174§ peg/min peg/min peg/min peg/min peg/min peg/min peg/min CF 1. Hydropenia 3.363±88‡ 3.157±118‡ 2.674±97‡ 2.392±87‡ 2.144±79‡ 1.952±70‡ 3. ANF 5.503±56‡ 4.966±48‡ 4.524±4‡ 4.209±38‡ 3.907±48‡ 3.661±49‡ 4. Glucagon 5.443±66‡ 4.886±44‡ 4.489±52‡ 4.157±50‡ 3.89±80‡ 3.56±61 2.802±55 3. ANF 5.503±56‡ 4.966±48‡ 4.524±42‡ 4.209±38‡ 3.907±48\ddagger 3.661±49‡ 4. Glucagon 5.443±66‡ 4.886±44‡ 4.489±52‡ 4.157±50‡ 3.89±80‡ 3.547±12₹ 5. Alkalosis 2.992±71 $\frac{1}{2}$ 2.794±58 $\frac{1}{2}$ 2.526±69 $\frac{1}{2}$ 2.270±61 $\frac{1}{2}$ 2.01±6±63 $\frac{1}{2}$ 1.79±0.5 $\frac{1}{2}$ 1.4±0.6 $\frac{1}{2}$ 4. Glucagon 5.443±66‡ 4.886±44‡ 4.489±52‡ 4.157±50‡ 3.89±80‡ 3.547±12₹ 5. Alkalosis 2.992±71 $\frac{1}{2}$ 2.79±58 $\frac{1}{2}$ 7.7±0.5 $\frac{1}{2}$ 1.5±0.5 $\frac{1}{2}$ 1.4±0.6 $\frac{1}{2}$ 2. Euvolemia 4.1.5±0.4 31.4±0.5 2.7.4±0.4 2.5.1±0.5 22.8±0.5 20.7±0.7 3. ANF 5.1.2±0.7‡ 41.0±0.3‡ 36.7±0.2‡ 33.9±0.1‡ 31.2±0.3‡ 2.9±0.4 $\frac{1}{2}$ 4.0±0.4 $\frac{1}{2}$ 3.0±0.6 $\frac{1}{4}$ 3.7±0.5 $\frac{1}{2}$ 3.0±0.5 $\frac{1}{4}$ 3.4±0.6 $\frac{1}{4}$ 3.7±0.5 $\frac{1}{4}$ 3.5±0.3 $\frac{1}{4}$	5. Alkalosis	46.6±1.5 ‡ "	36.1±1.4 ‡ "	28.5±1.2‡"	27.0±1.1‡"	25.5±1.0‡"	23.9±0.8‡ ⁱ	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Cl⁻							
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	1. Hydropenia	118.6±0.6‡	138.9±1.8*	140.7±2.4*	139.4±1.8*	140.1±1.9	138.5±2.5	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	2. Euvolemia	113.4±0.4	131.8±1.3	132.9±2.2	132.2 ± 2.1	134.1 ± 2.1	135.5±2.5	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	3. ANF	107.6±1.2 ‡	121.1±0.7 ‡	123.2±1.2*	124.2±1.0*	125.1±0.7*	125.6±1.2*	
5. Alkalosis 96.8±0.6‡ ⁱⁱ 115.4±1.4‡§ 125.9±0.7* 127.2±1.3 129.7±2.8 133.1±5.1 peq/min	4. Glucagon	107.4±0.9‡	117.5±0.3‡	120.5±0.9*	123.5±1.2*	125.1±1.1*	124.9±1.5*	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	5. Alkalosis	96.8±0.6‡"	115.4±1.4 ‡ §	125.9±0.7*	127.2±1.3	129.7±2.8	133.1±5.1	
Delivery rates HCO ₃ 1. Hydropenia 740±31‡ 385±24‡ 199±16‡ 151±15‡ 110±15* 86±15* 2. Euvolemia 1,135±9 615±18 382±15 272±15 196±10 133±10 3. ANF 1,424±24‡ 882±14‡ 628±17‡ 484±9‡ 359±6‡ 266±13‡ 4. Glucagon 1,430±36‡ 883±25‡ 622±34‡ 485±30‡ 358±13* 263±12‡ 5. Alkalosis 1,437±28‡ 871±28‡ 569±21‡ 481±19‡ 396±18‡ 323±17‡8 peq/min peq/min peq/min peq/min peq/min peq/min peq/min peq/min CC ⁻ 1. Hydropenia 3,363±88‡ 3,157±118‡ 2,674±97‡ 2,392±87‡ 2,144±79‡ 1,952±70‡ 2. Euvolemia 4,704±37 4,141±43 3,634±39 3,311±47 3,056±61 2,802±55 3. ANF 5,503±56‡ 4,966±48‡ 4,524±42‡ 4,209±38‡ 3,907±48‡ 3,661±49‡ 4. Glucagon 5,443±66‡ 4,886±44‡ 4,489±52‡ 4,157±50‡ 3,839±80‡ 3,547±112‡ 5. Alkalosis 2,992±71‡ ^{II} 2,794±58‡ ^{II} 2,526±69‡ ^{II} 2,270±61‡ ^{II} 2,016±63‡ ^{II} 1,796±61‡ ^{II} ml/min nl/min nl/min nl/min nl/min nl/min nl/min nl/min H ₂ O 1. Hydropenia 28.7±0.7‡ 22.8±0.7‡ 19.0±0.5‡ 17.3±0.5‡ 15.6±0.5‡ 14.4±0.6‡ 2. Euvolemia 41.5±0.4 31.4±0.5 27.4±0.4 25.1±0.5 22.8±0.5 20.7±0.7 3. ANF 51.2±0.7‡ 41.0±0.3‡ 36.7±0.2‡ 33.9±0.1‡ 31.2±0.3‡ 29.2±0.4‡ 4. Glucagon 50.7±0.6‡ 41.6±0.4‡ 37.3±0.6‡ 33.7±0.5‡ 30.7±0.5‡ 28.4±0.7± 3. ANF 51.2±0.7‡ 41.0±0.3‡ 36.7±0.2‡ 33.7±0.5‡ 30.7±0.5‡ 28.4±0.7± 3. ANF 51.2±0.7‡ 41.0±0.3‡ 36.7±0.2‡ 33.7±0.5‡ 30.7±0.5‡ 28.4±0.7± 5. Alkalosis 30.9±0.6‡ ^{II} 24.3±0.7‡ ^{II} 20.1±0.6‡ ^{II} 17.7±0.4‡ ^{II} 15.5±0.3‡ ^{II} 13.5±0.3‡ 4. Glucagon 50.7±0.6‡ 41.6±0.4‡ 37.3±0.6‡ 33.7±0.5‡ 30.7±0.5‡ 28.4±0.7± 5. Alkalosis 30.9±0.6‡ ^{II} 24.3±0.7‡ ^{II} 20.1±0.6‡ ^{II} 17.7±0.4‡ ^{II} 15.5±0.3‡ ^{II} 13.5±0.3‡ 5. Alkalosis 30.9±0.6‡ ^{II} 24.3±0.7‡ ^{II} 20.1±0.6‡ ^{II} 17.7±0.4‡ ^{II} 15.5±0.3‡ ^{II} 13.5±0.3‡ 5. Alkalosis 30.9±0.6‡ ^{II} 24.3±0.7‡ ^{II} 20.1±0.6‡ ^{II} 17.7±0.4‡ ^{II} 15.5±0.3‡ ^{II} 13.5±0.3‡ 5. Alkalosis 30.9±0.6‡ ^{II} 24.3±0.7‡ ^{II} 20.1±0.6‡ ^{II} 17.7±0.4‡ ^{II} 15.5±0.3‡ ^{II} 13.5±0.3‡ 5. Alkalosis 30.9±0.6‡ ^{II} 24.3±0.7‡ ^{II} 20.1±0.6‡ ^{II} 17.7±0.4‡ ^{II} 15.5±0.3‡ ^{II} 13.5±0.3‡ 5. Alkalosis 30.9±0.6‡ ^{II} 24.3±0.7‡ ^{II} 20.1±0.6‡ ^{II} 17.7±0.4‡ ^{II} 15.5±0.3‡ ^{II} 13.5±0.3‡ 5. Alkalosis 30.9±0.6‡ ^{II} 24.3±0.7‡ ^{II} 20.1		peq/min	peq/min	peq/min	peq/min	peq/min	peq/min	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Delivery rates							
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	HCO ₃							
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	1. Hydropenia	740±31‡	385±24‡	199±16‡	151±15‡	110±15*	86±15*	
3. ANF $1,424\pm24$ 882 ± 14 628 ± 17 484 ± 9 359 ± 6 266 ± 13 4. Glucagon $1,430\pm36$ 883 ± 25 622 ± 34 485 ± 30 $358\pm13^*$ 263 ± 12 5. Alkalosis $1,437\pm28$ 871 ± 28 569 ± 21 481 ± 19 396 ± 18 323 ± 17 peq/min peq/min peq/min peq/min peq/min peq/min peq/min peq/min CI ⁻ 1. Hydropenia $3,363\pm88$ $3,157\pm118$ $2,674\pm97$ $2,392\pm87$ $2,144\pm79$ $1,952\pm70$ 2. Euvolemia $4,704\pm37$ $4,141\pm43$ $3,63\pm39$ $3,311\pm47$ $3,056\pm61$ $2,802\pm55$ 3. ANF $5,503\pm564$ $4,966\pm484$ $4,524\pm424$ $4,209\pm384$ $3,907\pm484$ $3,661\pm494$ 4. Glucagon $5,443\pm664$ $4,886\pm444$ $4,489\pm524$ $4,157\pm504$ $3,839\pm804$ $3,547\pm1122$ 5. Alkalosis $2,992\pm714^{\mu}$ $2,794\pm584^{\mu}$ $2,526\pm694^{\mu}$ $2,270\pm614^{\mu}$ $2,016\pm634^{\mu}$ $1,796\pm614^{\mu}$ 4_2O 1 1 1 1 1 1 1	2. Euvolemia	1,135±9	615±18	382±15	272±15	196±10	133±10	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	3. ANF	1,424±24‡	882±14‡	628±17‡	484±9‡	359±6‡	266±13‡	
5. Alkalosis $1,437\pm28$ 871 ± 28 569 ± 21 481 ± 19 396 ± 18 323 ± 17 peq/minpeq/minpeq/minpeq/minpeq/minpeq/minpeq/minpeq/minCl ⁻ .1. Hydropenia $3,363\pm88$ $3,157\pm118$ $2,674\pm97$ $2,392\pm87$ $2,144\pm79$ $1,952\pm70$ 2. Euvolemia $4,704\pm37$ $4,141\pm43$ $3,634\pm39$ $3,311\pm47$ $3,056\pm61$ $2,802\pm55$ 3. ANF $5,503\pm56$ $4,966\pm48$ $4,524\pm42$ $4,209\pm38$ $3,907\pm48$ $3,661\pm49$ 4. Glucagon $5,443\pm66$ $4,886\pm444$ $4,489\pm52$ $4,157\pm50$ $3,839\pm80$ $3,547\pm1124$ 5. Alkalosis $2,992\pm71$ $2,794\pm58$ $2,526\pm69$ $2,270\pm61$ $2,016\pm634^{\parallel}$ $1,796\pm614^{\parallel}$ n/min n/min n/min n/min n/min n/min n/min H_2O1. Hydropenia 28.7 ± 0.7 22.8 ± 0.7 19.0 ± 0.5 17.3 ± 0.5 15.6 ± 0.5 14.4 ± 0.6 2. Euvolemia 41.5 ± 0.4 31.4 ± 0.5 27.4 ± 0.4 25.1 ± 0.5 22.8 ± 0.5 20.7 ± 0.7 3. ANF 51.2 ± 0.7 41.0 ± 0.3 36.7 ± 0.2 33.9 ± 0.1 31.2 ± 0.3 29.2 ± 0.4 4. Glucagon 50.7 ± 0.6 41.6 ± 0.4 37.3 ± 0.6 33.7 ± 0.5 30.7 ± 0.5 28.4 ± 0.7 5. Alkalosis 30.9 ± 0.6 41.6 ± 0.4 37.3 ± 0.6 33.7 ± 0.5 30.7 ± 0.5 28.4 ± 0.7 5. Alkalosis 30.9 ± 0.6 24.3 ± 0.7 20.1 ± 0.6 17.7 ± 0.4 15.5 ± 0.3 13.5 ± 0.3 <td>4. Glucagon</td> <td>1,430±36‡</td> <td>883±25‡</td> <td>622±34‡</td> <td>485±30‡</td> <td>358±13*</td> <td>$263 \pm 12 \pm$</td>	4. Glucagon	1,430±36‡	883±25‡	622±34‡	485±30‡	358±13*	$263 \pm 12 \pm$	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	5. Alkalosis	1,437±28‡	871±28‡	569±21‡	481±19‡	396±18‡	323±17‡§	
$\begin{array}{c} Cl^- \\ 1. \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ $		peq/min	peq/min	peq/min	peq/min	peq/min	peq/min	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Cl⁻							
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1. Hydropenia	3,363±88‡	3,157±118‡	2,674±97‡	2,392±87‡	2,144±79‡	1.952±70±	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2. Euvolemia	4,704±37	4,141±43	3,634±39	3,311±47	3.056±61	2.802 ± 55	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	3. ANF	5,503±56‡	4,966±48‡	4,524±42‡	$4,209 \pm 38 \pm$	3.907±48±	$3.661 \pm 49 \pm$	
5. Alkalosis $2,992\pm71\ddagger^{ }$ $2,794\pm58\ddagger^{ }$ $2,526\pm69\ddagger^{ }$ $2,270\pm61\ddagger^{ }$ $2,016\pm63\ddagger^{ }$ $1,796\pm61\ddagger^{ }$ nl/min nl/min nl/min nl/min nl/min nl/min nl/min nl/min H2O1. Hydropenia $28.7\pm0.7\ddagger$ $22.8\pm0.7\ddagger$ $19.0\pm0.5\ddagger$ $17.3\pm0.5\ddagger$ $15.6\pm0.5\ddagger$ $14.4\pm0.6\ddagger$ 2. Euvolemia 41.5 ± 0.4 31.4 ± 0.5 27.4 ± 0.4 25.1 ± 0.5 22.8 ± 0.5 20.7 ± 0.7 3. ANF $51.2\pm0.7\ddagger$ $41.0\pm0.3\ddagger$ $36.7\pm0.2\ddagger$ $33.9\pm0.1\ddagger$ $31.2\pm0.3\ddagger$ $29.2\pm0.4\ddagger$ 4. Glucagon $50.7\pm0.6\ddagger$ $41.6\pm0.4\ddagger$ $37.3\pm0.6\ddagger$ $33.7\pm0.5\ddagger$ $30.7\pm0.5\ddagger$ $28.4\pm0.7\ddagger$ 5. Alkalosis $30.9\pm0.6\ddagger^{ }$ $24.3\pm0.7\ddagger^{ }$ $20.1\pm0.6\ddagger^{ }$ $17.7\pm0.4\ddagger^{ }$ $15.5\pm0.3\ddagger^{ }$ $13.5\pm0.3\ddagger$	4. Glucagon	5,443±66‡	4,886±44‡	4,489±52‡	$4,157\pm50$	3.839±80±	3.547±112±	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	5. Alkalosis	2,992±71‡"	2,794±58‡"	2,526±69‡"	2,270±61‡"	2,016±63‡"	1,796±61‡	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		nl/min	nl/min	nl/min	nl/min	nl/min	nl/min	
1. Hydropenia $28.7\pm0.7\ddagger$ $22.8\pm0.7\ddagger$ $19.0\pm0.5\ddagger$ $17.3\pm0.5\ddagger$ $15.6\pm0.5\ddagger$ $14.4\pm0.6\ddagger$ 2. Euvolemia 41.5 ± 0.4 31.4 ± 0.5 27.4 ± 0.4 25.1 ± 0.5 22.8 ± 0.5 20.7 ± 0.7 3. ANF $51.2\pm0.7\ddagger$ $41.0\pm0.3\ddagger$ $36.7\pm0.2\ddagger$ $33.9\pm0.1\ddagger$ $31.2\pm0.3\ddagger$ $29.2\pm0.4\ddagger$ 4. Glucagon $50.7\pm0.6\ddagger$ $41.6\pm0.4\ddagger$ $37.3\pm0.6\ddagger$ $33.7\pm0.5\ddagger$ $30.7\pm0.5\ddagger$ $28.4\pm0.7\ddagger$ 5. Alkalosis $30.9\pm0.6\ddagger^{\parallel}$ $24.3\pm0.7\ddagger^{\parallel}$ $20.1\pm0.6\ddagger^{\parallel}$ $17.7\pm0.4\ddagger^{\parallel}$ $15.5\pm0.3\ddagger^{\parallel}$ $13.5\pm0.3\ddagger$	H ₂ O							
2. Euvolemia 41.5 ± 0.4 31.4 ± 0.5 27.4 ± 0.4 25.1 ± 0.5 22.8 ± 0.5 20.7 ± 0.7 3. ANF $51.2\pm0.7\ddagger$ $41.0\pm0.3\ddagger$ $36.7\pm0.2\ddagger$ $33.9\pm0.1\ddagger$ $31.2\pm0.3\ddagger$ $29.2\pm0.4\ddagger$ 4. Glucagon $50.7\pm0.6\ddagger$ $41.6\pm0.4\ddagger$ $37.3\pm0.6\ddagger$ $33.7\pm0.5\ddagger$ $30.7\pm0.5\ddagger$ $28.4\pm0.7\ddagger$ 5. Alkalosis $30.9\pm0.6\ddagger$ $24.3\pm0.7\ddagger$ $20.1\pm0.6\ddagger$ $17.7\pm0.4\ddagger$ $15.5\pm0.3\ddagger$ $13.5\pm0.3\ddagger$	1. Hydropenia	28.7±0.7‡	22.8±0.7‡	19.0±0.5‡	17.3±0.5±	15.6±0.5±	14.4+0.6t	
3. ANF $51.2\pm0.7\ddagger$ $41.0\pm0.3\ddagger$ $36.7\pm0.2\ddagger$ $33.9\pm0.1\ddagger$ $31.2\pm0.3\ddagger$ $29.2\pm0.4\ddagger$ 4. Glucagon $50.7\pm0.6\ddagger$ $41.6\pm0.4\ddagger$ $37.3\pm0.6\ddagger$ $33.7\pm0.5\ddagger$ $30.7\pm0.5\ddagger$ $28.4\pm0.7\ddagger$ 5. Alkalosis $30.9\pm0.6\ddagger$ $24.3\pm0.7\ddagger$ $20.1\pm0.6\ddagger$ $17.7\pm0.4\ddagger$ $15.5\pm0.3\ddagger$ $13.5\pm0.3\ddagger$	2. Euvolemia	41.5±0.4	31.4±0.5	27.4±0.4	25.1±0.5	22.8±0.5	20.7±0.7	
4. Glucagon $50.7\pm0.6\ddagger$ $41.6\pm0.4\ddagger$ $37.3\pm0.6\ddagger$ $33.7\pm0.5\ddagger$ $30.7\pm0.5\ddagger$ $28.4\pm0.7\ddagger$ 5. Alkalosis $30.9\pm0.6\ddagger$ $24.3\pm0.7\ddagger$ $20.1\pm0.6\ddagger$ $17.7\pm0.4\ddagger$ $15.5\pm0.3\ddagger$ $13.5\pm0.3\ddagger$	3. ANF	51.2±0.7‡	41.0±0.3‡	36.7±0.2‡	33.9±0.1‡	31.2±0.3±	29.2±0.4±	
5. Alkalosis $30.9\pm0.6\pm^{\parallel}$ $24.3\pm0.7\pm^{\parallel}$ $20.1\pm0.6\pm^{\parallel}$ $17.7\pm0.4\pm^{\parallel}$ $15.5\pm0.3\pm^{\parallel}$ $13.5\pm0.3\pm^{\parallel}$	4. Glucagon	50.7±0.6‡	41.6±0.4‡	37.3±0.6‡	33.7±0.5‡	30.7±0.5‡	28.4±0.7±	
	5. Alkalosis	30.9±0.6‡ ^{II}	24.3±0.7‡"	20.1±0.6‡	17.7±0.4‡"	15.5±0.3‡ ^{II}	13.5±0.3‡ ¹	

Table II. Anion Concentration and Delivery Rates as a Function of PCT Length

* P < 0.05 group 2 vs. groups 1, 3, 4, and 5. $\ddagger P < 0.001$ group 2 vs. groups 1, 3, 4, and 5. \$ P < 0.05 group 5 vs. group 3 or 4. $\parallel P < 0.001$ group 5 vs. group 3 or 4.



Figure 1. Axial profiles for tubular fluid/ultrafiltrate (TF/UF) concentration ratios for inulin, chloride, and bicarbonate in A for euvolemic group 2; B for ANF and glucagon hyperfiltration groups 3 and 4; and C for alkalotic group 5. Solid lines in each case depict mean values for hydropenic Group 1.

peq/min) resulted in a proportional increase in bicarbonate reabsorption in the 1 mm of the PCT, from 354 ± 21 to 520 ± 12 peq/mm · min (P < 0.001) (*hexagons* and *squares*, Figs. 2 and 3). Fractional reabsorption therefore remained constant at 0.5 in the initial millimeter segment (*hexagons* and *squares*, Fig. 4). In the 2nd mm, the increase in flow rate resulted in a smaller rise in transport and fractional reabsorption of the delivered load fell. In the 3rd to 5th mm, bicarbonate reabsorption was lower than in the 1st mm in hydropenia, expressed in both absolute (Figs. 2 and 3) and fractional (Fig. 4) terms, but increased in proportion to load in euvolemia.

When ANF (group 3) or glucagon (group 4) caused a further increase in SNGFR and filtered bicarbonate load (to $1,424\pm24$ and $1,430\pm36$ peq/min, respectively), bicarbonate reabsorption remained static in the 1st mm of the PCT, 542 ± 14 and 547 ± 29 peq/mm \cdot min (*triangles* and *inverted triangles*, Figs. 2 and 3).



Figure 2. Bicarbonate transport as a function of PCT length for hydropenic group 1 (*hexagons*), euvolemic group 2 (*squares*), ANF-treated group 3 (*triangles*), glucagon-treated group 4 (*inverted triangles*), and alkalotic group 5 (*circles*).

Therefore, fractional reabsorption declined in this segment to about 0.4 (*triangles*, Fig. 4). A similar response, though at lower levels, was observed in the 2nd mm. In qualitative contrast, the 3rd to 5th mm of the PCT showed a further increase in absolute bicarbonate transport in response to the increased delivered bicarbonate load with only a slight fall in the fraction of delivered load reabsorbed for each millimeter. The present free-flow bicarbonate reabsorptive data in the late (3rd to 5th mm) PCT agree quite well with previous microperfusion data (*dashed lines* in Figs. 3 and 4) (6).

Effect of alkalemia on bicarbonate transport. During chronic metabolic alkalosis (group 4), the rise in glomerular ultrafiltrate bicarbonate concentration was offset by a fall in SNGFR (Table II), so that filtered bicarbonate load $(1,437\pm28 \text{ peq/min})$ was not significantly different from that of groups 3 and 4 which had normal acid-base status. As shown in Table III and Fig. 5, bicarbonate reabsorption was similar in the alkalotic group (*circles*) in the 1st mm, $565\pm12 \text{ peq/mm} \cdot \text{min}$, compared with the normal pH groups (*triangles*). The same was true for the 2nd mm. However, bicarbonate reabsorption was reduced by 20–40% in the alkalotic animals in each of the 3rd- to 5th-mm segments despite higher luminal bicarbonate concentrations (Table II). As



Figure 3. Bicarbonate transport by each PCT segment as a function of the delivered bicarbonate load to that segment for hydropenic group 1 (*hexagons*), euvolemic group 2 (*squares*), ANF-treated group 3 (*triangles*), and glucagon-treated group 4 (*inverted triangles*). Dashed line derived from microperfusion data of Alpern et al. (6).



Figure 4. Reabsorbed fraction of delivered bicarbonate load by each PCT segment as a function of the delivered bicarbonate load to that segment for hydropenic group 1 (hexagons), euvolemic group 2 (squares), ANF-treated group 3 (triangles), and glucagon-treated group 4 (inverted triangles). Dashed line derived from microperfusion data of Alpern et al. (6).

a result of this inhibition of late PCT acidification, cumulative absolute bicarbonate reabsorption along the entire PCT length was significantly (P < 0.05) reduced in group 5 (1,115±46) compared with groups 3 and 4 (1,201±33 and 1,180±39 peq/min).

Bicarbonate transport as a function of load in the 1st mm in all five groups are combined in Fig. 6. It is apparent that acidification can rise to very high levels, to $\sim 550 \text{ peq/mm} \cdot \text{min}$, but then saturates when load is raised further by an increase in flow or concentration.

Flow dependency of chloride transport. The transpithelial chloride concentration gradient decreased as flow and filtered chloride load increased in groups 1-4 (Table II and Fig. 1 A and B) and increased somewhat in the alkalotic group 5 animals (Fig. 1 C).

Compared with hydropenia (*hexagons*), when filtered chloride load was increased in euvolemia (group 2), chloride transport in the 1st mm almost tripled, to 585 ± 21 peq/mm \cdot min (*squares*, Fig. 7 and *solid squares*, Fig. 8), and fractional chloride reabsorption actually increased to 0.12 (Fig. 9). This flow-induced stimulation of chloride transport occurred to a similar degree



Figure 6. Bicarbonate transport in the 1st mm of the PCT as a function of the filtered bicarbonate load for hydropenic group 1 (*hexa*gons), euvolemic group 2 (squares), ANF-treated group 3 (triangles), glucagon-treated group 4 (inverted triangles), and alkalotic group 5 (circles).

but at a lesser delivered chloride load in the 2nd mm (stippled symbols, Figs. 8 and 9). Chloride transport was changed relatively little in response to the increase in flow up to euvolemic values in the 3rd to 5th mm of the PCT in groups 1 and 2 (open hexagons and squares, Figs. 7 and 8). Fractional chloride transport in these groups therefore declined (Fig. 9). With a further increase in luminal flow rate and chloride delivery after ANF or glucagon administration (groups 3 and 4), no further augmentation of absolute chloride reabsorption was observed in either the early or late PCT (triangles and inverted triangles, Figs. 7 and 8) and hence fractional chloride reabsorption as a function of delivered chloride load declined in all PCT segments (Fig. 9). The relatively modest load dependence of chloride transport in the late PCT is in reasonable agreement with microperfusion studies in which the late PCT has been perfused at varying rates with sodium chloride-containing solutions (dashed lines, Figs. 8 and 9) (12). Chloride transport in the 1st mm in group 5 was similar to group 1 (Table II and hexagons and circles, Figs. 7 and 8) at comparable filtered loads, suggesting that alkalemia did not obviously affect this transport system.



Figure 5. Bicarbonate transport as a function of PCT length for normal ANF-treated group 3 (*triangles*) and glucagon-treated group 4 (*inverted triangles*) compared with alkalotic group 5 (*circles*).



Figure 7. Chloride transport as a function of PCT length for hydropenic group 1 (*hexagons*), euvolemic group 2 (squares), ANF-treated group 3 (triangles), glucagon-treated group 4 (*inverted triangles*), and alkalotic group 5 (circles).



Figure 8. Chloride transport by each PCT segment as a function of the delivered chloride load to that segment for hydropenic group 1 (*hexagons*), euvolemic group 2 (squares), ANF-treated group 3 (triangles), glucagon-treated group 4 (*inverted triangles*), and alkalotic group 5 (circles). Dashed line derived from microperfusion data of Green et al. (12).

Flow dependence of water transport. As SNGFR rose from hydropenia to euvolemia (groups 1 and 2), absolute water reabsorption in the 1st mm of the PCT increased markedly, from 5.9 \pm 0.4 to 10.1 \pm 0.4 nl/mm · min (Table III and hexagons and squares, Figs. 10 and 11). The fraction of water reabsorbed in the 1st mm actually rose slightly as flow increased, from 0.21 to 0.25 (Fig. 12). A quantitatively less flow-dependent response in absolute water reabsorption was observed in the remaining PCT (Figs. 10 and 11) so that water reabsorption as a fraction of delivered volume load for the 3rd to 5th mm declined (Fig. 12). A further increase in SNGFR by ANF and glucagon (groups 3 and 4) evoked no change in absolute water reabsorption in the 1st mm and only small increments in reabsorption in the remaining PCT (triangles and inverted triangles, Figs. 10 and 11) so that fractional reabsorption of delivered volume load declined in all millimeter segments studies (Fig. 12). The relatively poor load dependence of water transport in the late PCT agrees



Figure 9. Reabsorbed fraction of delivered chloride load by each PCT segment as a function of the delivered bicarbonate load to that segment for hydropenic group 1 (hexagons), euvolemic group 2 (squares), ANF-treated group 3 (triangles), glucagon-treated group 4 (inverted triangles), and alkalotic group 5 (circles). Dashed line derived from microperfusion data of Green et al. (12).



Figure 10. Water transport as a function of PCT length for hydropenic group 1 (*hexagons*), euvolemic group 2 (*squares*), ANF-treated group 3 (*triangles*), glucagon-treated group 4 (*inverted triangles*), and alkalotic group 5 (*circles*).

reasonably well with data previously obtained by in vivo microperfusion (*dashed lines*, Figs. 11 and 12) (6).

Discussion

These studies examined the response of the early versus late PCT transport systems for bicarbonate, chloride, and water to alterations in luminal flow rate and to luminal and peritubular anionic composition. In the following discussion, the early PCT will refer principally to the 1st mm of the superficial PCT. Maunsbach (1) has stated that the initial millimeter of the rat PCT contains exclusively S_1 cells. The 3rd to 5th mm of the accessible superficial PCT, which will subsequently be referred to as the late PCT, contains only S_2 cells (1). The transition from S_1 to S_2 cells is not abrupt according to Maunsbach (1). The 2nd mm of the PCT probably contains a mixture of both cell types and would therefore be expected to exhibit transport characteristics intermediate between the early and late PCT, as was observed in the present studies.

Axial heterogeneity of bicarbonate reabsorption: response to alteration in luminal flow rate. Bicarbonate reabsorption in the

Figure 11. Water transport by each PCT segment as a function of the delivered water load to that segment for hydropenic group 1 (*hexagons*), euvolemic group 2 (squares), ANF-treated group 3 (triangles), and glucagon-treated group 4 (inverted triangles). Dashed line derived from microperfusion data of Alpern et al. (6).



Figure 12. Reabsorbed fraction of delivered water load by each PCT segment as a function of the delivered water load to that segment for hydropenic group 1 (*hexagons*), euvolemic group 2 (*squares*), ANF-treated group 3 (*triangles*), and glucagon-treated group 4 (*inverted triangles*). Dashed line derived from microperfusion data of Alpern et al. (6).

rat late PCT is effected by proton secretion and exhibits saturation kinetics (5, 6, 11, 17, 17-20). Major independent determinants of acidification in the late PCT include the luminal bicarbonate concentration (5), luminal flow rate (6), and peritubular bicarbonate concentration/pH (19). The present freeflow micropuncture study as well as others (8, 10) quantitatively demonstrated the flow dependence of bicarbonate reabsorption in the late PCT previously shown using in vivo microperfusion (compare *dashed line* representing previous microperfusion data and *symbols* representing present data in the 3rd to 5th mm of the PCT in Figs. 3 and 4). Whereas microperfusion studies indicate that bicarbonate absorption in the late PCT is saturable at ~200 peq/mm · min (5, 6, 19), this level cannot be reached under physiologic free-flow conditions owing to insufficient bicarbonate delivery rates even after ANF and glucagon (groups 3 and 4).

With increasing bicarbonate load caused by glomerular hyperfiltration induced by either ANF or glucagon, bicarbonate reabsorption in the early PCT qualitatively resembled that in the late PCT by showing saturation kinetics (Figs. 3 and 6). The saturability of early PCT bicarbonate reabsorption in the physiologic range of filtered bicarbonate loads is consistent with the conclusion reached by Corman et al. (10), though they did not directly measure bicarbonate reabsorption in the early PCT, but is in apparent contradiction with the conclusion of Maddox and Gennari (8). In the latter work, however, a systematic examination of bicarbonate reabsorption in the initial millimeter of the PCT at high bicarbonate deliveries was not undertaken. At a filtered bicarbonate load of 1,200-1,600 peq/min, Maddox and Gennari reported that bicarbonate reabsorption at 1 mm of tubule length was \sim 550 peq/min, in excellent agreement with our results. To examine the reabsorptive response to a further increase in flow rate, data were reported for volume ex-

Table III. Absolute Anion and Water Transport Rates as a Function of PCT Length

	Millimeter segment					
Group	lst	2nd	3rd	4th	5th	
	peq/mm • min	peq/mm • min	peq/mm • min	peq/mm • min	peq/mm • min	
HCO ⁻ 3						
1. Hydropenia	354±21‡	186±17	48±10*	41±7*	24±3‡	
2. Euvolemia	520±12	233±22	109±11	76±6	73±10	
3. ANF	542±14	254±16	144±11*	125±12*	93±8*	
4. Glucagon	547±29	261±38	137±17	127±17*	95±17	
5. Alkalosis	565±12*	302±12*§	89±8§	85±7§	73±9	
	peq/mm • min	peq/mm · min	peq/mm • min	peq/mm · min	peq/mm • mir	
Cl-						
1. Hydropenia	206±55‡	483±94	282±42	248±40	192±35	
2. Euvolemia	585±21	507±70	323±26	254±22	254±17	
3. ANF	537±18	443±54	315±32	302±21	246±22	
4. Glucagon	557±22	397±13	332±8	319±38	291±45	
5. Alkalosis	198±32‡"	268±24*§	256±18§	253±16	220±23	
	nl/mm · min	nl/mm · min	nl/mm · min	nl/mm · min	nl/mm · min	
H ₂ O						
1. Hydropenia	5.9±0.4‡	3.8±0.4	1.7±0.2	1.7±0.2	1.2±0.2*	
2. Euvolemia	10.1±0.4	4.1±0.5	2.3±0.2	2.3±0.1	2.1±0.2	
3. ANF	10.2±0.5	4.3±0.5	2.9±0.2	2.6±0.2	2.1±0.1	
4. Glucagon	9.1±0.4	4.3±0.2	3.6±0.2*	3.0±0.4	2.3±0.3	
5. Alkalosis	6.7±0.3‡ [∥]	4.2±0.3	2.3±0.2§	2.2±0.2	2.0±0.2	

* P < 0.05 group 2 vs. groups 1, 3, 4, and 5. $\ddagger P < 0.001$ group 2 vs. groups 1, 3, 4, and 5. \$ P < 0.05 group 5 vs. group 3 or 4. $\parallel P < 0.001$ group 5 vs. group 3 or 4.

panded animals in which filtered bicarbonate load exceeded 1,600 peq/min. However, only three data points for bicarbonate reabsorption within the 1st mm at these high filtered bicarbonate loads were presented; one of the points was below and two were above the level that had been already described for bicarbonate reabsorption at the lower filtered load of 1,200–1,600 peq/min. Thus, a rigorous conclusion regarding the saturability of acidification in the initial millimeter of the PCT could not be reached from data presented in that work.

There are two interesting differences between the acidification rates in the early and late PCT. The first difference is that the level of saturation of bicarbonate transport is achieved in the early but not late PCT by the filtered bicarbonate load that occurs in a normal euvolemic animal. An increment in filtered bicarbonate load above normal (e.g., as induced by ANF or glucagon) results in further bicarbonate reabsorption solely in the late PCT. Maintenance of proximal glomerulotubular balance for bicarbonate reabsorption (flow-dependent acidification) at supernormal flow rates is therefore a function of the late but not early PCT. The second, more important, difference is that the absolute magnitude of the bicarbonate reabsorptive capacity in the early PCT, about 550 peq/mm · min, is two and one-half to three times the maximal rate in the late PCT (5, 6, 19). In fact, early PCT acidification capacity is more than 1 order of magnitude higher than maximal rates which have been reported in any distal nephron segment under normal conditions (2, 3).

The present studies did not elucidate whether such high rates of acidification in the early PCT were effected by amplification of the same processes resident in the late PCT. S₁ cells have greater membrane surface area (1) and could potentially contain more of the same luminal and peritubular transporters required for acidification in the S₂ cells. It is also possible that the early PCT might recruit a different mechanism for boosting bicarbonate reabsorption (37). Further work will be required to identify the mechanism(s) responsible for the higher early PCT acidification process and to provide a more precise definition of the kinetics of transport in this segment than can be obtained using free-flow micropuncture techniques.

When taken together, the micropuncture and microperfusion data have shown that bicarbonate reabsorption of the entire superficial PCT can eventually be saturated in response to progressively increasing luminal flow. If maximal rates of transport in each of the five 1-mm segments are sequentially taken as 550, 350, 200, 200, and 200 peq/mm · min from Fig. 3, a maximal reabsorptive capacity of the entire PCT would be $\sim 1,500$ peq/ min. This rate of bicarbonate reabsorption is never reached under physiologic free-flow conditions because the requisite SNGFR $(\geq 75 \text{ nl/min})$ and filtered bicarbonate load $(\geq 2,000 \text{ peq/min})$ cannot be acutely achieved. At lower, physiologic SNGFRs, bicarbonate reabsorption in the entire proximal convoluted tubule demonstrates very good flow dependence (8, 17, 33). Nevertheless, it would seem reasonable to consider bicarbonate transport kinetically similar (load-dependent but saturable) to transport processes for other sodium cotransported solutes in the PCT (e.g., glucose and amino acids).

Axial heterogeneity of bicarbonate reabsorption: response to alkalemia. In agreement with previous predictions from this laboratory (17, 18), late but not early PCT bicarbonate reabsorption was found to be inhibited by alkalemia. The suppressed rate of bicarbonate reabsorption in the late PCT during alkalemia in the present studies agreed very well with that previously defined by in vivo microperfusion, $\sim 80 \text{ peq/mm} \cdot \text{min}$ (19). Inhibition of bicarbonate reabsorption was observed despite concurrent high luminal bicarbonate concentration (two to three times normal), potassium deficiency, and extracellular volume contraction (5, 17). Alkalemia resets the maximal rate of late PCT acidification and prohibits further stimulation by yet higher luminal bicarbonate concentration (19). Alkalemia suppresses late PCT acidification (19, 38, 39), presumably by impairing bicarbonate exit from the cell (because of the hyperbicarbonatemia or possibly the reabsorbate alkalinity) resulting in cellular alkalinization (R. J. Alpern, personal communication). The reason for the relative sparing of the early PCT from this inhibitory effect of alkalemia is unknown but certainly deserving of further study. It should be noted, however, that when more prolonged metabolic alkalosis and hypokalemia occurs in association with tubular hypertrophy, the quantitative and perhaps qualitative effects of alkalemia on segmental bicarbonate reabsorption can be altered (40).

The results considered collectively suggest that bicarbonate reabsorption during chronic metabolic alkalosis may be maximal in both the early and late PCT. In the early PCT, bicarbonate reabsorption was already at a maximal level (\sim 550 peq/ $mm \cdot min$) during the normal state (groups 2-4) and was not reduced by alkalemia (group 5); in the late PCT, bicarbonate reabsorption was reduced by alkalemia and rendered unresponsive to further stimulation by a high luminal bicarbonate concentration and delivery. The thesis that absolute bicarbonate reabsorption over the entire proximal convoluted tubule length is at a maximal level during chronic metabolic alkalosis is supported by observations that an increase in SNGFR and filtered bicarbonate load by volume expansion (20) or by ANF (34) resulted in no reabsorptive stimulation. It has therefore been proposed that the glomerular hypofiltration that occurs during chronic metabolic alkalosis (20, 34) is critical for the maintenance of the alkalotic state by preventing filtered bicarbonate load from exceeding the PCT reabsorptive capacity.

Axial heterogeneity of chloride transport. Chloride transport in the late PCT is effected by parallel active and passive processes (9, 11, 41, 42). Transcellular transport of chloride is electroneutral and exquisitely sensitive to the peritubular protein concentration (9, 11, 41). Paracellular chloride transport is governed by the magnitudes of the junctional chloride permeability and the transepithelial electrochemical gradient, principally the chloride concentration gradient (9, 11). Contradictory microperfusion evidence has been presented on whether active chloride transport in the late PCT is (12-14) or is not (14-16) flow dependent. Even when found, the magnitude of the rise in chloride transport is small compared with the increase in chloride load, similar to the present free-flow results (compare dashed line representing previous microperfusion data and symbols representing present data in the 3rd to 5th mm in Figs. 8 and 9) (12). A rigorous statement regarding flow dependence of late PCT chloride transport is not possible for several reasons. First, the transepithelial chloride gradients in these studies were not equivalent (the late PCT transepithelial chloride gradient declined from about 23 to 20 to 18 meq/liter in hydropenia, euvolemia, and ANF and glucagon groups, respectively, and was ≥ 30 meq/liter in the microperfusion studies). A small flow-induced change in active transport might have been offset by a directionally opposite

change in chloride diffusion. Second, peritubular factors may also have been changed, which could affect active chloride transport. Nevertheless, although a definitive mechanistic conclusion cannot be reached, inspection of Figs. 7–9 reveals that the relatively low rate of absolute chloride reabsorption in the late PCT under free-flow conditions (<300 peq/mm \cdot min) increased only modestly, with a decline in the fraction reabsorbed, as delivery rose.

Chloride transport in the early PCT differed from that in the late PCT both quantitatively and qualitatively. First, there was a marked augmentation in chloride transport in transition from the low filtered chloride loads of groups 1 and 5 to the normal level of group 2 (Figs. 7 and 8), unrelated to chemical concentration gradients. The fractional chloride reabsorption actually rose to as high as 0.12 (Fig. 9). Indeed, as chloride load increased to the euvolemic level, most of the increment in absolute chloride reabsorption for the entire PCT, 544 peq/min (from 1,404±189 to 1,948±175 peq/min), was attributable to enhancement of chloride transport in the initial millimeter (379 peq/min). A further increase in chloride load with ANF or glucagon induced no more chloride transport, indicating apparent saturation of this process. Puzzling aspects of the load-dependent chloride reabsorptive response in the early PCT include the fact that the fractional rate of transport actually increased as delivery rose and transport in the 2nd mm required a lower delivered load for augmenting transport than the 1st mm. Second, the maximum rate of chloride reabsorption in the 1st mm was very high, 585 peq/mm · min, similar to the rate of bicarbonate reabsorption in this segment and even rivalling the rate of chloride transport in the thick ascending limb of Henle (43).

The mechanism(s) responsible for this robust and flow-dependent chloride reabsorptive process in the early PCT was not defined in the present experiments. The early PCT may possess more of the presently unidentified transporters that effect chloride transport in the late PCT (e.g., more apical NaCl cotransporters or parallel exchangers such as Na⁺/H⁺ and Cl⁻/OH⁻ or Na⁺/ H⁺ and Cl⁻/formate⁻ with appropriate increase in peritubular transport systems) (42, 44). Alternatively, a different mechanism may be responsible for this early flow-dependent PCT chloride transport. For instance, there may substantial electrodiffusion of chloride in the early PCT, driven by the lumen-negative potential difference generated by sodium-coupled organic reabsorption. Such a mechanism for chloride transport coupled to electrogenic organic reabsorption has been thought unlikely for the rabbit early PCT (9) because a lumen-negative potential difference in the setting of a high sodium/chloride permeability would simply result in sodium recycling. However, appropriate permeability measurements have not yet been performed in the rat.² Such a mechanism would explain the early PCT chloride transport flow-dependence and saturability (in that transport of glucose and other organic solutes is flow dependent and saturable). Clearly, further study of this important transport mechanism is required.

Axial heterogeneity of water transport. Water reabsorption in the PCT is effected principally by the osmotic gradient (luminal hypotonicity and possibly peritubular hypertonicity) generated by reabsorption of sodium bicarbonate, sodium chloride, and organic solutes (11, 45). Flow dependence of volume reabsorption in the PCT has been of great investigative interest for many years (46). In the late PCT during microperfusion, water reabsorption increases with load. However, the proportionality between water reabsorption and delivery has often been found not to be well maintained (46) (i.e., glomerulotubular balance has been less than perfect), in accord with the present results (compare dashed lines representing microperfusion data and symbols representing present free-flow data in Figs. 11 and 12). In any event, the absolute rate of water reabsorption (<3 nl/ mm · min) and the reabsorbed fraction of water delivered in the late PCT as a function of water delivery (<0.1) were relatively low under all free-flow conditions.

In the early PCT, on the other hand, a rise in SNGFR and filtered solute loads from a hydropenic to a euvolemic level was accompanied by excellent load-dependent solute transport and water reabsorption. Water reabsorption increased to 10.1 nl/ mm \cdot min in the euvolemic state, a rate four to five times higher than observed under normal conditions in the late PCT (5-8). This water reabsorptive rate exceeds that which normally occurs in any other segment of the entire nephron. In addition, the increase in absolute water reabsorption in the early PCT in the transition from the hydropenic to euvolemic state was proportional to the increased SNGFR; maintenance of excellent fractional water reabsorption at a high level (0.20–0.25). Glomerulotubular balance was perfect and fully a quarter of the glomerular ultrafiltrate was reabsorbed in the 1st mm of the nephron under conditions of low-to-normal SNGFR.

The early PCT reabsorbed a greater fraction of delivered volume than the late PCT and tended to exhibit better glomerulotubular balance in the low-to-normal SNGFR range. However, a further increase in SNGFR with ANF or glucagon revealed no higher water reabsorptive capacity and fractional water reabsorption then declined. This lack of flow-dependent reabsorption in both the early and late PCT when the SNGFR rose above normal caused a disproportionately large fraction ($\sim 80\%$) of the increment in filtered sodium and water load to be transmitted out of the PCT.

These findings emphasize the complicated nature of water reabsorption in the PCT: (a) there is an axial gradient in the capacity for solute and water reabsorption; (b) there appears to be a heterogeneous, nonlinear, water-reabsorptive response as a function of length to a change in luminal flow and anion composition; (c) and there can be differential regulation of solute and water reabsorption in the early versus late tubule by peritubular factors. Such complex kinetics and determinants of transport as a function of length may explain some of the disparity in reported results regarding flow dependency of whole PCT volume reabsorption (46).

In conclusion, the early superficial PCT is distinguished from the late PCT by having high-capacity, flow-responsive but sat-

^{2.} The quantity of organics reabsorbed in the early PCT can be estimated if it is assumed: (a) that the constituents of the reabsorbate besides sodium bicarbonate and sodium chloride are principally organics solutes; and (b) that the reabsorbate is approximately isosmotic (300 mosmol/kg H₂O) (44). The organic solute flux can then be estimated as (300)(H₂O reabsorption) $- 2(HCO_3^- + Cl^-$ reabsorption), and was 656, 820, 902, and 522 pmol/mm · min in the 1st mm of the PCT in groups 1–4, respectively. These organic solute reabsorption rates would be more than sufficient to account for the quantity of chloride reabsorbed if the paracellular pathway in this nephron segment were relatively chloride-selective (9).

urable, anion- and volume-reabsorptive processes relatively unaffected by alkalemia.

Acknowledgments

We thank Floyd C. Rector, Jr., M.D., for his continuing support and advice. These studies were performed by Dr. Liu in partial fulfillment of the requirements for the degree of Ph.D. in Physiology, University of California, San Francisco.

These studies were supported in part by a Clinical Investigator Award (1-K08-AM-10115) and grants from the National Institute of Arthritis, Diabetes, and Digestive Diseases (DK-37423 and DK-27045) and from Wyeth Laboratories.

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