Influence of tolbutamide on renal function in man. – Über den Einfluß von Tolbutamid auf die Nierenfunktion des Menschen
The effect of tolbutamide 1 g i.v., or 8 g of glucose and 8 g of fructose (as control) in hypertonic solution on renal hemodynamics, concentrating ability and extracellular electrolytes was studied in 31 adults during slightly hypertonic diuresis. The results were compared with the data obtained previously (Mertz, 1963) after 4 units of insulin i.v.
Tolbutamide, glucose, fructose, and insulin had no significant effect on either inulin- and PAH-clearance or on the filtration fraction. The previously described antidiuretic effect of insulin was only observed in 1 of 10 persons given i.v. glucose. Tolbutamide and fructose were inert in this respect. There was no significant change of the renal concentrating ability (urine volume/min, U/P0sm, Ch2o) and of the plasma osmolarity in any of the 3 groups. During the acute experiment tolbutamide, glucose, and fructose induced a significant fall of the serum level and of the renal excretion of potassium. There was also a clear diminution of renal sodium excretion during tolbutamide infusion.
It is therefore assumed that: (1) The antidiuretic effect of insulin is linked to an elevation of the peripheral insulin activity (concentration) and (2), the effect of tolbutamide is not only due to the endogenous release of insulin (as already postulated by Creutzfeldt and Soling, 1960). The peripheral action of insulin after glucose infusion is subminimal or absent.
References
Author’s address: D. P. Mertz, Medizinische Poliklinik der Universität, Freiburg i. Br. (Deutschland).
Hereditary nephrogenic diabetes insipidus in a female infant (complete form).- Familiärer nephrogener Diabetes insipidus mit voller Ausprägung bei einem weiblichen Säugling
The nephrogenic vasopressin-resistant diabetes insipidus is a congenital and familial tubular disorder, which usually appears in the males of the affected families. It therefore is considered to be transmitted by a sex-linked recessive gene defect. We have now observed a female infant with the complete form of this disease. At the age of two months the infant became repeatedly dehydrated, vomited and ran high fever. Despite her hyperelectrolytemia (Na = 174 mEq/l and Cl = 140 mEq/l), the urine remained diluted with a maximal osmolality of 80 mOsm/kg t/¼O. Vasopressin did not reduce the urine flow nor increase the osmolality. Clearance studies revealed otherwise normally functioning kidneys, the acido-genesis was not impaired.
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Further Section
Nephron 1965;2:48-61

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Her father has a mild form of nephrogenic diabetes insipidus. He suffers from polydipsia and polyuria and has a maximal urinary osmolality of 770 mOsm/kg H₂O. The infant’s parents are consanguine as they have the same great-grandparents.

We know of only 7 more proved cases of the complete form of nephrogenic diabetes insipidus in females in the literature. In only two cases, including our one, was a familial trait obvious. Genetic considerations make it important to distinguish clinically between the complete and intermediate forms of nephrogenic diabetes insipidus. Therefore the following classification is presented:

Table I

<table>
<thead>
<tr>
<th>Maximal urinary Vasopressin-concentration test</th>
<th>Uosm/Posm</th>
<th>Uosm (mOSUL/kg %O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete form of neph. diab. ins. (homozygote or hemizygote)</td>
<td>&lt; 1</td>
<td>&lt; 295 φ</td>
</tr>
<tr>
<td>Intermediate form of neph. diab. ins. (heterozygote)</td>
<td>1-3</td>
<td>295-850 (+)</td>
</tr>
<tr>
<td>Normal</td>
<td>&gt; 3</td>
<td>&gt; 850 +</td>
</tr>
</tbody>
</table>

Authors’ address: Dr. J. Brodehl and L. Braun, Univ.-Kinderklinik, Bonn (Deutschland).

Arterial angiotensin levels in edematous patients


The renin-angiotensin system is known as one of the major mechanisms in the regulation of aldosterone secretion and excretion. This relationship has been investigated in 21 patients with gross edema relevant to states of secondary hyper-aldosteronism.

The arterial angiotensin level was determined by a sensitive and specific method recently deserved by Boucher et al. (1). According to this method, the mean normal level is 6.3 nanograms (millimicrograms) for 100 ml of plasma, with a range of 0 to 35 nanograms. Detectable levels of angiotensin were found in only 30% of normal subjects.

Results

Twelve out of thirteen edematous cardiac patients presented angiotensin levels above normal range for a mean level of 232 ng. Ten of these were studied also after natriuretic treatment and total or partial relief of their edema; eight out of ten exhibited an important lowering of their angiotensin levels; the mean level decreased from 232 ng to 78 ng for 100 ml of plasma. It is of interest to emphasize that most of these patients were normotensive despite the high levels of circulating angiotensin.

Two out of three nephrotic patients had initial values above normal range.

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Summaries – Resumes

ARTERIAL ANGIOTENSIN LEVELS IN NORMAL SUBJECTS AND EDEMATOUS PATIENTS

ANGIOTENSIN

Ng/100ml PLASMA

300-

200

100-
Four out of five cirrhotic patients had initial values within normal range. The increase in activity of angiotensinase as reported by others, would explain a normal angiotensin level in the peripheral blood of these patients.

These preliminary results strongly suggest a possible role of the renin-angio-tensin system in the pathogenesis of cardiac and nephrotic edemas.

Reference
Author’s address: Dr. Jacques de Champlain, Hôtel-Dieu de Montreal, 3840, rue Saint-Urbain, Montreal iS (Canada).

The relationship of ‘Chronic Pyelonephritis’ to chronic potassium deficiency

A review of the literature was made of the multiple functional and structural de-arrangement of the kidney of acute potassium deficiency in man and animals. Next, thirty-five patients with prolonged potassium depletion reported in the literature were reviewed. Hydropic vacuolar degeneration was found in the kidneys of twenty out of thirty-five potassium deficient patients. In a large portion of these patients either pyelonephritis or interstitial fibrosis was found.

In Individual Segments of the Nephron

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– 20 millivolts in the proximal tubule, a potassium concentration equal to or lower than that of plasma is prim a facie evidence of active transport if solvent drag effect is excluded. Certainly solvent drag could in no way result in a reduction in potassium concentration below that filtered, and for solvent drag to produce no change in potassium concentration would require absolutely free permeability of the tubule cell to potassium with no steric hindrance to the passage of that ion. Others repeating the experiments in Necturus, however, could not confirm either of these results (47). The concentration of potassium at all sites in the proximal tubule was found to be considerably higher than glomerular fluid potassium concentration, the mean tubule fluid:plasma ratio being 1.6. Since this ratio corresponded to the simultaneous inulin concentration ratio, no net potassium transport was apparent from these experiments. Additional studies were done using the stopped-flow modification (17) of classical micropuncture technique. In these experiments, tubules were filled with a solution which contained no potassium, yet after 20 minutes (normal proximal tubule fluid transit time in Necturus), the final tubular potassium concentration was 6.5 mM/1. In the face of this high final potassium concentration in experiments where no potassium was initially present, impermeability to potassium cannot be cited as the reason for comparable ratios of inulin and potassium found in the other experiments. Rather, a sizable net influx of potassium occurred. When the transtubular electrical potential of 20 millivolts is considered, the potassium concentration ratio across the Necturus proximal tubule is close to that predicted from the Nernst equation for passive ion distribution. At the luminal face, however, where the potential difference is 52 millivolts, lumen positive to cell, passive distribution demands a luminal potassium concentration of 14 mEq/1 at equilibrium. This requires, of course, that the reported intratubular potassium concentration of 110 mM/1 is correct, that none is compartmentalized at higher concentration at the expense of general cell water, and all is free to exert its full chemical activity. Another premise [which may be incorrect (48)] is that the ionic composition of interstitial fluid is accurately reflected in the concentration of ions in plasma. One must assume from these experiments that an active absorptive mechanism exists at the luminal membrane. It is possible, however, that membrane permeability is such that insufficient time had elapsed to permit full passive equilibration, or that the above ‘ground rules’ are incorrect.

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An immunoassay method for urinary albumin at low concentrations
A simple immunological method for estimating the albumin concentration in human urine is described. The method is the same in principle as that of Hales and Randle (1) and Morgan and Lazarow (2) for measuring insulin in human plasma.

To 0.1 ml of the urine under investigation a small quantity of 125I-albumin (human) and of anti-human albumin serum raised in the guinea pig is added. The 125I-albumin present in the system is arranged always to be in excess of the binding capacity of the antibody so that only part of it is complexed. These soluble antigen-antibody complexes are precipitated by an anti-guinea pig globulin serum raised in the rabbit. The precipitin is collected and when its radioactivity is compared with that of standard albumin solutions treated similarly, the unknown albumin concentration in the urine can be deduced.

The method is particularly sensitive at low albumin concentrations and urines containing large amounts of protein have to be diluted before assay. Evidence is supplied showing that the reproducibility obtained by the method is satisfactory.

The advantages of the method are its simplicity and its capacity to measure albumin concentration to one tenth of a milligram per 100 ml over the range of albumin concentrations encountered in human urines; it is thus particularly useful at albumin concentrations around the normal where quantitative methods utilizing small volumes of unconcentrated urine are lacking.

References
Author’s address: Dr. H. Keen, Dept. of Medicine, Guy’s Hospital, London S.E. i (England).

Skeletal, intestinal and renal calcium dynamics in hyperparathyroidism

The effects of parathyroid hormone on bone formation, bone resorption, intestinal absorption of calcium and renal tubular transport of calcium and phosphorus were measured before and after treatment in two patients with parathyroid adenomas and in a third with a hyperparathyroidlike state secondary to a localized broncho-genie carcinoma. All patients underwent simultaneous nine-day balance and calcium47 kinetic studies. Renal clearances of creatinine and phosphorus were determined in all three patients and of calcium in one.

Skeletal turnover ranged from low-normal to four times normal. The fall of the serum calcium to normal within ninety minutes following the removal of parathyroid adenomas in two subjects could only be explained by an immediate reduction in bone resorption rather than by a change in renal excretion or intestinal absorption of calcium.

Intestinal absorption of calcium was increased in all and promptly fell following treatment. Endogenous fecal calcium bore no relation to the level of serum calcium and was within normal limits in all patients.

The percent renal tubular reabsorption of phosphorus (normal range being 78 to 90%) rose from 73 and 81% preoperatively to 99 and 97% respectively during the first two days after removal of parathyroid adenomas in two patients. By the fourth post-operative day, however, the %TRP had fallen to 83 and 92%. The changes in serum calcium preceded those of serum phosphorus by at least fifteen hours suggesting that changes in serum calcium are not secondary to changes in serum phosphorus.

The percent renal tubular reabsorption of calcium immediately fell from 99 to 93% despite a 25% reduction in the filtered load of calcium following the removal of a parathyroid adenoma in
one subject. This change preceded the increase in the tubular reabsorption of phosphorus by six hours and is consistent with a reduction in circulating parathormone causing a reduced renal tubular reabsorption of calcium. That other unknown factors also influence the tubular transport of calcium is evidenced by the subsequent rise in the %TRCa during the next five days without a significant change in filtered load.

Authors’ addresses: F.W. Lañarity and O.H. Pearson, Departments of Medicine and Pathology, Western Reserve University, School of Medicine, Cleveland, Ohio eUSA).

The effect of antimetabolites on canine renal homografts: Current status
By Zukoski, C.F.

The homograft reaction elicited by canine renal homografts can be reduced or suppressed by the administration of various antimetabolites to allow long term survival of the recipient. The initial success achieved with 6-mercaptopurine by Zukoski et al. (1) and others led to a further search for other antimetabolites which would give a higher percentage of long term survivors. The following medications have been screened by Zukoski et al. (2, 3): 6-mercaptopurine (6-MP), 6-MP riboside, 6-MP plus 8-azaguaine, 8-azaguaine, 5-fluouracil, azaserine, 6-azauracil, methotrexate, 6-methyl MP, azathioprine (Imuran or B.W. 57-322), urethane plus 6-azauracil, cyclophosphamide and vinblastine sulfate. In all these experiments the medication was given orally to bilateral nephrectomized renal homografted dogs and therapy was begun the day of transplantation. Prednisolone has given significant survival in several animals (4). Another dog has survived for over six months on prednisolone therapy (5). The simultaneous administration of prednisolone with 6-methyl MP or azathioprine has given some prolongation but not the additive result of either drug alone (5).

In a few dogs adult acquired tolerance (treatment with a medication and then withdrawal of the therapy) for renal homografts has been achieved with 6-methyl MP (6) in one dog which lived 735 days and with prednisolone (4) in one dog now living 935 days. The 6-methyl MP dog developed membraneous glomerular nephritis and advanced vascular lesions (7) similar to those reported in human renal homografts. This 6-methyl MP dog is no longer considered to have been rendered tolerant to its homografted kidney but as one which had had its homograft response markedly suppressed. The vascular and glomerular changes are assumed to be a form of delayed homograft response.

Of the many drugs screened to date in the canine renal homograft system, azathioprine, 6-methyl MP and 6-MP have been proven to achieve the highest percentage of long term survivors. A need exists for a more reliable antimetabolite for management of clinical renal homografts. The most advantageous regimen for administering these antimetabolites has not been clearly established.

References
Distribution of arginase within the kidneys of several vertebrate species


(1) Arginase activity was determined in kidney homogenates from sheep, goat, dog, rat, frog, tadpole, mudpuppy, turtle and chicken. In mammals, the intra-renal distribution of arginase was compared to that of urea under different conditions of renal urea excretion.

In dog, rat, sheep and goat different but species-characteristic patterns of intrarenal arginase distribution were found. Intra-renal arginase distribution did not appear related to that of urea itself, nor was its activity responsive to dietary-induced alterations of renal urea excretion.

Renal arginase activity was extremely high in the dorsal portion of the adult frog kidney, and its activity was not altered by doses of di-nitro-phenol which were sufficient to inhibit renal tubular urea secretion. Renal arginase activity was markedly lower in whole kidney homogenates from premetamorphic tadpoles in which the tubular secretory system for urea had not yet appeared. Similarly, the enzyme activity of Necturus kidney was relatively low.

Lowest arginase activities were obtained in homogenates of whole chicken kidney.

These data imply that renal arginase may contribute to the renal tubular secretory process for urea in the frog. No statement may be made regarding its possible contribution to mechanisms of urea excretion by mammalian kidney.

Author’s address: Dr. Bodil Schmidt-Nielsen, Dept. of Biology, Western Reserve Univ. Cleveland, Ohio (USA).
Renal hemodynamic effects of hypertonic mannitol infusions
The effects of intravenous administration of 5 ml/min of a 20% mannitol solution to operated
anesthetized dogs was investigated. In normotensive animals, the infusion resulted in a prompt
fall in the extraction ratio of PAH, an increase in renal blood flow, and a reduction in glomerular
filtration rate. In dogs made hypotensive by bleeding, administration of the mannitol solution,
either prevented the marked renal vasoconstriction usually accompanying hemorrhagic
hypotension, or restored renal blood flow and to a lesser extent glomerular filtration rate toward
control values. The observed effects of the infusion are believed to be the result of renal
vasodilatation, especially of the efferent arterioles. The mechanism whereby hypertonic mannitol
infusion produces this effect is unknown. In more recent studies by Goldberg and Lilienfield
(unpublished), it was demonstrated that this effect of mannitol cannot be prevented by nerve
blockade, nor is it due to any direct chemical effect of mannitol itself on the renal vessels. It is
concluded that changes in the viscous properties of the blood itself play an important role in the
reduced renal resistance during mannitol infusion. In addition, there is the possibility that the
diuresis induced increased renal interstitial pressure lowers renal arteriolar resistance because of
decreased transmural pressure.
Author’s address: Dr. Lawrence S. Lilienfield, Dept. of Physiology and Biophysics, Georgetown
University Medical Center, Washington, D.C. (USA).

Intrarenal distribution of nutrient blood flow determined with Krypton85 in the unanesthetized
dog
By Thorburn, G.D.; Kopald, H.H.; Herd, A.; Hollenberg, M.; O’Morchoe, C.C. and Barger,
A method has been described for the measurement, by means of Kr85, of intrarenal nutrient
blood flow distribution in the unanesthetized dog. Injection of the isotope

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into the renal artery is followed by a multiexponential disappearance curve which can be
obtained by external monitoring with a scintillation detector. In acute experiments
autoradiographs have demonstrated that the first exponential component represents cortical blood
flow; the second, outer medullary blood flow; the third, inner medullary blood flow; and the
fourth, hilar and perirenal fat blood flow. The average cortical blood flow in 65 experiments in
five kidneys of four unanesthetized dogs was 472 ml/100 g/min, the outer medullary 132 ml/100
g/min, and the inner medullary 17 ml/100 g/min. Eighty per cent of the radioactivity was
distributed initially to the cortex, 16% to the outer medulla, and 2% to the inner medulla. The
hilar and perirenal fat, which receives approximately 2% of the initial radioactivity, was
estimated to have a flow rate of 21 ml/100 g/min. In addition, a method for the rapid
determination of serial cortical blood flow rates has been described. The importance of these
findings has been discussed with reference to the anatomy of the kidney, and to the
countercurrent concept as it applies to passive reabsorption of lipid soluble substances, and to the
maintenance of an osmotic gradient.
Author’s address: Dr. A. Clifford Barger, Dept. of Physiology, Harvard Medical School, 25
Shattuck Street, Boston //, Mass. (USA).
Effects of papaverine on cell separation in the mammalian kidney papilla
Investigations have revealed that within the kidney, blood in the medulla is separated into cell-rich and cell-poor moieties. One possible explanation for this separation is that some myogenic sphincterlike mechanism in the medullary vessels impedes red cell passage into the papilla, shunting cell-rich blood to the outer medulla. Consequently one should be able to alter the hematocrit of the blood in the papillary vessels by an agent which could alter this mechanism. Such an agent is the smooth muscle relaxant, papaverine. Studies were performed in 16 mongrel hydropenic dogs (8 control and 8 following papaverine administration). Control dogs were anesthetized with pentobarbital, peritoneum incised and loose ties placed around both intact renal pedicles. Cr51 tagged erythrocytes and I131 albumin were then injected intravenously. After 40 min, pedicles were tied, and the kidneys excised and frozen. Sections from cortex, medulla, and papilla were analyzed for Cr51 and I131. In the experimental animals, papaverine was administered by continuous intravenous drip at a rate of 40 mgm/min during the entire procedure. Between the control group and the papaverine group the only statistically significant difference was an increase in the red cell content (Cr51) and a decrease in the albumin content (I131) in the papilla. These results are compatible with the existence of some myogenic mechanism in the partitioning of a cell-rich and a cell-poor fraction of the blood in the renal medulla. The significance of this mechanism has yet to be determined.

Author’s address: Dr. Lawrence S. Lilienfield, Cardiovascular Research Division, Department of Medicine, Georgetown University Hospital, Washington, D.C. (USA).

Mechanisms of intrarenal hemodynamic changes following acute arterial occlusion

The hemodynamic response of the kidney to acute arterial occlusion is poorly understood. The purpose of the present study was to determine intrarenal hemo-

57 dynamic changes in intact and isolated kidneys following arterial occlusion. The relative roles of metabolic, myogenic, and tissue pressure influences on the post-occlusion response were evaluated. The response of the kidney to occlusion was found to be complex, depending on the interaction of a variety of physical and humoral forces. Increases in renal resistance appeared to be due, in part, to adrenergic agents and were enhanced by extending time of occlusion and lowering the arterial pressure. The combined effects of prevenous dilatation and diminished tissue pressure resulted in a decreased resistance following shorter periods of occlusion. Prevenous dilatation was accounted for by depressed vascular sensitivity to pressor agents and the presence of vasodilator substances. Changes in venous segment resistance were found to be of primary importance in both the autoregula-tory phenomenon and the postocclusion hyperemic response to short (15 sec) occlusion periods. The complete nature of the postocclusion ischemic response is not clear. It is not dependent on renal innervation and therefore appears to have no counterpart in other vascular beds. The tendency for a post-occlusion ischemic response to occur at low arterial pressures, coupled with the effect of increased time of occlusion on intensifying the severity of ischemia, may account for the particular susceptibility of the kidney to injury during prolonged systemic hypotension or shock.

Author’s address: Lerner B. Hinshaw, Renal Physiology Section, Civil Aeromedical Research Institute, Oklahoma City, Okla. (USA).

Effect of ureteral blockade on renal blood flow and urinary concentrating ability
Complete blockade of the ureter in dogs subjected to saline loading (0.85-10.0% NaCl) resulted in an increase in total renal blood during the period of blockade which appeared to be related to the antecedent diuresis and increment in ureteral pressure. This was accompanied by a progressive decrease in extraction of para-aminohippurate (PAH) and a greater decrease in creatinine extraction. The change in Epah showed a close inverse correlation to the change in renal blood flow (RBF). This afforded a possible explanation for the increment in RBF, for the increased perfusion of vascular circuits of the A-V communicating type would account for such a correlation. Evidence was supplied which suggested that such pathways involved the medullary vascular circuits. This was based on the observation that the concentrating ability of the kidney was impaired by the period of occlusion. The most likely mechanism for this would be maintained (or increased) vascular perfusion of the vasa recta system, in the face of markedly curtailed glomerular filtration, conditions resulting from ureteral blockade.

Author's address: Dr. Ewald E. Selkurt, Dept. of Physiology, Indiana University School of Medicine, Indianapolis, Ind. (USA).

Kinetics of p-aminohippurate secretion in the rabbit

This study extends to the living rabbit the kinetic analysis of p-aminohippurate (PAH) transport reported for slices in work previously published from this laboratory (Amer. J. Physiol. 196: 86-92, 1959). The proposed technique permits the calculation of the size and turnover rate of the PAH secretory pool in vivo. The secretory pool is here defined as the cellular solute compartment with which secreted solute equilibrates during its transcellular movement from plasma into tubular urine. The experiments are performed with anesthetized rabbits which have been allowed to reach steady state with regard to urine flow, glomerular filtration rate and PAH clearance at a low steady plasma level of PAH. Tracer amounts of C14-labelled PAH are then infused into the thoracic aorta in such a manner that a constant specific activity of arterial PAH is maintained. Under these conditions the rate of isotopic equilibration of urine and plasma may be used to calculate the parameters of the secretory pool. Direct chemical determination of the PAH content of kidneys after completion of the experiment confirmed the correctness of the calculated size of the pool. By analyzing the kinetics of tracer excretion before and after the infusion of various drugs, the effect of such compounds on the secretory pool could be studied. The inference was drawn from these experiments that the pool is coextensive with the PAH accumulated in the cells and that it consists of free rather than bound solute. In agreement with our earlier views (Amer. J. Physiol. 196: 83-85, 1959), it could further be concluded that similar carrier mechanisms are responsible for influx of PAH from intersti-tium into the pool, and for efflux from the pool into the lumen of the tubule.

Author’s address: Dr. E. C. Foulkes, May Institute, and Department of Physiology, University of Cincinnati College of Medicine, Cincinnati, Ohio (USA).

Allocation of cardiac output to limb and kidney during hypotensive procedures

Cardiac output, and renal and femoral venous outflows were measured simultaneously and continuously by rotameters during hemorrhage and inferior vena caval obstruction in dogs anesthetized with chloralose. Control observations (18 dogs) were mean aortic blood pressure 118 mm Hg, cardiac output 1.3 l/m2, renal blood flow 114 ml/min, femoral blood flow 46
ml/min. Acute reductions in cardiac output of 45 to 68% resulted in an immediate increase in femoral and renal fractions of the cardiac output. The femoral fraction increased from a control of 5% to 9% (hemorrhage) and 11.5% (caval obstruction). The renal fraction of cardiac output increased from a control of 11.1% to 13.3% (hemorrhage) and 15.7% (caval obstruction). Further augmentation of the femoral flow fraction with reduction of the renal flow fraction was accomplished by baroreceptor area de-nervation or guanethidine. The skeletal muscle bed is a primary recipient of baro-receptor mediated reflex nervous activity. Following guanethidine-induced reduction of sympathetic vasoconstrictor activity of the femoral bed, the femoral flow pattern was converted to a renal flow pattern. Guanethidine, which reduced or eliminated sympathetic vasoconstrictor activity altered regional flow fractions during acute reductions of cardiac output according to their resting sympathetic nervous activity. A regional bed having high tone (skeletal muscle) will increase its flow fraction whereas a regional bed having low tone (kidney) will decrease its flow fraction following intravenous guanethidine (5-10 mg/kg). The partition of cardiac output during acute hypotensive procedures in this experimental setting was determined by differential vasoconstrictor activity, possibly by neurohumoral agents which selectively influence certain vascular beds, and by an intrinsic property of the blood vessel wall which determines in part its response to acute reduction in flow.

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Reference

Author’s address: Dr. J.C. McGiff, Departments of Pharmacology and Medicine, Schools of Medicine, University of Pennsylvania, Philadelphia, Pa. (USA).

The renal excretion of folic acid

The renal excretion of tritiated folic acid was explored using a single renal intra-arterial injection in the dog. Renal tubular reabsorption of folic acid was demonstrated. The initial reabsorption mechanism from tubular lumen to cell exhibited saturation. When this mechanism was completely saturated the proportion of folic acid filtered was shown to represent a relatively constant fraction of concomitantly administered inulin. The proportion filtered was shown to correspond to the proportion of folic acid not bound to plasma proteins. The initial reabsorptive mechanism was shown to be inhibited by methotrexate. A large dose of unlabeled folic acid was shown to displace reabsorbed tritiated folic acid into the urine from renal tubular cells. This displacement demonstrated storage of tritiated folic acid under these circumstances, rather than rapid transport into the blood stream. The characteristics of this reabsorptive mechanism (saturation, inhibition, and counter-transport) are compatible with a mobile membrane carrier-transport system for folic acid abutting upon the tubular lumen.

Author’s address: Dr. C.A. Goresky, McGill University Medical Clinic, The Montreal General Hospital, Montreal, Quebec (Canada).

Effects of certain inhibitors on renal excretion of salt and water

The direct proportionality between renal oxygen consumption and sodium reabsorption suggests a linkage between cation transport and the electron transport system (ETS). We have studied the effects of in vitro inhibitors of the ETS on sodium reabsorption in the dog kidney. Compounds known to block C½ consumption or reduce tissue levels of adenosine triphosphate (ATP) were
infused in milli-molar quantities into a renal artery of anesthetized dogs. We observed a unilateral diuresis following the administration of cyanide, antimycin-A and iodoacetamide; no diuresis was observed following administration of 2,4-dinitrophenol, azide, and phlorizin. These latter agents block the synthesis or facilitate the degradation of ATP. Negative results were also observed with phthiocerol (a naphthoquinone), malonate, and Amytal, inhibitors of specific substrates of ETS. We interpret our results as follows. Inhibition of sodium reabsorption by cyanide and antimycin-A supports the hypothesis that renal cation transport is dependent in part upon oxidative metabolism. The failure of phlorizin and 2,4-dinitrophenol to affect sodium reabsorption suggests that cation transport may be independent of ATP synthesis or concentration in renal tissues.

Author’s address: Dr. Richard H. Kessler, Dept. of Physiology, Cornell University Medical College, 1300 York Avenue, New York 21, N.Y. (USA).

Effects of certain quinones on renal excretion of sodium

Effects of albumin infusion on renal function in the dog

Serum albumin (25%) was infused into anesthetized dogs undergoing a saline diuresis. No significant effect was seen on arterial pressure, but renal venous pressure was elevated slightly. GFR remained unchanged, while CpaH, renal plasma flow, total renal blood flow, and flow to medullary tissue increased significantly Accompanying these changes were marked declines in Pah and creatinine extraction ratios. Urine volume, CNa, and COSm declined appreciably during albumin infusion; T/min tended to decrease. The ratio of Na and osmolar constituents in renal venous blood to that in arterial blood increased above unity, and calculations indicated that at this time Na was washed from the kidney. TmpAh remained unchanged during albumin infusion. It is concluded that during albumin infusion, there is an increase in plasma volume and renal blood flow accompanied by a diversion of part of this blood through agglomerular regions, possibly through A-V anastomoses, as evidenced by the accompanying decrease in Ecr and Epah. This could involve increased perfusion of the medullary papillary zone, including the vasa recta vessels, supported by the observations that during albumin infusion there is a washout of osmotic constituents, primarily Na, presumably from a zone of high Na concentration.
Handling of urea and related compounds by the renal tubules of the frog
A high arginase activity is found in the kidney of the adult frog Rana catesbeiana which actively
secretes urea. Urea accumulates in the kidney in concentrations around seven to eight times the
blood concentration. To test whether the kidney arginase
causes significant formation of urea in tubular cells at normal plasma arginine levels, C14 urea,
chemical urea, and creatinine clearances were measured. C14 urea and chemical urea clearances
were identical, both being about seven times the GFR. 2,4-Dinitrophenol (DNP) inhibited the
active secretion of urea, but C14 and chemical urea clearances remained identical to each other.
When arginine was administered, urea was formed in the kidney and excreted in the urine at the
rate of 35 µM/g kidney/h. The chemical urea clearance was then about twice the C14 urea
clearance. DNP administered with arginine caused the C14 urea clearance to fall below the GFR
but did not inhibit the formation of urea as shown by the chemical urea clearance being three
times the GFR. Compounds chemically related to urea were handled in different ways by the
frog kidney. Acetamide and methylurea were not secreted and did not accumulate in the kidney.
DNP had little or no affect on their excretion. Thiourea was found to be actively secreted and to
accumulate in the kidney. DNP inhibited thiourea secretion. It is concluded that urea is normally
actively transported across the tubular wall and that formation of urea in the tubular cells is
insignificant.
Effect of carbonic anhydrase inhibition on proximal tubular bicarbonate reabsorption
Samples of fluid from the proximal tubule were collected for the measurement of pH and
bicarbonate concentration before and after the administration of acetazolamide (Diamox).
Samples collected before acetazolamide were consistently more acid than plasma with the most
acid samples coming from the more distal portion of the proximal tubule. After the intravenous
administration of acetazolamide, the pH and bicarbonate concentration were consistently higher
than in plasma. Bicarbonate concentrations as high as 2.8 times that in plasma were observed.
The rise in proximal tubular fluid bicarbonate concentration after acetazolamide is presumably
due to a reduction in the rate of bicarbonate reabsorption out of proportion to any impairment
in proximal tubular fluid volume reduction.
Evidence against immune mechanism in aminonucleoside nephrosis in rats
Various animal and laboratory studies failed to demonstrate an immunologic basis for the
nephrotoxic action of aminonucleoside (P-A) of puromycin in rats. These studies consisted of
passive transfer of whole serum, beta globulin, and gamma globulin from P-A-treated rats to
normal rats. Complement fixation and precipitation studies with nephrotic sera were also
negative. Cortisone, nitrogen mustard, and removal of 70% of the liver did not prevent or
ameliorate the proteinuria of P-A-treated rats. P-A did not inhibit regeneration of liver tissue. The results of these experiments suggest that P-A does not produce nephrosis in the rat by means of an immune mechanism.

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