Further Section

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Summaries – Résumés

Failure to demonstrate a hormonal inhibitor of proximal sodium reabsorption

The experiments described in this paper were undertaken independently in Bethesda, London, and Cologne in an attempt to identify the existence of a plasma natriuretic factor (‘third factor’).

In the Bethesda study, micropuncture studies were performed on rats infused with blood obtained from hydropenic dogs before and after they received large infusions of isotonic saline. While the dog plasma was infused, fractional sodium reabsorption of individual tubules was determined using the recollection technique. The plasma infusion protocol was followed in an additional 4 antidiuretic rats and sodium reabsorption was estimated by the shrinking drop method of Gertz.

In another series of experiments dialyzed plasma of saline-loaded and non-saline-loaded dogs was directly injected into proximal tubules and the rate of absorption assayed by the shrinking drop technique. These experiments were performed in double blind fashion. In the London and Cologne protocols, peripheral and jugular venous blood samples were obtained from conscious dogs before and after the infusion of large amounts of isotonic saline. The urine volume and sodium concentration were determined after the infusion of the two types of plasma samples infused in an alternating sequence. Both normal Wistar rats and animals with hereditary diabetes insipidus were used in this study. These plasma samples were dialyzed and injected directly into the proximal tubule. Sodium absorption was estimated by the shrinking drop technique, the identity of each sample remaining unknown to the experimenter until completion of the study.

Fractional sodium absorption by the proximal tubule was not found to be different during infusion of natriuretic plasma and during infusion of hydropenic plasma whether studied by free flow micropuncture methods or the shrinking drop technique. No increase in the urine volume or the rate of sodium excretion was observed during the period of natriuretic plasma infusion. Dialysates of natriuretic plasma also failed to inhibit proximal sodium reabsorption.

Furthermore, the authors were unable to detect sodium absorptive inhibitory activity in plasma obtained from dogs during the ‘escape’ phase of chronic deoxycorticosterone acetate administration. In summary, the authors were unable to detect an inhibitor of proximal sodium reabsorption in the plasma or dialysates of plasma, from saline-loaded animals.

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Oxygen cost of sodium reabsorption in proximal and distal parts of the nephron

The relationship between changes in tubular sodium reabsorption and changes in renal oxygen consumption (Na/Cs) was determined in dogs made anemic, as

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the arteriovenous difference in oxygen saturation was more than doubled by antecedent bleeding. Tubular sodium reabsorption was reduced by 45 ± 3%, and oxygen consumption by 36 ± 4%
after blocking distal sodium transport with ethacrynic acid and chlorothiazide. On the basis of these data it could be calculated that $34 \pm 5$ Eq Na$^+$ were transported in the distal nephron per/mol O$_2$ consumed. Similar Na/O$^{\frac{7}{8}}$ ratios were obtained by reducing proximal sodium reabsorption by lowering glomerular filtration rate after blocking distal sodium reabsorption. During infusion of chlorothiazide and ethacrynic acid, oxygen consumption was not further decreased by reduction of net proximal sodium reabsorption with mannitol infusion. This observation supports the hypothesis that energy-dependent sodium reabsorption in the proximal tubules is not reduced during mannitol diuresis. Na/O$^{\frac{7}{8}}$ was not affected by angiotensin in doses which halved renal blood flow, or by sodium sulphate or ferrocyanate in doses raising serum sodium by 40-50 mEq/l. The results are consistent with similar stoichiometric relationships between sodium reabsorption and oxygen consumption in the proximal and distal parts of the nephron.

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The relationship between the renal handling of phosphate and bicarbonate in man


Having previously noted that measures which caused an increase in urinary bicarbonate excretion and a rise in urinary pH caused a simultaneous phosphate diuresis, the authors formally studied the relationship between the renal handling of phosphate and bicarbonate in 13 normal male volunteers, 2 patients with classical renal tubular acidosis, and 1 patient with central diabetes insipidus. The effects of acetazolamide, sodium bicarbonate, saline and mannitol infusions and parathyroid extract on urine pH, electrolyte excretion, titratable acidity, urinary ammonium, and urine volume were determined. Bicarbonate diuresis, however induced, invariably was associated with a phosphate diuresis. Urine pH always rose in association with phosphaturia and bicarbonate diuresis. Parathyroid extract administered acutely also produced a bicarbonate diuresis and phosphaturia, but the magnitude of phosphaturia at any level of bicarbonate excretion was greater than that observed with any of the other agents used. It is unlikely that the phosphaturia was caused by primary changes in systemic acid base balance, however, since plasma pH, PCO$_2$ and bicarbonate concentrations either did not change or varied randomly while both bicarbonate and phosphate diuresis occurred. They suggest that the dependence of phosphate excretion upon bicarbonate excretion rests upon the preferential transport of the monovalent phosphate ion whose rate of reabsorption is directly influenced either by proximal tubular fluid pH, by the proximal tubular load of bicarbonate ion, or both.

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Increase in serum potassium resulting from the administration of hyper-tonic mannitol and other solutions


One liter of 10% mannitol solution in 0.5 normal saline was infused in four young normal men at a rate of 10 ml per minute. The subjects were on a prescribed diet containing 100 gm of protein, 80 mEq/Na and a potassium intake of 50, 140, or 200 mEq/daily. Six additional subjects who were not on this metabolic diet received 12.5% mannitol, 11 subjects received 1 liter of 2.25% NaCl, 13 subjects were given 10% mannitol in 75 mM/sodium bicarbonate, and 10 subjects were given 385 mM/sodium bicarbonate. All solutions were given in a volume of 11 at a rate of 10
ml/min. Additionally, 8 subjects received 2 l of isotonic saline, 7 received the same volume of isotonic mannitol, and 5 received isotonic sodium bicarbonate over a period of 90 min. Serum potassium concentration in response to hypertonic mannitol infusion in both hydropenic fasting volunteers and non-fasting normally hydrated volunteers rose approximately 0.7 mEq/l. Hypertonic saline also caused a comparable rise in serum potassium concentration. When mannitol was given with bicarbonate instead of saline, however, serum potassium concentration did not rise significantly. Isotonic saline infusion did not produce a significant rise in serum potassium concentration. The authors recognize that they are unable to determine the mechanism by which hypertonic solutions in the study produced a rise in serum potassium concentration. They feel, however, that expansion of extracellular fluid volume alone is not responsible since comparable volume expansion with isotonic saline did not produce a significant rise in saline concentration. They suggest, instead, that the rise in serum potassium concentration observed is more likely the result of a dilutional decrease in serum bicarbonate concentration with resulting acidosis and the transfer of intracellular potassium to the extracellular space.

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Mechanism of natriuretic action of bradykinin
Infusing bradykinin into the renal arteries of anesthetized dogs at graded dosage, the authors were able to confirm the natriuretic and diuretic effect of this agent, and demonstrated the expected decrease in renal vascular resistance and increase in renal blood flow. An increase in free water clearance, commonly attributed to decreased proximal tubule reabsorption of sodium, was observed. While reduced sodium reabsorption in the proximal tubule also might explain the increased sodium excretion, the authors found that bradykinin did not produce natriuresis in the absence of an increase in renal blood flow. In an attempt to evaluate the contribution of renal hemodynamics to the natriuretic response of bradykinin, its effect was studied in the autoperefused dog-kidney preparation. Under these circumstances, infusion of bradykinin caused a decrease in renal vascular resistance but no natriuresis when blood flow was constant. Natriuresis was observed without significant alteration in PAH clearance so long as blood flow was increased to maintain perfusion pressure constant during the bradykinin infusion. When renal blood flow was held constant with an aortic clamp during infusion of the peptide, sodium excretion decreased although glomerular filtration rate was unchanged. The authors interpret their findings to indicate that the natriuretic action of brady-kinin is related to an increase in renal blood flow and does not result from any direct interference with active tubular reabsorption of sodium. Their conclusion is consistent with the studies of Khairallah and Turner (Pharmacologist 7: 152, 1965) who found no effect of bradykinin on sodium transport in isolated tissues.

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The occurrence and assay of renin in human urine
As reported by Brown et al. (Lancet 2: 709, 1964), an enzyme is found in urine which is capable of reacting with renin substrate at pH 7.5 to form a peptide pressor substance. Since this material is not dialysable, is heat labile, and is susceptible to inactivation by renin-specific
antibody, it is indistinguishable from plasma renin. The finding of large amounts of renin in urine at concentrations comparable to those found simultaneously in plasma raise important diagnostic and physiological implications. In the present study, however, evidence has been presented that the high renin concentrations in normal urine reported previously are the artifactual result of the interfering action of pepsin forming pepsitensin from renin substrate. Appropriate control experiments showed the recovery of renin to be effectively complete. With the methods used in this study, the renin concentration in normal random male urine was found to average only 7% of the plasma concentration. It appears that further studies of urinary renin activity will need to take the interfering action of pepsin into account. The relationship between urinary renin and plasma renin activities in situations where plasma renin titers are elevated remains unelucidated.

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Studies on the role of angiotensin in experimental renovascular hypertension: An immunologic approach
The effect of immunization of rats against angiotensin using an angiotensin-carbodiimide-albumin complex was assessed in rats made hypertensive with DOCA and saline administration, animals made hypertensive by clipping one renal artery, and others made hypertensive by clipping one renal artery and removal of the contralateral kidney. Prior to immunization, DOCA rats showed an exaggerated response to both angiotensin amide and angiotensin acid. Those made hypertensive by clipping one renal artery showed depressed responses, while those with renal arterial hypertension and contralateral nephrectomy showed a normal response to angiotensin amide and depressed responsiveness to angiotensin acid. These findings suggested that different mechanisms might be involved in the three types of hypertension under study. Following immunization, none of six rats made hypertensive with DOCA and saline, and none of five mock immunized

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animals showed a depression of blood pressure after immunization. Of 20 rats with renal hypertension, 11 were shown by radio-immuno assay to have a significant antibody titer. Of these 11 rats, seven showed a persistant reduction in blood pressure, while three of the remaining four had had a significant fall in pressure earlier after immunization. None of the nine renal hypertensive rats without demonstrable antibodies had a reduction in blood pressure at the time of antibody determination and only one had demonstrated a reduction in blood pressure earlier. The renal hypertensive rats all were refractory to angiotensin injected after immunization. From these findings, the authors conclude that angiotensin plays a primary role in acute and chronic hypertension in rats with renal arterial constriction.

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The prevention of acute renal failure in the rat by long term saline loading: A possible role of the renin-angiotensin axis
Numerous published reports suggest that the renin-angiotensin axis may play a significant role in the development of acute renal failure. This study was undertaken to determine whether renin
depletion modifies the development of glycerol-induced myohemoglobinuric acute renal failure in the rat. Rats receiving one percent saline instead of tap water for as little as two weeks have been shown to have a very low renin content, both in kidney tissue and peripheral blood. Animals in this study were placed on the saline regimen for some two months to assure renin depletion. Water drinking rats and animals receiving 10 percent glucose solution in place of tap water served as controls. These rats were than given 10 ml/kg of 50% glycerol injected intramuscularly and developed comparable degrees of myohemoglobinuria. The BUN concentration of water and saline drinking rats 24 hours after glycerol injection was 75 ± 14 mg% and 43 ± 6 mg% respectively. Forty-eight hours after injection, water drinking rats had a BUN of 94-98 mg% while glucose drinking animals had a mean BUN concentration of 112 mg%. The BUN of saline drinking animals was not statistically different from that of normal control animals, indicating that the slight rise in BUN observed at 24 hours represented only transient renal insufficiency. Although it is unproved that the suppression of renin activity was responsible for the impressive degree of protection imparted by chronic saline loading in this study, the results lend strong support to that possibility. While other features associated with chronic saline loading, e. g., alterations in plasma volume, serum sodium concentration, urine volume, and other parameters studied in these experiments might be implicated, the results of control experiments made these unlikely causes of the protection observed. It is suggested that depletion of renin associated with chronic saline loading may have played a protective role and that the renin-angiotensin axis may be a potent factor in the development of glycerol induced acute renal failure in the rat.

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Book Reviews – Livres nouveaux
Progress in nephrology.
Comptes rendus, fort bien présentés, d’un Symposium où ont été exposés les travaux de près de 200 chercheurs. L’abondance des titres explique que certains sujets aient été déjà présentés et que d’autres n’aient pas encore atteint la maturité nécessaire à une réunion Internationale. Mais ces quelques faiblesses sont compensées et adoublé, par l’intérêt de certains chapitres tels ceux consacrés aux transferts de l’urée, à l’anatomie pathologique extrarénale de l’urémie et à l’étiologie toxique de quelques néphropathies. G. Richet
Bases statistiques pour la recherche médicale et biologique.
F. Gremy, D. Salmon:
L’ouvrage est divisé en deux parties, les principes du calcul statistique et l’application à des problèmes pratiques. Un effort particulier a été fait pour la clarté de l’ouvrage qui le rend très pédagogique. Chaque chapitre est divisé en paragraphes bien séparés, et terminé par un resume concis. Les formules mathématiques essentielles sont mises en valeur. Les exemples sont tires de travaux reals auxquels ont contribué les auteurs. Ce livre sera certainement très utile au biologiste en lui per-
mettant de résoudre au mieux les problèmes rencontrés de manière courante en experimentation. R. Ardaillou


Traité ayant bénéficié de la collaboration de physiologistes et de pharmacologistes mondialement reconnus, rédigé en allemand ou en anglais selon les chapitres. L'originalité de cet ouvrage est de rassembler des notions précises sur le mode d'action, enzymatique ou moléculaire, des diurétiques, notions difficiles à trouver ailleurs. G. Richet


Comptes rendus en allemand d'un symposium sur les diurétiques, tenu en octobre 1968. Le délai de parution enlève une partie de l'intérêt, le sujet étant sans cesse mouvant. G. Richet