RENAL ENDOCRINOPATHIES

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A hormone is a substance which is produced by specific cells in response to various physiological stimuli and that elicits a set of specific physiological responses from target organ(s). Using this definition, it is clear that there are numerous disease states in which the kidney, as an endocrine organ, has a central role in the pathogenesis of the disease process. The "renal endocrinopathies" can be divided conveniently into imbalance states resulting from abnormal production of hormones made by the kidney (erythropoietin, 1,25-dihydroxy vitamin D_2, renin-angiotensin) or abnormal responses by the kidney to hormones synthesized elsewhere (mineralocorticoids, parathyroid hormone, antidiuretic hormone). Prostaglandins do not satisfy the classical definition of a hormone since the prostaglandins with renal effects are synthesized, degraded and have their action in the kidney per se. Prostaglandins are more accurately considered as "messengers", and therefore, they will not be considered in the present review.

Hormones Produced by the Kidney

Erythropoietin

Erythropoietin (EPO) is a substance that is formed in response to hypoxic and anemic stress to accelerate the rate of red cell formation. The biochemical events between the interaction of EPO with its bone marrow receptor on ultimate increase in erythropoiesis are incompletely understood. The structure of EPO has not been established, but it appears to be a glycoprotein. Its molecular weight probably is in the neighborhood of 32,000 $\pm$ 10,000. This is a soft figure since even the present

preparations of serum or tissue EPO are impure as evidenced by numerous electrophoretic bands. However, human urinary EPO has been recently purified to apparent homogeneity. It is some 100 X more potent with respect to biologically active units per mg of protein than previous preparations. Its molecular weight as determined by SDS-gel electrophoresis is 39,000. A radioimmunoassay has been developed recently for the homogeneous preparation of human urinary EPO.

There are two basically different schools of thought with respect to the origin of erythropoietin. One such school feels that kidney, in response to a stimulus, elaborates erythrogenic factor (REF), which in turn activates an inactive normally circulating protein resulting in the formation of EPO. In support of this theory are those studies which show the absence of REF and EPO in kidneys during early hours of hypoxia while the serum values of REF rise prior to the rise of serum EPO. Further support of this theory has been the failure of a number of investigators to find erythropoietin in normal kidneys. Also in support of the extrarenal production of EPO are those studies which have demonstrated the presence of EPO levels in nephrectomized rodents and man. In most of these studies the EPO titers became evident only after intense stimulation.

The second school has maintained that erythropoietin is produced by renal tissue <u>per se</u>. This concept received its initial major support when it was demonstrated that kidneys removed from 3 hr hypoxic rabbits generated significantly more erythropoietin than kidneys from non-hypoxemic rabbits when perfused with serum free tissue culture mixture. More recently significant amounts of EPO have been extracted from the kidneys of normal rats, dogs, and cattle. It is significant that care

was taken in these studies to carefully wash the kidneys free of serum to obviate the potential criticism that a renal factor was acting on serum to convert a previously inactive molecule into EPO. These latter studies put forth strong evidence favoring the kidney as the major site of erythropoietin production. Failure of previous studies to demonstrate EPO in kidneys from normal animals may reflect variations in assay techniques for EPO. In the most recent study EPO was assayed from kidneys by three independent and different bioassay techniques. Presently studies are not available to localize which renal cell type is responsible for synthesis of EPO.

Though animal studies suggest that the hematocrit can be increased by the intravenous administration of erythropoietin-like material, and a number of patients have been reported with nephrogenic polycythemia, nevertheless, erythropoietin research has not advanced to the level yet where it can be of benefit clinically to those patients with anemia on the basis of low erythropoietin levels.

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Vitamin D_3

A renal metabolite of vitamin D_3, 1,25-dihydroxy vitamin D_3 (1,25-$(OH)_2D_3$), must be classified as a hormone since its primary function is to mobilize calcium from the bone and increase calcium reabsorption from the intestine. The synthesis of 1,25-$(OH)_2D_3$ from precursor 25-OH D_3 is regulated by the activity of D_3-1α-hydroxylase. The exact cell type where D_3-1α-hydroxylase is produced is not known. However, it is known that 1,25-$(OH)_2D_3$ is produced by some component of renal cortical cells.

The factors which regulate the synthesis of D_3-1α-hydroxylase has been a subject of a number of recent papers. There now seems to be general agreement that parathryoid hormone (PTH) and phosphate directly modulate the activity of D_3-1α-hydroxylase. Both PTH and hypophosphatemia increase the synthesis of 1,25-$(OH)_2D_3$ via regulation of D_3-1α-hydroxylase. Other factors have been postulated to regulate the level of D_3-1α-hydroxylase, but none have been proven to have a direct effect. It now appears that the serum level of calcium modulates the D_3-1α-hydroxylase via the intermediary effect on PTH. Also it is not clear, although a recent study suggests, whether prolactin and growth hormone effect the synthesis of 1,25-$(OH)_2D_3$ directly or whether these effects are in some way expressed through variations in serum PTH or phosphate concentrations.

Once the 1,25-$(OH)_2D_3$ is released into the blood stream it has two main target tissues. In the small intestine it promotes net reabsorption of calcium. The exact nature of interaction of 1,25-$(OH)_2D_3$ with the small intestine and its effect on calcium translocation have received much recent attention, but the final details have not been elucidated. It is known that 1,25-$(OH)_2D_3$, and not its precursors, can be localized

in nuclear and chromatin fraction of intestinal cells. There appears to be a nice correlation between the degree of saturation of chromatin binding sites and the level of net calcium transport. It has been suggested that an increase in intestinal 1,25-$(OH)_2D_3$-chromatin fraction leads to an increase in the synthesis of RNA, which then increases the synthesis of those proteins which are responsible for calcium transport. In addition to 1,25-$(OH)_2D_3$ increasing calcium transport, it has been shown that this same hormone increases phosphate transport out of the small intestine. 1,25-$(OH)_2D_3$ also causes a net decrease in bone calcium and phosphate but the mechanism(s) by which this is accomplished has not been determined in the same detail as those factors which lead to decreased calcium and phosphate transport across the small intestine. It is known, however, that in chronic renal disease with decreased 1,25-$(OH)_2D_3$ there is reduced skeletal response to PTH and defective mineralization of osteoid.

Though many symptom complexes and disease states can be either directly or indirectly related to a decrease in the active form of vitamin D, perhaps the most incapacitating set of symptoms are related to bone metabolism. A decrease in 1,25-$(OH)_2D_3$ is assocated with a wide spectrum of bone diseases (rickets, osteomalacia, osteopenia). Recent studies suggest that treatment of patients with renal osteodystrophy with 1,25-$(OH)_2D_3$ or its active, less expensive analog, 1α-OH-D_3, may be useful in improving the symptoms and signs of the bone involvement.

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Renin-angiotensin system

The current state of knowledge favors the view that the juxtaglomerular apparatus has the necessary biochemical machinery for the synthesis of renin, renin substrate (angiotensinogen), and the necessary converting enzyme(s) to degrade angiotensin I to octapeptide angiotensin II. Angiotensin II has a number of target organs including the adrenal cortex (stimulates aldosterone release); dipsogenic center (promotes thirst); pituitary gland (increases release of ADH); and smooth muscles (increases contractility). Thus it is clear that angiotensin II is a hormone with various target organs.

It is also clear that angiotensin has renal effects as well. The renal vasculature is quite sensitive to the vasoconstrictor effects of AII. The response to AII may be enhanced by salt loading while it is reduced by salt depletion, renal artery stenosis, and pregnancy. The vasoconstrictor activity of AII could be of physiological importance. However, the evidence seems to suggest that AII does not have as pivotal a role in the autoregulation of renal blood flow since autoregulation occurs in kidneys which have been depleted of renin. Also the role of

AII in the regulation of glomerular filtration rate by the tubuloglomerular feedback mechanism is controversial. The recent biochemical, physiological and histological studies are most consistent with the view that as the rate of distal delivery of fluid is increased there is activation of mechanisms which lead to afferent arteriole vasoconstriction, which in turn leads to a decrease in SNGFR. Since AII is produced in the macula densa, and since AII is a potent local vasoconstrictor, it is attractive to postulate that AII either directly or indirectly is responsible for the afferent vasoconstriction as originally suggested by Thurau and coworkers. There is no convincing data to suggest that AII has a direct nonhemodynamic effect on salt and water transport although it is possible that part of the antinatriuresis seen with AII can be explained by AII stimulating the renal release of prostaglandins, while part of the kaliuretic effect probably is related to secondary hyperaldosteronism.

A number of patients have been recognized recently with renin secreting tumors of juxtamglomerular cell origin. The syndrome resulting from a specific increase in renin and angiotensin presents itself with typical findings. Patients generally have been well except for the gradual development of hypertension in the range of 190-210/100-140. Aldosterone secretion rates are high, and serum potassium levels are moderately reduced (general range of 2.6-3.5 mEq/L). The localization of the tumor can be made by differential renal vein renin assays. It is not unusual to have a complete recovery with nephrectomy from the metabolic consequences of renin secreting tumors.

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Hormones Where the Kidney is the Target Organ

Mineralocorticoids

Aldosterone is the principal human mineralocorticoid hormone. Its production and release is stimulated by angiotensin, hyperkalemia, and ACTH. In contrast to previous concepts, it is doubtful that physiological variation in sodium concentration influences the synthesis of aldosterone though a decrease in total body sodium will increase the production of aldosterone as mediated through volume controlled increase in angiotensin release.

Aldosterone has three separate direct effects on the renal tubule epithelium. Most of the work has examined the effect of aldosterone on sodium transport. Here the direct evidence suggests that the main target tissue for aldosterone is the cortical collecting tubule. The evidence is two-fold. First, cortical collecting tubules harvested from rabbits which have received DOCA have a much more negative potential than do tubules from adrenalectomized rabbits. Second, cortical collecting

tubules from rabbits which have been pretreated with DOCA or in which the endogenous mineralocorticoids are stimulated, have a higher net efflux of sodium as determined from isotopic fluxes than do tubules harvested from adrenalectomized rabbits or rabbits which have suppressed mineralocorticoid levels. No convincing evidence exists to demonstrate that aldosterone affects sodium transport across other nephron segments. The second general effect of aldosterone is its ability to modulate chloride transport across the cortical collecting tubule. When cortical collecting tubules are harvested from DOCA-treated animals they may act as diluting segments. From the simultaneus measurements of transepithelial PD it can be determined that mineralocorticoids affect chloride transport as well as sodium transport. The third general area where aldosterone has a direct effect on the kidney is its ability to modulate the hydro-osmotic effect of vasopressin. Without aldosterone cortical collecting tubules are unable to respond normally to supramaximal amounts of ADH while aldosterone is able to restore fully to normal the ability of the collecting duct to respond to ADH. This may partly explain the concentration defect seen in mineralocorticoid deficient states. It is also known that aldosterone has an effect on acid-base balance but direct studies have not elucidated the mechanism of increased ammonia and hydrogen excretion as caused by hyperaldosteronism.

Primary aldosteronism (Conn's syndrome) is a discrete clinical entity which is characterized by hypertension and hypokalemic alkalosis. Edema is not a clinical feature of this syndrome since patients are analogous to the "DOCA escape" state which has been well described in experimental animals. The hallmark laboratory finding is the combination of hypersecretion of aldosterone with hyposecretion of renin. Primary

aldosteronism is an uncommon cause of hypertension. When it does occur, surgery is the treatment of choice for a discrete unilateral adenoma while spironolactones are often effective for those patients with bilateral adrenal hyperplasia.

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Parathyroid Hormone

Parathyroid hormone (PTH) is synthesized and stored in the parathyroid gland as a precursor proparathyroid hormone. The synthesis of biologically active PTH from pro-PTH is largely governed by intracellular concentrations of calcium and magnesium. Also, in the absence of changes in calcium or magnesium concentrations, hormones such as glucagon, calcitonin and beta adrenergic stimulants may increase the release of PTH. PTH has three primary target organs: bone (stimulates osteoclastic reab-

sorption and depresses osteoblastic activity); intestine (increases calcium reabsorption which may be direct or mediated via vitamin D); and kidney (to be discussed below).

Parathyroid hormone has a number of different renal effects. The effect on phosphate transport has been examined most extensively. It is now quite clear that PTH directly inhibits phosphate transport across the proximal tubule though the magnitude of the effect on convoluted vs straight portion may be dependent on the species. A number of investigators have also demonstrated significant PTH responsive phosphate transport beyond the surface accessible distal tubule. Thus it is evident that PTH exerts its phosphaturic effect on both the proximal and distal nephron segments. The data with respect to the effect of PTH on the transport of calcium is less clear. It is well appreciated that hyperparathyroid patients have hypercalciurea. The hypercalciurea occurs in spite of increased net calcium reabsorption by the nephron. Several laboratories have attempted to localize the site of the PTH effect on calcium reabsorption. Early micropuncture studies suggested that PTH has its effect on segments beyond the surface distal tubule punctures. More direct recent in vitro microperfusion studies have shown that PTH does not influence calcium transport out of the cortical thick ascending limb of Henle but does enhance calcium transport out of the distal convoluted tubule and cortical collecting duct segments. Hypercalciurea occurs in spite of increased distal reabsorption of calcium because the increased filtered load of calcium exceeds the increased tubular transport capacity of calcium. The effects of PTH on bicarbonate transport also has been a subject of significant interest. There seems to be general agreement that fractional excretion of bicarbonate is increased in chronic as well

as acute hyperparathyroidism. This would be in agreement with the not too infrequent observation that hyperchloremic acidosis is seen in patients with hyperparathyroidism. The bulk of current data suggest that PTH decreases bicarbonate and volume reabsorption in the proximal tubule, but these findings are not firm due to difficulties inherent with previous bicarbonate measurements. Indeed a recent micropuncture study with a model of chronic hyperparathyroidism failed to see any effect on bicarbonate reabsorption in the proximal tubule after the animals were parathyroidectomized. Thus additional studies are required before it can be established whether PTH affects HCO_3 reabsorption across the proximal tubule.

Clinically the symptoms of primary hyperparathyroidism are mainly related to the kidney (nephrolithiasis) or bone (osteitis fibrosa cystica). The nephrologist, however, is usually confronted with symptoms associated with secondary hyperparathyroidism. The frequency of bone pain and arthralgias in patients with chronic renal failure is quite variable between hemodialysis centers and different countries. In Dallas, parathyroidectomies have been performed on 55 patients for bone pain out of a total chronic hemodialysis population of 580. Also soft tissue and visceral calcification is being appreciated at greater frequency. Whether the pruritis seen in chronic renal failure is related to calcinosis cutis is not known, but parathyroidectomy often is paliative. Presently we do not have a satisfactory medical treatment of patients with severe secondary hyperparathyroidism. Management of the early symptoms of secondary hyperparathyroidism include judicious use of active forms of vitamin D and careful dietary limitations of phosphate intake in association with the use of phosphate binding gels. Occasional dietary calcium supplementation is necessary.

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Antidiuretic Hormone

Antidiuretic hormone (ADH) is synthesized in the supraoptic and paraventricular hypothalamic nuclei. The synthesized ADH is then bound to "transporting" protein, neurophysins. The combination of neurophysin and ADH is then transferred by connecting axons to the posterior pituitary gland. The free ADH is then released into the circulation in response to various stimuli which include: increased osmolality, decreased volume, angiotensin II, hypokalemia and various neurotransmitters (α-stimulators increase ADH; nicotine increases ADH; mecamylamine and pentolinium inhibit the ADH rise due to osmotic stimuli). A proportional rise in serum osmolality seems to be the most potent stimulus for release of ADH.

The renal effects of ADH have been well examined. The main target of ADH is the collecting duct. The receptor for ADH is located on the basolateral surface. After attachment, adenylate cyclase is activated, which is responsible for the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cyclic AMP). Cyclic AMP then increases the luminal permeability to water although the exact mechanisms by which this is accomplished are not clear. Perhaps microtubules play a role in increasing the luminal water permeability as suggested by recent data. Cyclic AMP mediated water flow can also be increased by inhibition of phosphodiesterase, which is responsible for the degradation of cyclic AMP. Vasopressin also stimulates adenylate cyclase in the medullary and cortical thick ascending limb of Henle. However, the significance of this observation is not clear since it does not increase water movement across the thick limb of Henle. The hydroosmotic effect of ADH can be modulated by a number of factors. Perhaps the most important of these are the prostaglandins. Prostaglandin inhibitors increase the hydroosmotic effects of ADH with a resultant increase in water reabsorption which results in more concentrated urine, while states with increased prostaglandin synthesis have exactly the opposite effects on water movement. Vasopressin also has been shown to augment sodium transport across the collecting tubule although this effect is transient. These findings are in opposite direction as would be expected from clinical observations where patients with elevated ADH levels have increased fractional excretion of sodium.

The clinical features of patients with excess or decreased amounts of circulating ADH have been well characterized. The syndrome of inappropriate ADH secretion, SIADH, typifies the metabolic defect of patients with excess ADH. These patients present with decreased serum

sodium concentration, inappropriately concentrated urine and increased urinary sodium. The primary difficulty in making the diagnosis of SIADH is to determine whether the elevation of ADH is appropriate or not. Thus clinical states such as decreased effective volume, renal salt wasting, Addison's disease and use of various diuretics must be ruled out. There are a number of etiologies of SIADH which include a wide variety of tumors, pulmonary disorders and central nervous system disorders. At present there are no known direct inhibitors of ADH. The best approach to these patients would be a direct cure of the etiology of SIADH. This, however, is often not possible and therefore these patients will benefit from restriction of water intake coupled with liberal intake of salt. Some patients with SIADH have benefited from the oral use of lithium salts. However, more recent studies have shown that demeclocycline (600-1200 mg per day) is superior to lithium in the treatment of SIADH. The physiological basis for this treatment is that elevated levels of lithium and demeclocylcine inhibit adenylate cyclase.

The syndrome of vasopressin sensitive diabetes insipidus (DI) presents with findings diametrical to those of SIADH. In DI the hallmark of the syndrome is hypernatremia with inappropriately dilute urine. The syndrome occurs when 90% of the supraoptic nuclei are destroyed whether by surgical ablation, tumors, trauma, vascular accidents, or various infections. The treament in these patients is the administration of vasopressin as such, or one of the new long-acting vasopressin analogues, 1-deamino 8-D arginine vasopressin, DDAVP.

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APPENDIX

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TWO SCHOOLS OF THOUGHT WITH RESPECT TO BIOGENESIS OF ERYTHROPOIETIN

I. KIDNEY ⟶ Erythrogenin

Inactive Circulating Protein ⟶ Erythropoietin

II. KIDNEY ⟶ Erythropoietin

RENAL DISEASES WITH INCREASED ERYTHROPOIESIS-STIMULATING ACTIVITY

A. Non-Neoplastic

1. Solitary or multiple renal cysts
2. Polycystic disease
3. Hydronephrosis

B. Neoplastic

1. Hypernephroma
2. Adenoma

UNANSWERED QUESTIONS

1. Why should there be an overproduction of EPO into a cyst?

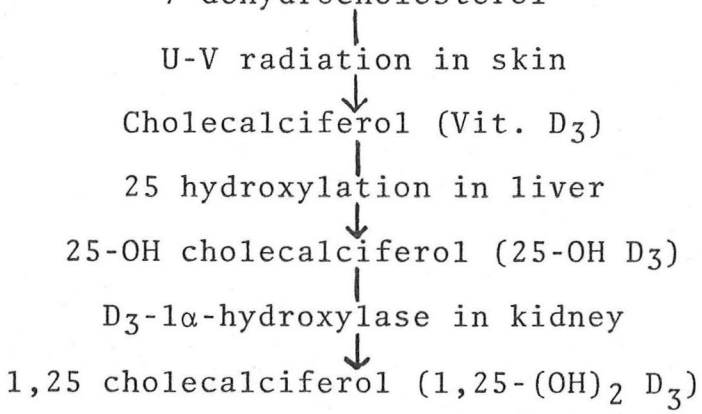
2. How does EPO get out of the cyst?

3. Is there some unidentified serum factor which regulates the release of EPO?

4. We now have 6 post-transplant patients with erythrocytosis - Why?

An eight month old boy was admitted to the hospital for evaluation of convulsions. Physical findings revealed retarded growth and findings consistent with rickets. He also had biochemical manifestations of vitamin D deficiency: hypocalcemia (6.0 mg%); hypophosphatemia (3.2 mg%); increased alkaline phosphatase activity (1527 μ/L; nl for this age group < 800 μ/L); hyperaminoaciduria; and radiological findings of rickets. Urine cyclic AMP excretion rate was markedly elevated, (38 nmol/mg Ca, upper limit of nl for this age group is 11.7 nmol/mg Ca). All of the pathologic findings were corrected by the oral intake of 2,700 IU vitamin D_2 daily for 4 1/2 months.

PRODUCTION OF METABOLICALLY ACTIVE VITAMIN D



FACTORS WHICH MODULATE D_3-1α-HYDROXYLASE

A. Direct Effect

   a. ↑ PTH → ↑ hydroxylase

   b. ↓ serum phosphate → ↑ hydroxylase

   c. ↑ growth hormone ? ↑ hydroxylase

   d. ↑ sex hormones ? ↑ hydroxylase

B. Indirect Effect

   a. ↓ serum Ca^{++} → ↑ PTH → ↑ hydroxylase

TARGET TISSUES OF $1,25(OH)_2 D_3$

A. Intestine

   1. Promotes calcium reabsorption

   2. Promotes phosphate reabsorption

B. Bone

   1. Necessary for permissive action of PTH

18 y/o male was admitted to University of Michigan Medical Center (Arch. Int. Med., 1972) for evaluation of hypertension (190-200/100-140) of five years duration. Apart from polydipsia/polyurea he had no other symptoms or abnormal physical findings. Abnormal laboratory findings included hypokalemia (3.1 - 3.8 mEq/L); alkalosis (HCO_3 = 26-38 mEq/L); elevated aldosterone excretion rates (44.1 µg/d which is 4X nl on 120 mEq Na diet); PRA and angiotensin were 2X in right as contrasted to left renal vein.

TARGET TISSUES OF ANGIOTENSIN

1. Adrenal cortex (stimulates aldosterone release)
2. Dipsogenic center (promotes thirst)
3. Smooth muscles (increases contractility)
4. Renal medulla (increases PGE_2 production)
5. Renal macula densa (regulates GFR)

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STIMULI OF ALDOSTERONE PRODUCTION AND RELEASE

1. Angiotensin
2. Hyperkalemia
3. ACTH

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SYNTHESIS AND RELEASE OF PTH

IS GOVERNED BY:

1. Calcium
2. Magnesium
3. Glucagon
4. Calcitonin
5. Beta Adrenergic Stimulants

RENAL EFFECTS OF PTH

1. Inhibits phosphate transport
   a. proximal tubule
   b. distal tubule
2. Enhances calcium reabsorption
   a. distal convoluted tubule
   b. cortical collecting duct
3. Increases fractional excretion of bicarbonate

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