The kidney as an endocrine organ

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Information seulement

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The kidney as an endocrine organ

Summary. Three hormonal substances which can be synthesized within the kidney (renin, prostaglandins, and erythropoietin) are discussed with reference to site of production, mode of action, clinical importance and the relationship between these substances. Finally, the close connexion between the endocrine functions of the kidney and the adrenal gland is described.

It is not commonly known that the kidneys in addition to their excretory capacity also perform an important endocrine function. In the following paper, three humoral substances will be discussed which can be synthesized in the kidney, and whose biological activities are of importance to the organism. These substances are: renin, the prostaglandins, and erythropoietin.

Renin

Renin is a nondialyzable protein with a molecular weight of appr. 45,000 which is synthesized within the juxtaglomerular apparatus.
of the kidney. The latter consists of the afferent and the efferent arterioles, the macula densa — a cell cluster at the base of the distal tubule —, the granulated juxtaglomerular cells which are partly located in the walls of the afferent arterioles, the non-granulated juxtaglomerular cells which are designated also as "polkissen" or "apparatus of Goormaghtigh", the mesangium cells located between the afferent and the efferent arterioles, and finally of the adrenergic and probably also the cholinergic nerve endings (36).

Renin originates most likely within the juxtaglomerular cells where it was demonstrable by immunofluorescence microscopy. The activity of this enzyme is being tested in vivo on hand of the rising blood pressure in the rat. During recent years it has become possible to measure directly, with the aid of radio-immunological methods, the amount of angiotensin formed by renin.

Renin acts as peptidase by splitting off four amino acids (leucine, valine, tyrosine, and serine) from the tetradecapeptides, the constituents of the angiotensinogens formed in the liver, thus producing the decapptide angiotensin I. The latter is being converted, mainly in pulmonary circulation (by a converting enzyme), into the octapeptide angiotensin II which is fairly rapidly catabolized by nonspecific angiotensinases into inactive peptides (36).

The actions of angiotensin II (Table 1) involve the autonomic nervous system, and the catecholamine metabolism in that angiotensin II by way of central and peripheral sympathetic stimulation causes the blood pressure to rise, and releases epinephrine and norepinephrine from the adrenal medulla as well as from the peripheral storage terminals (33, 34).
Table 1. Effects of angiotensin II

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<th>1. Autonomic nervous system and catecholamine metabolism:</th>
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<td>- Increase of central and peripheral sympathetic blood pressure;</td>
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<td>- Release of epinephrine and norepinephrine from the adrenal medulla and the peripheral storage terminals.</td>
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<td>2. Heart and circulation:</td>
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<td>- Increase of resistance in the peripheral arteries;</td>
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<td>- Increase of central venous pressure;</td>
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<td>- Decrease of pulse rate and cardiac output.</td>
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<td>3. Kidney:</td>
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<td>- Anti-natriuretic, anti-kaliuretic, and anti-diuretic in normotonic individuals;</td>
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<td>- Natriuretic, kaliuretic and diuretic in hypertensive patients, and in patients with secondary aldosteronism.</td>
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<td>4. Adrenal:</td>
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<td>- Stimulation of aldosteron production.</td>
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<td>5. Metabolism:</td>
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<td>- Increase of serum glucose;</td>
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<td>- Increase of free fatty acids and glyceride in serum.</td>
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In the cardiovascular system, angiotensin II elicits increased resistance in the peripheral arteries, elevation of the central venous pressure, and the reflectory decrease of pulse rate and cardiac output (36).

In normotonic individuals, anti-natriuresis, anti-kaliuresis, and anti-diuresis is observed after administration of angiotensin II, whereas in hypertensive patients, and in patients with secondary hyper-aldosteronism, natriuresis, kaliuresis and diuresis are demonstrable (36).
The metabolic effects of angiotensin II consist of increased glycogenolysis and probably also lipolysis with augmentation of glucose, free fatty acids and glyceride levels in the serum.

An important function of angiotensin II is the stimulation of aldosterone production in the zona glomerulosa of the adrenal cortex. Here, similarly to the other stimuli (potassium and ACTH*), it participates at a very early stage in aldosterone biosynthesis, namely already in the conversion of cholesterol into Δ5-pregnenolone. Another effective stimulus for aldosterone formation is sodium deficiency which, by way of increased release of renin or angiotensin, and also by direct participation in the transformation of corticosterone into aldosterone, can influence the biosynthesis of this hormone (25).

At present, opinions still differ as to the regulation of renin secretion. Five factors in all are being held responsible for the release of renin (31, 36):

1. Baroreceptors, located in the walls of the afferent arterioles, which react to pressure fluctuations during renal perfusion;

2. Chemoreceptors, located at the macula densa, which respond to changes of sodium concentration in the predistal tubular urine, or in the cells of the macula densa;

3. Volume receptors, presumably located in the ventricles, the large veins and arteries, or in the kidneys or the vicinity of the macula densa;

4. Neural stimuli (e.g., sympathetic tone, catecholamine level;

5. A renin-releasing hormone.

*ACTH = adrenocorticotropic hormone
Experimental as well as clinical findings can be cited for all these renin secretion-stimulating factors.

For clarification of the role played by the renin-angiotensin-aldosterone system, it is essential to relate to those diseases which manifest changes within this system (22). Such diseases cannot be discussed in detail here (cf. 22). However, it should be pointed out that the renin-angiotensin-aldosterone system is stimulated especially by loss of sodium, potassium or water (24, 27-30, 37, 39) as it occurs in Addison's disease, the Bartter syndrome, diabetes insipidus, hemorrhage, or upon reduction of perfusion pressure in the kidney as well as of the blood circulation in the renal cortex (35, 46) which is the case in renovascular hypertension, and in accelerated or malignant hypertension; conversely, suppression of the renin-angiotensin system or also of aldosterone can be observed (35, 46) with positive sodium and water levels (e.g., in primary hyperaldosteronism, Cushing's syndrome, pseudo Conn's syndrome). These facts suggest that renin activity is closely related to arterial blood pressure as well as to sodium and water metabolism. It has been attempted therefore to relate the extent of plasma-renin activity to the arterial pressure, the sodium concentration in serum and urine, and to the plasma volume. However, in this manner, completely divergent correlations can be established between plasma-renin activity on the one hand, and each of the four factors mentioned (43). For example, in renovascular hypertension, renin concentration and blood pressure are increased; with Conn's syndrome, there is hypertension, but renin is diminished; the latter is elevated in Addison's disease while blood pressure is in most instances
decreased; and in Parkinson's disease, low renin content and low 
blood pressure may coincide (22). Similar interrelations exist with 
respect to potassium concentration in serum and urine, and partly also 
in regard to plasma volume. On the basis of our own investigations 
and the findings of other authors we nevertheless favor the opinion 
that the volume plays a very important part as the regulating factor 
in the renin-angiotensin-aldosterone system (31, 32, 43).

Thus evaluating the possible significance of the renin-angio-
tensin-aldosterone system, three characteristics can be distinguished 
(after Lee):

1. The system as hypertensive-provoking factor: e.g., reno-
vascular hypertension, hypertension due to diseases of the parenchyme 
or to renal tumors, primary hyperaldosteronism;

2. The system as hypertensive-aggravating factor: e.g., accel-
erated or malignant hypertension, pheochromocytoma;

3. The system as homeostatic factor: e.g., primary hyperaldo-
steronism, Addison's disease, edema, hemorphages, Bartter syndrome.

Of definite importance is the third property, namely the homeo-
static factor which is concerned with stabilizing sodium levels and 
plasma volume. Viewed from this aspect, the first two factors may 
even be possibly integrated with the third because, due to the changes 
in renal arteries and arterioles that occur in renovascular and mali-
gnant hypertension, a disturbed homeostasis is being simulated which pro-
vokes the kidney into excessive renin production.
It is therefore our opinion that renin or the renin-angiotensin-aldosterone system fulfills a vital regulating function in sodium and water metabolism in that it mainly serves the maintenance of the volume (probably of the effective, circulating blood volume), and in that it may elicit arterial hypertension as a consequence of misinformation received by the kidneys or the juxtaglomerular apparatus (38).

Prostaglandins

The prostaglandins belong to a hormonal system which has been investigated more closely only in recent years. BERGSTROM et al. (4) succeeded in isolating prostaglandins, and in clarifying their structure; presently, sixteen such substances are known. The prostaglandins are unsaturated cyclic fatty acids and their presence has been established in diverse organs such as the brain, iris, thymus, heart, lungs, liver, pancreas, kidneys, prostate, and uterus. Their biological activities are extremely versatile (40). For example, they increase the pulse rate and the cardiac output, diminish the peripheral vascular resistance, reduce resistance in the bronchial system and can therefore be used therapeutically in asthma cases, they decrease the arteriovenous oxygen difference, influence norepinephrine release, and increase the activity of nonvascular smooth muscles so that they can be utilized to induce abortion. Furthermore, prostaglandins affect carbohydrate and lipometabolisms in various ways, and influence histamine, heparin, and serotonin liberation as well as the thrombocyte
aggregation (40). In these respects, the effect of the individual prostaglandin can vary greatly from that of another; for example, the prostaglandins PGA and PGE are capable of lowering the arterial blood pressure, while the prostaglandins PGF may induce hypertension.

In the kidney, prostaglandins are most probably synthesized in the osmiophilic lipid granula of interstitial cells of the renal medulla (17). At the renal level they induce natriuresis, kaliuresis, and diuresis, increase PAH- and urea clearance, block the water permeability of the tubular cells which is increased by antidiuretic hormones, induce shifting of the corticomedullary blood distribution, and stimulate renin secretion (Table 2). We were able to observe the last-mentioned effect in the dog after prostaglandin E\textsubscript{1} administration (Fig. 1) (44, 45). The effect of the prostaglandins is possibly mediated in the same manner as that of other hormones, namely by the adenyl cyclase system (6, 40).

It has been discussed whether the prostaglandins are to be considered as a vasodepressor principle of the kidneys. According to present opinion, the kidneys can cause hypertension not only because of increased diminished sodium and water excretion, or production of vasopressor substances such as renin, but also by reduced synthesis of vasodepressor agents (46). The latter possibility is greatly substantiated mainly by the occurrence of hypertension after bilateral nephrectomy which is known as 'renoprival hypertension'. It is interesting that the development of renoprival hypertension can be inhibited in experimental animals by prostaglandins, and that these substances are capable of markedly lowering the blood pressure which, in experimental renal hyper-

*) PAH = para-aminohippuric acid
tension, is caused by constriction of a renal artery, or by perinephritis (18). Furthermore, prostaglandin infusion markedly lowered the blood pressure of a patient with accelerated refractory hypertension (15).

Table 2. Effects elicited by prostaglandins upon the kidney

1. Natriuresis, kaliuresis, diuresis;
2. Increased PAH- and urea clearance;
3. Blockade of the water permeability (increased by antidiuretic hormone) of the tubular cells;
4. Shifting of corticomedullary blood distribution;
5. Stimulation of renin secretion;
6. Reduction of ureter peristalsis.

It is furthermore of interest whether the prostaglandins might be identical with a natriuretic factor. The natriuretic hormone in question is considered --next to the glomerular filtration rate and to the mineralocorticoid activity— as "the third factor" and thus as important for the regulation of sodium excretion (13). It is said to cause, for example, the renal escape phenomenon in primary aldosteronism and, due to reduced synthesis, to contribute to the development of edema. Since the prostaglandins also possess natriuretic and diuretic properties, and probably originate just like the natriuretic factor in the kidney (13), and since both substances inhibit the renal extraction
of PAH (40), it is tempting to assume their identity. However, this presumption is contradicted by the fact that the prostaglandins consist of dialyzable unsaturated fatty acids and have a molecular weight below 4,500 (15), whereas the natriuretic factor represents a thermoresistant, nondialyzable protein with a molecular weight between 5,000 and 70,000 (19). However, it was also reported recently that the natriuretic substance is dialyzable and that its molecular weight was established as being below 3,000 (5a).

The antagonism that exists between the prostaglandins and the renin-angiotensin system seems to be worth mentioning (40, 45). Angiotensin II increases peripheral vascular resistance, lowers the pulse rate as well as the cardiac output, stimulates norepinephrine release, diminishes (at least in normotonic patients) natriuresis and diuresis, and elevates the glucose level in the blood. By contrast, prostaglandins diminish the peripheral resistance, increase pulse rate and cardiac output, decrease norepinephrine stimulation, increase natriuresis and diuresis, and promote glycogenesis. In addition, PGE₁ can increase renin secretion, while angiotensin II diminishes plasma activity. As regards sites of origin and catabolism, there are also marked dissimilarities between renin and angiotensin on the one hand, and the prostaglandins on the other. Renin is produced in the renal cortex, and angiotensin II is being synthesized during pulmonary circulation of the blood, whereas the prostaglandins can be formed in the renal medulla and are thus subject to being rapidly metabolized in the lesser circulation. Which degree of importance should be attached to the biologic antagonism between angiotensin and the prostaglandins has not yet been clarified.
Erythropoietin

The third of the important hormonal substances that can be synthesized in the kidney is erythropoietin (32). It most probably originates in the granulated juxtaglomerular cells, as does renin. However, certain findings also indicate that the renal erythropoietic factor can be synthesized also in the glomerular capillaries or the tubular cells. Erythropoietin can be produced extrarenally as can renin; similarly to the action of the latter does the renal erythropoietic factor lead to the true hormone, erythropoietin, only by way of its enzymatic influence upon pro-erythropoietin, a substrate synthesized in the liver (10, 14). So far, attempts to obtain completely pure extracts of either erythropoietin or renin have not been successful. The molecular weight of the former lies between 27,000 and 70,000 (9).

It is the function of this hormone to regulate the activity of the red bone marrow. It has not yet been clarified whether erythropoietin causes the differentiation of a common stem cell of erythrocytes, leukocytes, and thrombocytes by erythropoiesis, or whether it stimulates hemoglobin synthesis in already slightly differentiated cells. Several findings seem to indicate that erythropoietin leads to an increase in messenger RNA, which promotes hemoglobin synthesis in immature cells. The consequences are macrocytosis and augmentation of the hemoglobin content in erythrocytes. The migration of reticulocytes from the marrow into the blood is accelerated by erythropoietin (9).

Erythropoietin as well as renin are subject to being regulated by neural impulses (3, 47), and the activity of both these humoral substances is influenced by stimulators and inhibitors (14, 20). Several
hormones (e.g., growth hormone, androgens, and thyroid hormones) promote erythropoiesis, probably by way of erythropoietin stimulation, whereas estrogens are blocking the effect of erythropoietin (14).

Erythropoietin synthesis can be adequately stimulated by hypoxemia, most probably mainly by hypoxemia of those cells which synthesize erythropoietin (3). Accordingly, increased erythropoietin activity is noted especially in patients with chronic pulmonary or cardiac diseases (32), as determined by measuring the rate of uptake of radioactive iron by the erythrocytes in polycythemic mice. Furthermore, renal diseases can entail both increased as well as decreased erythropoietin production. Thus, renal tumors can produce erythropoietin either directly, or stimulate its synthesis through local hypoxemia due to vessel restriction. Upon renal hystolysis due to inflammatory processes, there is marked regression of erythropoietin activity with consecutive renal anemia (26). Similarly motivated increases or diminutions are observed also in renin activity (46). Furthermore, in patients with tumors (e.g., pheochromocytoma, adrenocortical adenoma), as well as in connection with a paraneoplastic syndrome (e.g., carcinoma of the liver) an increase in erythropoietin content is demonstrable in the serum (23, 32, 41), whereas in polycythemia vera the erythropoietin is diminished in most cases (9).

Fig. 2: Endocrine functions of the kidney
Fig. 3: Hormonal interrelations between kidney and adrenal gland.

Diverse similarities between renin and erythropoietin have already been pointed out. It should be added, however, that the results of several investigations speak in favor of a joint stimulation of renin and erythropoietin. For example, high values were found for both hormones in experimental renal infarcts (1), the rejection crisis of kidney transplants in rabbits (2), as well as in patients with renovascular hypertension (5), or the Bartter syndrome (12). We tend to believe that here the activity of both the stimuli for renin and for erythropoietin secretion coincided, namely the hypovolemia which diminishes circulation in the renal cortex, and local renal hypoxemia, so that both hormones, despite possibly having been stimulated at the same time, were stimulated by way of different mechanisms. This view has been strengthened by experimental findings, but also by our own investigations. Administration of a saluretic caused renin to increase, while increased adminis-
tration of sodium and DOCA* decreased renin without changing erythropoietin concentration (7). On the other hand, erythropoietin was increased upon reduced oxygen supply, or after cobalt injection, without any marked alteration of plasma-renin activity (7). We ourselves have observed in ten patients with primary or secondary polycythemia that renin activity was normal despite fluctuating erythropoietin levels (32), while in hypertensive patients we were unable to establish a clearcut correlation between plasma-renin activity and the indirect indications of the extent of erythropoietin concentration (42).

It can thus be established that the kidney is capable of synthesizing three important humoral substances which influence the sodium and water metabolism, the tonus of peripheral vessels, and erythropoiesis (Fig.2). Especially revealing seem to us the biologic correlations between these renal hormones and the hormones of the adrenal. Thus, angiotensin stimulates the adrenocortical aldosterone (25) and the catecholamines in the adrenal medulla (34) which can, in turn, increase renin production (47). Aldosterone and cortisol inhibit renin secretion by way of sodium and water retention (23), and possibly also by their direct effect upon the juxtaglomerular apparatus(11). The prostaglandins potentiate the effect of catecholamines (8) and possess, like cortisol, natriuretic and diuretic potencies (21, 44, 45). Finally, androgens increase the activity of the renal erythropoietic factor (Fig.3).

Thus, the production of such humoral substances as renin, prostaglandins, and erythropoietin by the kidney renders the latter capable of regulating the plasmatic and cellular constituents of the vessel contents as well as the tonus of these vessels, and to stabilize the cardio-

*) DOCA = desoxycorticosterone
vascular system especially in cooperation with the adrenal; it also maintains the homeostasis in the sodium and water metabolism. The renal as well as the adrenal hormones can react by themselves also through vascular and tubular foci upon the excretory functions of the kidneys (16, 23, 34, 36, 45) so that a close physiological relationship exists between the endocrine activity and the excretory functions of the kidney.

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33. The effect of angiotensin II infusions upon catecholamine excretion in the dog.

34. The epinephrine and norepinephrine excretion during angiotensin II infusion into the carotid artery of the anesthetized dog.

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