Editorial

Renal endocrinology: The new frontier

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It is obvious to every student of medicine that the kidney is essential for life. Its role in fluid and salt homeostasis, and in maintaining blood pressure is well known.[1] The physiologic role of the kidney, however, extends much beyond its excretory purpose. Its multiple endocrine functions, which are still being discovered and elucidated, are the focus renal endocrinology.

Renal endocrinology encompasses some of the most important aspects of hormone physiology and pathology. Surprisingly, though, this subject does not seem to have received due attention. Endocrine researchers, perhaps, have their hands full with the pandemic of diabetes and metabolic syndrome, or prefer to focus on the "classic" glands. Nephrologists, similarly, are busy with other renal disorders, which seem more "real" and life threatening than renal endocrine abnormalities.

It is difficult to separate the endocrine aspects of renal physiology from the science of nephrology, or the renal aspects of hormone structure and function from endocrinology. A focus on the subspecialty of renal endocrinology or endocrine nephrology, however, is certainly required, as it draws attention of medical practitioners to the oft missed, yet, essential details of this field. This issue of *IJEM* aims to achieve precisely this focus.

The kidney has multiple endocrine roles; it secretes various hormones and humoral factors: the hormones of the renin- angiotensin system (RAS), erythropoietin (EPO), and 1,25 dihydroxy vitamin D3. It also produces enzymes, such as kallikreins, which produce hormones in other, distant sites. The kidney is also an important producer of "local hormones" or autocrine and paracrine molecules, such as prostaglandins, endothelins, and adrenomedullin. Not only that, the kidney is the primary target organ for various hormones like aldosterone, angiotensin, and the natriuretic peptides.[1,2] It is also affected by other hormonal diseases. Nephropathy is well characterized in acromegaly, hyperparathyroidism, and diabetes, to name a few. Endocrinology and nephrology overlap in many other diseases, such as urolithiasis and certain genetic disorders.

The RAS is one of the most important aspects of renal endocrinology. While angiotensinogen is produced by the liver, and angiotensin is formed primarily in the pulmonary circulation, the proteolytic cascade of RAS begins with renin, which is released from the juxtaglomerular cells of the kidney, which has autocrine and paracrine effects. Apart from mechanical, tubular, and sympathetic signals which stimulate renin release, hormones also affect its production. Atrial natriuretic peptide (ANP) and vasopressin inhibit renin release, while angiotensin II, prostaglandin E2, and prostacyclin stimulate its release.[1-3] Thus, the kidney is a prime endocrine target organ, apart from stimulating hormone production in nonrenal sites.

Angiotensin-converting enzyme (ACE) is present in abundance in the proximal tubule brush border of the kidney, as well as other sites. ACE, also known as kininase II, plays a crucial role in the rate-limiting step of tissue (RAS) activity, and contributes to renal homeostasis.

The AT1 angiotensin receptors are expressed in the kidney, as well as other tissues, but the AT2 receptors are limited to the adrenal medulla, brain, and gonads. Through the AT1 receptors, the kidney again becomes an endocrine target organ. The significance of ACE extends far beyond RAS.

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Several workers have reported the association of ACE gene DD polymorphism with a higher risk of restenosis after coronary revascularization, and progression of renal disease, including diabetic nephropathy and IgA nephropathy.

The natriuretic peptides have been reviewed in detail in earlier issues of *IJEM*.[3] The kidney secretes another, less well-known, hormone called urodilatin, which is a form of ANP, extended at the N-terminal by four amino acids, and may act in regulating the tubular reabsorption in the distal nephron. The kidney is also one of the sites which produce C natriuretic peptide (CNP). The kidney is a target organ for these hormones as well. All three subtypes of natriuretic peptide receptors are expressed in the kidney. While GC-A and the clearance (C) receptors are found in the glomeruli, the GC-B receptor is present in the tubules. In general, the natriuretic peptides act like a mirror image of the RAS, and tend to antagonize the actions of RAS, both at systemic and local levels. The kidney therefore becomes a production ground, as well as a battle ground, for various hormones. Another important renal endocrine system is the kallikrein–kinin family, which includes kininogen, kallikreins, kinins, and kininases. Kininogen, synthesized in the liver, is degraded by kallikrein, in the kidney. This reaction leads to the formation of kinins, which act through B1 and B2 receptors. The B2 receptors are present in the kidney as well, and regulate renal salt handling: a high concentration of kininases in the proximal tubule prevents kinins from reaching the downstream nephron. However, kinin receptors are found in the collecting duct, and a paracrine role is proposed to explain their presence. The kidney also produces some amount of "nonrenal" hormones, such as adrenomedullin, a primarily adrenal medullary peptide, and the endothelins ET1, ET2, and ET3.[1,2]

A distinct aspect of renal endocrinology relates to the production of erythropoietin (EPO), and the regulation of erythropoiesis. EPO is produced in the interstitial cells of the renal cortex, near the base of the proximal tubule, in response to the sensing of oxygen deficiency. As chronic renal failure develops, EPO production falls, and "renal anemia" develops. EPO supplementation is an accepted form of hormone administration today. Controversies related to this have been highlighted in the current volume of *IJEM*.

Perhaps most attention has been paid to the wrongly named renal hormone, vitamin D, in recent years. Vitamin D is synthesized in the skin, upon exposure to near-ultraviolet light. The active form, 1,25(OH)2D which is the most biologically active metabolite, is synthesized in the mitochondria of renal proximal tubules. Another metabolite 24,25 (OH)2D is also formed in the kidney, as is 25,26(OH)2D. As discussed for other hormone families, the kidney is both a producer and target organ for vitamin D. 1,25(OH)2D decreases calciuria and phosphaturia by increasing electrolyte reabsorption at the level of proximal tubules. Vitamin D deficiency and excess have multiple clinical implications and these are discussed by various authors in this issue of *IJEM*.

The kidney is often affected by other endocrine diseases. Nephropathy is a distinct and well-characterized entity in diabetes mellitus. Other hormone abnormalities such as acromegaly, thyroid disorders, and hyperparathyroidism also affect the renal structure and function. These entities too form part of the study of renal endocrinology.

Growth and development in children, as well as nutrition are other areas of interest for renal endocrinologists. Appropriate hormonal treatment may restore normalcy. Similarly, fertility issues in patients with CKD, and also post-transplantation, deserve special attention by the renal endocrinologists.

The current issue of *IJEM* tries to bring together two dynamic and complementary superspecialties of medicine: nephrology and endocrinology. Exhaustive reviews, pioneering original articles, and interesting case reports showcase the wide spectrum and challenging vistas of renal endocrinology. Developments in diagnosis, semantics, and allied specialties are also discussed. The editors hope that this will encourage more original researchers in this field, not only in India, but across the globe.

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