Review Article

Reno-endocrinal disorders: A basic understanding of the molecular genetics

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ABSTRACT

The successful management of endocrine diseases is greatly helped by the complete understanding of the underlying pathology. The knowledge about the molecular genetics contributes immensely in the appropriate identification of the causative factors of the diseases and their subsequent management. The fields of nephrology and endocrinology are also interrelated to a large extent. Besides performing the secretory functions, the renal tissue also acts as target organ for many hormones such as antidiuretic hormone (ADH), atrial natriuretic peptides (ANP), and aldosterone. Understanding the molecular genetics of these hormones is important because the therapeutic interventions in many of these conditions is related to shared renal and endocrine functions, including the anemia of renal disease, chronic kidney disease, mineral bone disorders, and hypertension related to chronic kidney disease. Their understanding and in-depth knowledge is very essential in designing and formulating the therapeutic plans and innovating new management strategies. However, we still have to go a long way in order to completely understand the various confounding causative relationships between the pathology and disease of these reno-endocrinal manifestations.

Key words: Erythropoietin, molecular genetics, parathyroid hormone, renin, vitamin D

Introduction

The advancements in the medical field have been greatly propelled by the understanding of the molecular genetics and the basic nature of the disease. These modifications in the management have virtually enabled the ablation of the diseases which were once thought to be totally incurable. Majority of times, the approach has to be multidisciplinary in the appropriate management of the underlying pathology rather than just focusing on one target organ. The fields of nephrology and endocrinology are also interrelated to a large extent. Kidney performs several endocrine functions and secretes many hormones having diverse actions, for example, renin, erythropoietin (EPO), active form of vitamin D, and so on. Besides performing the secretory functions, the renal tissue also acts as target organ for many hormones such as antidiuretic hormone (ADH), atrial natriuretic peptides (ANP), and aldosterone. Understanding the molecular genetics of these hormones is important because the therapeutic interventions in many of these conditions are related to shared renal and endocrine functions, including the anemia of renal disease, chronic kidney disease, mineral bone disorders, and hypertension related to chronic kidney disease [Table 1]. The management of these pathological entities has changed substantially over the last two decades. The present review focuses on the molecular genetics of these reno-endocrinological interactions and the various therapeutic strategies.

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Endocrinal Functions of Renal Tissue

Besides performing the major functions of excretion of various metabolites, toxins, drugs, and urine, the role of renal tissue in the maintenance of endocrinological milieu is also immensely significant. Various hormones are regulated and secreted by the kidney which has a huge

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Table 1: Reno-endocrine disorder, related hormones, and their molecular and genetic basis

Reno-endocrinal disorder/dysfunction	Hormones involved	Molecular/genetic basis
Anemia	Erythropoietin	30.4 kDa glycosylated protein hormone *EPO* gene: 5.4-kb HindIII–BamHI fragment EPO receptor: Transmembrane receptor associated with tyrosine kinase Downstream molecules: JNK/p38 MAP kinase, JAK/STAT, and PI-3 kinase
Metabolic bone disease	Vitamin D Parathyroid hormone Disorders of calcium and phosphorus metabolism	Active vitamin D: $1,25(OH)_2D$ Enzyme: 1α-hydroxylase (CYP27B1) (proximal tubule) Vitamin D receptor (VDR): Nuclear receptor family Sodium–phosphate co-transporters: NPT2a (*SLC34A1*) and NPT2c (*SLC34A3*) PHEX: Phosphate-regulating enzyme with homologies to endopeptidases on the X-chromosome Fibroblast growth factor 23 (FGF23) Dentin matrix protein 1 (DMP1) *GALNT3*: UDP-*N*-acetyl-a-d-galactosamine: Polypeptide *N*-acetylgalactosaminyltransferase 3 Klotho: Transmembrane protein
Hypertension	Renin–angiotensin system	Prorenin, renin: Produced by the juxtaglomerular (JG) cells Angiotensin I, II Angiotensin converting enzyme (ACE) Renin receptor: 350 amino acid protein, binds renin, prorenin
Nephrogenic diabetes insipidus, syndrome of inappropriate diuresis	Vasopressin	Vasopressin v2 receptor Aquaporins: Membrane proteins AQP1, AQP2, AQP3, AQP4, AQP6, AQP7, and AQP11 X-linked NDI: V2 receptor gene Autosomal NDI: Genes of AQP2

physiological impact on the human body. Understanding of the molecular basis of renal disease helps in formulation of various therapeutic interventions. However, understanding the subject of genetic basis of disease is not so easy and the knowledge about various endocrinological aspects is essential to formulate the treatment strategies for these reno-endocrine dysfunctions. The various hormones secreted by the renal tissue and their various functions and pathological aspects are discussed in the following sections.

Erythropoietin

EPO is a 30.4 kDa glycosylated protein hormone and a member of the family of class 1 cytokines that is produced by kidney's peritubular cells in response to hypoxia.[1] Erythroid development and the survival of erythroid progenitors are hugely dependent upon the EPO and the obligatory growth functions of these hormones maintain the hormonal milieu. The endocrine functions of this renal hormone are mediated after secretion into systemic circulation and subsequent action on the receptors in the bone marrow. The revolution in reno-endocrine functions owes to the first native human EPO isolation in 1977[2] and thereafter the human gene was cloned in 1985.[3,4] The successful isolation of EPO was made possible from a genomic phage library by using mixed 20-mer and 17-mer oligonucleotide probes. The genetic sequence and entire coding of the gene is contained in a 5.4-kb HindIII–BamHI fragment. The microstructural aspect of this gene is represented by four intervening sequences (1562 base pairs) and five exons (582 base pairs). The functional aspects of these genes are highlighted in encoding for a 27 amino acid signal peptide and a 166 amino acid mature protein. Factor 2a (HIF-2a) gets induced by hypoxia, which ultimately regulates the secretion from the *EPO* gene.[1] The secretion is enhanced by the upregulation and stimulation of HIF-2a with detection of hypoxia and expression of a variety of hypoxic genes including *EPO*. The molecular stability is maintained by the carbohydrate moiety of EPO, whereas the 165 amino acid protein component is critical for receptor binding.[5-7] There are four discrete carbohydrate chains; three are N-linked oligosaccharides important for circulatory stability and the fourth one is a small O-linked chain of unclear function.[7-12] Hepatic tissue is the major production house for EPO during fetal life, and after birth, kidneys overtake this function of EPO production.[13-15] The binding of the EPO on receptors of red cell precursors leads to expression of a series of intracellular signals responsible for the erythroid development. The first successful cloning of EPO receptors was made possible in 1989, which established these receptors as the member of the cytokine superfamily of receptors. Till now, several splice variants of the EPO receptors have been identified and studied successfully.[15,16] Initially, EPO receptors were thought to be expressed only on erythropoietic precursor cells, but now it has been demonstrated that they are expressed in other tissues as well, including neuronal cells and endothelial cells.[17] It has also been demonstrated that EPO receptors are single transmembrane receptors that are constitutively associated with tyrosine kinase and these receptors homodimerize upon binding to EPO at the cell surface. The binding of the EPO to its receptors initiates a signal transduction cascade and leads to activation of Janus kinase 2 (JAK2).[18,19] At cellular level, the entire process progresses with a cascade of signal transduction and activation of multiple pathways including Ras/Mitogen

activated protein kinase (Ras/MAP kinase), JNK/p38 MAP kinase, Janus Kinase (JAK)/ Signal Transducer and Activator of Transcription (STAT), and PI-3 kinase.[20] Extensive studies have been carried out for knowing the interaction of STAT, an important intermediary in signal transduction, with JAK2. The findings of these studies have established that after phosphorylation, the activation of EPO-inducible genes occurs as STAT5 becomes activated and undergoes homodimerization and translocates to the nucleus.[20] The promotion of mitogenesis and differentiation is the ultimate net effect of this signaling cascade which results in enhanced survival of committed erythrocyte progenitors and precursors, in particular, the CFU-E.[21,22] The termination of this signaling cascade and return to basal values takes approximately 30–60minutes after the cessation of EPO stimulation.

The major pathological changes brought about by the deficiency of EPO include anemia in chronic kidney disease. At present, for the successful treatment of this disease entity, various EPO analogues have been developed for treatment of anemia. These progressive therapeutic advancements have been made possible with a thorough and basic understanding of the molecular genetics related to the EPO physiology.

Vitamin D, parathyroid hormone, and regulators of phosphate

The occurrence of secondary hyperparathyroidism in chronic renal failure has multifactorial causative factors which include, but are not limited to, phosphorus retention, vitamin D3 deficiency, and hypocalcemia. The resulting skeletal pathology leads to metabolic bone disease which has considerable morbidity and mortality.

The basic metabolic pathway is characterized by conversion of cholesterol to 7-dehydrocholesterol, which, in turn, is metabolized in the skin to vitamin D_3. In addition, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) are obtained from dietary sources. Vitamin D-binding protein (DBP) binds and carries vitamin D_2 and D_3. Once they gain access through the bloodstream to the liver, they are hydroxylated by CYP27A1 to 25(OH)D called calcidiol. Calcidiol is then converted in the kidney to 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] by the action of 1α-hydroxylase (CYP27B1).[23] Various studies have localized the enzyme to the proximal convoluted tubules.[24] In 1975, Haussler *et al.* demonstrated that active vitamin D binds to the nucleus (vitamin D receptor or VDR) of the principal cells of the small intestine.[25] The fact that human VDR is a member of nuclear receptor family could be established only after confirmation of full-length cDNA coding.[26] The observation that patients with renal dysfunction had abnormalities in calcium regulation was central to invoking a role for vitamin D deficiency in patients with kidney failure.[27] A partial improvement of hypocalcemia was observed after oral treatment with 1,25 vitamin D3. However, it was discovered that vitamin D can directly suppress parathyroid hormone (PTH) synthesis.[28]

The main function of the PTH is to regulate calcium and phosphorus homeostasis. However, in the kidney, the actions of PTH in the proximal tubule are quite different from those in the distal tubule. In the proximal tubule, PTH decreases the expression of two sodium–phosphate co-transporters, NPT2a (SLC34A1) and NPT2c (SLC34A3), thereby decreasing the reabsorption of phosphate and thus enhancing renal phosphate excretion.[29,30] In this part of the nephron, PTH also enhances expression of the renal 25-hydroxyvitamin D 1a-hydroxylase (CYP27B1), the enzyme that increases the production of the biologically active metabolite of vitamin D, $1,25(OH)_2D$. Thus, the intestinal absorption of calcium and phosphate is enhanced indirectly by the PTH. In the distal tubule, PTH increases the expression of *TRPV5*, a member of the transient receptor potential (TRP) cation channel subfamily V, thereby enhancing the reabsorption of calcium and thus minimizing renal calcium excretion.[31,32]

Molecular definition of rare genetic disorders characterized by either hypo- or hyperphosphatemia has really helped in the discovery of several proteins involved in the regulation of phosphate homeostasis. The significant aspect of this discovery led to the identification of phosphate-regulating enzyme with homologies to endopeptidases on the X-chromosome (PHEX),[33] fibroblast growth factor 23 (FGF23),[34] NPT2c (sodium-dependent phosphate co-transporter type IIc; NaPi-IIc),[35,36] dentin matrix protein 1 (DMP1),[37] and *GALNT3* (UDP-*N*-acetyl-a-d-galactosamine: Polypeptide *N*-acetylgalactosaminyltransferase 3).[38] Later on, it also helped in defining the roles of the fibroblast growth factor receptor 1 (FGFR1)[39,40] and Klotho, a transmembrane protein. Furthermore, additional proteins have been proposed to have roles in the regulation of phosphate homeostasis; these include soluble frizzled-related protein (sFRP4),[41] matrix extracellular phosphoglycoprotein (MEPE),[42] and fibroblast growth factor 7 (FGF7).[43] Molecular genetic studies, rather than traditional protein purification or expression cloning strategies, have provided important new insights into the regulation of phosphate homeostasis.

Renin–angiotensin

The control of blood pressure and hypertension has been the major function of the renin–angiotensin–aldosterone system (RAAS) and is a part of major hormonal regulatory system of renal tissue.[44] The classical renin–angiotensin system (RAS) begins with the biosynthesis of the glycoprotein hormone, renin, by the juxtaglomerular (JG)

cells of the renal afferent arteriole. Renin is encoded by a single gene and renin mRNA is translated into preprorenin, containing 401 amino acids.[45] In the JG cell endoplasmic reticulum, a 20 amino acid signal peptide is cleaved from preprorenin, leaving prorenin, which is packaged into secretory granules in the Golgi apparatus, where it is further processed into "active" renin by severance of a 46 amino acid peptide from the N-terminal region of the molecule. Mature, "active" renin is a glycosylated carboxypeptidase with a molecular weight of approximately 44 kDa and "active" renin is released from the JG cell by a process of exocytosis involving stimulus–secretion coupling. In contrast, the "inactive" prorenin is released constitutively across the cell membrane. The trypsin-like activation step converts prorenin to "active" renin.[46] Angiotensinogen is further converted to decapeptide angiotensin I (Ang I) by a catalytically enabled cleavage. Angiotensin-converting enzyme (ACE), a glycoprotein (molecular weight 180 kDa) with two active carboxy-terminal enzymatic sites, hydrolyzes the inactive Ang I into biologically active Ang II.[47]

The soluble and particulate forms are the two major molecular forms in which ACE exists. Bradykinin (BK), an active vasodilator and natriuretic autacoid, is metabolized to BK (1–7), an inactive metabolite by the ACE.[48] The production of a potent vasoconstrictor, Ang II, is mediated by the ACE, while it is responsible simultaneously for degrading a vasodilator; BK. The metabolism of substance P into inactive metabolites and fragments is also mediated by ACE.

The successful cloning of a renin receptor from the mesangial cells has been done and its functional significance has also been clarified.[49] The receptor is a 350 amino acid protein with a single transmembrane domain that specifically binds both renin and prorenin.[49] The binding of these hormones induces the activation of the extracellular signal-related mitogen-activated protein (MAP) kinase (extracellular signal-regulated kinase (ERK) 1 and ERK 2) associated with serine and tyrosine phosphorylation and a fourfold increase in the catalytic conversion of Ang to Ang I. The receptor is localized on renal mesangial cell membranes and in the subendothelial layer of both coronary and renal arteries, associated with vascular smooth muscle cells, and co-localizes with rennin.[49] The transformation of growth factor-b production via MAP kinase phosphorylation is mediated by the renin receptor in the renal mesangial cells.

The recognition of intrarenal RAS was first done in the 1970s and early 1980s when selective intrarenal inhibition of the RAS was demonstrated to increase glomerular filtration rate (GFR) and renal Na+ and water excretion.[50] The regulation of Na+ excretion and the long-term control of arterial BP have been attributed to intrarenal RAS as the fundamental mechanism.[51,52] Inappropriate activation of the intrarenal RAS prevents the kidney from maintaining normal Na+ balance at normal arterial pressures and is an important cause of hypertension.[51]

Renal Tissue as Endocrinal Receptor Organ

For many endocrinological functions, the kidney tissue acts as an endocrinological organ mediating a multitude of actions. These functions subserve to maintain an endocrinological milieu and their detailed actions are described as follows.

Antidiuretic hormone and aquaporins

The posterior pituitary gland secretes vasopressin which is a peptide hormone. The name "vasopressin" symbolizes the fact that this hormone can cause vasoconstriction in arterioles and thus increases arterial blood pressure. The antidiuretic function of this hormone has ascribed it a name of vasopressin and is also known as the antidiuretic hormone as it causes antidiuresis (decreases urinary water excretion) by increasing the water permeability of the renal tubules. It consists of nine amino acid residues and the amino acid sequence of arginine vasopressin is Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly. The distal tubule cells of the kidney and Arginine vasopresin (AVP) are responsible for maintaining the water homeostasis. The secretion of vasopressin from the posterior pituitary gland is stimulated by an increase in serum osmolality and reduction in effective circulating blood volume.

Vasopressin v2 receptor (v2R), which is located on the basolateral membrane of the principal cells of the renal collecting duct, is the binding site of vasopressin which then exerts its action after binding. The adenylate cyclase is activated by v2R, which then catalyzes the conversion of ATP to cyclic AMP. The increase in cyclic AMP level leads to the activation of protein kinase A (PKA), which in turn phosphorylates residue Ser256 of AQP2. Subapical storage vesicles that contain AQP2 translocate from the cytoplasm of principal cells to the apical plasma membrane and fuse with it as a consequence of AQP2 phosphorylation. Relocation of phosphorylated AQP2 to the cell membrane renders the cell water permeable.[53-55] AQP2 is shuttled back to the cell cytoplasm upon removal of the vasopressin stimulus, a process that restores the water impermeability of the cell. This internalization process consists of AQP2 retrieval into early endosomes that express early endosome antigen 1 and subsequent transferral of this water channel to storage vesicles that express Rab-11.

Aquaporins are a family of membrane proteins that function as water-permeable channels. Seven different aquaporins are known to be expressed in the human kidney: AQP1, AQP2, AQP3, AQP4, AQP6, AQP7, and AQP11. AQP2 is the most studied and for which the most data are available; it is a vasopressin sensitive and is expressed in the principal cells of the collecting duct. The impairment of AQP2 functions results in nephrogenic diabetes insipidus (NDI) and other water balance disorders. The expressed genetic defects other than that of AQP2 in aquaporins are rare in the kidney and are associated with either mild defects (as for AQP1 and AQP7) or with no obvious deleterious consequence. AQP3 and AQP4 are expressed in the basolateral membrane of the principal cells of the collecting duct and represent potential exit pathways from these cells for water entering via AQP2. Besides being water permeable, AQP6 and AQP7 are also permeable to anions and glycerol, respectively; therefore, AQP6 is suggested to be involved in acid secretion and AQP7 in glycerol metabolism.[56]

NDI is caused by the defects in vasopressin receptors and aquaporins. NDI can be classified into two types: Acquired and genetic. Genetic NDI is rare and has various patterns of inheritance, X-linked and autosomal recessive or dominant.[57] The mutations of the V2 receptor gene result in the X-linked pattern which is the most common cause of genetic NDI.[58] It may involve an incompetent receptor, misfolding of the vasopressin receptor in the endosomes, or the instability of the transcribed receptor. There are at least 183 putative mutations at multiple sites. The autosomal pattern results from gene defects of AQP2, which is located in chromosome region 12q13; approximately 35 mutations have been identified so far.[59]

The combination of free water retention and urinary solute excretion results in syndrome of inappropriate diuresis (SIADH).[60] AVP excess increases water permeability in the collecting duct, leading to approximately 7–10% increase in total body water.[61] AVP production in SIADH can occur either from the neurohypophysis or from ectopic production in the case of a malignancy.

Conclusions

These are just a few of the renal-endocrine disorders and their genetic and molecular basis. Their understanding and in-depth knowledge is very essential in designing and formulating the therapeutic plans and innovating new management strategies. However, we still have to go a long way in order to completely understand the various confounding causative relationships between the pathology and the disease of these reno-endocrinal manifestations. There are numerous other interactions involving the renal tissue and endocrine system, like insulin resistance, metabolic syndrome, hypogonadism, and so on, which are indirectly related with each other but are out of scope of this review.

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