Gene Technology
ISSN: 2329-6682
Gowder, Gene Technology 2014, 3:1
DOI: 10.4172/2329-6682.1000e109
Editorial Open Access

Renal Membrane Transport Proteins and the Transporter Genes

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Kidney

In humans, the kidneys are a pair of bean-shaped organs about 10 cm long and located on either side of the vertebral column. The kidneys constitute for less than 1% of the weight of the human body, but they receive about 20% of blood pumped with each heartbeat. The renal artery transports blood to be filtered to the kidneys, and the renal vein carries filtered blood away from the kidneys. Urine, the waste fluid formed within the kidney, exits the organ through a duct called the ureter. The kidney is an organ of excretion, transport and metabolism. It is a complicated organ, comprising various cell types and having a neatly designed three dimensional organization [1]. Due to structural complexity, the intact kidney is difficult to employ for adequate study of many biochemical, pharmacological and physiological processes. Primary cultures of proximal tubule cells have been considered as an appropriate model for the study of proximal tubule cell function or renal intact function [2].

Membrane Transport

Transporters are membrane proteins present in all living beings. These proteins regulate nutrients, ions, environmental toxins, and other xenobiotics. Transporters are located in intestinal, renal, and hepatic epithelia. Their function involves absorption and elimination of endogenous substances and xenobiotics [3, 4]. The epithelial layer of the renal tubules alters the volume and composition of filtrate by means of reabsorption and secretion. The surface of the epithelium is organized in such a way that the leakage of salt and water back into the tubule can be minimized. The prominent function of the epithelial layer is to handle ion, solute, and water homeostasis. Renal tubular reabsorption is due to the receptor-mediated endocytic pathway. Epithelial cells are polarized and possess membrane transport proteins [5]. Transporter expression can be regulated due to induction or downregulation of transporter mRNAs. In this editorial, recent research on the renal membrane transporters and their regulation has been discussed with reference to available Pubmed sources.

Genes

TCN1

This gene encodes vitamin B12-binding protein family. The transcobalamin-vitamin B (12) complex transport vitamin B12 from plasma and into the tissues. This complex may have high-affinity ligand for the endocytic receptor, megalin that is expressed in the proximal tubule [6].

KCND3

Voltage-gated potassium (Kv) channels are complicated channels with reference to their structural and functional point of view. Angiotensin receptor forms a complex with potassium channel alpha-subunit Kv 4.3 and regulates its intracellular distribution and gating properties [7]. Dihydropyridine Ca2+ channel antagonists / agonists may block Kv4.2, Kv4.3 and Kv1.4 K+ channels expressed in HEK293 cells [8].

AQP2

This gene regulates a water channel protein and it belongs to aquaporin family. Studies show that high sodium diet can increase angiotensin-II and thereby downregulates AQP2 expression. In this way, high sodium diet favors urinary sodium concentration [9]. AQP2 has a role in hereditary and acquired diseases affecting urine-concentrating mechanisms [10]. AQP2 regulates antidiuretic action of arginine vasopressin (AVP). The urinary excretion of this protein is considered to be an index of AVP signaling activity in the renal system. Aquaporins are also considered as markers for chronic renal allograft dysfunction [11].

AQP4

This gene encodes a member of the aquaporin family of intrinsic membrane proteins. These proteins function as water-selective channels in the plasma membrane. Aquaporin-4 (AQP4) is homologous proteins noticed in the basolateral plasma membrane of the kidney collecting duct, and they mediate the exit pathway for apically reabsorbed water [12]. Renal aquaporins (AQP1-4) concentration is downregulated and is in proportion to the degree of hydronephrosis graded by ultrasound in pediatric congenital hydronephrosis (CH) [13]. The upregulation of AQP4 is directly proportional to the onset and maintenance of salt-sensitive hypertension [14]. Vasopressin is involved in the regulation of AQP4 [15].

SLC1A6

It encodes high affinity glutamate and neutral amino acid transporters. These glutamate receptors are sensitive to dietary regulation [16]. They also function as anion channels [17]. Glutamate upregulates the open probability of the anion pore associated with glutamate transporters [18].

SLC12A5

K-Cl cotransporters are proteins and are involved in the maintenance of intracellular chloride concentrations. The electroneutral cation-chloride-coupled cotransporter gene family (SLC12) was identified initially in fish and then in mammals. This nine-member gene family involves two major branches, one including two bumetanide-sensitive Na (+)-K (+)-2Cl (-) cotransporters and the thiazide-sensitive Na (+): Cl (-) cotransporter. Two of the genes in this branch (SLC12A1 and SLC12A3), exhibit kidney-specific expression and function in renal salt reabsorption. The third gene (SLC12A2) of this family is expressed ubiquitously and plays a key role in epithelial salt secretion and cell volume regulation. The second branch constitutes four genes (SLC12A4- 7) regulate electroneutral K (+)-Cl (-) cotransporters [19]. K (+)-Cl (-) cotransporters (KCCs) play a fundamental role in epithelial cell function [20]. The Na (+)-K (+)-Cl (-) cotransporters (NKCCs), which belong to the cation-Cl (-) cotransporter (CCC) family, are able to translocate NH4 (+) across cell membranes [21].

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Received January 26, 2013; **Accepted** January 27, 2013; **Published** February 03, 2014

Citation: Gowder SJT (2014) Renal Membrane Transport Proteins and the Transporter Genes. Gene Technology 3: e109. doi: 10.4172/2329-6682.1000e109

TRPC1

The protein encoded by this gene, Transient Receptor Potential Canonical 1 (TRPC1) is a membrane protein that is permeable to calcium and other cations. Higher concentration of glucose increased the expression of TRPC6 and TRPC6-dependent Ca (2+) influx [22]. TRPC1 gene polymorphisms are associated with type 2 diabetes and diabetic nephropathy in Han Chinese population [23]. TRPC1 channels are associated to mechanosignaling during cell migration [24]. TRPC1 is regulated during the cell cycle progression and is involved in store-depletion-operated Ca (2+) entry (SOCE), regulatory volume decrease (RVD), and cell proliferation [25].

CLC3

This gene regulates a member of the voltage-gated chloride channel (ClC) family. The encoded protein is noticed in all cell types and is present in plasma membranes and in intracellular vesicles. ClC-3 channel/antiporter regulates nuclear factor (NF)-κB activation [26]. ClC-3 has nucleocytoplasmic shuttling dynamics and regulates the cell cycle in cancer cells [27]. CIC-3 plays a role in wound closure in Xenopus embryos [28]. ClC-3 Cl (-) channel involved in cell volume regulation and cell cycle [29]. Diabetes results in the alteration in the expression of ClC-3 channels. These changes result in the impaired kidney functions observed in diabetes [30].

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