Disorders of renal NaCl transport and implications for blood pressure regulation

Blood pressure and arterial hypertension

The requirement of a circulatory system is a consequence of the increasing size of multicellular organisms during evolution. Arterial blood pressure is a result of blood flow through the vasculature, which ensures the transportation of cells, nutrients, hormones, metabolites, O_2 , and CO_2 throughout the body. It is determined by the total mean flow in the circulation (cardiac output) and the peripheral resistance of the vasculature. Starting from 115 mm Hg, each difference of 20 mm Hg in systolic blood pressure is associated with a twofold increase in the risk of dying from stroke and ischemic heart disease [30]. Because the relationship between blood pressure and cardiovascular and renal events is continuous, the distinction between normal blood pressure and hypertension is somewhat arbitrary [5]. High blood pressure is the leading cause of death and disability-adjusted life years worldwide [33, 61]. Therefore, understanding of the regulation of blood pressure and identification of the genetic factors that contribute to blood pressure are of key relevance.

Role of NaCl in blood pressure and arterial hypertension

Because NaCl is the major osmotic constituent of the extracellular fluid (ECF), it largely determines ECF volume and cardiac output. Usually dietary Na^+ uptake matches Na^+ excretion. If this balance is disturbed, Na^+ loss leads to decreased blood pressure, whereas Na^+ retention leads to increased blood pressure. How

this can lead to chronic hypertension is still controversial. Although it is widely assumed that all pressor ‘sensitivity’ to dietary NaCl depends on its Na^+ , selective dietary loading of Na^+ without Cl^- has repeatedly failed to induce a pressor effect [62]. Because substitution of dietary NaCl with equimolar sodium bicarbonate leads to a reduction in blood pressure [34], there is evidence that renal Cl^- transport is an independent determinant of vascular volume and blood pressure regulation. The identification of genetic defects (■ Table 1) that are linked to altered renal Na^+ and Cl^- handling characterized by either decreased or increased blood pressure in rare monogenic disorders highlights the critical role of NaCl homeostasis in blood pressure regulation [32, 46].

Renal NaCl uptake and associated monogenic disorders

The basic functional unit of the kidney is the nephron, which consists of the glomerulus, where Na^+ and Cl^- are freely filtered, and the tubular system, which conveys the urine into the renal pelvis (■ Fig. 1). Along the passage of the tubular epithelium many constituents of the primary filtrate including Na^+ and Cl^- are reabsorbed by an orchestra of different transport systems. Most but not all of the filtered Na^+ is reabsorbed together with Cl^- . The segmental Cl^- handling differs from Na^+ and involves both paracellular and transcellular routes.

Roughly 67% of the filtered NaCl and water reabsorption takes place in near isotonic fashion in the proximal tubule (PT). The driving force is mainly

provided by the basolateral Na^+/K^+ -ATPase, which sets the electrochemical gradient to drive a number of apical transporters that mediate Na^+ and/or Cl^- entry such as Na^+ -dependent glucose transporters (SGLTs), the Na^+/H^+ exchanger NHE3/SLC9A3 [57], which exploits the downhill Na^+ gradient across the apical cell membrane generated by the Na^+/K^+ -ATPase, and the electrogenic Na^+/HCO_3^- co-transporter NBC1/SLC4A4, which is mutated in proximal renal tubular acidosis [21]. In addition, the blood pressure of Slc4a4 [16] and Slc9a3 [45] knockout mice was reduced. This example illustrates the enormous capacity of the downstream nephron to compensate for impaired proximal NaCl uptake. In fact, patients with SLC9A3 mutations mainly suffer from congenital secretory sodium diarrhea [24]. Further, a considerable part of Cl^- reabsorption in the PT occurs in a paracellular manner, which is driven by the lumen-negative transepithelial potential difference. An additional 25% of the Na^+ and Cl^- is reabsorbed by the $Na^+/K^+/2Cl^-$ co-transporter NKCC2/SLC12A1 [14] in the thick ascending limb of Henle’s loop, which is inhibited by loop diuretics such as furosemide and bumetanide. These drugs are widely used to treat hypertension and edema associated with congestive heart failure. To maintain NKCC2-mediated NaCl uptake, K^+ entering the cell via NKCC2 has to be recycled by the apical K^+ channel ROMK/KCNJ1. At the basolateral side, Na^+ leaves the cell via the Na^+/K^+ -ATPase, whereas Cl^- efflux is largely mediated by the Cl^- channel CLCNKB/CIC-K2 [20], which requires its β -subunit Bart-

tin/BSND [11]. Notably, mutations in SLC12A1 [50], KCNJ1 [51], CLCNKB [49] or BSND [2] can cause Bartter syndrome, which mimics the effects of loop diuretics with marked secondary hyperaldosteronism originating from renal salt-wasting with normal or low blood pressure, hypokalemia, and metabolic alkalosis. Gain-of-function mutations of the calcium sensing receptor CaSR, which is involved in parathyroid hormone secretion, renal calcium, and to some extent renal salt reabsorption, are another cause of Bartter syndrome [60]. Recently, a transient form of antenatal Bartter syndrome was identified, which is caused by MAGED2 mutations [28]. It is assumed that MAGED2 participates in the maturation of membrane proteins within the endoplasmic reticulum and thereby affects the expression of NKCC2, ROMK, and possibly other membrane proteins.

In the distal convoluted tubule (DCT) another 5% of the filtered Na^+ is taken up by the apical NaCl co-transporter NCC/SLC12A3 [15], which is highly sensitive to thiazide diuretics. NCC loss-of-function mutations are found in Gitelman syndrome patients [52], who generally have a low or normal blood pressure with low levels of chloride, potassium, and magnesium, and show decreased urinary calcium excretion. NCC regulation is critical, as familial hyperkalemic hypertension can be caused by mutations in WNK kinases WNK1 and WNK4 [63], both controlling NCC activity in the DCT [64]. Moreover, mutations in KLHL3 and CUL3 have been reported in patients with pseudohypoaldosteronism II featuring hypertension, hyperkalemia, and metabolic acidosis [4]. CUL3 and BTB-domain-containing kelch proteins, such as KLHL3, are components of cullin-RING E3 ligase complexes that ubiquitinate substrates such as WNK kinases and thereby control NCC activity [10, 47].

A salt-wasting renal tubulopathy similar to Gitelman syndrome is accompanied by epilepsy, ataxia, and sensorineural deafness in EAST syndrome, which is caused by mutations in the K^+ channel KCNJ10 [3]. KCNJ10 is expressed basolaterally in the DCT and connecting tubule of the kidney [42].

Finally, the remaining 3% enter the collecting system, which consists of the connecting tubule and the collecting duct (CD) and is under control of the renin-angiotensin-aldosterone system, antidiuretic hormone/vasopressin, and natriuretic peptides (NPs), which are released from the heart in response to pressure and volume overload and inhibit renal sodium reabsorption. Therefore, the distal tubule plays an essential role in the fine tuning of salt, electrolyte, water, and acid-base balance. Its epithelium comprises two main cell types, principal cells and intercalated cells [37].

In the connecting tubule and CD, Na^+ reabsorption is largely achieved through the apical epithelial sodium channel ENaC [6], in tandem with the basolateral Na^+/K^+ -ATPase, both expressed in connecting tubule cells and principal cells of the CD. Aldosterone increases both Na^+ entry through ENaC and basolateral Na^+ extrusion via the Na^+/K^+ ATPase. Notably, mutations in the β - [48] or γ -subunit [19] of ENaC, which result in an increased number of these channels in the apical cell membrane, cause Liddle syndrome with severe early onset hypertension, whereas loss of function mutations in the α -, β - or γ -subunit cause pseudohypoaldosteronism type I [8, 54]. Pseudohypoaldosteronism type I is characterized by salt wasting and severe hypotension. Thereby, the mutation-phenotype correlation for ENaC illustrates the concept of activating and inactivating mutations resulting in opposite phenotypes (hyper- versus hypotension).

Because approximately 50% of Na^+ absorption in the cortical collecting duct of rats is insensitive to amiloride but sensitive to thiazides [56], a second mechanism independent of principal cells and ENaC was suspected. First evidence that intercalated cells are also involved in NaCl homeostasis came from the targeted inactivation of the apical $\text{HCO}_3^-/\text{Cl}^-$ exchanger pendrin/Slc26a4 of type B intercalated cells, which protected mice against mineralocorticoid-induced hypertension and favored hypotension upon NaCl depletion [58, 59]. Moreover, overexpression of pendrin induced arterial hypertension in mice fed on a high salt

medgen 2019 · 31:1–7
<https://doi.org/10.1007/s11825-019-0232-8>
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Abstract

Hypertension is one of the major risk factors for cardiovascular disease in industrialized societies. Substantial progress has been made in understanding its epidemiology, its pathophysiology, and its associated risks such as coronary artery disease, stroke, and heart failure. Because there is consensus that the abnormal retention of sodium by the kidney is a major important pathophysiological event in hypertension, this review focuses on mechanisms of renal NaCl transport and associated genetic disorders.

Keywords

Hypertension · Sodium chloride · Kidneys · Hypertonia · Ion transport

Störungen des renalen NaCl-Transports und Auswirkungen auf die Blutdruckregulation

Zusammenfassung

Bluthochdruck ist einer der entscheidenden Risikofaktoren für die Entwicklung von kardiovaskulären Erkrankungen in Industrienationen. Das Wissen zur Epidemiologie, Pathophysiologie und die hiermit assoziierten Risiken haben in den vergangenen Jahren erheblich zugenommen. Eine inadäquate Natriumretention durch die Niere gilt als eine wesentliche Ursache einer arteriellen Hypertonie. Diese Übersichtsarbeit fasst daher die renalen NaCl-Transportmechanismen und damit assoziierte erbliche Erkrankungen zusammen.

Schlüsselwörter

Bluthochdruck · Natriumchlorid · Niere · Hypertonie · Ionentransport

diet [23]. Mutations in SLC26A4 result in Pendred syndrome, the most common syndromic form of deafness, associated with developmental abnormalities of the cochlea, sensorineural hearing loss, and diffuse thyroid enlargement [13]. Although hypertension was not

Table 1 Genes linked with blood pressure regulation/pathological conditions				
Gene	Full gene name	Syndrome/animal model	Defective/altered function	Ref.
<i>Proximal tubule</i>				
SLC9A3	Solute carrier 9, member 3 (NHE3)	Mouse: blood pressure reduced, hyperaldosteronism	Apical transporter using sodium gradient for urinary acidification	[45]
SLC4A4	Solute carrier 4, member 4 (NBC1)	Mouse: blood pressure reduced, hyperaldosteronism	Apical transporter using sodium gradient for bicarbonate recovery	[16]
<i>Thick ascending limb</i>				
SLC12A1	Solute carrier 12, member 1 (NKCC2)	Bartter syndrome type 1	Apical ion transport	[50]
KCNJ1	Potassium inwardly-rectifying channel, subfamily J, member 1 (ROMK)	Bartter syndrome type 2	Apical potassium recycling	[51]
CLCNKB	Chloride channel, voltage-sensitive Kb (ClC-K2)	Bartter syndrome type 3	Basolateral chloride exit in TAL	[49]
BSND	Barttin CLCNK-type accessory beta subunit	Bartter syndrome type 4	Correct membrane targeting of CLCNK channels	[2]
CASR	Calcium-sensing receptor	Hypocalcemia with Bartter syndrome	CASR activation inhibits ROMK in rats, hyperprostaglandinism	[60]
MAGED2	Melanoma antigen, family D, 2	Transient Bartter syndrome 5	Regulates stability of NKCC2 and ROMK in the unborn and during early life	[28]
UMOD	Uromodulin	Variant associated with blood pressure	GPI-anchored glycoprotein secreted by cleavage into urine	[40]
<i>Distal convoluting tubule</i>				
SLC12A3	Solute carrier 12, member 3 (NCC)	Gitelman syndrome	Apical ion transport	[52]
WNK1	WNK lysine-deficient protein kinase 1	PHA1C	Phosphorylation NCC	[63]
WNK4	WNK lysine deficient protein kinase 4	PHA1B	Regulation of WNK1 activity by phosphorylation	[63]
KLHL3	Kelch-like 3	PHA1D	E3 Ubiquitin ligase	[4]
CUL3	Cullin 3	PHA1E	E3 Ubiquitin ligase	[4]
KCNJ10	Potassium inwardly rectifying channel, subfamily J, member 10	EAST syndrome (SeSAME syndrome)	Basolateral potassium recycling with impact on NCC regulation	[3]
<i>Cortical collecting duct</i>				
SLC26A4	Solute carrier family 26, member 4 (PDS)	Mouse: blood pressure changed if challenged	Apical ion transport	[13]
SLC4A8	Solute carrier family 4, member 8 (NDCBE)	Mouse: blood pressure changed if challenged	Apical ion transport	[29]
SCNN1A	Sodium channel, nonvoltage-gated 1 alpha (ENaC alpha)	Liddle syndrome, PHAI	Apical localization in principal cells	[8]
SCNN1B	Sodium channel, nonvoltage-gated 1 beta (ENaC beta)	Liddle syndrome, PHAI	Apical localization in principal cells	[48]
SCNN1G	Sodium channel, nonvoltage-gated 1 gamma (ENaC gamma)	Liddle syndrome, PHAI	Apical localization in principal cells	[19]
NEDD4L	Neural precursor cell expressed, developmentally down-regulated gene 4-like	Variant associated with blood pressure	Ubiquinates ENaC subunits	[36]
<i>Aldosterone axis</i>				
CYP11B2	Cytochrome P450, family 11, subfamily b, polypeptide 2 (aldosterone synthase)	Familial hyper-/hypoaldosteronism	Aldosterone synthesis	[31]
CYP11B1	Cytochrome P450, family 11, subfamily b, polypeptide 1 (11-beta-hydroxylase)	Aldosteronism, glucocorticoid-re-mediable	Aldosterone synthesis	[31]
NR3C2	Nuclear receptor family 3, group C, member 2 (mineralocorticoid receptor)	Hypertension, PHAI	Aldosterone receptor	[17]
KCNJ5	Potassium inwardly rectifying channel, subfamily J, member 5	Familial hyperaldosteronism type III	Regulation of aldosterone production	[9]

Table 1 (Continued)

Gene	Full gene name	Syndrome/animal model	Defective/altered function	Ref.
CACNA1D	Calcium channel, voltage-dependent, L-type, alpha, 1D subunit	PASNA	Regulation of aldosterone production	[1]
CACNA1H	Calcium channel, voltage-dependent, L-type, alpha, 1H subunit	Familial hyperaldosteronism type IV	Regulation of aldosterone production	[44]

Genes are sorted according to the localization of the respective proteins along the nephron or listed as genes encoding extrarenal proteins. For some genes, the function has been resolved by animal models, but no human disorder has yet been reported. For many genes, the expression is not limited to the kidney. Owing to space limitations, extrarenal functions are not discussed in this review

PHA pseudohyperaldosteronism, **PASNA** Primary aldosteronism, seizures, and neurological abnormalities (PHA with seizures and neuronal abnormalities), **TAL** thick ascending limb

reported in a small retrospective analysis of patients with Pendred syndrome [35], it is still unclear whether Pendred syndrome protects against the development of hypertension. Furthermore, studies on isolated cortical collecting tubules suggested a second mechanism of Na⁺ reabsorption different than ENaC, which was blocked by thiazide diuretics, although NCC is absent from CDs. Because isolated CDs of mice, which lack the Na⁺-dependent Cl⁻/HCO₃⁻ exchanger Ndcbe/Slc4a8, were devoid of ENaC-independent NaCl reabsorption [29], thiazide-sensitive NaCl uptake in the CD likely results from the functional coupling of pendrin and Slc4a8. The basolateral NaCl exit is independent of the Na⁺/K⁺-ATPase but critically relies on the presence of the basolateral V-ATPase and Ae4/Slc4a9 [7].

Excessive aldosterone secretion causes hypokalemia and hypertension, whereas too little aldosterone results in hyperkalemia and hypotension. Mutations that affect aldosterone synthesis result in severe hypotension [41]. Glucocorticoid-remediable aldosteronism is caused by a gene duplication arising by unequal crossing over between two closely related genes involved in adrenal steroid biosynthesis, i.e., aldosterone synthase (encoded by CYP11B2) and 11-β-hydroxylase (encoded by CYP11B1) [31]. As a consequence, regulatory sequences of 11-β-hydroxylase are fused with the coding sequences for aldosterone synthase thus leading to early onset of hypertension with normal or elevated aldosterone levels despite suppressed plasma renin activity. Normally, 11-β-hydroxylase protects the mineralocorticoid receptor (encoded by NR3C2) from cortisol by metabolizing it to cortisone.

Because cortisol is also able to effectively activate the mineralocorticoid receptor, patients lacking the 11-β-hydroxylase develop apparent hyperaldosteronism with early onset hypertension and hypokalemia in the virtual absence of aldosterone. Chronic consumption of licorice can result in a similar condition, because a metabolite of licorice inhibits 11-β-hydroxylase [53]. Mutations in the mineralocorticoid receptor gene itself cause autosomal-dominant pseudohypoaldosteronism type I with severe hypotension [17].

Adrenocortical adenomas can lead to the autonomous secretion of aldosterone responsible for primary aldosteronism and secondary arterial hypertension. Notably, somatic mutations in genes regulating intracellular ionic homeostasis and membrane potential are a recurrent finding in aldosterone-producing adenomas [1, 9, 44, 65]. As β-catenin mutations are frequent in both aldosterone- and cortisol-producing adenomas [55], the Wnt/β-catenin pathway appears to play an important role in adrenal tumorigenesis.

Common variants and renal NaCl uptake

The numerous monogenic disorders caused by mutations in genes involved in NaCl homeostasis outlined above and the potency of antihypertensive agents such as thiazides, ACE inhibitors and AT1 and mineralocorticoid receptor blockers in the treatment of hypertension confirm the concept that hypertension is primarily a renal disorder characterized by abnormal handling of sodium [18] (and chloride). As another proof of concept, it has been shown that rare heterozygous

mutations in the genes encoding NCC, NKCC2, and ROMK reduce blood pressure in participants of the Framingham Heart Study [25]. Whether more common variants in genes involved in NaCl homeostasis play a role in blood pressure control in the larger population is not yet finally solved. Several genome-wide association studies (GWAS) have been carried out to detect such common genetic variations with modest effect sizes. The largest cardiovascular genetic association study to date, with over 1 million participants, demonstrated more than 900 different genetic loci [12]. Because of the small effects, causal relationships are often difficult to establish. Notably, one of these variants lies in the promoter region of UMOD [40], which is specifically expressed in the thick ascending limb. Mouse studies suggest a functional link between UMOD and NKCC2, because NKCC2-mediated transport was reduced in Umod knockout mice [38]. Another SNP maps close to SLC4A7 encoding the electroneutral sodium-bicarbonate co-transporter 1 [22], which is also expressed in the thick ascending limb. Functional data, however, may point to a vascular effect, because this SNP was associated with altered SLC4A7 expression and defective pH regulation in vascular smooth muscle cells [39]. NEDD4L, which encodes an ubiquitin ligase regulating the cell surface expression of ENaC by targeting it for degradation, may also contribute to blood pressure [36]. Finally, variants in NPR3 encoding the natriuretic peptide receptor C, which controls the clearance of natriuretic peptides [43], have been linked with variation in blood pressure regulation [22, 26].

Fig. 1 ◀ Ion transporters and their function within different nephron segments. **a** The nephron is the functional unit of the kidney, which comprises the glomerulus, the proximal tubule (PT), the Henle loop, the thick ascending limb (TAL), the distal convoluted tubule (DCT), the cortical collecting duct (CCD), and the medullary collecting duct (MCD). **b–e** Na^+ and Cl^- transport pathways are shown for the different nephron segments. **b** A significant amount of Na^+ is taken up via the sodium proton exchanger NHE3 and the electrogenic sodium bicarbonate cotransporter driven by the Na^+ gradient generated by the basolateral Na^+/K^+ -ATPase. Similarly, other transporters use the Na^+ gradient to recover amino acids, carbohydrates, and other metabolites from the primary filtrate in PT cells. Cl^- transport is driven by the transepithelial potential in a paracellular manner. **c** In cells of the thick ascending limb of the Henle loop, NKCC2 and ROMK cooperate to transport NaCl into cells fueled by the basolateral Na^+/K^+ -ATPase with ROMK mediating apical K^+ recycling. Cl^- exit is mediated by CLCNKB, which requires Barttin for proper membrane targeting. MAGED2 affects NKCC2 and ROMK membrane targeting in early development but is dispensable in later life. **d** In the DCT, the apical NCC transports Na^+ and Cl^- into the cell driven by the basolateral Na^+/K^+ -ATPase. NCC activity/membrane insertion is tightly regulated by WNK1, WNK4, KLHL3, and CUL3. **e** In the CCD and CD, principal cells use ENaC to recover Na^+ . Localization of ENaC at the apical membrane is negatively regulated by NEDD4L. Type B intercalated cells take up NaCl via coupling of NDCBE and pendrin, which is extruded basolaterally via CLCNKB and AE4. Notably, the transport is energized by the basolateral V-ATPase and does not require the Na^+/K^+ -ATPase

Future

Mendelian genetics helped to identify molecules that are crucial for renal NaCl homeostasis. Although their loss can cause extreme perturbations of blood pressure, the respective disorders are very rare and there is currently limited evidence that variants in the same genes play a common role in the determination of BP in the general population. Although the heritability of blood pressure from family studies is assumed to account for up to 50% [27], the collective effect of all loci identified by GWAS is thought to explain only roughly 2% of blood pressure heritability [22]. Therefore, the molecular mechanisms leading to hypertension are still poorly understood in the majority of patients. In addition to the few loci that can be

linked to NaCl handling, the vasculature appears to be an important target organ in the pathogenesis of hypertension. Whether such genetic risk scores based on GWAS data prove to be clinically useful, is as of yet unclear. From the current data, recommendations for lifestyle management should be for the whole population, rather than targeted using genetic information.

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Compliance with ethical guidelines

Conflict of interest. J. C. Hennings and C. A. Hübner declare that they have no competing interests.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all patients for whom identifying information is included in this article. All institutional and national guidelines for the care and use of laboratory animals were followed. This article does not contain any studies with human or animal subjects.

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Hier steht eine Anzeige.