



Renal metabolism and hypertension

Zhongmin Tian ¹ & Mingyu Liang ²✉

Hypertension is a leading risk factor for disease burden worldwide. The kidneys, which have a high specific metabolic rate, play an essential role in the long-term regulation of arterial blood pressure. In this review, we discuss the emerging role of renal metabolism in the development of hypertension. Renal energy and substrate metabolism is characterized by several important and, in some cases, unique features. Recent advances suggest that alterations of renal metabolism may result from genetic abnormalities or serve initially as a physiological response to environmental stressors to support tubular transport, which may ultimately affect regulatory pathways and lead to unfavorable cellular and pathophysiological consequences that contribute to the development of hypertension.

Hypertension continues to be a leading risk factor for disease burden worldwide, despite the availability of several preventive and therapeutic approaches¹. Hypertension substantially increases the risk of stroke, heart disease, chronic kidney disease, and cognitive decline^{2,3}. Most hypertensive patients need to take antihypertensive medications continuously, as a cure is not available. Millions of patients remain hypertensive despite taking three or more antihypertensive medications⁴. Numerous genetic, epigenetic, lifestyle, and environmental factors may contribute to the development of hypertension. Understanding the physiological and molecular mechanisms underlying blood pressure regulation and utilizing this mechanistic understanding to sub-group hypertensive patients for precision prevention and treatment are important challenges in medical and biomedical research³.

Cardiac output and total peripheral vascular resistance determine systemic blood pressure. Several organs and tissues, including kidneys, resistance arterioles, central nervous system, and immune system, contribute to the regulation of blood pressure by regulating cardiac output or vascular resistance. The kidneys may regulate bodily fluid volume and vascular resistance by directly altering renal tubular transport of fluid and sodium or indirectly, by altering renal hemodynamics or endocrine factors^{5,6}. Nearly all of the identified causal genes for Mendelian forms of human blood pressure abnormalities involve kidney function^{7,8}, and most of the commonly used animal models of hypertension present kidney abnormalities⁹.

In addition to its essential fueling and housekeeping functions, intermediary metabolism is increasingly recognized for its regulatory role in which metabolic pathways and intermediate products influence gene expression, signal transduction, and other regulatory pathways in the cell¹⁰. Alterations in intermediary metabolism have been associated with the development of various conditions, including cancer and heart disease^{11,12}. In the kidneys, intermediary metabolism and related cellular functions such as mitochondrial function play an essential role in the development of acute kidney injury and chronic kidney disease^{13,14}.

Most of the energy produced in the kidneys is used to support renal tubular transport¹⁵, which is essential for the long-term regulation of blood pressure. Changes in renal energy and substrate

¹The Key Laboratory of Biomedical Information Engineering of Ministry of Education, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an, Shaanxi, China. ²Center of Systems Molecular Medicine, Department of Physiology, Medical College of Wisconsin, Milwaukee, WI, USA. ✉email: mliang@mcw.edu

metabolism may influence tubular transport by altering adenosine triphosphate (ATP) availability and levels of other metabolic intermediates with regulatory function. Therefore, renal energy and substrate metabolism might be important for regulating blood pressure and the development of hypertension. Moreover, energy and substrate metabolism might provide new interventional targets for the prevention or treatment of hypertension.

In this review, we provide a brief overview of renal metabolism and its association with tubular transport, summarize studies in humans and animal models that have examined renal energy and substrate metabolism in blood pressure regulation and hypertension, and outline challenges and opportunities in this exciting research area.

Renal metabolism

The structure and function of the kidneys are highly compartmentalized. The primary functional unit of the kidneys is the nephron. The number of nephrons averages ~1 million in a human kidney. Each nephron consists of a glomerulus and a Bowman's capsule connected serially to a proximal tubule, a loop of Henle, and a distal convoluted tubule, and several nephrons drain into a shared collecting duct.

A variety of substrates may be used as fuel in the kidneys. Major biochemical pathways relevant to renal substrate metabolism are summarized in Fig. 1A. Several of the metabolic pathways shown in Fig. 1A are targets of approved or investigational drugs. Prominent examples of these drugs and the pathways that they target are shown in Fig. 1B.

Renal metabolism is characterized by several important and, in some cases, unique features. Previous reviews have thoroughly described the intricate relation between renal metabolism and tubular transport^{16–19}. The following section highlights salient points and recent studies in this area that are particularly relevant to understanding the role of renal metabolism in hypertension:

First, the kidneys have a high metabolic rate. The metabolic rate in the human kidneys has been estimated to be >400 kcal/kg tissue/day, which is the same as the heart, twice as high as the liver and the brain, and much higher than other organs²⁰. Second, >80% of the oxygen consumed by the kidneys is used to support active transport machinery, primarily Na⁺/K⁺-ATPase located on the basolateral membrane of tubular cells¹⁵. Na⁺/K⁺-ATPase generates electrochemical gradients that directly or indirectly drive most of the remaining transport activities in the tubule. Third, blood flow and tissue oxygenation vary substantially between kidney regions. The renal cortex receives a blood flow that exceeds its metabolic needs but is necessary for the bulk filtration at glomeruli that is essential for removing whole-body metabolic wastes²¹. The partial pressure of oxygen (PO₂) is ~50 mmHg in the renal cortex. Tissue PO₂ decreases gradually into the renal medulla, reaching 10–15 mmHg in the renal inner medulla¹⁹. Fourth, substances used as fuel for energy may differ between the kidneys and other organs. For example, arterial –venous blood sampling and isotope tracing experiments in pigs indicate that circulating citrate contributes to the tricarboxylic acid (TCA) cycle most prominently in the kidneys and to an extent that is similar to glutamine and lactate²².

Nephron segment metabolism and physiology

Each nephron segment has distinct physiological characteristics, and substrate utilization and metabolic pathway activities vary substantially between nephron segments and are generally consistent with oxygen availability (Fig. 1C). In regions where PO₂ is high, nephrons use primarily oxidative phosphorylation to produce ATP, whereas segments where PO₂ is low rely mainly on glycolysis. However, the current understanding of nephron

segmental metabolism is mainly based on studies that measured specific substrate utilization, ATP production, and abundance or activities of a small number of metabolic enzymes in nephron segments isolated from rats, mice, and other animal models^{17–19,23}. One should be cautious with extrapolating these findings to nephron segmental metabolism *in vivo* because metabolism is highly dynamic and dependent on the cellular milieu and anatomical context.

The proximal tubule reabsorbs ~65% of the filtered NaCl and water and nearly all filtered glucose and amino acids²¹. Part of this reabsorption may occur passively through the paracellular space¹⁹. Na⁺/K⁺-ATPase activity per unit length of the tubule segment and mitochondrial density and enzyme abundance in the proximal tubule are lower than or similar to the thick ascending limb of the loop of Henle and the distal convoluted tubule, but higher than other nephron segments²³. Free fatty acids appear to be a significant energy source for the proximal tubule (Fig. 1C). Other substances that the proximal tubule may use as fuel include glutamine, lactate, and ketone bodies^{17–19,23}. The proximal tubule has significant gluconeogenic capabilities^{17–19,23}. Gluconeogenesis may compete with Na⁺/K⁺-ATPase for ATP in the proximal tubule.

The thick ascending limb of the loop of Henle reabsorbs 20–25% of the filtered NaCl without reabsorbing water²¹. Glucose may be the primary energy source in thick ascending limb, even though lactate, fatty acids, and ketone bodies may also contribute. Glycolytic capabilities are present in the thick ascending limb and subsequent nephron segments and largely absent in the proximal tubule^{17–19,23}. The thin descending and ascending limbs of the loop of Henle do not have significant active transport²¹.

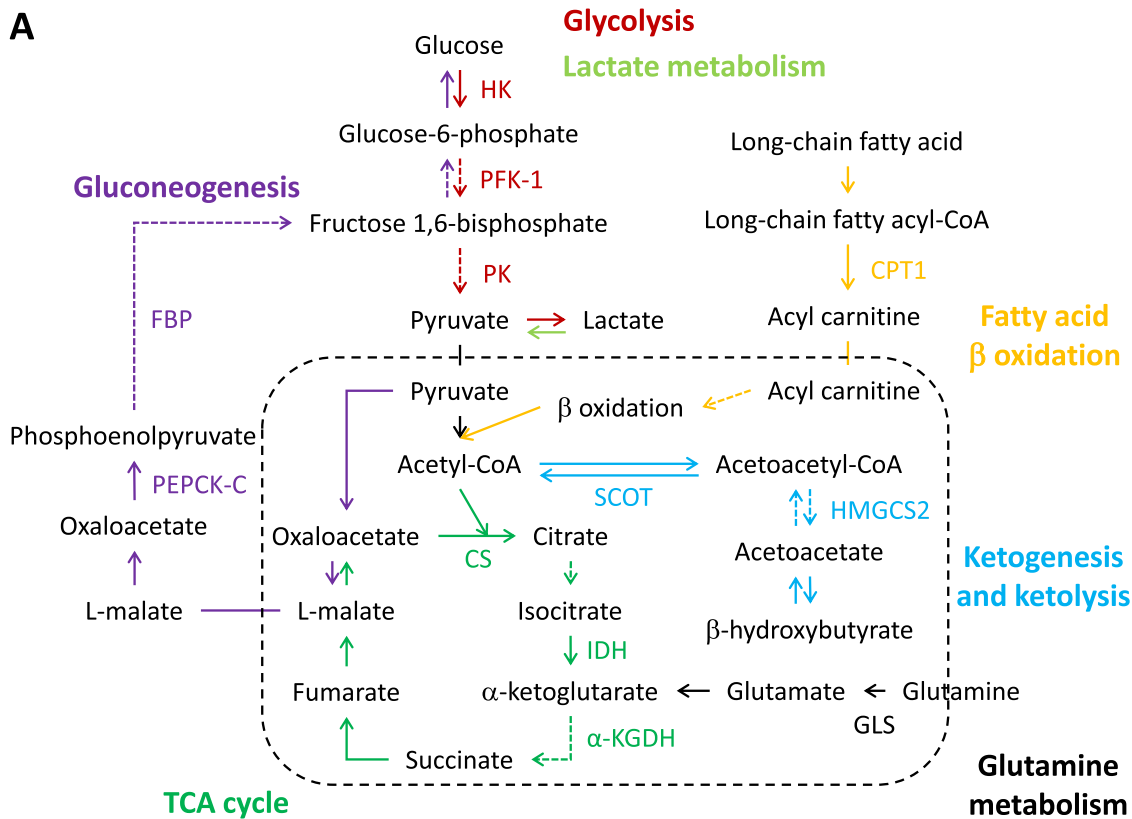
The distal convoluted tubule and the collecting duct reabsorb 5–10% of the filtered sodium and are the final segments that may control sodium excretion and urine flow rate²¹. Substrate utilization in the cortical collecting duct is qualitatively similar to the thick ascending limb^{17–19,23}. The importance of glucose as the main energy source appears to increase, and that of fatty acids decreases, as the collecting duct progresses to the renal inner medulla region.

Comprehensive transcriptome and proteome analyses have provided global views of mRNA and protein abundance of metabolic enzymes in kidney regions and nephron segments^{24–27}, which are generally consistent with results of previous targeted analyses of enzyme activity, protein abundance, or substrate utilization.

Role of renal metabolism in hypertension

Renal metabolism in human hypertension. Tissue oxygenation levels are determined by oxygen supply and consumption and may reflect tissue metabolic activities. Oxygen consumption is determined by aerobic metabolism, which, in the kidneys, is largely determined by tubular transport activity. Oxygen supply to kidney tissue regions is determined by blood flow.

Renal regional tissue oxygenation levels in humans may be measured by blood oxygenation level-dependent magnetic resonance imaging (BOLD-MRI)²⁸. A BOLD-MRI analysis in 10 normotensive subjects and eight untreated hypertensive patients indicated that a low-salt diet increased renal medullary tissue oxygenation levels in both groups when compared with a high-salt diet²⁹. In the normotensive group, renal medullary oxygenation was correlated positively with proximal tubular reabsorption of sodium and negatively with distal sodium reabsorption. In another study examining patients with hypertension, renal medullary tissue oxygenation levels were significantly lower in a group of 20 African Americans compared with 29 Americans of European descent³⁰. Furosemide, which inhibits



B

Select drugs

- Glycolysis
 - 2-Deoxyglucose
- Gluconeogenesis
 - Metformin
- Fatty acid β oxidation
 - Trimetazidine
 - Perhexiline
- Ketogenesis
 - Insulin
- Glutamine metabolism
 - CB-839

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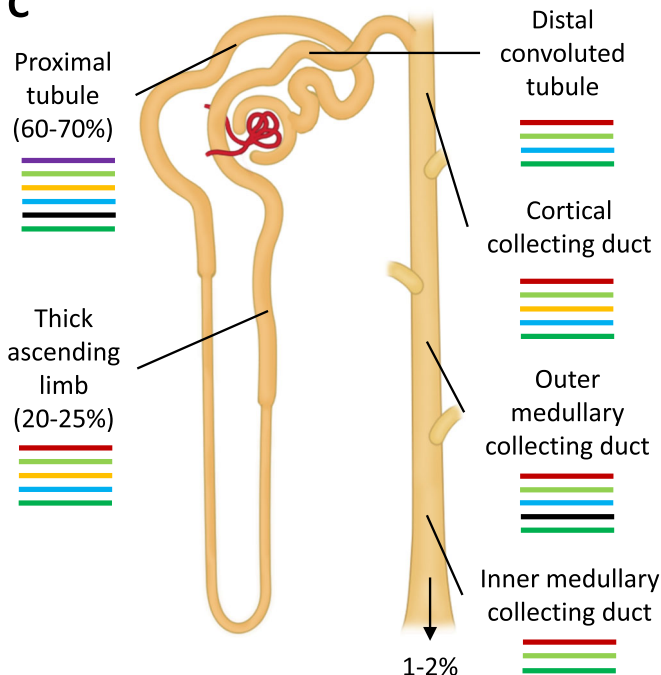


Fig. 1 Renal metabolism and nephron segments. A Major metabolic pathways in the kidney. To make the figure comprehensible, only rate-limiting or key enzymes are shown, and arrows that contain multiple enzymatic steps are shown as dashed arrows. The box surrounded by the dashed line indicates mitochondria. FBP fructose 1,6-bisphosphatase, PEPCK-C cytosolic phosphoenolpyruvate carboxykinase, HK hexokinase, PFK-1 phosphofructokinase-1, PK pyruvate kinase, CPT1 carnitine palmitoyltransferase I, HMGCS2 mitochondrial HMG-CoA synthetase, SCOT succinyl-CoA:3-ketoacid-CoA transferase, GLS glutaminase, CS citrate synthase, IDH isocitrate dehydrogenase, α -KGDH α -Ketoglutarate dehydrogenase. **B** Examples of approved or investigational drugs targeting the metabolic pathways. **C** Major metabolic pathways in nephron segments. Colors of bars correspond to the colors of pathway names in panel A. The percentages indicate the percent of the filtered sodium reabsorbed or excreted.

sodium reabsorption in the thick ascending limb, increased medullary tissue oxygenation to similar levels in the two groups, suggesting that the thick ascending limb in African Americans might have greater reabsorptive activities and consume more oxygen³⁰. The salt sensitivity level was not known for the individuals examined in this previous study; however, blood pressure in African Americans is more likely to be salt-sensitive compared with Americans of European descent³¹.

The Dietary Approaches to Stop Hypertension (DASH)-Sodium trial examined the effect of ~30 days of 50, 100, or 150 mmol of sodium intake on blood pressure using a randomized, crossover study design³². The trial demonstrated that higher sodium intake significantly increased blood pressure. A targeted metabolomic analysis identified a significant inverse correlation between urinary levels of β -aminoisobutyric acid (BAIBA), a metabolite of thymine and valine, and systolic blood pressure in a subset of DASH-Sodium subjects on the low- or high-sodium intake³³. BAIBA was previously reported to be inversely correlated with cardiometabolic risk factors in the Framingham Heart Study cohort³⁴. Positive correlations were identified for cystine, citrulline, homocysteine, and lysine with systolic blood pressure and cystine with diastolic blood pressure in the DASH-Sodium participants³³. Urinary levels of several metabolites including fumarate, a TCA cycle intermediate, appeared to be able to classify the participants as salt-sensitive or salt-insensitive³³.

In the absence of a change in glomerular filtration or tubular reabsorption and secretion of a metabolite, a dissociation of changes in urinary and plasma levels of the metabolite would suggest the intrarenal synthesis or catabolism of the metabolite has been altered. Renal handling of a metabolite, including intrarenal metabolism, may also influence plasma levels of the metabolite. Several studies have identified serum or plasma metabolites that are associated with blood pressure or hypertension or predictive of incident hypertension^{35–37}. These metabolites include amino acids, such as glycine and serine, lactate, phospholipids, and fatty acids. The role of the kidneys in determining circulating levels of these metabolites and the effect of these metabolites on renal function remain to be examined.

Genetic factors associated with intermediary metabolism and hypertension. Several DNA sequence variations that influence intermediary metabolism or mitochondrial function have been shown to contribute to the development of hypertension or are associated with blood pressure in humans. A homoplasmic mutation substituting cytidine for uridine immediately 5' to the mitochondrial tRNA^{Leu} anticodon causes a cluster of maternally inherited diseases, including hypertension³⁸. Mitochondrial tRNAs are required for the translation of proteins, including several components of the electron transport chain, encoded by the mitochondrial genome. Other mutations in mitochondrial tRNAs also reportedly cause maternally inherited hypertension, and these mutations decrease the efficiency of mitochondrial oxygen utilization³⁹.

Genome-wide association studies involving as many as 1 million humans have identified >1000 genomic loci that are significantly associated with blood pressure^{40,41}. The >26,000 single-nucleotide polymorphisms (SNPs) in these loci include nonsynonymous and potentially damaging SNPs in 63 genes⁴². In total, 12 of the 63 genes are known to be involved in intermediary metabolism or mitochondrial function (Table 1).

Most of the blood pressure-associated SNPs are in noncoding regions of the genome and may influence blood pressure by influencing gene expression. An expression quantitative trait locus (eQTL) is a DNA sequence variant for which individuals

Table 1 Metabolism-related genes containing common amino acid sequence variations that are associated with human blood pressure^a.

Gene symbol	Gene name
<i>ADO</i>	2-aminoethanethiol dioxygenase
<i>APOE</i>	Apolipoprotein E
<i>DBH</i>	Dopamine beta-hydroxylase
<i>DDHD2</i>	DDHD domain containing 2
<i>ERAP1</i>	Endoplasmic reticulum aminopeptidase 1
<i>F2</i>	Coagulation factor II, thrombin
<i>IMMT</i>	Inner membrane mitochondrial protein
<i>MTHFR</i>	Methylenetetrahydrofolate reductase
<i>PPRC1</i>	Peroxisome proliferator-activated receptor gamma, coactivator-related 1
<i>PRKAG1</i>	Protein Kinase AMP-activated non-catalytic subunit gamma 1
<i>PTPMT1</i>	Protein tyrosine phosphatase, mitochondrial 1
<i>RHOT2</i>	Ras homolog family member T2
<i>SULT1C3</i>	Sulfotransferase family 1C member 3
<i>TNXB</i>	Tenascin XB

^aThese genes are known to be involved in intermediary metabolism or mitochondrial function based on the gene functional annotation retrieved using the Database for Annotation, Visualization and Integrated Discovery (DAVID). In addition, these genes contain nonsynonymous and potentially damaging single-nucleotide polymorphisms associated with human blood pressure with genome-wide significance⁴².

possessing different alleles of the variant show different expression levels of a gene in one or more tissues⁴². Several hundred blood pressure-associated SNPs are eQTLs in kidney regional tissues or tissues included in the Genotype-Tissue Expression Project for 50 genes that are known to influence the physiology of blood pressure regulation⁴². In total, 23 of these 50 genes are known to be involved in intermediary metabolism or mitochondrial function (Table 2).

The specific role of the kidneys in mediating the effect of these mitochondrial or nuclear DNA sequence variations and associated metabolic enzymes on blood pressure remains to be investigated. Hypertension is not an indication for renal biopsy, and hypertension often occurs together with other disease conditions, making it difficult to study the role of renal molecular or metabolic changes in the development of human hypertension. Nonetheless, a gene expression microarray analysis shows substantial downregulation of amino acid catabolism and synthesis, and fatty acid oxidation in kidneys biopsied from patients with hypertensive nephrosclerosis compared with healthy controls, which is associated with lower urine excretion of several amino acids⁴³.

These aforementioned analyses performed in human subjects indicate that hypertension or blood pressure salt sensitivity is associated with changes in renal regional tissue oxygenation and energy and substrate metabolism, especially amino acid metabolism. Energy and substrate metabolism may contribute to the effect of rare and common genetic variants on blood pressure in humans.

Renal metabolism in animal models of hypertension. Animal models are essential for hypertension research, since it is not possible to model blood pressure regulation adequately with any in vitro experimental system⁴⁴. Renal metabolism has been studied in several animal models of hypertension, especially the Dahl salt-sensitive (SS) rat and the spontaneously hypertensive rat (SHR). The SS rat is the most widely used genetic model of human salt-sensitive hypertension³¹. SS rats exhibit a rapid and progressive increase of blood pressure within days upon exposure to a high-salt diet. The kidneys, including the renal medulla, play

Table 2 Metabolism-related genes that may mediate the effect of common noncoding DNA sequence variations on human blood pressure^a.

Gene symbol	Gene name	GTEx eQTL	eQTL kidney region
ACE	Angiotensin I converting enzyme	Yes	Glom, TI
ADM	Adrenomedullin	Yes	
AGT	Angiotensinogen	Yes	Glom, TI
AVP	Arginine vasopressin	Yes	
CYP11B1	Cytochrome P450 family 11 subfamily B member 1		Glom
CYP4F12	Cytochrome P450 family 4 subfamily F member 12		TI
DDAH1	Dimethylarginine dimethylaminohydrolase 1		TI
DRD5	Dopamine receptor D5		TI
ENPEP	Glutamyl aminopeptidase	Yes	
ERAP1	Endoplasmic reticulum aminopeptidase 1	Yes	Glom, TI
ERAP2	Endoplasmic reticulum aminopeptidase 2	Yes	Glom, TI
GCH1	GTP cyclohydrolase 1	Yes	
LNPEP	Leucyl and cysteinyl aminopeptidase	Yes	Glom
LRP5	LDL receptor-related protein 5	Yes	
MME	Membrane metalloendopeptidase		Glom
NISCH	Nischarin		Glom
NOS3	Nitric oxide synthase 3	Yes	
NPPA	Natriuretic peptide A	Yes	Glom
NPR2	Natriuretic peptide receptor 2	Yes	
PDE4D	Phosphodiesterase 4D		Glom
PIK3R1	Phosphoinositide-3-kinase regulatory subunit 1		TI
SLC2A5	Solute carrier family 2 member 5		TI
TACR3	Tachykinin Receptor 3		TI

GTEx Genotype-Tissue Expression Project, eQTL expression quantitative trait locus, Glom glomerulus, TI renal tubulointerstitial compartment.

^aThese genes are known to be involved in intermediary metabolism or mitochondrial function based on the gene functional annotation retrieved using the Database for Annotation, Visualization and Integrated Discovery (DAVID). In addition, these genes are eQTL genes for human blood pressure-associated single-nucleotide polymorphisms with genome-wide significance, and they are known to be physiologically important for blood pressure regulation based on Gene Ontology⁴².

an essential role in the development of salt-induced hypertension in SS rats^{45,46}. SHR exhibit gradual and spontaneous increases in blood pressure with age.

Metabolic pathways are prominent findings of global, agnostic analyses of the kidneys from animal models of hypertension, similar to findings from human kidney biopsies with hypertensive nephrosclerosis⁴³. An RNA-seq analysis of the renal outer medulla identified nine pathways that were altered between SS rats on a diet containing 0.4% salt and after seven days on the same diet containing 4% salt²⁴. Seven of the nine pathways were involved in amino acid metabolism, and another was peroxisome proliferator-activated receptor (PPAR) signaling, which is a potent regulator of cellular metabolism. Another RNA-seq analysis of the renal outer medulla comparing SS rats on the 0.4% salt diet and after 14 days on the 4% salt diet identified eight pathways that included PPAR signaling and five pathways involved in amino acid metabolism⁴⁷.

Oxygen metabolism and mitochondrial bioenergetics. Renal hypoxia may occur in hypertension and contribute to the development of hypertensive renal injury⁴⁸. Whether changes in oxygen metabolism in the kidneys contribute to the development of hypertension is less clear. Renal oxygen metabolism is altered in SHR^{49,50}. Renal inner medullary blood flow is reduced in prehypertensive SHR⁵¹. PO₂ is significantly lower in the outer cortical proximal and distal convoluted tubules but not in the efferent arterioles of SHR when compared with normotensive Wistar Kyoto (WKY) rats⁵². Kidneys of SHR exhibit a sharp reduction in the oxygen utilization efficiency with significantly higher oxygen consumption for a unit of tubular sodium reabsorption⁵². Nitric oxide (NO) may decrease oxygen consumption by inhibiting several mitochondrial enzymes, including aconitase, electron transport chain complexes I and II, and cytochrome oxidase⁵³. Stimulators of endogenous NO production decrease

renal cortical oxygen consumption more prominently in WKY than they do in SHR⁵⁴. This difference between SHR and WKY could be eliminated by the superoxide scavenger tempol. Basal oxygen consumption rate, ATP synthesis-linked oxygen consumption rate, and maximum and reserve respiration are higher in renal proximal tubule cells in primary culture from SHR⁵⁵. Treatment with dichloroacetate, an inhibitor of pyruvate dehydrogenase kinase, increases pyruvate dehydrogenase activity and systolic blood pressure in 3–4 weeks old SHR and WKY rats⁵⁵.

SS rats exhibit elevated reabsorption activities in the tubular loop that includes the thick ascending limb, which may contribute to the impaired pressure natriuresis in SS rats^{56,57}. High-salt diet decreases cell surface Na⁺-K⁺-2Cl⁻ cotransporter (NKCC2) expression and furosemide-sensitive oxygen consumption, an index of NKCC2-sensitive sodium reabsorption, in the thick ascending limb of salt-resistant (SR) rats but not in SS rats⁵⁸. Renal medullary blood flow is decreased in SS rats within a few days after the start of a high-salt diet^{59,60}.

Mitochondrial alterations have been reported in the kidneys of SS rats (Fig. 2). Longer mitochondria (>2 μm), which may indicate healthier mitochondria, account for a significantly smaller fraction of mitochondria in medullary thick ascending limbs of the loop of Henle, but a larger fraction in proximal tubules, in SS rats compared with salt-insensitive consomic SS.13^{BN} rats and Sprague-Dawley (SD) rats⁶¹. These changes occur before the development of substantial hypertension and overt renal injury. The oxygen consumption rate of intact medullary thick ascending limb cells and state 3 respiration of mitochondria isolated from the renal outer medulla are lower in SS rats than in SS.13^{BN} rats fed an 8% NaCl diet for 7 days⁶². Proteomic analysis of mitochondria isolated from medullary thick ascending limbs identified several proteins as differentially expressed between the two rat strains⁶². ATP contents of mitochondria isolated from the renal cortex or medulla are

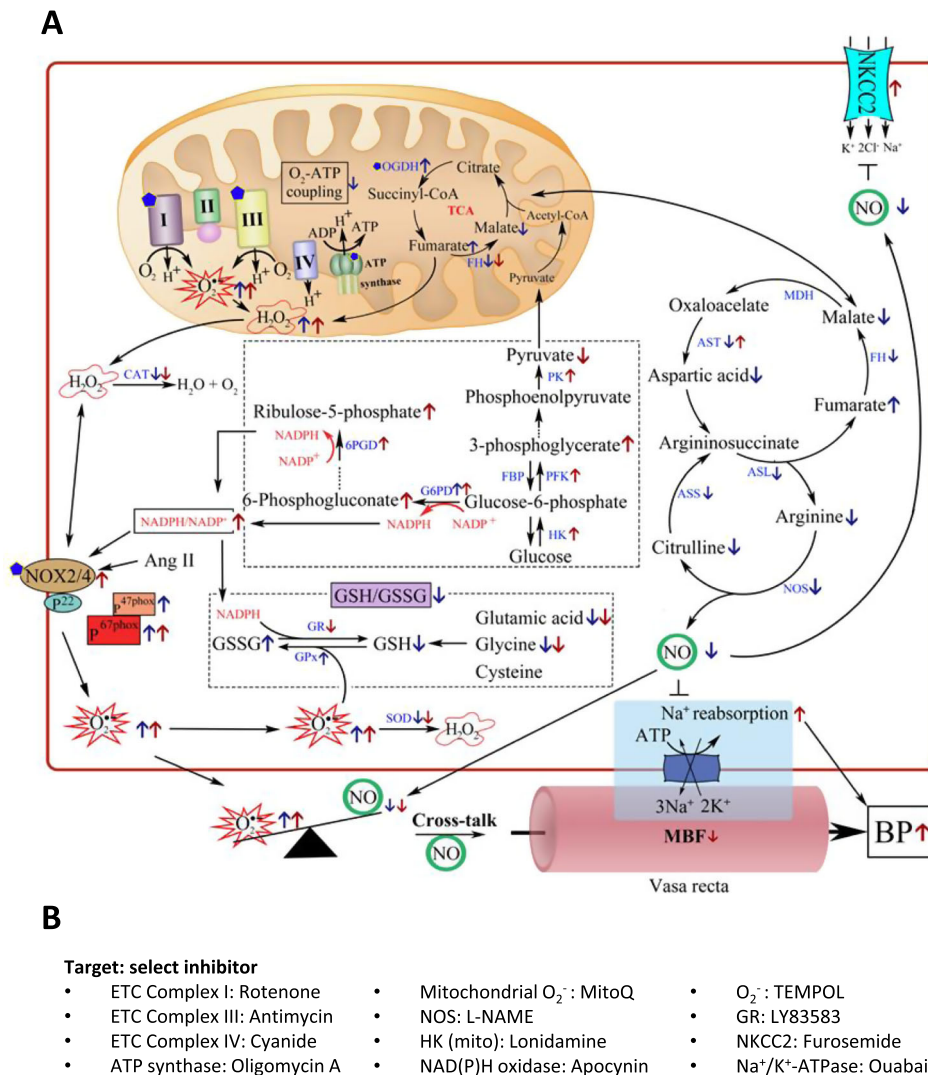


Fig. 2 Renal metabolic mechanisms of hypertension in Dahl salt-sensitive (SS) rats. A Renal metabolic mechanisms of hypertension. This figure is primarily based on data obtained from analyses of the renal medulla or the medullary thick ascending limb of the loop of Henle in SS rats. Some of the indicated changes also occur in the renal cortex. The blue arrows represent increased or decreased content (or activity) in SS rats relative to salt-insensitive rats, including SS-13^{BN} rats. The red arrows represent increased or decreased content (or activity) in SS rats fed a high-salt diet. Blue pentagons represent sites of reactive oxygen species generation. Black arrow and inverted T mark (⊥) represent positive and negative influence, respectively. Some of these regulatory relations and their causal role in the development of hypertension remain to be tested in the specific context of SS kidneys. TCA tricarboxylic acid cycle, OGDH α-ketoglutarate dehydrogenase, FH, fumarase; MDH, malic dehydrogenase; ASS, argininosuccinate synthetase; ASL, argininosuccinate lyase; AST, aspartate aminotransferase, NOS nitric oxide synthase, HK hexokinase, PFK phosphofructokinase, G6PD glucose-6-phosphate dehydrogenase, 6PGD 6-phosphogluconate dehydrogenase, GSH glutathione, GSSG glutathione disulfide, GR glutathione reductase, GPx glutathione peroxidase, NKCC2 Na-K-2Cl cotransporter, SOD superoxide dismutase, CAT catalase, MBF medullary blood flow. **B** Examples of chemical inhibitors of components of the metabolic mechanisms shown in panel (A). Other inhibitors may be available, and the inhibitors listed may have additional targets. ETC electron transport chain, L-NAME L-N^G-nitro arginine methyl ester.

similar between SS and SS.13^{BN} rats on a 0.4% salt diet, while mitochondrial membrane potential and ATP production rate are lower in SS rats⁶³. Treatment with a 4% NaCl diet for 7 or 21 days resulted in lower ratios of ATP/ADP, GTP/GDP, and NADH/NAD⁺ in the glomeruli, but not the cortical tissue, of SS rats⁶⁴. These studies suggest structural and functional changes might occur in mitochondria in kidneys of hypertension models.

Changes in renal oxygen metabolism or mitochondrial bioenergetics may lead to changes in the level of substrate metabolic intermediaries, which in turn influence blood pressure regulation, as discussed in later sections of this article. Changes in renal oxygen metabolism and mitochondrial bioenergetics may also lead to changes in reactive oxygen species (ROS) production (Fig. 2). Excessive ROS, particularly superoxide and hydrogen

peroxide, is present in the kidneys of animal models of hypertension and may contribute to the development of hypertension through several mechanisms, such as decreasing NO bioavailability^{46,65}. NAD(P)H oxidase is upregulated and ROS scavenging enzymes superoxide dismutase and catalase are downregulated in the kidneys of SS rats on a high-salt diet⁶⁶⁻⁶⁸. In mitochondria, electron “leaks” from the electron transport chain may lead to a one-electron reduction of O₂ and the generation of superoxide⁶⁹⁻⁷¹. Mitochondrial ROS may contribute to the development of hypertension and mitochondria-targeted antioxidants may attenuate hypertension⁷²⁻⁷⁶. Uncoupling proteins (UCP) allow proton leakage back across the inner mitochondrial membrane without generating ATP and could lower oxygen utilization for ATP production and increase oxygen

consumption. Mice null for the redox-sensitive chaperone DJ-1 exhibit hypertension and an upregulation of renal UCP2 expression. UCP2 knockdown by renal subcapsular infusion of a siRNA attenuates hypertension and increases serum NO metabolite levels in these mice⁷⁷. How the changes in renal oxygen metabolism and mitochondrial bioenergetics in hypertensive animal models may change mitochondrial ROS production remains to be investigated.

The TCA cycle. Proteomic analysis of the renal cortex and medulla identified fumarase as one of the proteins that showed the most substantial differences in expression between SS and SS.13^{BN} rats²⁶. Fumarase converts fumarate to L-malate in the TCA cycle. The gene that encodes fumarase, *Fh*, contains a nucleotide difference between the SS allele and the BN allele that results in the presence of lysine at amino acid position 481 in SS rats and glutamic acid in BN and SS-13^{BN} rats⁷⁸. Despite an apparent compensatory increase in fumarase abundance in SS rats, total fumarase activity in the kidneys is significantly lower in SS rats compared with SS.13^{BN} rats^{78,79}. Transgenic overexpression of fumarase in SS rats attenuates salt-induced hypertension⁸⁰. The knockdown of renal fumarase in SD rats using a siRNA delivered directly into the renal medullary interstitium exacerbates salt-induced hypertension⁸⁰. Intravenous infusion of a fumarate precursor in SS.13^{BN} rats results in a fumarate excess in the renal medulla comparable with that seen in SS rats and significantly exacerbates salt-induced hypertension in SS.13^{BN} rats⁷⁸. Renal medullary H₂O₂ contributes to the development of salt-induced hypertension in SS rats⁸¹. Fumarate increases the levels of H₂O₂ in the renal medulla in vivo and cultured human renal epithelial cells in vitro, the mechanism of which remains unclear^{78,82}. NADPH oxidase-derived ROS may downregulate fumarase and increase fumarate in mouse glomeruli⁸³, potentially forming a vicious cycle between fumarate and ROS.

L-malate is converted to oxaloacetate by malate dehydrogenase. Oxaloacetate may be combined with acetyl-CoA to form citrate in the TCA cycle but can also be converted to aspartate via aspartate transaminase. Aspartate may be combined with citrulline by argininosuccinate synthase to form argininosuccinate, which is converted to L-arginine and fumarate by argininosuccinate lyase. L-arginine is the substrate for NO synthase (NOS) for the generation of NO and citrulline. Renal NO protects against the development of hypertension through its vasodilatory effect as well as direct inhibition of sodium reabsorption at several nephron segments^{84,85}. L-arginine, given systemically or directly into the renal interstitium, substantially attenuates hypertension in SS rats^{86,87}. Aspartate, citrulline, L-arginine, and NO levels are reduced in the kidneys of SS rats compared with SS.13^{BN} rats⁷⁹. Oral supplementation with L-malate or aspartate in SS rats reverses the reduction of these metabolites in the kidneys and attenuates salt-induced hypertension⁷⁹. A heterozygous mutation in *Nos3* that results in haploinsufficiency of eNOS exacerbates hypertension and renal injury in SS rats. Transgenic overexpression of fumarase in these rats increases NO and the ratio of L-arginine/citrulline in the renal outer medulla and abolishes hypertension and renal injury that may be attributed to *Nos3* heterozygous mutation⁸⁸. In addition, oral malate supplementation attenuates high-salt-induced elevation of H₂O₂ and lipid peroxidation in the renal medulla of SS rats⁸².

These findings suggest that fumarase insufficiency in SS rats might contribute to the predisposition to developing salt-sensitive hypertension by decreasing NO and increasing H₂O₂ in the kidneys (Fig. 2). In salt-insensitive humans or animals, a high-salt diet may elicit adaptive responses in renal metabolism that prevent the development of hypertension. Pre-existing defects in salt-sensitive individuals, such as fumarase insufficiency, may

hinder such adaptive responses to high-salt intake, resulting in the development of hypertension.

Other TCA cycle components in the kidneys also may be involved in the regulation of blood pressure. Intravenous injection of succinate into rats and mice induces hypertension via activation of the renin-angiotensin system, and this response is abolished in GPR91-deficient mice⁸⁹. The activation of succinate receptor GPR91 could trigger renin release from macula densa cells in the distal convoluted tubule^{90,91}. Circulating succinate is associated with the elevation of blood pressure in SHR⁹². Succinate increases in the plasma, but not in the renal medulla of SS rats, compared with SS.13^{BN} rats^{78,93}.

DNA methylation and demethylation in the renal medulla are involved in the development of hypertension in SS rats^{94,95}. DNA demethylation catalyzed by ten-eleven translocase requires α -ketoglutarate. Circulating citrate may be a significant source of energy in the kidney²². Despite these advances, the precise role of these TCA cycle intermediates in the kidneys in the development of hypertension remains to be investigated.

Carbohydrate metabolism. The proximal tubule normally has low, if any, glycolytic activity^{23,25}. However, proximal tubule cells in primary culture from SHR showed a higher extracellular acidification rate than cells from WKY rats, suggesting elevated glycolytic activity and capacity in SHR⁵⁵. Lactate levels in renal cortical homogenate are slightly higher in SHR than WKY⁵⁵.

Several metabolites and enzymes in the glycolysis and pentose phosphate pathways of glucose catabolism, including 3-phosphoglycerate, 6-phosphogluconate, and ribulose-5-phosphate, are elevated in the kidneys of SS rats fed a high-salt diet (Fig. 2)^{82,96}. The pentose phosphate pathway produces NADPH from NADP. The NADPH/NADP ratio is higher in SS rats fed a high-salt diet⁹⁶. NADPH is a limiting factor for the activity of NADPH oxidase that produces superoxide, and 6-phosphogluconate dehydrogenase may directly interact with the NADPH oxidase complex⁹⁷⁻⁹⁹.

Methylglyoxal (MG) may be produced as a side product of glycolysis. MG could react with lysine, arginine, and cysteine residues of proteins to form irreversible advanced glycation end products¹⁰⁰. Plasma and renal levels of MG and renal levels of MG-induced advanced glycation end products were higher in SHR than WKY rats¹⁰¹. MG increases blood pressure and exacerbates renal injury and oxidative stress in SS rats on a 1% NaCl diet, and these effects were attenuated by the angiotensin II receptor blocker candesartan¹⁰².

High plasma levels of insulin may contribute to hypertension by stimulating renal tubular sodium reabsorption^{103,104}. SS rats exhibit signs of insulin resistance¹⁰⁵. Whether this insulin resistance contributes to sodium retention or hypertension in SS rats is not clear. Fasting plasma glucose and plasma insulin levels, renal insulin receptor mRNA levels, and insulin-binding parameters are similar between SS and SR rats fed either low- or high-salt chow^{105,106}. Notably, the mechanisms underlying insulin resistance in SS rats did not appear to involve canonical insulin signaling¹⁰⁷.

Amino acid metabolism. Systemic changes in amino acid levels are associated with hypertension, and fluid and sodium homeostasis. Lower plasma levels of a large number of amino acids were observed in a group of young hypertensive men compared with control³⁶. A combined treatment of a high-salt diet with saline drinking in mice causes broad changes in energy and substrate metabolism in the liver and skeletal muscle, including amino acid catabolism in the muscle¹⁰⁸. SS rats exhibit significant changes in plasma amino acid levels and skeletal muscle amino acid metabolism compared with SS.13^{BN} rats or in response to a high-salt diet, especially glycine, serine,

and threonine metabolism and alanine, aspartate, and glutamate metabolism^{93,109}. Serum levels of metabolites, including several amino acids and TCA cycle intermediates, have been reported to show circadian variation patterns that may be different between SHR and WKY rats¹¹⁰.

Renal metabolism of several amino acids may contribute to the development of hypertension by influencing blood pressure regulatory mechanisms. The relation of these amino acids with renal energy metabolism is largely unclear as amino acids, with the exception of glutamine, are not normally a key source of energy in the kidneys. However, it is possible that amino acids are used as fuel in the kidneys when renal metabolic abnormalities occur.

The antihypertensive effect of L-arginine, likely through enhancing NO production, is well-established in animal models. NO production and endothelial NOS expression are decreased in SHR compared with WKY^{111–113}. Perinatal dietary supplementation with L-arginine and antioxidants reduces blood pressure in SHR¹¹⁴. L-arginine alone, however, may not attenuate hypertension in SHR^{87,115}. Renal levels of L-arginine and NO are lower in SS rats⁷⁹. NOS activities in the renal outer medulla are lower in SS rats compared with SS.13^{BN} rats after six weeks of a high-salt diet⁶⁶. Activities of neuronal NOS are lower in SS rats than SR rats after four weeks of a high-salt diet¹¹⁶. L-arginine, administered through renal medullary interstitial infusion⁸⁶, intravenous infusion^{117,118}, intraperitoneal injections⁸⁷ or oral supplementation^{87,119,120}, increases the generation of NO and substantially attenuates hypertension in SS rats.

Renal L-arginine may come from the endogenous synthesis in the kidneys or circulating L-arginine. Circulating L-arginine mainly comes from intestinal absorption of protein-derived L-arginine and free L-arginine in the food¹²¹. Endogenous L-arginine is mainly synthesized in the liver and kidneys through the urea cycle. L-arginine synthesized in the liver does not reach the systemic circulation effectively because of the high activity of hepatic arginase^{122,123}. The lower level of renal L-arginine in SS rats might result, in part, from fumarase insufficiency and the subsequent reduction of L-arginine regeneration from citrulline and aspartate, as discussed earlier in this article (Fig. 2). L-arginine transport, which may be inhibited competitively by L-lysine, also appears to be involved in angiotensin II-induced renal cortical vasoconstriction in SD rats and low renal NO bioavailability in SHR^{113,124}.

Citrulline and aspartate are the substrates of endogenous L-arginine synthesis in the kidney. Citrulline is a nonessential amino acid mainly derived from intestinal glutamine breakdown. The liver does not take up citrulline^{125–127}; however, the kidneys may take up circulating citrulline and convert it to L-arginine. Argininosuccinate synthase is a rate-limiting enzyme in the citrulline-NO cycle, and its expression and activity can be induced by citrulline¹²⁸. Citrulline improves renal NO levels and attenuates hypertension in SS and SHR rats^{87,129,130}.

The metabolism of glycine, glutamate, and cysteine may be involved in the development of hypertension by influencing the homeostasis of glutathione (GSH), an important antioxidant, and glutathione disulfide (GSSG) (Fig. 2). The synthesis of GSH is regulated by cysteine availability and GSH/GSSG feedback inhibition¹³¹. Cysteine, delivered as its stable analog N-acetyl cysteine, has antihypertensive effects in humans and animal models and may work directly or through its storage form GSH to decrease oxidative stress¹³². Levels of glycine and glutamate in the renal medulla are lower in SS rats compared with SS.13^{BN} rats⁸². The ratio of GSH/GSSG is lower in the kidney, particularly the renal medulla, of SS rats compared with SS.13^{BN} rats⁸². Glutathione reductase is downregulated and glutathione peroxidase upregulated in the kidneys of SS rats on a high-salt diet^{66,96}.

The kidneys influence the body pool of another cysteine-related amino acid, taurine, by regulating tubular reabsorption of taurine¹³³. Taurine attenuates hypertension in humans and several animal models, including SS rats and SHR^{134–137}. Taurine reduces oxidative stress and elevates kallikrein in the kidney.

Catecholamines, including dopamine, norepinephrine, and epinephrine, play a significant role in regulating renal hemodynamics, renal tubular transport, and blood pressure. Catecholamines are metabolic products of the amino acid tyrosine. Renal proximal tubules and possibly the distal nephron may take up the tyrosine product 3,4-dihydroxyphenylalanine and convert it to dopamine¹³⁸.

Urinary levels of BAIBA, a nonprotein amino acid produced by catabolic metabolism of thymine or branched-chain amino acid valine, are inversely correlated with systolic blood pressure in humans on low- and high-sodium intakes as discussed earlier in this article³³. Treatment with BAIBA significantly attenuates salt-induced hypertension in SS rats³³. Alanine-glyoxylate aminotransferase-2 (AGXT2) is one of the enzymes involved in the metabolism of BAIBA. AGXT2 also may degrade asymmetric dimethylarginine, an endogenous inhibitor of NOS. AGXT2 knockout mice exhibit increased asymmetric dimethylarginine and reduced NO and develop hypertension¹³⁹. Treatment of SS rats with a high-salt diet downregulates valine and another branched-chain amino acid leucine in glomeruli⁶⁴.

The amount and source of dietary protein influence the development of hypertension^{47,140,141}. It remains to be investigated whether changes in renal metabolism, including amino acid metabolism, contribute to the effect of dietary protein on the development of hypertension.

Lipid metabolism. Obesity may contribute to the development of hypertension by altering the renal function through the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system¹⁴². Obesity is associated with abnormalities in bioenergetics in several organ systems, and β oxidation of fatty acids, a major fuel for the kidney, has been implicated in the development of renal injury. However, the role of renal bioenergetic metabolism of lipids in the development of hypertension is largely unclear.

Blood pressure, renal tissue content of triglycerides, and lipid droplets in tubular cells are greater in Otsuka Long-Evans Tokushima Fatty rats than Long-Evans Tokushima Otsuka rats. Treatment with a calcium channel blocker, benidipine, or an angiotensin type 1 receptor blocker, losartan, decreases blood pressure, reduces lipid accumulation in the kidneys, and increases the expression of carnitine palmitoyltransferase-1¹⁴³. Alport syndrome mice develop hypertension and exhibit cholesterol accumulation, dynamin-3 and LDL receptor upregulation, and defective mitochondria in the renal tubule¹⁴⁴. Osteopontin gene deletion reduces renal expression of dynamin-3 and LDL receptor and lowers blood pressure in Alport syndrome mice¹⁴⁴.

A high-salt diet leads to a decrease in the serum level of the ketone body β -hydroxybutyrate in fasting SS rats. Nutritional supplementation of β -hydroxybutyrate precursor, 1,3-butanediol, attenuates renal inflammation and hypertension in SS rats¹⁴⁵. It has been suggested that the cardiovascular and renal benefits of sodium-glucose cotransporter 2 (SGLT2) inhibitors might be in part because the inhibitors cause a shift in myocardial and renal fuel metabolism from fat and glucose oxidation to ketone bodies¹⁴⁶. It is unclear whether any such shift is relevant to the blood pressure-lowering effect of SGLT2 inhibition.

Non-energetic metabolism of lipids in the kidneys produces several metabolites that play significant roles in the regulation of blood pressure through their effects on renal hemodynamics and tubular transport. These metabolites include cytochrome P450

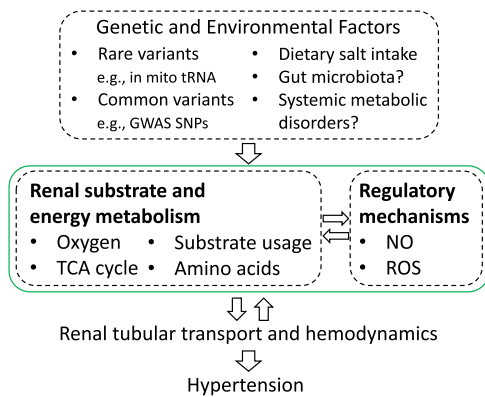


Fig. 3 The proposed overall mechanism by which renal energy and substrate metabolism contribute to the development of hypertension. It

is well-established that genetic and environmental factors influence renal tubular transport and hemodynamics, which, in turn, contribute to the development of hypertension and cause changes in renal energy and substrate metabolism. Recent advances in human and animal model research indicate that renal energy and substrate metabolism may also influence the development of hypertension, which may be mediated by novel effects of renal energy and substrate metabolism on regulatory substances including NO and ROS and subsequent effects on renal tubular transport and hemodynamics. Mito mitochondria, GWAS SNPs blood pressure-associated single-nucleotide polymorphisms identified by genome-wide association studies, TCA tricarboxylic acid, NO nitric oxide, ROS reactive oxygen species.

metabolites of arachidonic acids 20-hydroxyeicosatetraenoic acid and epoxyeicosatrienoic acids, cyclooxygenase metabolites prostaglandin E₂, prostaglandin I₂, and thromboxane A₂, and lipoxygenase metabolites leukotrienes, hydroxyeicosatetraenoic acids, and lipoxins. The role of these metabolites in the development of hypertension has been reviewed elsewhere^{147–149}.

Summary and perspectives

In summary, recent studies have led to several key advances in our understanding of the role of renal energy and substrate metabolism in the development of hypertension (Fig. 3). First, several rare and common genetic variants that influence blood pressure in humans may do so by affecting energy or substrate metabolism. Second, hypertension or blood pressure salt sensitivity is associated with changes in renal tissue oxygenation and substrate metabolism, especially amino acid metabolism, in both humans and well-established animal models. Third, renal energy and substrate metabolism may influence the development of hypertension via a range of mechanisms, some unexpected. For example, TCA cycle enzymes or intermediaries may influence hypertension by changing the level of amino acids, NO or ROS or binding to orphan receptors^{78,79,88,89}.

Renal energy and substrate metabolism are closely tied to renal hemodynamics and tubular transport. Changes in renal tubular transport or hemodynamics may alter energy demands or oxygen supply, leading to changes in renal energy metabolism. Emerging evidence reviewed in this article suggests that the reverse might also occur (Fig. 3). That is, alterations of renal energy and substrate metabolism may influence renal tubular transport and hemodynamics and thereby the regulation of blood pressure and the development of hypertension. These alterations of renal energy and substrate metabolism may result from inherent abnormalities, including genetic defects, attempts of the kidneys to respond to environmental stressors, such as high-salt intake, or a combination of internal and external factors. The alterations of renal energy and substrate metabolism may meet the energy

demand but disturb regulatory mechanisms, such as NO levels and redox balance, resulting in dysregulation of renal tubular transport and hemodynamics and the development of hypertension. It is an intriguing possibility that renal energy and substrate metabolism may influence blood pressure through mechanisms that are not dependent on bioenergetics alone.

Thorough investigation of the regulatory model shown in Fig. 3 requires concerted efforts of physiologists, biochemists, geneticists, and computational biologists and a molecular systems medicine approach^{94,150,151}. Going forward, it will be of primary importance to better understand the in vivo metabolic profiles and dynamics in the kidneys and nephron segments of animals and humans, and the investigation of genetic and environmental factors that lead to the development of hypertension by influencing these metabolic processes may help identify any pro-hypertensive regulatory dysfunctions that result from such metabolic abnormalities. Ultimately, it will be important to examine whether targeting these metabolic abnormalities may represent an advantageous therapeutic approach for certain subgroups of hypertensive patients. Recent studies have begun to shed light on these questions, but the study of the role of renal energy and substrate metabolism in the development of hypertension remains a largely open field.

Several exciting areas of research provide additional opportunities to explore the role of renal energy and substrate metabolism in hypertension (Fig. 3). Obesity, diabetes, and other systemic metabolic disorders are closely related to hypertension. New treatments for diabetes, such as SGLT2 inhibitors, have significant blood pressure-lowering effects¹⁵². Changes in the gut microbiota have also been shown to influence blood pressure¹⁵³. It would be interesting to understand how broad metabolic disturbances in patients with systemic metabolic disorders or altered gut microbiota may involve renal energy and substrate metabolism and whether the renal metabolic involvement might play a role in the development and progression of hypertension in these patients.

Received: 24 May 2020; Accepted: 18 January 2021;

Published online: 11 February 2021

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Acknowledgements

This work was supported by US National Institutes of Health grants HL116264-5244 and HL121233 and Advancing a Healthier Wisconsin Endowment (to M.L.) and National Natural Science Foundation of China grants Nos. 81770728 and 81570655 (to Z.T.). The authors thank Kristin Nord, Xuewei Zheng, and Meng Chen for assistance with references.

Author contributions

M.L. designed the structure of the article. Z.T. and M.L. wrote the article and prepared the figures.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to M.L.

Peer review information *Nature Communications* thanks the anonymous reviewer(s) for their contribution to the peer review of this work.

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