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Review

New advances in renal mechanisms of high fructose-induced salt-sensitive hypertension

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Abstract: Fructose intake has increased dramatically over the past century and the upward trend has continued until recently. Increasing evidence suggests that the excessive intake of fructose induces salt-sensitive hypertension. While the underlying mechanism is complex, the kidney likely plays a major role. This review will highlight recent advances in the renal mechanisms of fructose-induced salt-sensitive hypertension, including (pro)renin receptor-dependent activation of intrarenal renin-angiotensin system, increased nephron Na^+ transport activity via sodium/hydrogen exchanger 3 and Na/K/2Cl cotransporter, increased renal uric acid production, decreased renal nitric oxide production, and increased renal reactive oxygen species production, and suggest actions based on these mechanisms that have therapeutic implications.

Key words: fructose; salt-sensitive hypertension; intrarenal renin-angiotensin system; (pro)renin receptor; nephron ion transporter; uric acid; nitric oxide; reactive oxygen species

果糖诱导盐敏感性高血压的肾脏机制

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摘 要：从过去一个世纪以来，果糖的进食量急剧增加，并且与糖尿病、肥胖、肾衰、高血压等的发生密切相关。目前越来越多的证据证明过量的果糖饮食会引起盐敏感性高血压，其发生机制十分复杂，但是肾脏可能在其中扮演着重要的角色。本文主要阐述了果糖诱导盐敏感性高血压的肾相关机制，包括肾素原受体依赖的肾内肾素-血管紧张素系统的活化，肾内Na^+转运体钠氢交换子3 (sodium/hydrogen exchanger 3, NHE3)和Na-K-2Cl共转运体(Na/K/2Cl cotransporter, NKCC2)的活化，肾内尿酸产生的增加，肾内一氧化氮合成的降低，以及肾内活性氧产生的增加，并以此为理论依据提出潜在的治疗盐敏感性高血压的靶点或策略。

关键词：果糖；盐敏感性高血压；肾素原受体；肾内肾素-血管紧张素系统；Na/H交换子3；Na/K/2Cl共转运体；尿酸；一氧化氮；活性氧
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1 Introduction

Hypertension is the major risk factor for the high morbidity and mortality of cardiovascular disease and kidney disease. The number of adults with elevated blood pressure (BP) has increased from 594 million in 1975 to

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1.13 billion in 2015 [1]. More than 40% of persons > 25 years have hypertension (http://apps.who.int/iris/handle/10665/79059). It is the leading cause of death and disability globally [2], given that an estimated 1 600 million people a year, die from cardiovascular disease, and about 50% of them are caused by hypertension [3]. It is often referred to as "the silent killer" with low awareness, treatment and control rate, frequently displaying no overt symptomatology, and only 50% of the patients' BP were under control [3].

Increased salt intake represents a major environmental factor that contributes to pathogenesis of essential hypertension. Enhanced sensitivity of BP to salt intake is present in nearly half of Americans who are afflicted with hypertension, including approximately 75% of African American hypertensive patients [1–3]. A large epidemiological study performed by Elliott *et al*. showed that individual 24-hour urinary Na^+ excretion higher by 100 mmol was associated with systolic/diastolic BP higher than average by 6/3 mmHg [4]. Similarly, another large clinical trial performed by Cutler *et al*. showed that individual 24-hour Na^+ intake lower by 100 mmol was associated with systolic/diastolic BP lower than average by 5.8/2.5 mmHg [5]. High-salt (HS) diet is particularly prominent in China. It was reported that the 24-hour urinary Na^+ excretion of man/woman was 299/253 mmol in north China (Beijing) and the 24-hour salt intake of man in Tianjin was 254 mmol, while in the south China (Guangxi), the 24-hour salt intake of man/woman was 150/128 mmol, which corresponds to a higher incidence of hypertension and stroke in north China than that in south China [6, 7]. Thus, there appears to be a positive correlation relationship between salt intake and BP, and a better understanding of the mechanisms of salt-sensitive hypertension (SSH) is important for the prevention and control of hypertension.

Fructose is a monosaccharide that is widely present in natural food sources such as fruits, vegetables, and honey. In addition to hepatic origin, approximately 50% of the filtered fructose is reabsorbed in the proximal tubules (PTs) via the fructose transporters SGLT5, GLUT5 and GLUT2, and metabolized via fructokinase (KHK), which depletes adenosine triphosphate (ATP) and generates adenosine diphosphate (ADP), then stimulates adenosine monophosphate (AMP) deaminase and increases the degradation of nucleotides to form uric acid (UA) [8–10]. Intake of fructose has increased dramatically over the last century and the upward trend continued until recently since fructose has been used as sweet additives (https://www.ers.usda.gov/publications/pub-details/?pubid=90411) [11]. It has been nearly 31 years since Hwang *et al*. in 1987 for the first time showed that fructose-fed rats exhibit insulin resistance, hyperinsulinemia, hypertriglyceridemia, and hypertension [12]. Since then, more studies suggested that excessive fructose intake is linked to the epidemics of diabetes mellitus, obesity, renal failure, hypertension, and electrolyte dysregulation [13–17]. A number of studies have linked high-fructose (HF) feeding with hypertension and provided several possible mechanisms including increased sympathetic nervous system activity, circulating catecholamines, renin-angiotensin system (RAS) activity and angiotensin II (Ang II) levels, Na^+ reabsorption, secretion of endothelin-1, production of UA, and impaired endothelium-dependent relaxation, *etc*. These topics have been covered by a number of comprehensive reviews [18–21].

It has recently been shown that HF alone had no effect on BP but a combination of HF and HS diet induced SSH as assessed by using radiotelemetry [22–27]. We for the first time demonstrated an important role of (pro)renin receptor (PRR) in mediating HF-induced SSH in rats. Further evidence from our study and others suggests a potential mechanism involving overactivation of intrarenal RAS, and the mechanism may involve activation of ion transporters including sodium/hydrogen exchanger 3 (NHE3) [26, 27], Na/K/2Cl cotransporter (NKCC2) [17, 27], and Na^+-K^+-ATPase [28, 29], and increased renal reactive oxygen species (ROS) [30], increased renal UA production [27], and decreased renal nitric oxide (NO) [31]. Here, the major objective of this article is to review recent advances in this filed with emphasis on PRR and intrarenal RAS.

2 Renal PRR regulates intrarenal RAS during HF-induced SSH

The RAS has been known for about 120 years since renin was first discovered by Tigerstedt and Bergman in 1898 [32]. During the past decade, there has been a paradigm shift in our understanding of the RAS. Increasing evidence suggests a local RAS has been found in various target tissues including heart, blood vessels, brain, adrenal glands, and kidney [33, 34]. Strong evidence suggests that intrarenal RAS contains all the RAS components, including angiotensinogen (AGT), prorenin/renin, angiotensin-converting enzyme (ACE), Ang II type 1 receptor (AT1R), AT2R, AT4R, and PRR,

which play a crucial role in hypertension and kidney diseases [35, 36]. Aberrant activation of local RAS plays a pivotal role in the pathogenesis of hypertension as well as cardiovascular and renal disease. In particular, Dahl salt-sensitive rats showed suppressed circulating RAS but enhanced intrarenal RAS as reflected by increases of renal PRR, AGT, ACE, AT1R, and Ang II levels following HS loading, respectively reported by Kobori *et al*.[37] and Zhu *et al*.[38].

PRR, a new component of the RAS, was first cloned as a specific receptor for prorenin and renin by Nguyen *et al.* in 2002 [39]. Although Cousin *et al*. [40] and Yoshikawa *et al*. [41] respectively reported that PRR can be cleaved by furin or A Disintegrin and Metalloproteinase 19 (ADAM19) to generate soluble PRR (sPRR), Nakagawa *et al*. [42] recently reported that site-1 protease (S1P) is a dominant enzyme in the generation of sPRR. Full-length PRR is synthesized in endoplasmic reticulum and then cleaved by S1P in Golgi apparatus (Golgi), and furin in the *trans*-Golgi network to generate sPRR for extracellular secretion [42]. Consistently, our recent published data showed that S1P but not furin or ADAM19 is responsible for the sPRR generation induced by bovine serum albumin treatment, which plays an essential role in the regulation of renin activity [43]. It is increasingly evident that PRR/sPRR serves a multitude of functions [44] in regulating embryogenesis via vacuolar H^+-ATPase and Wnt/β-catenin signaling [45], balancing sodium via NADPH oxidase 4 (NOX4)/H_2O_2 signaling [46], regulating water via prostaglandin E2/prostaglandin E2 type 4 receptor signaling [47] or liver X receptor [48], modulating acid secretion via vacuolar H^+-ATPase [49], *etc*.

Despite some controversial reports, increasing evidence supports an important role of PRR in the pathogenesis of hypertension and the regulation of local RAS. For example, transgenic rats with human PRR overexpression in vascular smooth muscle cells [50] but not in the whole body [51] exhibited higher BP. Brain-specific PRR knockdown with short hairpin RNA attenuated age-dependent increases in mean arterial pressure in the spontaneously hypertensive rats [52] and Ang II-dependent hypertension [53]. Neuron-specific PRR knockout [54] and intracerebroventricular infusion of the PRR antagonist PRO20 (the first 20 amino acid residues of the prorenin prosegment, L^1PTRTATFERIPLKKMPSVR^{20}) [55] attenuated the development of deoxycorticosterone acetate-salt-induced hypertension. Within the kidney, PRR is expressed in multiple structures including the intercalated cells, mesangial cells, and renal vascular smooth muscle cells. Functional evidence is also available to support a Na^+- and water-retaining and pro-hypertensive action of renal PRR.

In HF model, local RAS is activated in aorta [56], kidney [56, 57], and skeletal muscle [58], as reflected by the upregulation of prorenin/renin, AT1R, Chymase, Ang I, and Ang II levels in these tissues. Consistent with this notion, we recently reported that HF intake significantly increased renal PRR expression and urinary sPRR excretion, in parallel with an increase of renal renin expression and urinary renin and Ang II levels, without affecting plasma Ang II concentrations [27]. Functional evidence demonstrated that PRR antagonism with PRO20 treatment effectively suppressed HF-induced activation of intrarenal RAS as well as SSH [27]. These results support the association between renal PRR and intrarenal RAS in the HF model.

The involvement of systemic RAS in the HF model is inconsistent. Iyer *et al*. reported that plasma Ang II levels of fructose-fed rats were significantly increased at the end of the second week and returned to basal levels at the end of the fourth week of dietary treatment [59]. However, in a rat model of 12-week HF treatment, we found no change in plasma Ang II concentrations [27]. Interestingly, the HS-induced suppression of plasma renin activity is blunted in fructose-fed animals [31, 60], suggesting that dysregulation of systemic RAS may contribute to HF-induced SSH. Future studies are necessary to examine possible coordination of systemic and intrarenal RAS during HF/HS intake.

3 Renal PRR regulates nephron ion transporters during HF-induced SSH

Renal PRR expression responded to changing Na^+ and K^+ balance [61–66], suggesting a potential role of renal PRR in regulation of electrolyte metabolism. Functional evidence demonstrated that renal PRR selectively regulated Ang II- or prorenin-stimulated epithelial Na^+ channel (ENaC) activity and expression [46, 67–69]. Additionally, we have recently reported that activation of renal PRR promoting K^+ secretion during a high K^+ load is via intrarenal renin-angiotensin-aldosterone system [65, 66]. Furthermore, HF intake caused Na^+ retention [70]. We found that PRO20 treatment inhibited HF-induced increase of plasma Na^+ and decrease of urinary Na^+ excretion, associated with suppressed urinary

renin and Ang II levels, and renal NHE3 and NKCC2 expression [27]. Therefore, these studies suggest that PRR-dependent activation of intrarenal RAS may contribute to HF-induced Na^+ retention.

Several studies have shown that fructose intake increased renal Na^+ reabsorption [70] via NHE3 and NKCC2 [17, 26, 27, 71] and Na^+-K^+-ATPase [28, 29], as well as enhanced the sensitivity of PT Na^+ reabsorption to Ang II [26, 72, 73], rendering increased salt sensitivity [17, 31]. In agreement with this notion, we reported that chronic HF intake significantly upregulated renal NHE3 and NKCC2 expression at both mRNA and protein levels as well as the *in vivo* NKCC2 activity and the later was assessed by examining the rapid diuresis and natriuretic responses to furosemide [27]. More importantly, the activation of NHE3 and NKCC2 by fructose was blocked by PRR antagonist PRO20 treatment, in parallel with the changes in the indices of intrarenal RAS and Na^+ retention [27]. These results suggest that PRR-dependent activation of intrarenal RAS may contribute to HF-induced SSH via stimulating ion transporters NHE3 and NKCC2. However, the detailed mechanism of how renal PRR activation mediates HF-induced SSH remains elusive. As discussed above, HF-promoted renal PRR expression has been found in a variety of renal structures including the PTs, the thick ascending limb (TAL), and the collecting duct (CD). Along this line, functional studies showed that multiple ion transporters including NHE3, NKCC2, thiazide-sensitive NaCl cotransporter, ENaCs, and Na^+-K^+-ATPase are under the regulation by PRR during HF feeding [28, 29]. Future studies are needed to determine the relative contribution of the PRR in a particular nephron site to HF-induced SSH and intrarenal RAS.

4 Renal UA regulates PRR and intrarenal RAS during HF-induced SSH

UA, an inert metabolic end-product of purine metabolism, has been recently incriminated in many chronic disease processes, such as hypertension, metabolic syndrome, obesity, non-alcoholic fatty liver disease, and kidney disease [74]. Recently, multiple studies showed that exogenous UA stimulated local RAS leading to oxidative stress in 3T3-L1 adipocytes [75], rat vascular smooth cell proliferation [76], human vascular endothelial cell dysfunction [77], and immortalized human mesangial cell proliferation [78], elevated serum UA increases BP and activates renal RAS [79, 80], suggesting a close link between UA and the RAS.

UA is a major metabolic end products of fructose metabolism and contributes to fructose-induced metabolic syndrome [74]. Besides its hepatic expression, the rate limiting enzyme for fructose metabolism, KHK, is highly expressed in the PTs and TALs where KHK-dependent production of UA contributes to proinflammatory response [81, 82]. Although several literatures reported HF-caused hyperuricemia contributes to fructose-induced hypertension [83, 84], the source of increased UA remains elusive. Some animal studies [8, 27] and a clinical study [85] have shown that HF intake did not demonstrate any elevation in serum UA, but exhibited enhanced urinary UA excretion. Furthermore, we found that allopurinol treatment attenuated HF-induced urinary UA excretion in parallel with suppressed SSH while plasma UA levels largely remained quite constant [27]. These results suggest an intriguing possibility that the UA of renal origin may be causally linked to the generation of SSH during HF intake. It is thus interesting to determine the mechanism of how HF affects local UA production in the kidney. To address this question, the use of nephron-specific deletion of KHK will be highly informative. Further studies in kidney-specific KHK knockout mice are needed to confirm the role of renal KHK-mediated UA production in HF-induced SSH.

Irrespective of the underlying mechanism, inhibition of UA production likely represents an effective antihypertensive intervention. Indeed, allopurinol lowers BP in adolescence with prehypertension [86] and also in adults with established hypertension [87]. We have also reported that allopurinol treatment effectively attenuated HF-induced SSH associated with suppression of renal PRR and intrarenal RAS as well as renal expression of NHE3 and NKCC2 [27].

5 Imbalance between ROS and NO contributes to HF-induced SSH

The pathogenesis of fructose-induced SSH may occur as a result of increased oxidative stress. It has been reported that increased oxidative stress was observed in fructose-fed rats, as reflected by increased aortic NOX [88], increased ventricular [89] and vascular superoxide anion production [89, 90], elevated free radical hydrogen peroxide levels [88], and stimulated urinary 8-isoprostane excretion [60]. Interestingly, in fructose-induced salt-sensitive animals, there is a further enhancement of oxidative stress [91], which may thereby lead to sympathoexci-

tation, at least in part, responsible for the blunted suppression of plasma renin activity by HS intake and the development of SSH. Along with this line, renal denervation attenuates NOX activity and ROS levels in the kidney[92], and cryoablation of the renal nerves significantly decreased plasma renin activity and SSH in fructose-fed rats[93]. Moreover, a recent study by Dornas *et al*. [30] provides a link between oxidative stress and NF-κB pathway, which may contribute to HF-induced SSH and renal injury.

UA acts as a pro-oxidant and once inside cells it stimulates production of ROS via NOX-dependent mitochondrial oxidant system [94], suggesting that UA-induced oxidative stress may be responsible for the BP elevation and the renal injury during HF intake. Of note, oxidative stress also leads to overstimulation of renal NHE3 by exaggerating Ang II signaling [95]. Overall, in fructose/salt models, renal UA-stimulated oxidative stress may contribute to the activation of intrarenal RAS and hence the activation of ion transporters, resulting in increased Na^+ reabsorption and retention.

Reduced NO bioavailability represents a major pathophysiological factor contributing to hypertension due to diverse etiologies. Inhibition of NO synthesis or genetic deletion of endothelial NO synthase (eNOS) resulted in elevated BP [96]. Diminished NO production has been reported in several animal models of hypertension [97, 98] as well as hypertensive individuals [99, 100]. The antihypertensive action of NO is attributed to vascular relaxation and inhibition of tubular ion transport [101–103]. Both the vascular tissues from fructose-fed rats and HF-treated isolated rat mesenteric vascular beds exhibit impaired endothelium-dependent relaxation [18], leading to enhanced vascular tone and elevated BP. In addition, renal medullary eNOS expression [24] and urinary NO metabolites NO_2/NO_3 excretion as a biomarker for renal NO [31] were reduced by HF/HS intake, which may contribute to decreased Na^+ excretion and increased Na^+ retention in HF/HS-fed rats . Of note, the cause and effect between the decreased NO excretion and the decreased Na^+ excretion in HF/HS model is still unknown.

6 Conclusion

It has been well established that fructose/salt intake induces hypertension likely via enhancement of renal Na^+ reabsorption. We have recently reported that the underlying mechanism involves UA-dependent activation of PRR and intrarenal RAS, which leads to increased renal Na^+ reabsorption via multiple renal ion transporters including NHE3, NKCC2, ENaCs, and Na^+-K^+-ATPase, ultimately resulting in elevated BP (Fig. 1). Targeting components of this pathway such as UA production, the activation of PRR or the intrarenal RAS, or ion transport may offer benefits for the patients with hypertension associated with HF and HS intake.

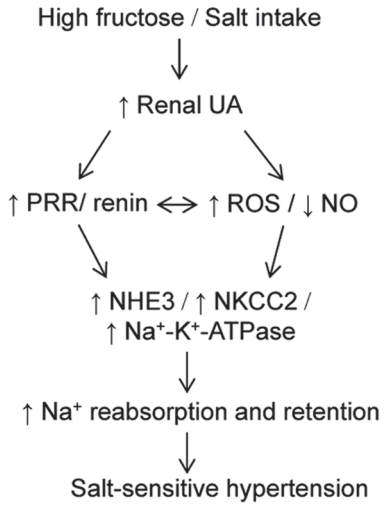

Fig. 1. The proposed renal mechanisms of fructose-induced salt-sensitive hypertension. Experimental evidence is available to demonstrate that high fructose/salt intake causes uric acid (UA)-dependent activation of (pro)renin receptor (PRR) and intrarenal renin-angiotensin system (RAS), along with the imbalance between intrarenal reactive oxygen species (ROS) and nitric oxide (NO), which leads to increased renal Na^+ reabsorption and retention via multiple renal ion transporters including sodium/hydrogen exchanger 3 (NHE3), Na/K/2Cl cotransporter (NKCC2), and Na^+-K^+-ATPase, ultimately resulting in elevated blood pressure.

REFERENCES

1 NCD Risk Factor Collaboration. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. Lancet 2017; 389(10064): 37–55.

2 Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG, Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J, Carnahan E, Chafe Z, Charlson

F, Chen H, Chen JS, Cheng AT, Child JC, Cohen A, Colson KE, Cowie BC, Darby S, Darling S, Davis A, Degenhardt L, Dentener F, Des Jarlais DC, Devries K, Dherani M, Ding EL, Dorsey ER, Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder G, Farzadfar F, Ferrari A, Finucane MM, Flaxman S, Fowkes FG, Freedman G, Freeman MK, Gakidou E, Ghosh S, Giovannucci E, Gmel G, Graham K, Grainger R, Grant B, Gunnell D, Gutierrez HR, Hall W, Hoek HW, Hogan A, Hosgood HD 3rd, Hoy D, Hu H, Hubbell BJ, Hutchings SJ, Ibeanusi SE, Jacklyn GL, Jasrasaria R, Jonas JB, Kan H, Kanis JA, Kassebaum N, Kawakami N, Khang YH, Khatibzadeh S, Khoo JP, Kok C, Laden F, Lalloo R, Lan Q, Lathlean T, Leasher JL, Leigh J, Li Y, Lin JK, Lipshultz SE, Londo S, Lozano R, Lu Y, Mak J, Malekzadeh R, Mallinger L, Marcenes W, March L, Marks R, Martin R, McGale P, McGrath J, Mehta S, Mensah GA, Merriman TR, Micha R, Michaud C, Mishra V, Mohd Hanafiah K, Mokdad AA, Morawska L, Mozaffarian D, Murphy T, Naghavi M, Neal B, Nelson PK, Nolla JM, Norman R, Olives C, Omer SB, Orchard J, Osborne R, Ostro B, Page A, Pandey KD, Parry CD, Passmore E, Patra J, Pearce N, Pelizzari PM, Petzold M, Phillips MR, Pope D, Pope CA 3rd, Powles J, Rao M, Razavi H, Rehfuess EA, Rehm JT, Ritz B, Rivara FP, Roberts T, Robinson C, Rodriguez-Portales JA, Romieu I, Room R, Rosenfeld LC, Roy A, Rushton L, Salomon JA, Sampson U, Sanchez-Riera L, Sanman E, Sapkota A, Seedat S, Shi P, Shield K, Shivakoti R, Singh GM, Sleet DA, Smith E, Smith KR, Stapelberg NJ, Steenland K, Stockl H, Stovner LJ, Straif K, Straney L, Thurston GD, Tran JH, Van Dingenen R, van Donkelaar A, Veerman JL, Vijayakumar L, Weintraub R, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams W, Wilson N, Woolf AD, Yip P, Zielinski JM, Lopez AD, Murray CJ, Ezzati M, AlMazroa MA, Memish ZA. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380(9859): 2224–2260.

3 Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 2017; 135(10): e146–e603.

4 Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, Marmot M. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group. BMJ 1996; 312 (7041): 1249–1253.

5 Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. Am J Clin Nutr 1997; 65(2 Suppl): 643S–651S.

6 Stamler J, Elliott P, Dennis B, Dyer AR, Kesteloot H, Liu K, Ueshima H, Zhou BF, INTERMAP Research Group. INTERMAP: background, aims, design, methods, and descriptive statistics (nondietary). J Hum Hypertens 2003; 17(9): 591–608.

7 Nan Y, Tian HG, Shao RC, Hu G, Dong QN, Pietinen P, Nissinen A. Assessment of sodium and potassium in processed foods in an urban area in China. Eur J Clin Nutr 1995; 49(4): 299–306.

8 Singh AK, Amlal H, Haas PJ, Dringenberg U, Fussell S, Barone SL, Engelhardt R, Zuo J, Seidler U, Soleimani M. Fructose-induced hypertension: essential role of chloride and fructose absorbing transporters PAT1 and Glut5. Kidney Int 2008; 74(4): 438–447.

9 Sugawara-Yokoo M, Suzuki T, Matsuzaki T, Naruse T, Takata K. Presence of fructose transporter GLUT5 in the S3 proximal tubules in the rat kidney. Kidney Int 1999; 56(3): 1022–1028.

10 Hallfrisch J. Metabolic effects of dietary fructose. FASEB J 1990; 4(9): 2652–2660.

11 Tappy L, Le KA. Metabolic effects of fructose and the worldwide increase in obesity. Physiol Rev 2010; 90(1): 23–46.

12 Hwang IS, Ho H, Hoffman BB, Reaven GM. Fructose-induced insulin resistance and hypertension in rats. Hypertension 1987; 10(5): 512–516.

13 Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, Hu FB. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA 2004; 292(8): 927–934.

14 Abdulla MH, Sattar MA, Abdullah NA, Hye Khan MA, Anand Swarup KR, Johns EJ. The contribution of alpha1B-adrenoceptor subtype in the renal vasculature of fructose-fed Sprague-Dawley rats. Eur J Nutr 2011; 50(4): 251–260.

15 Peredo HA, Andrade V, Donoso AS, Lee HJ, Puyo AM. Sodium molybdate prevents hypertension and vascular prostanoid imbalance in fructose-overloaded rats. Auton Autacoid Pharmacol 2013; 33(3–4): 43–48.

16 Palanisamy N, Venkataraman AC. Beneficial effect of

genistein on lowering blood pressure and kidney toxicity in fructose-fed hypertensive rats. Br J Nutr 2013; 109(10): 1806–1812.

17 Ares GR, Ortiz PA. Direct renal effects of a fructose-enriched diet: interaction with high salt intake. Am J Physiol Regul Integr Comp Physiol 2015; 309(9): R1078–R1081.

18 Tran LT, Yuen VG, McNeill JH. The fructose-fed rat: a review on the mechanisms of fructose-induced insulin resistance and hypertension. Mol Cell Biochem 2009; 332(1–2): 145–159.

19 Kretowicz M, Johnson RJ, Ishimoto T, Nakagawa T, Manitius J. The impact of fructose on renal function and blood pressure. Int J Nephrol 2011; 2011: 315879.

20 Soleimani M, Alborzi P. The role of salt in the pathogenesis of fructose-induced hypertension. Int J Nephrol 2011; 2011: 392708.

21 Abdulla MH, Sattar MA, Johns EJ. The relation between fructose-induced metabolic syndrome and altered renal haemodynamic and excretory function in the rat. Int J Nephrol 2011; 2011: 934659.

22 Brands MW, Garrity CA, Holman MG, Keen HL, Alonso-Galicia M, Hall JE. High-fructose diet does not raise 24-hour mean arterial pressure in rats. Am J Hypertens 1994; 7(1): 104–109.

23 Bezerra RM, Ueno M, Silva MS, Tavares DQ, Carvalho CR, Saad MJ, Gontijo JA. A high-fructose diet induces insulin resistance but not blood pressure changes in normotensive rats. Braz J Med Biol Res 2001; 34(9): 1155–1160.

24 Nishimoto Y, Tomida T, Matsui H, Ito T, Okumura K. Decrease in renal medullary endothelial nitric oxide synthase of fructose-fed, salt-sensitive hypertensive rats. Hypertension 2002; 40(2): 190–194.

25 D'Angelo G, Elmarakby AA, Pollock DM, Stepp DW. Fructose feeding increases insulin resistance but not blood pressure in Sprague-Dawley rats. Hypertension 2005; 46(4): 806–811.

26 Cabral PD, Hong NJ, Hye Khan MA, Ortiz PA, Beierwaltes WH, Imig JD, Garvin JL. Fructose stimulates Na/H exchange activity and sensitizes the proximal tubule to angiotensin II. Hypertension 2014; 63(3): e68–e73.

27 Xu C, Lu A, Lu X, Zhang L, Fang H, Zhou L, Yang T. Activation of renal (pro)renin receptor contributes to high fructose-induced salt sensitivity. Hypertension 2017; 69(2): 339–348.

28 Rukavina Mikusic NL, Kouyoumdzian NM, Uceda A, Del Mauro JS, Pandolfo M, Gironacci MM, Puyó AM, Toblli JE, Fernández BE, Choi MR. Losartan prevents the imbalance between renal dopaminergic and renin angiotensin systems induced by fructose overload. L-Dopa/dopamine index as new potential biomarker of renal dysfunction. Metabolism 2018; 85: 271–285.

29 Rukavina Mikusic NL, Kouyoumdzian NM, Del Mauro JS, Cao G, Trida V, Gironacci MM, Puyo AM, Toblli JE, Fernandez BE, Choi MR. Effects of chronic fructose overload on renal dopaminergic system: alteration of urinary L-dopa/dopamine index correlates to hypertension and precedes kidney structural damage. J Nutr Biochem 2018; 51: 47–55.

30 Dornas WC, Cardoso LM, Silva M, Machado NL, Chianca DA Jr, Alzamora AC, Lima WG, Lagente V, Silva ME. Oxidative stress causes hypertension and activation of nuclear factor- kappaB after high-fructose and salt treatments. Sci Rep 2017; 7: 46051.

31 Gordish KL, Kassem KM, Ortiz PA, Beierwaltes WH. Moderate (20%) fructose-enriched diet stimulates salt-sensitive hypertension with increased salt retention and decreased renal nitric oxide. Physiol Rep 2017; 5(7): pii: e13162.

32 Tigerstedt R, Bergman PG. Niere und kreislauf. Scand Arch Physiol 1898; 8: 223–271.

33 Navar LG, Kobori H, Prieto MC, Gonzalez-Villalobos RA. Intratubular renin-angiotensin system in hypertension. Hypertension 2011; 57(3): 355–362.

34 Suzaki Y, Prieto-Carrasquero MC, Kobori H. Intratubular renin-angiotensin system in hypertension. Curr Hypertens Rev 2006; 2(2): 151–157.

35 Zhuo JL, Ferrao FM, Zheng Y, Li XC. New frontiers in the intrarenal Renin-Angiotensin system: a critical review of classical and new paradigms. Front Endocrinol (Lausanne) 2013; 4: 166.

36 Yang T, Xu C. Physiology and pathophysiology of the intrarenal renin-angiotensin system: an update. J Am Soc Nephrol 2017; 28(4): 1040–1049.

37 Kobori H, Nishiyama A, Abe Y, Navar LG. Enhancement of intrarenal angiotensinogen in Dahl salt-sensitive rats on high salt diet. Hypertension 2003; 41(3): 592–597.

38 Zhu A, Yoneda T, Demura M, Karashima S, Usukura M, Yamagishi M, Takeda Y. Effect of mineralocorticoid receptor blockade on the renal renin-angiotensin system in Dahl salt-sensitive hypertensive rats. J Hypertens 2009; 27(4): 800–805.

39 Nguyen G, Delarue F, Burckle C, Bouzhir L, Giller T, Sraer JD. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. J Clin Invest 2002; 109(11): 1417–1427.

40 Cousin C, Bracquart D, Contrepas A, Corvol P, Muller L, Nguyen G. Soluble form of the (pro)renin receptor generated by intracellular cleavage by furin is secreted in plasma. Hypertension 2009; 53(6): 1077–1082.

41 Yoshikawa A, Aizaki Y, Kusano K, Kishi F, Susumu T, Iida S, Ishiura S, Nishimura S, Shichiri M, Senbonmatsu T. The (pro)renin receptor is cleaved by ADAM19 in the Golgi

leading to its secretion into extracellular space. Hypertens Res 2011; 34(5): 599–605.

42 Nakagawa T, Suzuki-Nakagawa C, Watanabe A, Asami E, Matsumoto M, Nakano M, Ebihara A, Uddin MN, Suzuki F. Site-1 protease is required for the generation of soluble (pro) renin receptor. J Biochem 2017; 161(4): 369–379.

43 Fang H, Xu C, Lu A, Zou C, Xie S, Zhou L, Su J, Liu M, Wang L, Wang W, Yang T. (Pro)renin receptor mediates albumin-induced cellular responses: role of site-1 protease-derived soluble (pro)renin receptor in renal epithelial cells. Am J Physiol Cell Physiol 2017; 313(6): C632–C643.

44 Zhu Q, Yang T. Enzymatic sources and physio-pathological functions of soluble (pro)renin receptor. Curr Opin Nephrol Hypertens 2018; 27(2): 77–82.

45 Cruciat CM, Ohkawara B, Acebron SP, Karaulanov E, Reinhard C, Ingelfinger D, Boutros M, Niehrs C. Requirement of prorenin receptor and vacuolar H^+-ATPase-mediated acidification for Wnt signaling. Science 2010; 327(5964): 459–463.

46 Lu X, Wang F, Liu M, Yang KT, Nau A, Kohan DE, Reese V, Richardson RS, Yang T. Activation of ENaC in collecting duct cells by prorenin and its receptor PRR: involvement of Nox4-derived hydrogen peroxide. Am J Physiol Renal Physiol 2016; 310(11): F1243–F1250.

47 Wang F, Lu X, Peng K, Fang H, Zhou L, Su J, Nau A, Yang KT, Ichihara A, Lu A, Zhou SF, Yang T. Antidiuretic action of collecting duct (pro)renin receptor downstream of vasopressin and PGE2 receptor EP4. J Am Soc Nephrol 2016; 27(10): 3022–3034.

48 Lu X, Wang F, Xu C, Soodvilai S, Peng K, Su J, Zhao L, Yang KT, Feng Y, Zhou SF, Gustafsson JÅ, Yang T. Soluble (pro)renin receptor via β-catenin enhances urine concentration capability as a target of liver X receptor. Proc Natl Acad Sci U S A 2016; 113(13): E1898–E1906.

49 Trepiccione F, Gerber SD, Grahammer F, López-Cayuqueo KI, Baudrie V, Păunescu TG, Capen DE, Picard N, Alexander RT, Huber TB, Chambrey R, Brown D, Houillier P, Eladari D, Simons M. Renal Atp6ap2/(Pro)renin receptor is required for normal vacuolar H^+-ATPase function but not for the renin-angiotensin system. J Am Soc Nephrol 2016; 27(11): 3320–3330.

50 Burckle CA, Jan Danser AH, Muller DN, Garrelds IM, Gasc JM, Popova E, Plehm R, Peters J, Bader M, Nguyen G. Elevated blood pressure and heart rate in human renin receptor transgenic rats. Hypertension 2006; 47(3): 552–556.

51 Rosendahl A, Niemann G, Lange S, Ahadzadeh E, Krebs C, Contrepas A, van Goor H, Wiech T, Bader M, Schwake M, Peters J, Stahl R, Nguyen G, Wenzel UO. Increased expression of (pro)renin receptor does not cause hypertension or cardiac and renal fibrosis in mice. Lab Invest 2014; 94(8): 863–872.

52 Shan Z, Shi P, Cuadra AE, Dong Y, Lamont GJ, Li Q, Seth DM, Navar LG, Katovich MJ, Sumners C, Raizada MK. Involvement of the brain (pro)renin receptor in cardiovascular homeostasis. Circ Res 2010; 107(7): 934–938.

53 Li W, Peng H, Cao T, Sato R, McDaniels SJ, Kobori H, Navar LG, Feng Y. Brain-targeted (pro)renin receptor knockdown attenuates angiotensin II-dependent hypertension. Hypertension 2012; 59(6): 1188–1194.

54 Li W, Peng H, Mehaffey EP, Kimball CD, Grobe JL, van Gool JM, Sullivan MN, Earley S, Danser AH, Ichihara A, Feng Y. Neuron-specific (pro)renin receptor knockout prevents the development of salt-sensitive hypertension. Hypertension 2014; 63(2): 316–323.

55 Li W, Sullivan MN, Zhang S, Worker CJ, Xiong Z, Speth RC, Feng Y. Intracerebroventricular infusion of the (Pro) renin receptor antagonist PRO20 attenuates deoxycorticosterone acetate-salt-induced hypertension. Hypertension 2015; 65(2): 352–361.

56 Dhar I, Dhar A, Wu L, Desai KM. Increased methylglyoxal formation with upregulation of renin angiotensin system in fructose fed Sprague Dawley rats. PLoS One 2013; 8(9): e74212.

57 Yokota R, Ronchi FA, Fernandes FB, Jara ZP, Rosa RM, Leite APO, Fiorino P, Farah V, Nascimento NRF, Fonteles MC, Casarini DE. Intra-renal angiotensin levels are increased in high-fructose fed rats in the extracorporeal renal perfusion model. Front Physiol 2018; 9: 1433.

58 Nagai Y, Ichihara A, Nakano D, Kimura S, Pelisch N, Fujisawa Y, Hitomi H, Hosomi N, Kiyomoto H, Kohno M, Ito H, Nishiyama A. Possible contribution of the non-proteolytic activation of prorenin to the development of insulin resistance in fructose-fed rats. Exp Physiol 2009; 94(9): 1016–1023.

59 Iyer SN, Katovich MJ, Raizada MK. Changes in angiotensin AT1 receptor density during hypertension in fructose-fed rats. Adv Exp Med Biol 1996; 396: 49–58.

60 Zenner ZP, Gordish KL, Beierwaltes WH. Free radical scavenging reverses fructose-induced salt-sensitive hypertension. Integr Blood Press Control 2018; 11: 1–9.

61 Matavelli LC, Huang J, Siragy HM. *In vivo* regulation of renal expression of (pro)renin receptor by a low-sodium diet. Am J Physiol Renal Physiol 2012; 303(312): F1652–F1657.

62 Huang J, Siragy HM. Sodium depletion enhances renal expression of (pro)renin receptor via cyclic GMP-protein kinase G signaling pathway. Hypertension 2012; 59(52): 317–323.

63 Quadri S, Siragy HM. Regulation of (pro)renin receptor expression in mIMCD via the GSK-3β-NFAT5-SIRT-1

signaling pathway. Am J Physiol Renal Physiol 2014; 307(305): F593–F600.

64 Rong R, Ito O, Mori N, Muroya Y, Tamura Y, Mori T, Ito S, Takahashi K, Totsune K, Kohzuki M. Expression of (pro)renin receptor and its upregulation by high salt intake in the rat nephron. Peptides 2015; 63: 156–162.

65 Xu C, Fang H, Zhou L, Lu A, Yang T. High potassium promotes mutual interaction between (pro)renin receptor and the local renin-angiotensin-aldosterone system in rat inner medullary collecting duct cells. Am J Physiol Cell Physiol 2016; 311(4): C686–C695.

66 Xu C, Lu A, Wang H, Fang H, Zhou L, Sun P, Yang T. (Pro) Renin receptor regulates potassium homeostasis through a local mechanism. Am J Physiol Renal Physiol 2017; 313(3): F641–F656.

67 Ramkumar N, Stuart D, Mironova E, Bugay V, Wang S, Abraham N, Ichihara A, Stockand JD, Kohan DE. Renal tubular epithelial cell prorenin receptor regulates blood pressure and sodium transport. Am J Physiol Renal Physiol 2016; 311(1): F186–F194.

68 Quadri S, Siragy HM. (Pro)renin receptor contributes to regulation of renal epithelial sodium channel. J Hypertens 2016; 34(3): 486–494.

69 Peng K, Lu X, Wang F, Nau A, Chen R, Zhou SF, Yang T. Collecting duct (pro)renin receptor targets enac to mediate angiotensin II-induced hypertension. Am J Physiol Renal Physiol 2017; 312(2): F245–F253.

70 Nandhini AT, Anuradha CV. Hoe 140 abolishes the blood pressure lowering effect of taurine in high fructose-fed rats. Amino Acids 2004; 26(3): 299–303.

71 Queiroz-Leite GD, Crajoinas RO, Neri EA, Bezerra CN, Girardi AC, Reboucas NA, Malnic G. Fructose acutely stimulates NHE3 activity in kidney proximal tubule. Kidney Blood Press Res 2012; 36(1): 320–334.

72 Gonzalez-Vicente A, Hong NJ, Yang N, Cabral PD, Berthiaume JM, Dominici FP, Garvin JL. Dietary fructose increases the sensitivity of proximal tubules to angiotensin ii in rats fed high-salt diets. Nutrients 2018; 10(9): pii: E1244.

73 Gonzalez-Vicente A, Cabral PD, Hong NJ, Asirwatham J, Yang N, Berthiaume JM, Dominici FP, Garvin JL. Dietary fructose enhances the ability of low concentrations of angiotensin II to stimulate proximal tubule Na^+ reabsorption. Nutrients 2017; 9(8): pii: E885.

74 Kanbay M, Jensen T, Solak Y, Le M, Roncal-Jimenez C, Rivard C, Lanaspa MA, Nakagawa T, Johnson RJ. Uric acid in metabolic syndrome: From an innocent bystander to a central player. Eur J Intern Med 2016; 29: 3–8.

75 Zhang JX, Zhang YP, Wu QN, Chen B. Uric acid induces oxidative stress via an activation of the renin-angiotensin system in 3T3-L1 adipocytes. Endocrine 2015; 48 (1): 135–142.

76 Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. J Hypertens 2008; 26 (2): 269–275.

77 Yu MA, Sánchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. J Hypertens 2010; 28(6): 1234–1242.

78 Albertoni G, Maquigussa E, Pessoa E, Barreto JA, Borges F, Schor N. Soluble uric acid increases intracellular calcium through an angiotensin II-dependent mechanism in immortalized human mesangial cells. Exp Biol Med (Maywood) 2010; 235(7): 825–832.

79 Perlstein TS, Gumieniak O, Hopkins PN, Murphey LJ, Brown NJ, Williams GH, Hollenberg NK, Fisher ND. Uric acid and the state of the intrarenal renin-angiotensin system in humans. Kidney Int 2004; 66(4): 1465–1470.

80 Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, Kang DH, Gordon KL, Watanabe S, Nakagawa T, Lan HY, Johnson RJ. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol 2002; 282(6): F991–F997.

81 Burch HB, Choi S, Dence CN, Alvey TR, Cole BR, Lowry OH. Metabolic effects of large fructose loads in different parts of the rat nephron. J Biol Chem 1980; 255(17): 8239–8244.

82 Cirillo P, Gersch MS, Mu W, Scherer PM, Kim KM, Gesualdo L, Henderson GN, Johnson RJ, Sautin YY. Ketohexokinase-dependent metabolism of fructose induces proinflammatory mediators in proximal tubular cells. J Am Soc Nephrol 2009; 20(3): 545–553.

83 Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, Ouyang X, Feig DI, Block ER, Herrera-Acosta J, Patel JM, Johnson RJ. A causal role for uric acid in fructose-induced metabolic syndrome. Am J Physiol Renal Physiol 2006; 290(3): F625–F631.

84 Sanchez-Lozada LG, Tapia E, Bautista-Garcia P, Soto V, Avila-Casado C, Vega-Campos IP, Nakagawa T, Zhao L, Franco M, Johnson RJ. Effects of febuxostat on metabolic and renal alterations in rats with fructose-induced metabolic syndrome. Am J Physiol Renal Physiol 2008; 294(4): F710–F718.

85 Angelopoulos TJ, Lowndes J, Sinnett S, Rippe JM. Fructose containing sugars do not raise blood pressure or uric acid at normal levels of human consumption. J Clin Hypertens (Greenwich) 2015; 17(2): 87–94.

86 Soletsky B, Feig DI. Uric acid reduction rectifies prehypertension in obese adolescents. Hypertension 2012; 60(5):

1148–1156.

87 Beattie CJ, Fulton RL, Higgins P, Padmanabhan S, McCallum L, Walters MR, Dominiczak AF, Touyz RM, Dawson J. Allopurinol initiation and change in blood pressure in older adults with hypertension. Hypertension 2014; 64(5): 1102–1107.

88 Nyby MD, Abedi K, Smutko V, Eslami P, Tuck ML. Vascular Angiotensin type 1 receptor expression is associated with vascular dysfunction, oxidative stress and inflammation in fructose-fed rats. Hypertens Res 2007; 30(5): 451–457.

89 Delbosc S, Paizanis E, Magous R, Araiz C, Dimo T, Cristol JP, Cros G, Azay J. Involvement of oxidative stress and NADPH oxidase activation in the development of cardiovascular complications in a model of insulin resistance, the fructose-fed rat. Atherosclerosis 2005; 179(1): 43–49.

90 Shinozaki K, Ayajiki K, Nishio Y, Sugaya T, Kashiwagi A, Okamura T. Evidence for a causal role of the renin-angiotensin system in vascular dysfunction associated with insulin resistance. Hypertension 2004; 43(2): 255–262.

91 Vasdev S, Gill V, Parai S, Gadag V. Fructose-induced hypertension in Wistar-Kyoto rats: interaction with moderately high dietary salt. Can J Physiol Pharmacol 2007; 85(3–4): 413–421.

92 Nagasu H, Satoh M, Kuwabara A, Yorimitsu D, Sakuta T, Tomita N, Kashihara N. Renal denervation reduces glomerular injury by suppressing NAD(P)H oxidase activity in Dahl salt-sensitive rats. Nephrol Dial Transplant 2010; 25(9): 2889–2898.

93 Soncrant T, Komnenov D, Beierwaltes WH, Chen H, Wu M, Rossi NF. Bilateral renal cryodenervation decreases arterial pressure and improves insulin sensitivity in fructose-fed Sprague-Dawley rats. Am J Physiol Regul Integr Comp Physiol 2018; 315(3): R529–R538.

94 Ejaz AA, Mu W, Kang DH, Roncal C, Sautin YY, Henderson G, Tabah-Fisch I, Keller B, Beaver TM, Nakagawa T, Johnson RJ. Could uric acid have a role in acute renal failure? Clin J Am Soc Nephrol 2007; 2(1): 16–21.

95 Banday AA, Lokhandwala MF. Oxidative stress causes renal angiotensin II type 1 receptor upregulation, Na^+/H^+ exchanger 3 overstimulation, and hypertension. Hypertension 2011; 57: 452–459.

96 Rees DD, Palmer RM, Moncada S. Role of endothelium-derived nitric oxide in the regulation of blood pressure. Proc Natl Acad Sci U S A 1989; 86(9): 3375–3378.

97 Lockette W, Otsuka Y, Carretero O. The loss of endothelium-dependent vascular relaxation in hypertension. Hypertension 1986; 8 (6 Pt 2): II61–II66.

98 Luscher TF, Vanhoutte PM. Endothelium-dependent contractions to acetylcholine in the aorta of the spontaneously hypertensive rat. Hypertension 1986; 8(4): 344–348.

99 Panza JA, Casino PR, Kilcoyne CM, Quyyumi AA. Role of endothelium-derived nitric oxide in the abnormal endothelium-dependent vascular relaxation of patients with essential hypertension. Circulation 1993; 87(5): 1468–1474.

100 Panza JA, Quyyumi AA, Brush JE Jr, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. N Engl J Med 1990; 323(1): 22–27.

101 Endemann DH, Schiffrin EL. Endothelial dysfunction. J Am Soc Nephrol 2004; 15(8): 1983–1992.

102 Ortiz PA, Garvin JL. Role of nitric oxide in the regulation of nephron transport. Am J Physiol Renal Physiol 2002; 282(5): F777–F784.

103 Garvin JL, Herrera M, Ortiz PA. Regulation of renal NaCl transport by nitric oxide, endothelin, and ATP: clinical implications. Annu Rev Physiol 2011; 73: 359–376.