Hypertension is present in ≈40% of the world’s population and is responsible for 12.8% of total deaths. In the United States, hypertension affects 32% (2011–2012) of the middle-age (40–59 years) adult population and is responsible for 35.6% of total deaths. However, these statistics do not include normotensive individuals who are salt sensitive. Almost half of the US population has hypertension, salt sensitivity, or both. Salt sensitivity, independent of the presence of hypertension, is a risk factor for not only cardiovascular morbidity and mortality but also other diseases, eg, asthma, gastric carcinoma, osteoporosis, renal dysfunction, and metabolic syndrome. Salt sensitivity may also interfere with the normal circadian rhythm of blood pressure. Failure of the normal night-time dip in blood pressure may be associated with an increase in cardiovascular morbidity and mortality.

The World Health Organization recommends reducing salt consumption to <5 g of NaCl per day in adults, to help prevent hypertension, heart disease, and stroke. In a recent meta-analysis of randomized controlled trials, it was concluded that in the normotensive population, there is no relationship between the amount of sodium restriction (136–188 mmol/d) and blood pressure level. However, in the prehypertensive and hypertensive populations, reduction in sodium intake (77–140 mmol/d) correlated with a decrease in blood pressure. Another meta-analysis indicated that a modest reduction in salt intake for ≥4 weeks causes a decrease in blood pressure levels in both hypertensive and normotensive individuals. In subjects with no history of hypertension, no association was found between dietary sodium or potassium intake with hypertension or prehypertension. However, a lower limit of the daily NaCl intake is not defined. This is important because the relationship between sodium intake and blood pressure may not be linear but more of a J-shaped curve. There is evidence for an increase in cardiovascular risk at low levels of sodium ingestion. Sodium restriction (<40 mmol/d) may increase the blood pressure in 15% to 20% of the population and may be more apparent in normotensive than hypertensive individuals. A failure to take into account the influence of genetics and epigenetics on blood pressure response to sodium or potassium intake may explain some of the conflicting results.

Hypertension and salt sensitivity are complex diseases caused by genetic and epigenetic predisposition and modified by environmental influences, such as sodium and potassium consumption and sedentary lifestyles. The precise genetic and epigenetic modifications that affect the regulatory mechanisms that lead to salt sensitivity are unknown. However, the importance of the kidney in blood pressure regulation is supported by renal transplantation studies in humans, rats, and mice. An inability of the kidney to excrete a sodium load would cause a positive sodium balance, an increase in blood pressure, and eventually hypertension.

Gastrorenal Axis

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The gastrointestinal tract is important in the regulation of blood pressure because it is the first organ exposed to ingested nutrients and most likely to initially react to a sodium load. Sensing the amount of ingested sodium by the stomach and other segments of the gastrointestinal tract may be an important mechanism by which sodium balance is regulated. Thus, the same amount of sodium given orally has been reported to be excreted more rapidly than that administered intravenously in some studies. The presence of a gut sodium sensor has been disputed, but this could be related to experimental conditions that could lead to contradictory signals. For example, an oral sodium load that leads to an increase in plasma osmolality would lead to an increase in vasopressin secretion that would result in a decrease in both urine flow and sodium excretion. However, even the study that reported no difference in the excretion of sodium given orally or intravenously does not dispute the presence of a sodium sensor in the gut.

Gastrin as the Effector of Gut Sodium Sensor

Neural mechanisms and gut hormones (eg, uroguanylin [Guca2b], cholecystokinin [CCK], and gastrin) have been proposed to mediate the natriuresis of an oral sodium load. However, the oral intake of sodium does not increase circulating prouroguanylin, proguanylin, and uroguanylin levels. Although Guca2b−/− mice have an impaired natriuretic response to an acute oral sodium load, blood pressure is only slightly increased and salt sensitivity is similar in Guca2b−/− and Guca2b+/− mice. CCK is natriuretic but circulating CCK levels are not increased by an oral sodium load, and CCK is not transported into renal tubules. However, the natriuresis after

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ingestion of a critical amount of sodium may be because of the secretion of the enterokine gastrin by G cells in the stomach and duodenum and released into the circulation.26,33 Gastrin is reabsorbed by renal cortical tubules to a greater extent than the other enterokines released after a meal.34,36 Once taken up by the kidney, gastrin then acts on its receptor, the CCK type B receptor (CCKBR) expressed in several nephron segments33–35 to decrease sodium transport. Gastrin is important in the regulation of sodium balance and blood pressure because various strategies to interfere with gastrin expression in mice (eg, germ-line deletion of Gast [ie, Gast−/− or Cckbr−/−]) or selective silencing of stomach Gast (using siRNA, unpublished data) prevents or minimizes the increase in sodium excretion after an oral sodium load. These mice also have increased blood pressure. Gast is also important in the expression of the salt-sensitive phenotype because Gut−/− mice on low sodium intake are normotensive but become hypertensive when sodium intake is increased36 (unpublished data).

In a preliminary communication, we reported that exposure of human stomach gastrin cells (G cells) to the ionophore monensin, which increases intracellular ions, including sodium, also increases gastrin mRNA and protein.40 Human G cells also express the D1 receptor,40 a member of the D1-like receptor family of dopamine receptors.41 D1-like receptor agonist stimulation increases gastrin mRNA in human G cells and colon adenocarcinoma cells (SW626) and a D1-like receptor antagonist blocks the ability of monensin to increase human gastrin transcription and secretion may require a functional D1-like receptor.

Gastrin is also important in the expression of the salt-sensitive phenotype because Gut−/− mice on low sodium intake are normotensive but become hypertensive when sodium intake is increased36 (unpublished data).

Dopamine is produced by the kidney, largely independent of renal nerves,41 from circulating l-3,4-dihydroxyphenylalanine (l-DOPA) that is decarboxylated to dopamine by aromatic amino acid decarboxylase (AADC).51,43,44 l-DOPA is filtered by the glomerulus and reabsorbed by the renal proximal tubule via at least 2 sodium-independent amino acid transporters, L-type amino acid transporter type 2 (LAT-2) and b0,+; LAT-1 may also participate, especially in the spontaneously hypertensive rat.45,46 B0,+ is present mainly in the apical membrane, whereas LAT-1 and LAT-2 are present mainly at the basolateral membranes of renal proximal tubules.46 Two sodium-dependent amino acid transporters (ASCT2 and BOAT1), expressed at the renal proximal tubular luminal membrane, may also be involved in the renal proximal tubular transport of l-DOPA.46 The expression of l-DOPA transporters is age dependent, sensitive to high salt intake, and regulated differently in normotensive and hypertensive animals. In renal proximal tubule cells from normotensive human and mouse, gastrin stimulates renal dopamine production by increasing the cellular uptake of l-DOPA, via the LAT-1.47 This selective deletion of the l-AADC gene in the mouse renal proximal tubules causes hypertension and salt sensitivity.48

Dopamine and Gastrin Receptors and Renal Sodium Transport

Renal dopamine production and dopamine receptors are important in the regulation of renal sodium transport and blood pressure.41 As aforementioned, preventing renal proximal tubule synthesis of dopamine causes salt-sensitive hypertension.44 Germline deletion of any of the 5 dopamine receptor subtypes in mice results in hypertension, the pathogenesis of which is subtype specific.41 Renal-selective silencing of dopamine receptor subtypes, eg, D1R, in mice also causes hypertension.48 Single nucleotide polymorphisms of the D1R gene, DRD1, have been reported to be associated with human essential hypertension.49,50

D1R and D2R and CCKBR can physically interact (Figures 1 and 2).37,38 This interaction in the kidney results in the inhibition of renal sodium transport (Figures 3 and 4).37,38 The natriuresis associated with high sodium diet in mice can be blocked by either a combined D1R and D2R antagonist, SCH23390, or a CCKBR antagonist, YF476 (Figure 3).37 The natriuretic effect of fenoldopam, a D1-like receptor (D1R and D2R) agonist, administered selectively into the kidney via infusion into the right suprarenal artery, can be blocked not only by a D1-like receptor (D1R and D2R) antagonist, SCH23390, but also by a CCKBR antagonist, CI-988, in normotensive Wistar–Kyoto rats.38 Conversely, the natriuretic effect of gastrin, also administered selectively into the kidney via infusion into the right suprarenal artery, can be blocked not only by the CCKBR antagonist CI-988 but also by the D1-like receptor antagonist, SCH23390 (Figure 4).38 In mice, the natriuretic effect of fenoldopam can also be blocked by another CCKBR antagonist, YF476 (Figure 3).37 We have also reported that the D1-like receptor agonist fenoldopam or gastrin can inhibit NHE3 and Na+K+ATPase activity in human renal proximal tubule cells.40,41,51,52 Gastrin and fenoldopam also interact to inhibit Na+, K+-ATPase activity in renal proximal tubule cells from Wistar–Kyoto rats. The synergistic interaction between D1-like receptors and CCKBR in renal proximal tubule cells from Wistar–Kyoto rats.
Thus, gastrin and D₁-like receptors interact to facilitate the interaction of D₁R and CCKBR to regulate each other’s expression. In the kidney, gastrin may increase renal dopamine production, in addition to positively interacting with the D₁R and the other D₁-like receptor, D₅R, to induce a natriuresis and diuresis. 37,38,47

Figure 2. Gastrin (A) or fenoldopam, a D₁-like receptor (D₁R and D₅R) agonist (B) increases the coimmunoprecipitation of cholecystokinin type B receptor (CCKBR) and D₁R in renal proximal tubule (RPT) cells from Wistar-Kyoto (WKY) but not from spontaneously hypertensive rats (SHR). The RPT cells were incubated with gastrin (1 nmol, A) or fenoldopam (100 nmol/L, B) for 15 min. Thereafter, the samples were immunoprecipitated with CCKBR antibodies and immunoblotted with D₁R antibodies (*P<0.05 vs control; n=3–5; 1-way factorial ANOVA, Holm–Sidak test). One immunoblot (72 kDa, A; 80 kDa, B) is depicted in the inset (lane 1=vehicle-treated RPT cells from WKY rat, lane 2=gastrin-treated RPT [A] or fenoldopam-treated RPT [B] cells from WKY rat, lane 3=vehicle-treated RPT cells from SHR, and lane 4=gastrin-treated RPT [A] or fenoldopam-treated RPT [B] from SHR). Reprinted from Chen et al. 36 Copyright © 2013, the American Heart Association, Inc.

rats was related to an increase in D₁R and CCKBR colocalization at the plasma membrane in these renal proximal tubule cells. These effects were much less or not observed in renal proximal tubule cells from spontaneously hypertensive rats. 38 The other D₁-like receptor, D₅R, also interacts with CCKBR to regulate each other’s expression. 37 In the kidney, gastrin may increase renal dopamine production, in addition to positively interacting with the D₁R and the other D₁-like receptor, D₅R, to induce a natriuresis and diuresis. 37,38,47

Figure 3. D₁-like receptors (D₁R and D₅R) and cholecystokinin type B receptor (CCKBR) interact to increase sodium excretion in BALB/c mice. Twenty-four-hour urinary sodium to creatinine ratio (UNa/UCr) was used to quantify natriuresis. The BALB/c mice were fed normal (NS, 0.4% NaCl, black open bar) or high salt (HS, 3% NaCl, red open bar) diet for 2 wk. The BALB/c mice on NS diet were subdivided into seven groups and intraperitoneally injected (0.5 mL) daily for 2 wk. Then the BALB/c mice on HS diet were subdivided into seven groups and intraperitoneally injected (0.5 mL) daily for 1 wk with vehicle (normal saline)=HS+Saline, SCH23390 (a D₁-like receptor antagonist, 0.1 mg/kg)=HS+SCH, YF476 (a CCKBR antagonist, 0.1 mg/kg)=HS+YF, fenoldopam (a D₁-like receptor agonist, 1 mg/kg)=HS+Fen, gastrin (a CCKBR ligand, 10 μg/kg)=HS+Gast, fenoldopam (1 mg/kg) with YF476 (0.1 mg/kg)=HS+Fen+YF, and gastrin (10 μg/kg) with SCH23390 (0.1 mg/kg)=HS+Gast+SCH. The BALB/c mice on NS diet were also injected intraperitoneally with 0.5-mL normal saline, daily for 1 wk=NS+Saline. The end of drug treatment, urine was collected for 24 h. n=5–7 per group, *P<0.05 vs NS+Saline, Student t test; **P<0.05 vs HS+Saline, 1-way factorial ANOVA, Duncan multiple range test. Reprinted from Jiang et al. 37 Copyright © 2016, The Authors (see: https://creativecommons.org/publicdomain/zero/1.0/).

excretion of an acute oral sodium load to prevent accumulation of sodium in the body and keep the blood pressure in the normal range (Figure 5). However, blood pressure is not increased in patients who have had gastric bypass. Indeed, the high blood pressure is normalized by gastric bypass in 38% in adults (Roux-en-Y gastric bypass surgery) 53 and 74% in adolescents (Roux-en-Y gastric bypass surgery and sleeve gastrectomy). 54 As it turns out, sleeve gastrectomy actually increases plasma gastrin levels after a mixed meal. 55 By contrast, Roux-en-Y gastric bypass surgery prevents the increase in plasma gastrin after a mixed meal 56 but either type of bypass surgery increases plasma levels of natriuretic enterokines, such as glucagon-like peptide-1. 57–59

G-Protein–Coupled Receptor Type 4

G-protein–coupled receptor kinases (GRKs) constitute a family of 7 serine/threonine protein kinases that phosphorylate specific agonist-activated G-protein–coupled receptors. 60–62 GRK-mediated receptor phosphorylation results in the desensitization of G-protein–coupled receptors that are subsequently resensitized and recycled to the plasma membrane. 61–63 Wild-type GRK4 is important in the desensitization and recycling of D₁R and D₅R to the plasma membrane of renal proximal tubules. 61,62 GRK4 plays a vital role in regulating dopamine-mediated natriuresis and renin–angiotensin system–mediated antinatriuresis. 61,63 However, a role of GRK4 in the regulation of CCKBR has not been reported.

GRK4 gene variants in humans (GRK4 A>G or A>C) are associated with hypertension in several but not in all ethnic groups. 64–77 The reasons leading to the differences among studies are not known. However, the negative studies could be the consequence of not taking into account salt sensitivity (in particular, GRK4 R65L and A486V) or assessing the role of GRK4 in conjunction with other single nucleotide polymorphisms of GRK4 and other genes. 61,63 It should be stated that GRK4 gene variants have also been associated with obesity associated with increased sodium intake (GRK4 486A>V), lower values of eGFR (GRK4 rs2488815, intronic), and hypertension in some diabetic subjects. 78–80
Only a few gene variants thought to be causal of hypertension in humans have been shown to produce hypertension in mice, e.g., AGT that encodes angiotensinogen, AGTR1 that encodes the AT1R, CYP11B2 that encodes aldosterone synthase, and UMOD that encodes uromodulin, and GRK4. These genes fulfill the criteria for ascribing a gene as causal of a complex disorder, such as hypertension. These include supporting data from linkage studies in several ethnic populations, comprehensive sequence analyses, in vitro studies using pertinent cell lines, and definitive evidence involving transgenics and gene knockout models.

The overexpression of human GRK4 γ gene variants (A>65 L, A>142 V, and A>486 V) in mice causes hypertension although salt sensitivity depends on which GRK4 γ variant is present. Overexpression of human GRK4, wild-type in mice results in normal blood pressure and salt resistance. By contrast, overexpression of human GRK4 142 V in mice causes salt-resistant hypertension, whereas overexpression of GRK4 486 V in mice causes salt-sensitive hypertension. Increased expression of AT1R in GRK4 142 V mice and production of reactive oxygen species in GRK4 486 V mice but not in GRK4 142 V mice contributes to the different blood pressure phenotype. GRK4 142 V also interacts with AT1R to increase vascular reactivity. GRK4 4R>65 L may also cause salt-sensitive hypertension (unpublished), especially in the presence of SLC4A5 gene variants. Therefore, GRK4 gene variants impair the ability of dopamine to inhibit renal sodium transport and impair the synergistic interaction between dopamine and gastrin.
between gastrin and dopamine in the kidney. The continued consumption of dietary sodium in face of an impaired ability to excrete the ingested sodium results in a positive sodium balance and eventually hypertension (Figure 6). The interaction between D1-like receptors and intracellular sodium in the stimulation of gastrin release may not be impaired in hypertension because GRK4 is not expressed in human G cells (unpublished studies). Indeed, the stimulatory effect of mixed meal on plasma gastrin levels is not different between hypertensive and normotensive subjects.95

Genome-wide association studies have identified only 2% of the genetic factors believed to influence blood pressure96; genome-wide association studies used screening platforms that did not consistently include CCKBR, GAST, and variants of other genes important in causing essential hypertension (eg, GRK4 variants that negatively regulate D1R and D3R).41,62,63,85 The chromosomal loci of CCKBR (11p15.5-p15.4) and GAST (17q21) are among the loci identified by genome-wide association studies that are linked to hypertension. However, CCKBR and GAST single nucleotide polymorphisms have not been associated with hypertension, and these variants are relatively infrequent (unpublished data). Nevertheless, abnormal gene/gene interactions among CCKBR, GAST, and DRD1 with GRK4 may explain the importance of GRK4 in the pathogenesis of essential hypertension. Moreover, an increasing number of studies show that the blood pressure response to antihypertensive medicines and adverse cardiovascular outcomes of antihypertensive treatment are influenced by the presence of GRK4 gene variants.95–103

Conclusions
Published and unpublished data suggest that gastrin produced by G cells in the stomach may be the effector of the sodium sensor in the stomach. D1-like receptors aid the ability of sodium to increase gastrin production by the stomach G cell. Circulating gastrin, taken up by renal proximal tubule cells, increases the renal production of dopamine. Gastrin and D1-like receptors interact to inhibit renal sodium transport, enabling the kidney to excrete a sodium load. GRK4 gene variants impair the function of D1R and D3R and abet the function of AT1R. These lead to enhancement of renal sodium reabsorption and impaired ability to excrete a sodium load that eventually leads to hypertension.

Perspectives
Ingested sodium is sensed by sodium channels in G cells of the stomach. An increase in intracellular sodium concentration, in conjunction with D1R in G cells, increases transcription of gastrin and also its releases into the stomach and circulation. Gastrin, via CCKBR, and dopamine via its 5 dopamine receptor subtypes (D1R, D2R, D3R, D4R, and D5R), synergistically inhibit renal tubular sodium transport resulting in a natriuresis. The presence of GRK4 gene variants (R>65 L, A142>V, and A486>V) decreases the function of some dopamine receptors (eg, D1R and D3R), impairing their ability to inhibit renal sodium transport. Positive sodium balance and increased vascular reactivity caused by GRK4 gene variants result in hypertension.

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Disclosures
R.A. Felder and P.A. Jose own Hypogen, Inc, which owns the rights to G-protein–coupled receptor type 4. G.M. Eisner is a member of the Advisory Board of Hypogen, Inc. The other authors report no conflicts.

References
1. http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en/Accessed. Accessed November 27, 2015.
2. Heron M. Deaths: Leading causes for 2012. Natl Vital Stat Rep. 2015;64:1–92.
3. Yoon SS, Fryar CD, Carroll MD. Hypertension prevalence and control among adults: United States, 2011–2014. NCHS Data Brief. 2015;220:1–8.
4. Mozaffarian D, Benjamin EJ, Go AS, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation. 2015;131:e29–322. doi: 10.1161/ CIR.0000000000000237.
5. Weinberger MH, Fineberg NS, Fineberg SE, Weinberger M. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. Hypertension. 2001;37(2 pt 2):429–432.
6. Aaron KJ, Sanders PW. Role of dietary salt and potassium intake in cardiovascular health and disease: a review of the evidence. Mayo Clin Proc. 2013;88:987–995. doi: 10.1016/j.mayocp.2013.06.005.
7. D’Elia L, Galletti F, Strausullo F. Dietary salt intake and risk of gastric cancer. Cancer Treat Res. 2014;159:83–95. doi: 10.1007/978-3-642-38007-5_6.
8. Ma Y, He FF, MacGregor GA. High salt intake: independent risk factor for obesity? Hypertension. 2015;66:843–849. doi: 10.1161/HYPERTENSIONAHA.115.05948.
9. Friedman O, Logan AG. Can nocturnal hypertension predict cardiovascular risk? Int J Blood Press Control. 2009;2:25–37.
10. O’Flynn AM, Madden JM, Russell AJ, Curtin RJ, Kearney PM. Isolated plantar flexion on NaCl-induced hypertension in Dahl rats. Hypertension. 1990;15:1092–1099.
11. Montasser ME, Douglas JA, Roy-Gagnon MH, Van Hout CV, Weir MR, Thijs L, Tikhonoff V, Seidlerová J, Institute of Medicine. Washington, DC: National Academies Press, 2013.
12. O’Flynn AM, Madden JM, Russell AJ, Curtin RJ, Kearney PM. Isolated nocturnal hypertension and subclinical target organ damage: a systematic review of the literature. Hypertens Res. 2015;38:570–575. doi: 10.1038/hr.2015.43.
13. www.who.int/global.../global-status-report-ncds. 2014. Accessed November 27, 2015.
14. Graudal N, Hubeck-Graudal T, Jürgens G, McCarron DA, BF, van der Weerth A, Jonas V, CCKB/gastrophin derivatives labelled with 111In: radiolabelling, affinity profile and pharmacokinetics in rats. Nucl Med Biol. 2007;34:633–641. doi: 10.1016/j.nucmedbio.2007.05.002.
15. Pignea JR, Tarasova NI, Kopp JA, Asico LD, Jose P, Farnsworth DW, Mechiček Č, Wank SA. Postprandial changes in renal function are mediated by elevated serum gastrin acting at cholecystokinin type B receptors (CCKBR) in the kidney (Abstract). Gastroenterology. 1996;110:A160A.
16. Menshaghara L, Lazzinickova A, Lazzinick M. Preclinical evaluation of gastrin derivatives labelled with 111In: radiolabelling, affinity profile and pharmacokinetics in rats. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2014;158:544–551. doi: 10.1515/bpmed-2013.005.
17. Jiang X, Chen W, Liu X, Wang Z, Liu Y, Felder RA, Gildea JJ, Jose PA, Qin C, Yang Z. The synergistic roles of cholecystokinin B and dopamine D5 receptors on the regulation of renal sodium excretion. PLoS One. 2016;11:e0146641. doi: 10.1371/journal.pone.0146641.
18. Chm Y, Asico LD, Zheng S, Villar VA, He D, Zhou L, Zeng C, Jose PA. Gastrin and D1 dopamine receptor interact to induce natriuresis and diuresis. Hypertension. 2013;62:927–933. doi: 10.1161/HYPERTENSIONAHA.113.01094.
19. von Schenck T, Ahrens M, de Weerth A, Bobrowski C, Wolf G, Jonas L, Jocks T, Schulz M, Bläker M, Neumaier M, Stahl RA. CCKB/gastrophin receptors mediate changes in sodium and potassium absorption in the isolated perfused rat kidney. Kidney Int. 2000;58:995–1003. doi: 10.1046/j.1523-1755.2000.00257.x.
20. Gildea JJ, Xu P, Zhang C, Wang DB, Tran HT, Felder RA. Intestinal cell gastrin inhibits renal NHE3 and NaKATPase in concert with the renal D1R. Hypertension. 2015;66:A807.
21. Curtis JJ, Luke RG, Duster PL, Kasgarian M, Whelchel JD, Jones P, Diethelm AG. Remission of essential hypertension after renal transplantation. N Engl J Med. 1983;309:1009–1015. doi: 10.1056/NEJM198102273090702.
22. Bianchi G, Fox U, Di Francesco GF, Giovannetti AM, Pagetti D. Blood pressure changes produced by kidney cross-transplantation between spontaneously hypertensive rats and normotensive rats. Clin Sci Mol Med. 1974;47:435–448.
23. Morgan DA, DiBona GF, Mark AL. Effects of interferon renal transplantation on NaCl-induced hypertension in Dahl rats. Hypertension. 1990;15:436–442.
44. Zhang MZ, Yao B, Wang S, Fan X, Wu G, Yang H, Yin H, Yang S, Harris RC. Intrarenal dopamine deficiency leads to hypertension and decreased longevity in mice. J Clin Invest. 2011;121:2845–2854. doi: 10.1172/JCI57324.

45. Quiñones H, Collazo R, Moe OW. The dopamine precursor L-dihydroxyphenylalanine is transported by the amino acid transporters bCAT and LAT2 in renal cortex. Am J Physiol Renal Physiol. 2004;287:F74–F80. doi: 10.1152/ajprenal.00237.2003.

46. Pinto V, Pinho MJ, Soares-da-Silva P. Renal amino acid transport systems and essential hypertension. FASEB J. 2013;27:2927–2938. doi: 10.1096/fj.12-224998.

47. Jiang X, Zhang Y, Yang Y, Asisdo LD, Chen W, Felder RA, Armando I, Jose PA, Yang G. Gastrin stimulates renal dopamine production by increasing the renal tubular uptake of L-DOPA. http://www.ishrd.org/2015/touch/logging abstract_show.asp?id=45&fromurl=http%3A%2F%2Fwww.ishrd.org%2F2015%2Fouch2%2Fprogram2.asp%3Flag%3Dpp%26session id%3D48. Accessed November 25, 2017.

48. Zhang Y, Cuevas S, Asisdo LD, Escano C, Yang Y, Pascua AM, Wang X, Jones JE, Grandy D, Eissner G, Jose PA, Armando I. Deficient dopamine D2 receptor function causes renal inflammation independently of high blood pressure. PLoS One. 2012;7:e38745. doi: 10.1371/journal.pone.0038745.

49. Fung MM, Rana BK, Tang CM, Shima T, Nievergelt CM, Rao F, Salem MJ. Very small leptin-expressing neurons with the characteristics of a sympathetic cell type in human brainstem. J Neurosci. 2009;29:10191–10198. doi: 10.1523/JNEUROSCI.2603-09.2009.

50. Padmanabhan S, Menini C, Lee WK, Laing S, Brambilla P, Sega R, Perego R, Grassi G, Ceriselli D, Delles C, Mancia G, Dominiczak AF. The effects of sex and method of blood pressure measurement on genetic associations with blood pressure in the PAMELA study. J Hypertens. 2010;28:465–477. doi: 10.1097/JHJ.0b013e32833594d7.

51. Liu T, Konkalmatt PR, Yang Y, Jose PA. Gastrin decreases Na+, K+ATPase activity via a PI3 Kinase- and PKC-dependent pathway in human renal proximal tubule cells. Am J Physiol Endocrinol Metabol. 2016. doi: 10.1152/ajpendo.00360.2015.

52. Liu T, Jose PA. Gastrin induces sodium-hydrogen exchanger 3 phosphorylation and mTOR activation via a phosphoinositide 3-kinase/- protein kinase C-dependent but AKT-independent pathway in renal proximal tubule cells derived from a normotensive male human. Endocrinology. 2013;154:865–875. doi: 10.1210/en.2012-1813.

53. Puzziferri N, Roshek TB III, Mayo HG, Gallagher R, Belle SH, Livingston EH. Long-term follow-up after bariatric surgery: a systematic review. JAMA. 2014;312:934–942. doi: 10.1001/jama.2014.10706.

54. Inge TH, Courcoulas AP, Jenkins TM, Michalsky MP, Helmrath MA, Puzziferri N, Roshek TB III, Mayo HG, Gallagher R, Belle SH, Livingston EH. Long-term follow-up after bariatric surgery: a systematic review. JAMA. 2014;312:934–942. doi: 10.1001/jama.2014.10706.

55. Przeworska R, Brand ML, Harmon CM, Zeller MH, Chen MK, Xanthakos SA, Horlick EH. Long-term follow-up after bariatric surgery: a systematic review. JAMA. 2014;312:934–942. doi: 10.1001/jama.2014.10706.

56. Lohmueller KE, Wijmenga C, Zhang H, Maillard M, Bochud M, Staessen JA, Kuznetsova T, Zhang H, Maillard M, Bochud M. Low blood pressure in white Americans is associated with the DRD1 proline-rich tyrosine kinase 4 gene. Hypertension. 2004;43:224–229. doi: 10.1161/HYPERTENSIONAHA.103.003665.

57. Villar VA, Jones JE, Armando I, Alaines-Saloma C, Yu P, Pascua AM, Keever L, Arnaldo FB, Wang Z, Luo Y, Felder RA, Jose PA, Gastrin coupled receptor kinase 4 (GKR4) regulates the phosphorylation and function of the dopamine D3 receptor. J Biol Chem. 2009;284:21425–21434. doi: 10.1074/jbc.M109.036681.

58. Liu T, Konkalmatt PR, Yang Y, Jose PA. Gastrin decreases Na+, K+ATPase activity via a PI3 Kinase- and PKC-dependent pathway in human renal proximal tubule cells. Am J Physiol Endocrinol Metabol. 2016. doi: 10.1152/ajpendo.00360.2015.

59. Przeworska R, Brand ML, Harmon CM, Zeller MH, Chen MK, Xanthakos SA, Horlick EH. Long-term follow-up after bariatric surgery: a systematic review. JAMA. 2014;312:934–942. doi: 10.1001/jama.2014.10706.
92. Abiola O, Lee ST, Kim WJ, Park SE, Park SW, Kim JW, Park CY. Genetic variation in CYP17A1 is associated with arterial stiffness in diabetic subjects. *Exp Diabetes Res.* 2012;2012:827172. doi: 10.1155/2012/827172.

91. Jain S, Vinaikonda G, Fiering SN, Kumar A. A haplotype of human angiotensinogen gene containing -217A increases blood pressure in transgenic mice compared with -217G. *Am J Physiol Regul Integr Comp Physiol.* 2008;295:R1849–R1857. doi: 10.1152/ajpregu.90637.2008.

90. Diao Z, Armando I, Asico L, Cuevas S, Jose P, Wang X. Increased renal oxidative stress in hGRK4γ transgenic mice. *J Biol Chem.* 2013;288:37048–37056. doi: 10.1074/jbc.M113.520023.

89. Wang Z, Armando I, Asico LD, Escano C, Wang X, Lu Q, Felder RA, Jose PA. Human G protein-coupled receptor kinase 4 (GRK4) in pathogenesis of salt sensitivity, salt sensitive hypertension and response to antihypertensive treatment. *Int J Mol Sci.* 2015;16:5741–5749. doi: 10.3390/ijms16035741.

88. Rayner B, Ramesar R, Levitt N, Lombard C, Charlton K. G-protein-coupled receptor kinase 4 polymorphisms predict blood pressure response to dietary modification in Black patients with mild-to-moderate hypertension. *J Hum Hypertens.* 2012;26:334–339. doi: 10.1038/jhh.2011.33.

87. Chen K, Fu C, Chen C, Liu J, Ren H, Han Y, Yang J, He D, Zhou L, Yang Z. Basal and postprandial serum levels of gastrin in normotensive and hypertensive adults. *Clin Exp Hypertens.* 2013;35:74–78. doi: 10.3109/10641963.2012.690474.

86. Padmanabhan S, Caulfield M, Dominiczak AF. Genetic and molecular aspects of hypertension. *Circ Res.* 2015;115:937–959. doi: 10.1161/CIRCRESAHA.115.303647.

85. Rayner B, Ramesar R, Levitt N, Lombard C, Charlton K. G-protein-coupled receptor kinase 4 polymorphisms predict blood pressure response to dietary modification in Black patients with mild-to-moderate hypertension. *J Hum Hypertens.* 2012;26:334–339. doi: 10.1038/jhh.2011.33.

84. Jain S, Prater A, Pandey V, Rana N, Kumar A. A haplotype of human angiotensin receptor type 1 associated with human hypertension increases blood pressure in transgenic mice. *J Biol Chem.* 2013;288:37048–37056. doi: 10.1074/jbc.M113.520023.

83. Mopidevi B, Kaw MK, Puri N, Ponnula M, Jain S, Rana A, Keetha NR, Khuder SA, Fiering SN, Kumar A. Variable transcriptional regulation of the human aldosterone synthase gene causes salt-dependent high blood pressure in transgenic mice. *Circ Cardiovasc Genet.* 2015;8:30–39. doi: 10.1161/CIRCGENETICS.114.000694.

82. Jain S, Janas S, Lanzani C, et al; Swiss Kidney Project on Genes in Hypertension (SKIPOGH) team. Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. *Nat Med.* 2013;19:1655–1660. doi: 10.1038/nm.3384.

81. Jain S, Vinukonda G, Fiering SN, Kumar A. A haplotype of human angiotensin II type 1 receptor-mediated hypertension via renal histone deacetylase type 1 inhibition. *Hypertension.* 2016;67:325–334. doi: 10.1161/HYPERTENSIONAHA.115.05962.

80. Yang SJ, Lee ST, Kim WJ, Park SE, Park SW, Kim JW, Park CY. Genetic variation in CYP17A1 is associated with arterial stiffness in diabetic subjects. *Exp Diabetes Res.* 2012;2012:827172. doi: 10.1155/2012/827172.

79. Jain S, Prater A, Pandey V, Rana N, Kumar A. A haplotype of human angiotensin receptor type 1 associated with human hypertension increases blood pressure in transgenic mice. *J Biol Chem.* 2013;288:37048–37056. doi: 10.1074/jbc.M113.520023.