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Gastro-renal axis

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Introduction

Hypertension is present in about 40% of the world's population and is responsible for 12.8% of total deaths (1). In the USA, hypertension affects 32% (2011 to 2012) of the middle-age (40-59 years) adult population and is responsible for 35.6% of total deaths (2-4). However, these statistics do not include normotensive individuals who are salt-sensitive. Almost half of the US population has hypertension, salt sensitivity, or both (5). Salt sensitivity, independent of the presence of hypertension, is a risk factor not only for cardiovascular morbidity and mortality (5, 6) but also for other diseases, e.g., asthma, gastric carcinoma, osteoporosis, renal dysfunction, and metabolic syndrome (7, 8). Salt sensitivity may also interfere with the normal circadian rhythm of blood pressure (9). Failure of the normal night-time dip in blood pressure may be associated with an increase in cardiovascular morbidity and mortality (9, 10).

The World Health Organization recommends reducing salt consumption to less than 5 g of NaCl per day in adults, to help prevent hypertension, heart disease, and stroke (11). In a recent meta-analysis of randomized controlled trials, it was concluded that in the normotensive population, there is no relation between the amount of sodium restriction (136-188 mmol/day) and blood pressure level. However, in the prehypertensive and hypertensive populations, reduction in sodium intake (77-140 mmol/day) correlated with a decrease in blood pressure (12). Another meta-analysis indicated that a modest reduction in salt intake for 4 or more weeks causes a decrease in blood pressure levels in both

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hypertensive and normotensive individuals (13). In subjects with no history of hypertension, no association was found between dietary sodium or potassium intake with hypertension or prehypertension (14). However, a lower limit of the daily NaCl intake is not defined (15). 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 very low levels of sodium ingestion (16, 17). Sodium restriction (<40 mmol/day) may increase the blood pressure in 15 to 20% of the population and may be more apparent in normotensive than hypertensive individuals (18, 19, 20). 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 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 (21), rats (22, 23), and mice (24, 25). An inability of the kidney to excrete a sodium load would cause a positive sodium balance, an increase in blood pressure, and eventually hypertension.

Gut sodium sensing

The gastrointestinal tract is important in the regulation of blood pressure since it is the first organ exposed to ingested nutrients and most likely to initially react to a sodium load (26, 27). 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 (27). Thus, the same of amount of sodium given orally has been reported to be excreted more rapidly than that administered intravenously in some studies (28, 29). The presence of a gut sodium sensor has been disputed, but this could be related to experimental conditions that could lead to contradictory signals (27, 30). 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 (31). 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 (29).

Gastrin as the effector of gut sodium sensor

Neural mechanisms (27) and gut hormones (e.g., uroguanylin [Guca2b], cholecystokinin [CCK], gastrin) have been proposed to mediate the natriuresis of an oral sodium load (26-28, 30). However, the oral intake of sodium does not increase circulating prouroguanylin, proguanylin, uroguanylin levels (29, 32). Although, *Guca2b*$^{-/-}$ mice have an impaired natriuretic response to an acute oral odium load, blood pressure is only slightly increased and salt sensitivity is similar in *Guca2b*$^{-/-}$ and *Guca2b*$^{+/+}$ mice (32).

CCK is natriuretic but circulating CCK levels are not increased by an oral sodium load (33) and CCK is not transported into renal tubules (34). However, the natriuresis following

ingestion of a critical amount of sodium may be due to the secretion of the enterokine gastrin by G-cells in the stomach and duodenum and released into the circulation (26, 35). 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 segments (35, 37, 38, 39) 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 (e.g., germ-line deletion of *Gast* (i.e., $Gast^{-/-}$) (35) or *Cckbr* (37) 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 $Gast^{-/-}$ mice on low sodium intake are normotensive but become hypertensive when sodium intake is increased (35 and 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 D_1 receptor (40), a member of the D_1-like receptor family of dopamine receptors (41). D_1-like receptor agonist stimulation increases gastrin mRNA in human G-cells and colon adenocarcinoma cells (SW626) and a D_1-like receptor antagonist blocks the ability of monensin to increase human G-cell gastrin mRNA (40, 42). Therefore, the ability of intracellular sodium to increase gastrin transcription and secretion may require a functional D_1-like receptor.

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) (41, 43, 44). L-DOPA is filtered by the glomerulus and reabsorbed by the renal proximal tubule via at least two sodium-independent amino acid transporters, L-type amino acid transporter type 2 (LAT-2) and rBAT/b0,+; LAT-1 may also participate, especially in the spontaneously hypertensive rat (45, 46). B0,+ is present mainly in the apical membrane while 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 B0AT1), 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). The selective deletion of the *L-AADC* gene in the mouse renal proximal tubules causes hypertension and salt sensitivity (44).

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 five dopamine receptor subtypes in mice results in hypertension, the pathogenesis

of which is subtype-specific (41). Renal-selective silencing of dopamine receptor subtypes, e.g., D_2R, in mice also causes hypertension (48). Single nucleotide polymorphisms of the D_1R gene, *DRD1*, have been reported to be associated with human essential hypertension (49, 50).

D_1R and D_5R 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 D_1R and D_5R antagonist, SCH23390, or a CCKBR antagonist, YF476 (Figure 3) (37). The natriuretic effect of fenoldopam, a D_1-like receptor (D_1R and D_5R) agonist, administered selectively into the kidney via infusion into the right suprarenal artery, can be blocked not only by a D_1-like receptor (D_1R and D_5R) 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 D_1-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 D_1-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 D_1-like receptors and CCKBR in renal proximal tubule cells from Wistar-Kyoto rats was related to an increase in D_1R 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 D_1-like receptor, D_5R, 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 D_1R and the other D_1-like receptor, D_5R, to induce a natriuresis and diuresis (37, 38, 47). Thus, gastrin and D_1-like receptors interact to facilitate the 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 following a mixed meal (55). By contrast, Roux-en-Y bypass surgery prevents the increase in plasma gastrin following a mixed meal (56) but either type of bypass surgery increases plasma levels of natriuretic enterokines, such as glucagon-like peptide-1 (GLP-1) levels (57-59).

G protein-coupled receptor type 4 (GRK4)

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 which are subsequently resensitized and recycled to the plasma membranes (41, 60-63). Wild-type GRK4 is important in the desensitization and recycling of D_1R and D_3R

to the plasma membrane of renal proximal tubules (41, 63). GRK4 plays a vital role in regulating dopamine-mediated natriuresis and renin-angiotensin system-mediated antinatriuresis (41, 61). However, a role of GRK4 in the regulation of CCKBR has not been reported.

GRK4 gene variants in humans (GRK4 A>65L, A>142V, and A>486V) are associated with hypertension in several but not 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 (GRK4 R65L and A486V, in particular) or assessing the role of GRK4 in conjunction with other single nucleotide polymorphisms of GRK4 and other genes (41, 61). 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 (81), *AGTR1* that encodes the AT_1R (82), *CYP11B2* that encodes aldosterone synthase (83), *UMOD* (84) that encodes uromodulin, and *GRK4* (85-90). These genes fulfill the criteria for ascribing a gene as causal of a complex disorder, such as hypertension (91, 92). 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 GRK4γ gene variants (A>65L, A>142V, and A>486V) in mice causes hypertension, although salt sensitivity depends on which is GRK4γ variant is present (85-90). Overexpression of human $GRK4_\gamma$ wild-type in mice results in normal blood pressure and salt resistance (88). By contrast, overexpression of human $GRK4_\gamma$142V in mice causes salt-resistant hypertension (85, 86) while overexpression of $GRK4_\gamma$486V in mice causes salt-sensitive hypertension (88, 90). Increased expression of AT_1R in $GRK4_\gamma$142V (86) and $GRK4_\gamma$486V (90) and production of reactive oxygen species in $GRK4_\gamma$486V (90) but not in $GRK4_\gamma$142V (89) contribute to the different blood pressure phenotype. $GRK4_\gamma$142V also interacts with AT_1R to increase vascular reactivity (87). GRK4 R>65L may also cause salt-sensitive hypertension (unpublished), especially in the presence of SLC4A5 gene variants (68). Therefore, GRK4 gene variants impair the ability of dopamine to inhibit renal sodium transport and impair the synergistic interaction 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 D_1-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 (93).

Genome-wide association studies have identified only 2% of the genetic factors believed to influence blood pressure (94); genome-wide association studies used screening platforms

that did not consistently include *CCKBR*, *GAST*, and variants of other genes important in causing essential hypertension (e.g., G protein-coupled receptor kinase 4 [*GRK4*] variants which negatively regulate D_1R and D_3R [41, 62, 63, 85]). The chromosomal loci of *CCKBR* (11p15.5-p15.4) and *GAST* (17q21) are among the loci identified by GWAS 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

In summary, 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. D_1-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 D_1-like receptors interact to inhibit renal sodium transport, enabling the kidney to excrete a sodium load. GRK4 gene variants impair the function of D_1R and D_3R and abet the function of AT_1R. These lead to enhancement of renal sodium reabsorption and impaired ability to excrete a sodium load that eventually leads to hypertension.

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Perspectives

Ingested sodium is sensed by sodium channels in G-cells of the stomach. An increase in intracellular sodium concentration, in conjunction with D_1R in G-cells, increases transcription of gastrin and also its release into the stomach and circulation. Gastrin, via CCKBR, and dopamine via its five dopamine receptor subtypes (D_1R, D_2R, D_3R, D_4R, and D_5R), synergistically inhibit renal tubular sodium transport resulting in a natriuresis. The presence of *GRK4* gene variants (R>65L, A142>V, A486>V), decrease the function of some dopamine receptors (e.g., D_1R and D_3R), impairing their ability to inhibit renal sodium transport. Positive sodium balance and increased vascular reactivity caused by *GRK4* gene variants result in hypertension.

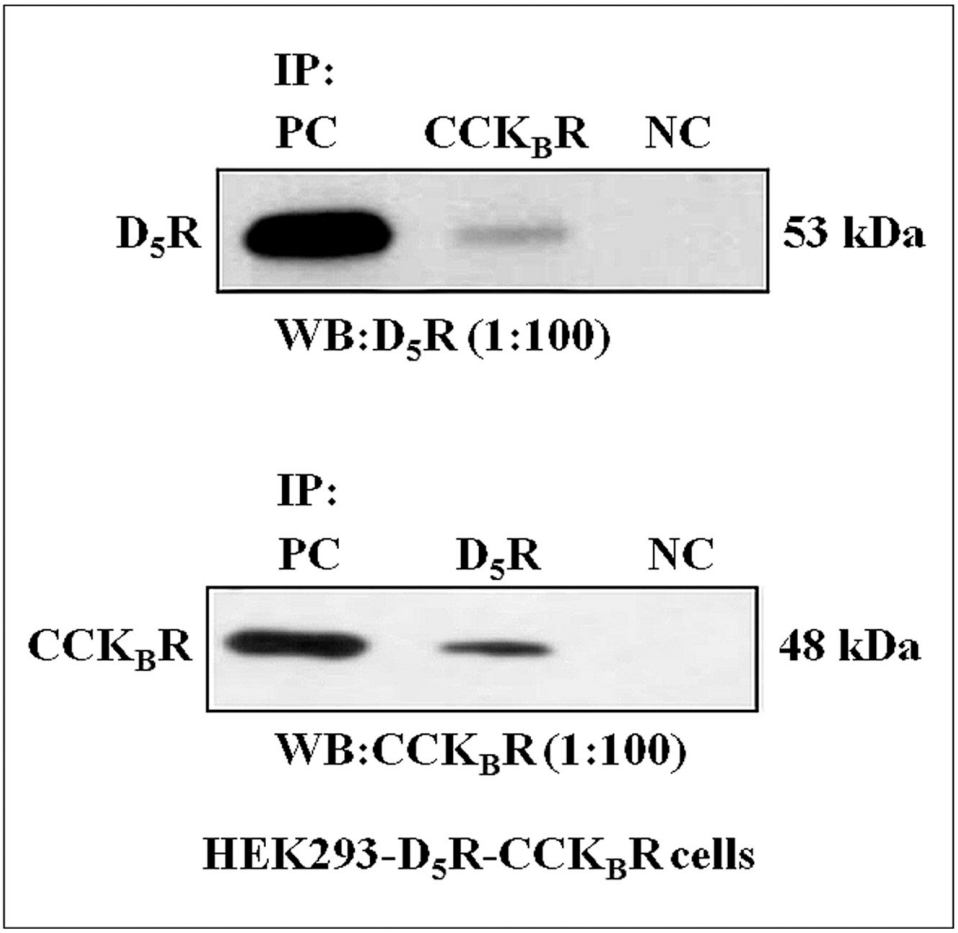

Figure 1.

D$_5$R and CCKBR physically interact in HEK293-D$_5$R-CCKBR cells. HEK293 cells stably overexpressing full-length human D$_5$R and CCKBR were generated in our laboratory (37). Whole cell lysates were subjected to immunoprecipitation (IP) with mouse anti-D$_5$R antibody, mouse anti-CCKBR antibody, or non-immune mouse serum (negative control). Immunoprecipitated complexes were analyzed by immunoblotting (western blot, WB), using rabbit anti-D$_5$R antibody or rabbit anti-CCKBR antibody. PC: positive control; NC: negative control. These experiments were repeated three times with similar results (from Jiang et al [37])

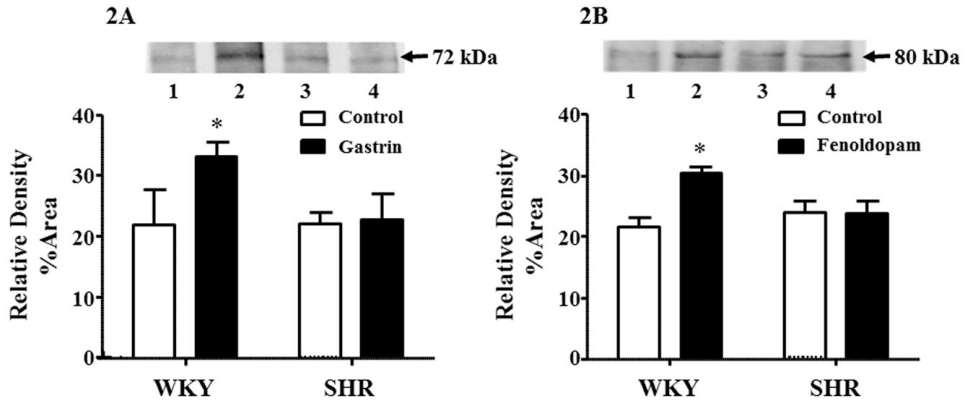

Figure 2.

Gastrin (**A**) or fenoldopam, a D_1R and D_5R agonist, (**B**), increases the coimmunoprecipitation of CCKBR and D_1R in renal proximal tubule (RPT) cells from Wistar-Kyoto (WKY) but not spontaneously hypertensive rats (SHR). The RPT cells were incubated with gastrin (10^{-9} M, **A**) or fenoldopam (10^{-7} M, **B**) for 15 min. Thereafter, the samples were immunoprecipitated with CCKBR antibodies and immunoblotted with D_1R antibodies (*P<0.05 vs control; n=3–5; one-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 (**A**)- or fenoldopam (**B**)-treated RPT cells from WKY rat, lane 3=vehicle-treated RPT cells from SHR, and lane 4=gastrin (**A**)- or fenoldopam (**B**)-treated RPT cells from SHR) (from Chen et al [38]).

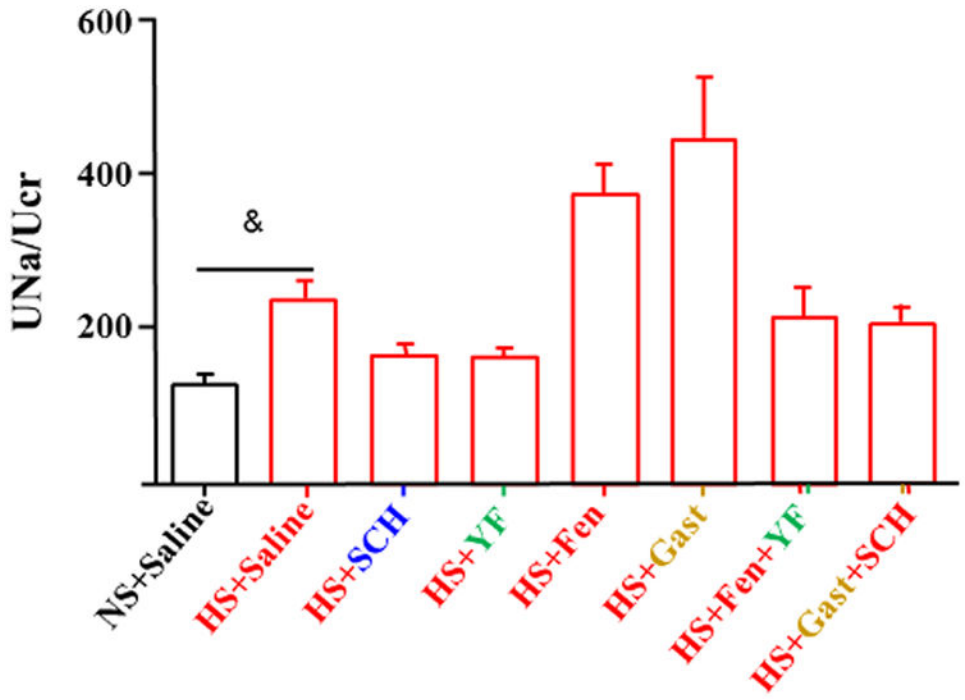

Figure 3.

D_1-like (D_1R and D_5R) receptors and CCKBR interact to increase sodium excretion in BALB/c mice. 24-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 two weeks. Then the BALB/c mice on **HS** diet were subdivided into seven groups and intraperitoneally injected (0.5 ml) daily for one week with vehicle (normal saline)=**HS+Saline**, SCH23390 (a D_1-like receptor antagonist, 0.1 mg/kg)=**HS+SCH**, YF476 (a CCKBR antagonist, 0.1 mg/kg)=**HS+YF**, fenoldopam (a D_1-like receptor agonist, 1mg/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 one week=**NS+Saline**. At the end of drug treatment, urine was collected for 24 hours. n = 5–7/group, $^{\&}P<0.05$ vs NS+Saline, Student's t test;*$P<0.05$ vs HS+Saline, one-way factorial ANOVA, Duncan's multiple range test (from Jiang et al [37])

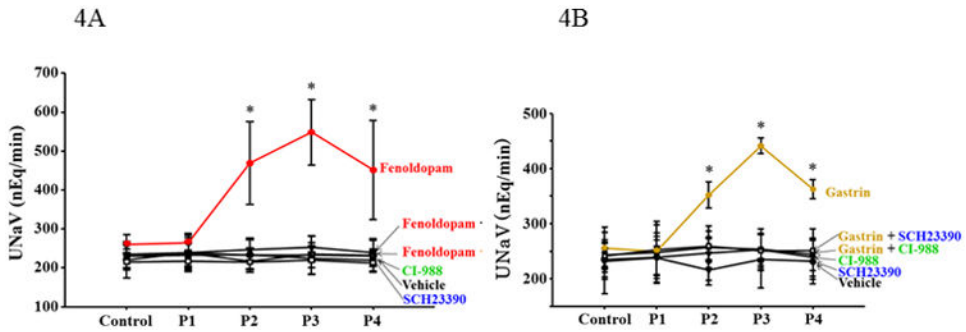

Figure 4.

Gastrin and D_1-like (D_1R and D_5R) receptors interact to increase sodium excretion (UNaV) in Wistar-Kyoto rats. There are five periods: Control and Periods 1-4; each period lasted 40 min. During the Control and Period 4 (P4), only the vehicle (saline) was infused.

A. Gastrin-mediated (1.0 μg/kg per minute; n=5) increase in sodium excretion is blocked by either the D_1-like receptor antagonist, SCH23390 (0.4 μg/kg per minute; n=5) or CCKBR antagonist, CI-988 (1.0 mg/kg per minute; n=5). During period 1 (P1), the vehicle (saline) was infused in the gastrin group, CI-988 in the CI-988 group, and SCH23390 in the SCH23390 group. During Period 2 (P2) and Period 3 (P3), gastrin was infused in the Gastrin group, gastrin and CI-988 in the Gastrin + CI-988 group, and gastrin and SCH23390 in the gastrin and SCH23390 group.

B. Fenoldopam-mediated (1.0 μg/kg per minute; n=5) increase in sodium excretion is blocked by either the CCKBR antagonist, CI-988 (1.0 mg/kg per minute; n=5) or D_1-like receptor antagonist, SCH23390 (0.4 μg/kg per minute; n=5). During period 1 (P1), the vehicle (saline) was infused in the gastrin group; CI-988 in the CI-988 group, and SCH23390 in the SCH23390 group. During Period 2 (P2) and Period 3 (P3), fenoldopam was infused in the Fenoldopam group, fenoldopam and CI-988 in the Fenoldopam + CI-988 group, and fenoldopam and SCH23390 in the Fenoldopam + SCH23390 group.

Data are expressed as mean ±SEM.*P<0.05 vs other groups (one-way factorial ANOVA, Holm–Sidak test) (from Chen et al [38])

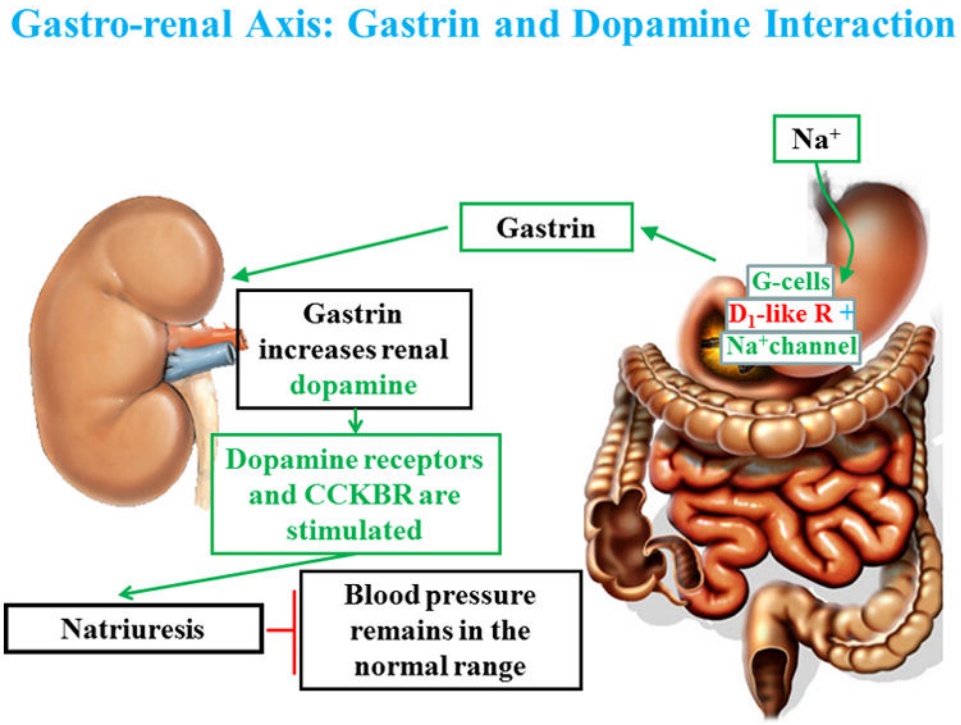

Figure 5.

Ingested sodium is sensed by sodium channels in G-cells of the stomach. An increase in intracellular sodium concentration, in conjunction with D_1R, in G-cells increases transcription of gastrin and also the release of gastrin into the stomach and the circulation for a few hours. An increase in ingested sodium also stimulates the synthesis of L-DOPA by enterochromaffin cells. Circulating gastrin and L-DOPA are taken up by renal proximal tubule cells, via amino acid transporters, e.g., LAT-1, and converted to dopamine by aromatic amino acid decarboxylase, a process that is facilitated by gastrin. Gastrin, via CCKBR, and dopamine, via its five dopamine receptor subtypes (D_1R, D_2R, D_3R, D_4R, and D_5R), inhibit renal tubular sodium transport resulting in a natriuresis. The excess sodium that is ingested is excreted and blood pressure remains in the normal range. D_1-like R = D_1-like receptors. Note: The drawings of the gastrointestinal tract and kidney were obtained from the Internet.

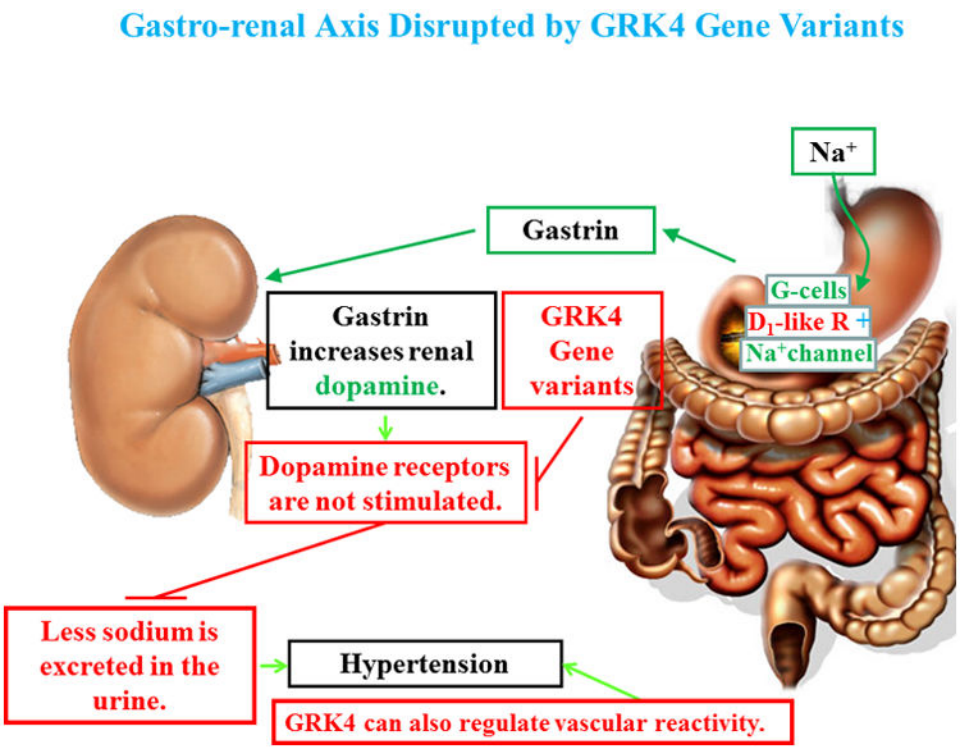

Figure 6.

In the presence of GRK4 gene variants (R>65L, A142>V, A486>V), some dopamine receptors (e.g., D_1R, D_3R) are constitutively desensitized, impairing the function of these dopamine receptors. Less sodium is excreted, sodium balance is increased, and blood pressure eventually increases that may reach hypertensive levels. GRK4 gene variants can also increase vascular reactivity. GRK4 gene variants may not affect gastrin secretion by stomach G-cells because these cells do not express GRK4. Note: The drawings of the gastrointestinal tract and kidney were obtained from the Internet.