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The importance of the gastrorenal axis in the control of body sodium homeostasis

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Abstract

Hypertension develops with chronically increased sodium intake when sodium that accumulates in the body can no longer be sequestered, extracellular fluid is expanded, and compensatory neural, hormonal, and pressure-natriuresis mechanisms fail. Sensing the amount of ingested sodium, by the stomach, is one mechanism by which sodium balance is regulated. The natriuresis following the ingestion of a certain amount of sodium may be due to an enterokine, gastrin, secreted by G-cells in the stomach and duodenum and released into the circulation. Circulating gastrin levels are 10–20-fold higher than those for cholecystokinin. Of all the gut hormones circulating in the plasma, gastrin is the one that is reabsorbed to the greatest extent by renal tubules. Gastrin, via its receptor, the cholecystokinin type B receptor (CCKBR), is natriuretic, in mammals including humans, caused by inhibition of renal sodium transport. Germline deletion of gastrin (*Gast*) or *Cckbr* gene in mice causes salt-sensitive hypertension. Selective silencing of *Gast* in the stomach and duodenum impairs the ability to excrete an oral sodium load and also increases blood pressure. Thus, the gastro-renal axis, mediated by gastrin, can complement pronatriuretic hormones, such as dopamine to increase sodium excretion after an oral sodium load. These studies in mice may be translatable to humans because the chromosomal loci of *CCKBR* and *GAST* are linked to human essential hypertension. Understanding the role of genes in the regulation of renal function and blood pressure may lead to the tailoring of anti-hypertensive treatment based on genetic make-up.

Keywords

dopamine; gastrin; gastro-renal axis; salt sensitivity

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Competing Interests

None

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Introduction

Forty percent of the world's population has hypertension and is responsible for about 12.8 % of annual deaths (Alwan, 2010). However, these statistics do not distinguish salt-sensitive from salt-resistant hypertension or include normotensives who are salt-sensitive. Almost half of the US population has hypertension, salt sensitivity, or both (Sullivan, 1991, Weinberger et al, 2001). Salt sensitivity, independent of blood pressure, is a risk factor for cardiovascular morbidity and mortality (Weinberger et al, 2001) and other diseases, e.g., asthma, gastric carcinoma, osteoporosis, and renal dysfunction (de Wardener et al, 2002, Franco et al, 2006). Salt sensitivity has also been claimed to interfere with the normal circadian rhythm of blood pressure (Logan et al, 2009). A normal dip in nocturnal blood pressure - a 10% fall in blood pressure relative to day time blood pressure - is important because the failure of the normal night-time dip in blood pressure is associated with an increase in cardiovascular morbidity and mortality (Logan et al, 2009, O'Brien E, 2009).

The World Health Organization recommends reducing sodium consumption to less than 87 mmol per day in adults, to help prevent hypertension, heart disease, and stroke (www.who.int/global.../global-status-report-ncds, 2014). 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 the decrease in blood pressure (Graudal et al, 2015). Another meta-analysis indicated that a modest reduction in salt intake for 4 or more weeks causes a decrease in blood pressure levels in in both hypertensive and normotensive individuals (He et al, 2013). However, these meta-analyses do not take into account the influence of genetics and epigenetics on blood pressure response to sodium intake. A lower limit of the daily NaCl intake is also not defined (Institute of Medicine, 2013), although the relationship between sodium intake and blood pressure may not be linear but more of a J-shaped curve. There is an increase in cardiovascular risk at very low levels of sodium intake (Mente et al, 2014). 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 (Ruppert et al, 1993, Montasser et al, 2011, Gildea et al, 2013).

Hypertension and salt sensitivity are complex diseases that are probably caused by genetics, epigenetics, and lifestyles, e.g., excessive sodium consumption and sedentary lifestyles. The precise genetic modifications that affect the regulatory mechanisms that lead to salt sensitivity in human essential hypertension remain unknown. However, the importance of the kidney in blood pressure regulation (Hall et al, 2012) is supported by renal transplantation studies in humans (Curtis, 1983), rats (Bianchi et al, 1974, Morgan et al, 1990), and mice (Crowley et al 2005, Asico et al 2011). An inability of the kidney to excrete a sodium load would cause a positive sodium balance (Hall et al 2012).

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Gut sodium sensing

There is a growing appreciation of a role of the gastrointestinal tract in the regulation of blood pressure because it is the first organ exposed to ingested nutrients and most likely to initially react to sodium load (Michell et al, 2008, Furness et al, 2013). Sensing the amount of ingested sodium may be an important mechanism by which sodium balance is regulated (Michell et al, 2008). Indeed, given the same amount of sodium load, an oral load may be more rapidly excreted than an intravenous load (Carey, 1978, Preston et al, 2012). The presence of a gut sodium sensor has been disputed (Furness et al, 2013, Andersen et al, 2000). However, a discrepancy between the rapidity of sodium excretion following an oral or an intravenous administration of sodium does not dispute the presence of a gut sodium sensor (Preston et al, 2012)

Gastrin as the effector of gut sodium sensor

Neural mechanisms (Furness et al, 2013), including the activation of the parasympathetic and inhibition of the sympathetic nervous system (Mailman, 1980), and gut hormones (e.g., uroguanylin [Guca2b], cholecystokinin [CCK]) have been proposed to mediate the natriuresis of an oral sodium load. However, the oral intake of sodium may not increase circulating proguanylin, prouroguanylin, or uroguanylin (GUCA2B) (Lorenz et al, 2003, Preston et al, 2012). *Guca2b*$^{-/-}$ mice have an impaired natriuretic response to an acute oral but not an intravenous sodium load. However, the blood pressure sensitivity to an increase in sodium intake is similar *Guca2b*$^{-/-}$ and *Guca2b*$^{+/+}$ mice. Inactivating GUCA2B variants in humans are also not associated with salt-sensitive hypertension. CCK is natriuretic but circulating CCK levels are not increased by oral sodium load and CCK is not reabsorbed by renal tubules (Melis et al, 2007). By contrast, the natriuresis following ingestion of a certain amount of sodium may be due to gastrin secreted by G-cells in the stomach and duodenum and released into the circulation (Michell et al, 2008, Pisegna et al, 1996). The oral intake of sodium, even in the absence of food, can stimulate gastrin secretion (Survé & Håkanson, 1998). Sodium, in conjunction with D_1-like receptors in G-cells of the stomach, increases the expression of gastrin (Gildea et al, 2014, 2015).

The normal fasting plasma gastrin levels range from 100 to 200 pg/ml; the meal-stimulated blood gastrin concentration is about 2–4.5-fold higher, equivalent to a concentration of about 400 pM (Li et al, 2014 Saqui-Salces et al, 2012). Among the radiolabeled analogues of several enterokines (CCK, gastrin, bombesin, neurotensin, and somatostatin), gastrin is taken up and retained to the greatest extent by renal proximal tubules (100–1000-fold), presumably by reabsorption from the glomerular filtrate (Melis et al, 2005, Melicharova et al, 2014). Thus, gastrin levels in the kidney after feeding may be in the nanomolar range, concentrations we have used to study the ability of gastrin to inhibit NHE3 and Na^+, K^+-ATPase activities in human renal proximal tubule cells (Li & Jose, 2013, Li et al, 2016). Gastrin then acts on its receptor, the cholecystokinin B receptor, CCKBR, expressed in several nephron segments (Calam et al, 1987, Pisegna et al, 1996, von Schrenck et al 2000) to decrease renal sodium transport. Gastrin has also been shown to decrease ileal absorption of sodium by increasing its (sodium) secretion into the ileal lumen. The direct inhibitory effect of gastrin on sodium transport in the intestines may be complemented by gastrin-

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mediated stimulation of cholinergic nerves or inhibition of sympathetic nerves (Mailman, 1980). Gastrin is important in the natriuresis associated with high salt diet because a CCKBR antagonist, YF476, abrogates the natriuresis in salt-resistant BALB/c mice fed 3% NaCl diet for two weeks (Jiang et al, 2016). Gastrin is important in the regulation of sodium balance and blood pressure because germ-line deletion of *Gast* (i.e., $Gast^{-/-}$) (Pisegna et al, 1996) or *Cckbr* (Yang et al, 2012, Jiang et al, 2016) or silencing *Gast* using siRNA selectively in the stomach (unpublished data) in mice 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 salt sensitivity because $Gast^{-/-}$ mice on low sodium intake are normotensive but become hypertensive with normal or high sodium intake (Pisegna et al, 1996 and unpublished data).

Gastrin needs a functioning renal dopaminergic system to exert is natriuretic effect. $Gast^{-/-}$ mice have decreased renal dopamine production (unpublished data). The natriuretic effect of gastrin, 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. Moreover, the natriuretic effect of fenoldopam, a D_1-like receptor agonist, also administered selectively into the kidney, via infusion into the right suprarenal artery, can be blocked not only by a D_1-like receptor antagonist, SCH23390, but also by a CCKBR antagonist, CI-988, in normotensive Wistar-Kyoto rats (Chen et al, 2013). Gastrin and fenoldopam also interact to inhibit Na^+-K^+-ATPase activity in renal proximal tubule cells from Wistar-Kyoto rats. By contrast, the synergism between D_1-like receptors and CCKBR in the regulation of renal sodium transport, *in vivo* and *in vitro,* in Wistar-Kyoto rats is not observed in spontaneously hypertensive rats. The synergistic interaction between D_1-like receptors and CCKBR in renal proximal tubule cells from Wistar-Kyoto rats was related to a gastrin-induced 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 (Chen et al, 2013). The increased sodium excretion in mice fed a high salt diet is also abrogated by D_1-like receptor or CCKBR antagonists (Jiang et al, 2016). We have also reported that the D_1-like receptor agonist fenoldopam, or gastrin, inhibits NHE3 activity in human renal proximal tubule cells (Armando et al, 2011, Chen et al, 2013, Liu et al, 2013).

Products of the fermentation of nutrients by gut microbiota can influence blood pressure by regulating expenditure of energy, intestinal metabolism of catecholamines, and gastrointestinal and renal ion transport, and thus, salt sensitivity (Jose & Raj, 2015). Increased sodium transport in the gastrointestinal tract may contribute to salt sensitivity (Lienhard et al, 2012, Spencer et al, 2014, Li et al, 2015). Gastrin and dopamine can also decrease ion transport in the gastrointestinal tract. Dopamine, via D_1-like receptors, inhibits jejunal Na^+-K^+-ATPase activity in young (20 days) but not older normotensive rats that is greater in those fed low than normal or high salt diet. The inhibitory effect of dopamine on jejunal Na^+-K^+-ATPase activity is not observed in spontaneously hypertensive rats (Lucas-Teixeira et al, 2000). However, the ability of dopamine to inhibit jejunal Na^+-K^+-ATPase activity persists in obese Zucker rats fed a high salt diet (Lucas-Teixeira et al 2002). In adult rats and dogs, gastrin can inhibit jejunal Na^+-K^+-ATPase activity (Mailman, 1980, Sharon et al, 1981). Although, gastrin does not inhibit electrolyte transport in the colon (Cummings,

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1975), gastrin-releasing peptide stimulates sodium secretion in the distal colon (Traynor TR & O'Grady, 1996). D_1-like receptors also simulate duodenal mucosal bicarbonate secretion (Safstein, 1993). Whether or not gastrin and dopamine interact to regulate intestinal ion transport remains to be determined.

Genome-wide association studies (GWAS) have identified only 2% of the genetic factors believed to influence blood pressure (Padmanabhan et al, 2015). This may be related to the fact that GWAS used screening platforms that did not consistently include genes that may be important in blood pressure regulation; e.g., *CCKBR*, *GAST*, and variants of other genes important in causing essential hypertension (e.g., G protein-coupled receptor kinase 4 [*GRK4*] which negatively regulates D_1R and D_3R [Armando et al, 2011]). Nevertheless, the chromosomal loci of *CCKBR* (11p15.5-p15.4) and *GAST* (17q21) are among those identified by GWAS that are linked to hypertension. However, *CCKBR* and *GAST* single nucleotide polymorphisms have not been associated with hypertension.

In summary, published and unpublished data suggest that gastrin produced by G-cells may be the effector of the sodium sensor in the stomach. However, the identification of the sodium sensor in the stomach remains to be determined. The presence of sodium sensors in other segments of the gastrointestinal tract also needs to be determined.

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New Findings

What is the topic of this review?

Sensing the amount of ingested sodium is one mechanism by which sodium balance is regulated. This review describes the role of gastrin in the cross-talk between the stomach and the kidney following the ingestion of sodium.

What advances does it highlight?

Neural mechanisms and several gut hormones, including cholecystokinin and uroguanylin, have been suggested to mediate the natriuresis after an oral sodium load. It is proposed that gastrin produced by G-cells via its receptor, cholecystokinin B receptor, interacts with renal D_1-like dopamine receptors to increase renal sodium excretion.