Hypertension is one of the most prevalent multifactorial cardiovascular disorders caused by both genetic and environmental factors. Overwhelming evidence shows that abnormal sodium regulation because of either hereditary factors or overconsumption of salt may lead to salt-sensitive hypertension. Sodium regulation is complex mainly because of its dependence on neuronal, hormonal, and local factors. Hormonal regulation involves a complex array of both natriuretic and antinatriuretic hormones affecting renal sodium reabsorption. During normal sodium intake, antinatriuretic hormones predominate whereby renin–angiotensin–aldosterone system maintains positive sodium balance by increasing renal sodium absorption mainly because of the activation of tubular sodium transporters. However, under sodium replete conditions, natriuretic factors, such as dopamine, nitric oxide, and arterial natriuretic peptide, inhibit renal tubular sodium transporters, leading to increased sodium excretion. The kidney, especially the renal proximal tubule, which is responsible for ≥60% of total renal sodium reabsorption, is critical in the regulation of sodium balance. Reports from our laboratory and others have shown that dopamine produced by the kidney is critically involved in the excretion of an Na⁺ load. Dopamine, via D1-like (composed of D1 receptor [D1R] and D5 receptor subtypes) and D2-like receptors (composed of D2 receptor, D3 receptor, and D4 receptor subtypes), increases sodium excretion secondary to a decrease in the activity of renal sodium transporters in several nephron segments, including the proximal tubules, thus preventing volume expansion and maintaining the blood pressure in the normal range. Chen et al have shown that ≥50% of basal sodium excretion in moderately volume expanded states is mediated by the paracrine action of renal dopamine exerted on D1Rs. Dopamine, via D1R, inhibits the activity of Na⁺/K⁺-ATPase in the basolateral membrane and Na⁺/H⁺ exchanger 3 in the apical membrane of renal proximal tubular cells. A defective D1R function is involved in the pathogenesis of hypertension because it has been shown that pharmacological blockade of dopamine receptors decreases Na⁺ excretion and increases blood pressure. Decreased renal dopamine production in the basal state or failure of dopamine production to increase in response to an Na⁺ load has also been reported in those with hypertension, prehypertension, and even in those with a family history of hypertension in some ethnic groups. Furthermore, inactivation of any dopamine receptor gene in mice results in hypertension in mice.

It is well established that an upregulation of antinatriuretic factors or a downregulation of natriuretic factors disrupts the renal sodium homeostasis and contributes to both salt-sensitive and salt-independent hypertension. However, apart from neuronal role in sodium regulation, little is known about the contribution of other organ systems to sodium homeostasis or blood pressure regulation. This is despite the fact that salt intake can modulate gastric hormone levels and an oral NaCl load produces a much stronger diuresis and natriuresis than an intravenous infusion of NaCl of similar magnitude. It is reported that the natriuresis after ingestion of a certain amount of Na⁺ may be caused by gastrin, an enterokine, secreted by G cells in the stomach and duodenum and released into the circulation, which is taken up by renal cortical tubules to a greater extent than the other enterokines released. Gastrin via cholecystokinin B receptor expressed in several nephron segments decreases Na⁺ transport and regulates blood pressure because mice lacking gastrin (ie, Gast−/−), systemically or only in the gut, or functional gastrin receptors (eg, Cckbr−/−, cholecystokinin B receptor blockade) do not increase Na⁺ excretion after an oral Na⁺ load and have increased blood pressure. Gastrin is also important in salt sensitivity because Gast−/− mice on low Na⁺ intake are normotensive but become hypertensive with normal or high Na⁺ intake. Although several other gut hormones (eg, cholecystokinin, uroguanylin) could potentially mediate natriuresis in response to an oral NaCl load because it has been shown that a high NaCl intake increases renal uroguanylin expression, oral sodium consumption may not always increase circulating uroguanylin levels, and cholecystokinin is not taken up by renal tubules.

The present study by Chen et al identifies a novel gastrointestinal-renal interaction using a genetic animal model of essential hypertension. It is reported that gastrin needs a functioning renal dopaminergic system because gastrin colocalizes with the enzymes that synthesize dopamine, and Gast−/− mice have decreased renal dopamine production. Also, inhibition of dopamine synthesis prevents gastrin-induced natriuresis of an oral Na⁺ load, despite functional gastrin receptor. This study by Chen et al reconfirms the gastrin–dopamine links by providing a potential mechanism at receptor level. They also found a physical interaction between the proximal tubular D1R and gastrin receptor using the immunoprecipitation study. Treatment of proximal tubules from Wistar-Kyoto

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rats with gastrin increased D1-like receptor expression in the cell membrane, whereas fenoldopam, a D1R agonist, increased gastrin receptor in the cell membrane. Thus, stimulation of one receptor increases the cellular distribution of the other receptor into the cell membrane. This is physiologically relevant as blockade of D1 or gastrin receptors abolishes the fenoldopam-mediated increase in proximal tubular Na/K-ATPase, which leads to increased sodium excretion and prevents increase in blood pressure.

modulated by oxidative stress, whereas the renin-angiotensin–aldosterone system is positively regulated by oxidative milieu. Taken together, the present study makes an important contribution to our understanding of hormonal regulation of renal sodium excretion by providing a novel gastric-renal interaction involving gastrin–dopamine receptor signaling to regulate sodium excretion and consequently blood pressure during high sodium intake (Figure).

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**Disclosures**

None.

**References**

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