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COMMENTARY

Interaction between Gα12 and Gα13 protein subunits and dopamine receptors in renal proximal tubules

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The cells of the renal proximal tubules (RPTs) have high aromatic L-amino-acid decarboxylase activity. Filtered or circulating L-3,4-dihydroxyphenylalanine can be converted to dopamine after uptake into this extraneuronal compartment, without being subsequently converted to norepinephrine.[1] Peripheral dopamine has been characterized as an important modulator of both renal sodium excretion and blood pressure by acting directly on renal epithelial ion transport and by modulating the secretion/release of other hormonal/humoral molecules. These hormonal and humoral molecules include aldosterone, catecholamines, renin and vasopressin, each of which contribute to the regulation of sodium homeostasis and blood pressure. In addition, other hormones may interact with dopamine produced in RPTs to increase (for example, atrial natriuretic peptide) or decrease (for example, angiotensin) its inhibitory effect on tubular sodium reabsorption. The actions of endogenous renal dopamine on water and electrolyte transport are modest under euvolemic conditions, but become magnified during moderate sodium excess. Thus, following a moderate acute or chronic sodium load, up to 50% of sodium excretion is mediated by dopamine produced by the RPTs.[2]

The natriuretic effect of peripheral dopamine is exerted by two major receptor classes, D_1-like and D_2-like receptors, which belong to the rhodopsin-like family of membrane receptors called G-protein-coupled receptors (GPCRs). GPCRs have specific resultant actions due to their heterotrimeric G-protein subunits composed of α, β and γ.[2,3] D_1-like receptors include D_1 and D_5 subtypes, which stimulate adenylyl cyclase. D_1 couples to Gαs and Gαq, whereas D_5 couples to Gαs, Gα12 and Gα13.[4–6] The linkage of G-protein subunits to the specific D_1-like receptor is tissue specific. D_2-like receptors include D_2, D_3 and D_4 subtypes, which are coupled to Gαi. Gαi subunits inhibit adenylyl cyclase and calcium channel activities.[2,7] In RPTs, D_1, D_3, D_4 and D_5 receptors are expressed. Although the quantitative contribution of a particular dopamine receptor subtype to renal sodium transport in RPTs has not been studied previously, most *in vivo* studies suggested that dopamine-induced natriuresis is mediated principally by D_1-like receptor subtypes. In fact, a number of studies evidenced that the activation of D_1-like receptors in RPTs decreases sodium reabsorption by the inhibition of both the Na^+/HCO_3^- co-transporter and Na^+-K^+-ATPase activities in the basolateral membranes. Moreover, D_1-like receptors in RPTs demonstrate inhibition of the Na^+-H^+ antiporter (NHE3), the Na^+-Pi co-transporter and the Cl^-/HCO_3^- antiporter in the apical membranes. Evidence has been provided suggesting that the dopamine-induced natriuretic response resulting from activation of tubular D_1-like receptors is diminished in both spontaneously hypertensive rats and in humans with essential hypertension. This compromised natriuretic response in hypertension was described to result from alterations occurring at the receptor level as well as at the cellular signaling pathway level, which ultimately decreases tubular sodium reabsorption.[8]

The effects of the D_2-like receptors, independent of the D_1-like receptors, on sodium excretion were not consistent, ranging from natriuresis to antinatriuresis and no effect. This lack of consistency was attributed to the use of drugs with poor D_2-like receptor subtype selectivity. However, the current perception is that D_2-like receptors may function synergistically with D_1-like receptors in RPTs, where they may potentiate the inhibitory effects of D_1-like receptors on NHE3, the Na^+-Pi co-transporter and Na^+-K^+-ATPase activities.[9] In the rat kidney, the major D_2-like receptor in RPTs is the D_3 receptor. The mechanisms underlying the interaction between D_3 and D_1 receptors were recently investigated using immortalized RPT cells.[10] In these studies, the D_3 receptor agonist PD128907 increased the immunoreactive expression of the D_1 receptors in a concentration-dependent and time-dependent manner. These data suggest synergism between D_3 and D_1 receptors capable of acutely increasing sodium excretion. In addition, co-immunoprecipitation of the D_3 and D_1 receptors in RPT cells was observed.[10] Together, these results indicate that the natriuretic effects of D_3 receptor activation in RPT cells could be due, at least in part, to D_3 receptor-mediated increases in D_1 receptor expression, specifically, total and cell surface membrane expression. Additionally, these results indicate direct D_3 and D_1 receptor interaction. The interaction between D_3 and D_1 receptors was impaired in RPT cells from spontaneously hypertensive rats, which provided evidence favoring their combined contribution to compromised sodium excretion and increased blood pressure in this rat hypertension model.[10]

In this issue of *Hypertension Research*, Zhang *et al.*[11] report on their findings that D_3 receptors in RPTs could bind to the fourth family member of the G-protein subunit (Gα12 and Gα13) when activated by the D_3 receptor-selective agonist PD128907. This binding was accompanied by the co-localization and co-immunoprecipitation of the D_3 receptor and Gα12 and Gα13 in renal brush border membranes and RPT cells. The compound PD128907 inhibited the Na^+-K^+-ATPase in RPTs in a concentration-dependent

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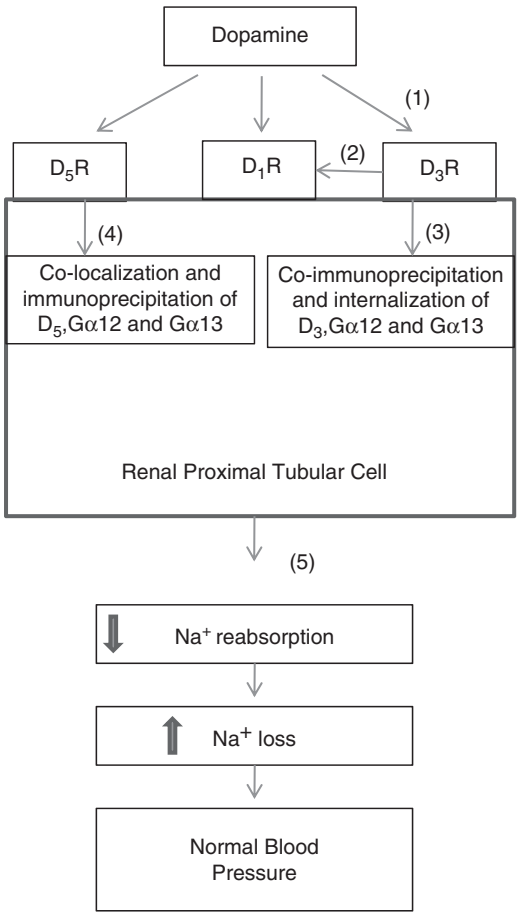

Figure 1 The interaction of Gα12 and Gα13 with dopamine receptors in the renal proximal tubules (RPTs). While experiencing conditions of moderately increased NaCl intake, the renal D_1, D_3 and D_5 receptors are stimulated by dopamine in the kidney (1). D_3 receptor stimulation increases the immunoreactive expression of D_1 receptors (2). Stimulation of the D_3 receptors is accompanied by increased co-immunoprecipitation and internalization of Gα12 and Gα13 with the D_3 receptors (3). Stimulation of the D_5 receptors is accompanied by co-localization and immunoprecipitation of Gα12 and Gα13 with the D_5 receptors (4). D_1, D_3 and D_5 receptor activation decreases sodium reabsorption and contributes to blood pressure control (5). It is suggested that both the D_1-like (D_5) and D_2-like (D_3) receptors may participate in the regulation of sodium transport by hampering Gα12 and Gα13 actions because Gα12 and Gα13 stimulate sodium transport by modulating the activities of the Na^+-K^+-ATPase and NHE3 in RPTs.

manner. Gα12 and Gα13 are known to stimulate sodium reabsorption in RPTs by increasing pump and transporter activity (more specifically, Na^+-K^+-ATPase and NHE3). Therefore, these results indicate that the association of the D_3 receptors with Gα12 and Gα13 may be one of the mechanisms underlying the natriuretic effect induced by stimulation of the D_3 receptors in RPT cells.

As previously mentioned, Gα12 and Gα13 were already linked to the D_5 receptor, but not to the D_1 receptors.[6] A linkage to the D_5 receptors was found in RPTs in native kidneys, in immortalized RPT cells and in HEK293 cells heterologously expressing the D_5 receptor. Laser confocal microscopy revealed the co-localization of the D_5 receptor with Gα12 and Gα13 at the brush border membranes and subjacent areas. In these elegant experiments, the authors also provided evidence that the D_1-like agonist fenoldopam increased the interaction between the D_5 receptor with both Gα12 and Gα13 in brush border membranes.[6] These results, when viewed together with the findings reported by Zhang *et al.*[11] in this issue, indicate that Gα12 and Gα13 may represent a common intracellular pathway of D_1-like (D_5) and D_2-like (D_3) receptors in RPT cells (see Figure 1). Because D_1-like and D_2-like receptors may function synergistically in RPT cells, it would be interesting to examine the influence of D_1 stimulation on the co-localization of D_3 receptors with Gα12 and Gα13. In addition, as the interaction between D_3 and D_1 receptors is impaired in RPT cells from spontaneously hypertensive rats, it would be interesting to examine the linkage between D_3 receptors and Gα12 and Gα13 in RPT cells in this rat hypertension model.

Gα12 and Gα13 are expressed in other locations besides brush border membranes and subjacent areas to RPT cells. Gα12 is expressed in the ascending limb of the loop of Henle and cortical collecting ducts. Gα13 is expressed in the distal tubules, the medullary collecting duct and the juxtaglomerular apparatus.[6] Therefore, the results by Zhang *et al.*[11] reinforce the view that each of the dopamine receptor subtypes—alone or by interacting with the other dopamine receptor subtypes, other GPCRs and G-protein subunits—regulate tubular sodium transport uniquely. Accordingly, the ultimate natriuretic effect of dopamine will be the sum of the interactions among the D_1-like and D_2-like dopamine receptors, other GPCRs, such as endothelin and angiotensin receptors, and G-protein subunits. Knowledge of the regulatory pathways involving differential G-protein subunit linkages on different dopamine receptors may provide new approaches to the pharmacological regulation of sodium excretion and blood pressure control.

1 Soares-da-Silva P, Pestana M, Fernandes MH. Involvement of tubular sodium in the formation of dopamine in the human renal cortex. *J Am Soc Nephrol* 1993; **3**: 1591–1599.
2 Hussain T, Lokhandwala MF. Renal dopamine receptors and hypertension. *Exp Biol Med (Maywood)* 2003; **288**: 134–142.
3 Schiöth HB, Fredriksson R. The GRAFS classification system of G-protein coupled receptors in comparative perspective. *Gen Comp Endocrinol* 2005; **142**: 94–101.
4 Kimura K, White BH, Sighu A. Coupling of human D-1 dopamine receptors to different guanine nucleotide binding proteins: evidence that D-1 dopamine receptors can couple to both Gs and Go. *J Biol Chem* 1995; **270**: 14672–14678.
5 Sidhu A, Kimura K, Uh M, White BH, Patel S. Multiple coupling of human D5 dopamine receptors to guanine nucleotide binding proteins Gs and Gz. *J Neurochem* 1998; **70**: 2459–2467.
6 Sheng S, Yu P, Zeng C, Wang Z, Yang Z, Andrews PM, Felder RA, Jose PA. Gα12 and Gα13-protein subunit linkage of D5 dopamine receptors in the nephron. *Hypertension* 2003; **41**: 604–610.
7 Holmes A, Lachowicz JE, Sibley DR. Phenotypic analysis of dopamine receptor knockout mice; recent insights into the functional specificity of dopamine receptor subtypes. *Neuropharmacology* 2004; **47**: 1117–1134.
8 Hussain T, Lokhandwala MF. Dopamine-1 receptor G-protein coupling and the involvement of phospholipase A2 in dopamine-1 receptor mediated cellular signaling mechanisms in the proximal tubules of SHR. *Clin Exp Hypertens* 1997; **19**: 131–140.
9 Eklof AC. The natriuretic response to a dopamine DA1 agonist requires endogenous activation of dopamine DA2 receptors. *Acta Physiol Scand* 1997; **160**: 311–314.
10 Zeng C, Wang Z, Li H, Yu P, Sheng S, Wu L, Asico L, Hopfer U, Eisner G, Felder R, Jose P. D3 dopamine receptor directly interacts with D1 dopamine receptor in immortalized renal proximal tubule cells. *Hypertension* 2006; **47**: 573–579.
11 Zhang Y, Fu C, Asico LD, Villar VAM, Ren H, He D, Wang Z, Yang J, Jose PA, Zeng C. Role of $G\alpha_{12}$- and $G\alpha_{13}$-protein subunit linkage of D_3 dopamine receptors in the natriuretic effect of D_3 dopamine receptor in kidney. *Hypertens Res* 2011; **34**: 1011–1016.