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Dopamine coordinates the effect of natriuretic and antinatriuretic factors

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Abstract:
Living organisms are dependent on a precise regulation of water and sodium. The stability of the internal environment is maintained through a series of feedback mechanisms, in response to changes within the organism as well as to changes in the external environment. Many organs in the body participate in sodium- and water turn over, but the kidney is the only organ in the body that excretes or retains sodium and water in a regulated fashion. Salt retention is a risk factor in the development of hypertension which may lead to renal insufficiency, heart failure and cerebrovascular catastrophes.

The traditional view has been that hypertension is caused by an excess of factors that produce vasoconstriction and sodium retention. This hypothesis has been modified after reports showing that a low availability of vasodilative, natriuretic factors also predisposes to hypertension. The precision by which sodium balance is regulated suggests an intricate interaction between modulatory factors released from intra- and extrarenal sources. Intrarenally produced dopamine has a central role in this interactive network. Dopamine acts as an autocrine and paracrine factor to inhibit the activity of renal tubular Na^+, K^+-ATPase as well as of a number of tubular sodium influx pathways. Other natriuretic factors activate the renal dopamine system via a heterologous recruitment of dopamine-1 like (D1R) to the plasma membrane, whereas dopamine counteracts the effect of antinatriuretic factors via unknown mechanisms.

Prolactin regulates fluid transport across the plasma membrane by unknown mechanisms. Prolactin interacts with dopamine in various tissues. Here we report that prolactin induces a dramatic nine fold increase in urinary sodium excretion associated with a decrease in renal proximal tubular Na^+, K^+-ATPase activity. These effects were abolished by a D1R antagonist. We found that prolactin signals via similar pathways as D1R in the renal proximal tubules, including protein kinas A, protein kinase C and PI3 kinase activation and that prolactin induced a heterologous recruitment of D1R to the plasma membrane. These results suggest that the renal dopamine system has a permissive role for prolactin.

Dopamine acting on the D1 family of receptors, and angiotensin II, acting on AT1 receptors, exert opposite effects on sodium excretion. Recent studies have shown that the AT1 receptor and the D1 receptor form a dimer, where they act as a unit of opposites. Here we report that the power of the AT1 receptor and D1 receptor interaction is increased by the AT1 receptor antagonist losartan**.** Losartan caused significant increase of the plasma membrane expression of D1 receptors. We conclude that the effect of losartan bound AT1 receptors on D1 receptor plasma membrane expression can be attributed to the function of the AT1 receptor-D1 receptor heterodimer. Taken together these results indicate that losartan will, by binding to the AT1 receptor, exert allosteric effects on its protomer, the D1 receptor, resulting in activation of D1 receptor signaling. Allosteric modulation within a heterodimer, where a structural modification in one protomer will affect the structure and function of the other protomer, has been intensively studied in the past decade, and is generally considered to be an important indirect mechanism for control of receptor function. To test the concept of allosteric interaction between the losartan bound AT1 receptor and the D1 receptors in an in vivo model, we compared the antihypertensive effects of losartan alone and with co-treatment of losartan and a D1 receptor antagonist in rats with experimental hypertension. We found that addition of a D1 receptor antagonist significantly attenuated the antihypertensive effect of losartan.

Not only G protein coupled receptors but also a classic tyrosine receptor, the prolactin receptor, exert its salt-regulating effect by heterologous recruitment and associated activation of renal D1 receptors. The finding that an AT1R antagonist can activate D1R signaling and that this effect is dependent on AT1 receptor and D1 receptor interaction is a novel finding and has potential pharmacologic implications.

***Key words**: Dopamine, Prolactin, Angiotensin, Na^+, K^+-ATPase, Losartan*

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