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HYPERTENSION

AT_2R activation counteracts hypertension

Sustained activation of the renin–angiotensin system (RAS), which controls Na^+ excretion and blood pressure (BP), by infusion of angiotensin II (ang II), leads to Na^+ retention and hypertension in rats. New data from Robert Carey and colleagues show that C-21, a highly selective angiotensin AT_2 receptor (AT_2R) agonist, induces natriuresis and lowers blood pressure in rats with ang II-induced hypertension.

The researchers previously reported that acute AT_2R activation with C-21 induced natriuresis in wild-type rats. "Because our previous work showed that AT_2R is active mainly when the RAS is activated, we hypothesized that activation of the AT_2R with C-21 in a model of ang II-dependent hypertension would reduce BP by increasing Na^+ excretion," explains Carey. Indeed, the researchers found that activation of AT_2R by systemic and renal C-21 administration prevents the initial renal Na^+ retention seen with ang II infusion and lowers BP over the 7 days of ang II exposure. C-21 was equally effective in lowering BP whether administered before or 3 d after ang II exposure. "Importantly, we showed that ang II-induced hypertension cannot only be prevented but also treated after the hypertension is established," says Carey.

> "ang II-induced hypertension can not only be prevented but also treated after the hypertension is established"

To investigate the cellular mechanisms by which C-21 administration normalizes BP and natriuresis, Carey and colleagues monitored the cellular trafficking of AT_2R and two major renal proximal tubule sodium transporters, sodium–hydrogen exchanger 3 (NHE-3) and sodium–potassium-transporting ATPase (NKA). They found that C-21 increases Na^+ excretion and lowers BP by internalizing and inactivating NHE-3 and NKA. "We also found that the effect of C-21 is likely to be reinforced by recruitment of AT_2R to the apical plasma membrane of renal proximal tubule cells, where binding to the agonist can occur," adds Carey.

Natriuresis induced by C-21 was additive to the effects of diuretics that act in the distal tubule (chlorothiazide) or the cortical collecting duct (amiloride), suggesting that C-21 inhibits Na^+ transport specifically in the renal proximal tubule. "AT_2R agonists might reinforce diuresis and natriuresis when combined with other existing diuretics," says Carey.

The researchers now plan to investigate the effects of C-21 in rats exposed to desoxycorticosterone acetate and salt, a volume expansion model of hypertension, and in the transgenic m(Ren 2)27 rat, in which tissue-specific overexpression of components of the RAS causes hypertension.

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ORIGINAL ARTICLE Kemp, B.A. *et al.* AT_2 receptor activation prevents sodium retention and reduces blood pressure in angiotensin II-dependent hypertension. *Circ. Res.* http://dx.doi.org/10.1161/CIRCRESAHA.116.308384 (2016)