Interplay Between Sodium and Calcium Regulatory Hormones
A Clinically Relevant Research Field

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Sodium and calcium homeostasis are tightly regulated by endocrine systems. Of particular importance are effects of the renin–angiotensin–aldosterone system (RAAS) on sodium and of parathyroid hormone (PTH) and vitamin D on calcium homeostasis.

Although previous investigations studied the relationship between the RAAS and PTH in the setting of either absolute aldosterone excess, that is, primary aldosteronism (PA), or absolute PTH excess, that is, primary hyperparathyroidism, Brown et al. addressed this issue in study participants without absolute PTH excess, that is primary hyperparathyroidism, aldosterone excess, that is, primary aldosteronism (PA), or between the RAAS and PTH in the setting of either absolute homeostasis.

The research group around Brown identified the expression of the angiotensin II (AngII) type I receptor and of the mineralocorticoid receptor (MR) in normal parathyroid glands and increased 2- to 4-fold in adenomatous parathyroid glands. Although low serum calcium levels are the physiological stimulus for the synthesis and secretion of PTH by the parathyroid glands, the data by Brown et al. suggest an additional direct regulatory impact of the RAAS on PTH. This hypothesis was substantiated by an increase of PTH and aldosterone after AngII infusions and a decrease of both hormones after a single dose of the angiotensin-converting enzyme (ACE) inhibitor captopril.

In view of a lacking effect of aldosterone infusion on PTH levels, Brown et al. concluded that AngII might mediate the acute effects of the RAAS on PTH secretion, whereas aldosterone might mediate long-term effects on PTH via genomic MR-related mechanisms. With this in line, MR antagonists by spironolactone treatment for 6 weeks modestly but significantly lowered PTH, as well as serum calcium and blood pressure levels, supporting the hypothesis of a clinically relevant aldosterone-PTH interplay. These data need confirmation in larger randomized controlled trials but are the first piece of evidence to hypothesize that MR antagonists significantly affect PTH in patients without PA.

The findings of Brown et al. might not be generalizable to the broad community as all 4 substudies in this post hoc analysis were performed in a rather small sample (n=10–27) of obese/overweight patients (body mass index, 29.5–37.1 kg/m²) with low vitamin D levels (16.6–22.6 ng/mL). Brown et al. acknowledged that their data are limited because of missing detailed electrolyte assessment, including magnesium and ionized and urinary calcium, as well as urinary sodium. Moreover, the potassium administration to avoid hypokalemia after aldosterone infusion (substudy 3) might have impact on aldosterone secretion and distorted effects on PTH levels. Although the experiments by Brown et al. give insights into acute treatment effects, it remains unclear whether the impact on PTH remains clinically significant in the long-term and with more physiological dosing regimens.

Aldosterone-mediated effects on epithelial and nonepithelial tissues depend on MR sensitivity and signaling, which is modulated by sodium. Novel evidence indicates that in states of high dietary salt intake, aldosterone promotes reabsorption of sodium and increases calcium (and magnesium) excretion in the renal distal tubule followed by PTH secretion. This mechanism might explain why the relationship between circulating aldosterone and PTH levels varies depending on dietary salt intake reflected by 24-hour urinary sodium excretion. It might therefore be interesting to see whether the effects of AngII on PTH secretion are similarly modulated by varying dietary salt intake.

Considering the wide use of MR antagonists, the above-discussed findings may have significant clinical implications: PTH excess has adverse effects on bone health, and accumulating evidence suggests that PTH is an independent cardiovascular risk factor. Thus, lowering PTH by MR antagonism may have beneficial effects. This is supported by the observation in patients with chronic heart failure that the use of MR antagonists is associated with reduced fracture risk. Several routes of crosstalk between aldosterone and the pathways regulated by AngII may contribute to target organ damage. Aldosterone upregulates ACE, pronounces AngII-related effects, and AngII in turn stimulates aldosterone secretion. With this in line, MR antagonism decreased gene expression of the angiotensin II type I receptor and ACE. In view of the findings by Brown.

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et al, it is tempting to speculate that decreased levels of PTH after MR antagonism may be, in part, the result of an attenuated interplay between aldosterone and AngII.

In patients with PA, treatment with either MR antagonists or adrenalectomy does not only normalize elevated PTH levels but is also associated with improved bone mineral density and decreased fracture risk.\(^5\)\(^6\) Whether beneficial effects of MR antagonism on cardiovascular health are related to its PTH modifying effect remains, however, to be evaluated in further studies. Apart from this, PTH levels may also serve as an additional tool for the diagnosis of PA, and in particular for aldosterone-producing adenomas.\(^5\)\(^7\)

Another mechanism explaining the mutual interplay between the RAAS and PTH was proposed by Maniero et al\(^3\): patients with PA show an increased responsiveness of the parathyroid glands to hypocalcemia. This research group further demonstrated the expression of both type 1 PTH receptors in the aldosterone-producing adrenocortical nodules, as well as expression of the MR in the nuclei of parathyroid adenoma and even in normal parathyroid cells. The presence of the MR in the nuclei of parathyroid cells indicates that aldosterone may modulate PTH secretion. In addition to this, Brown et al suggest that there may be a direct effect of the RAAS on PTH secretion probably mediated by AngII. Although the above-mentioned mechanisms may all work in concert to affect PTH, the situation seems to be even more complex when considering that Vaidya et al have previously shown that there exists an interaction with vitamin D status, that is, that the effect of the RAAS on PTH differs according to the prevailing vitamin D status. The authors suggested that according to their previous findings, vitamin D3 therapy might augment the tissue (vascular and adrenal) response to AngII infusion and marginalized the influence of an ACE inhibition on PTH.\(^4\) This interaction is also of interest because activation of the vitamin D receptor has been shown to directly suppress renin expression in the kidneys.\(^9\)

In conclusion, there exists accumulating evidence for a mutual interplay between the RAAS and the vitamin D-PTH axis (Figure). The pathophysiological background of the high prevalence of cardiovascular disease found in patients with inappropriately elevated aldosterone and PTH levels, in parallel to low vitamin D, is an ongoing research issue with high clinical relevance in different settings.

Considering the wide use of RAAS blocking agents, the results of ongoing randomized controlled trials evaluating
the clinical effects of ACE-inhibitors or MR antagonists on PTH, bone metabolism and cardiovascular disease are awaited with high interest. One study currently investigates the effects of Vitamin D Administration on Plasma Renin Activity in Patients With Stable Chronic Heart Failure (VitD-CHF). The Renin-Angiotensin-Aldosterone System and Parathyroid Hormone Control (RAAS-PARC) Study examines PTH-lowering effects of ACE-inhibitors. Another study explores the acute modulating effect of cinacalcet on the RAAS in healthy volunteers. Finally, the Effect of Eplerenone on Parathyroid Hormone (EPATH) Study evaluates the effect of MR antagonism by eplerenone on PTH levels and cardiovascular risk factors in patients with primary hyperparathyroidism.10

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