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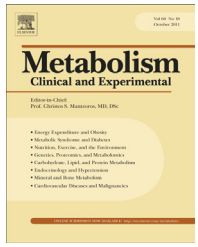

Aldosterone and parathyroid hormone interactions as mediators of metabolic and cardiovascular disease

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ABSTRACT

Inappropriate aldosterone and parathyroid hormone (PTH) secretion is strongly linked with development and progression of cardiovascular (CV) disease. Accumulating evidence suggests a bidirectional interplay between parathyroid hormone and aldosterone. This interaction may lead to a disproportionally increased risk of CV damage, metabolic and bone diseases.

This review focuses on mechanisms underlying the mutual interplay between aldosterone and PTH as well as their potential impact on CV, metabolic and bone health.

PTH stimulates aldosterone secretion by increasing the calcium concentration in the cells of the adrenal zona glomerulosa as a result of binding to the PTH/PTH-rP receptor and indirectly by potentiating angiotensin 2 induced effects. This may explain why after parathyroidectomy lower aldosterone levels are seen in parallel with improved cardiovascular outcomes.

Aldosterone mediated effects are inappropriately pronounced in conditions such as chronic heart failure, excess dietary salt intake (relative aldosterone excess) and primary aldosteronism. PTH is increased as a result of (1) the MR (mineralocorticoid receptor) mediated calciuretic and magnesiuretic effects with a trend of hypocalcemia and hypomagnesemia; the resulting

Abbreviations: CV(D), cardiovascular (disease); MR, mineralocorticoid receptor; PTH(R), parathyroid hormone (receptor); PA, primary aldosteronism; HF, heart failure; CaSR, calcium sensing receptor; p(s)HPT, primary (secondary) hyperparathyroidism; RA(A)S, renin angiotensin (aldosterone) system; VDR, vitamin D receptor; $1,25(OH_2)D_3$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ROS, reactive oxygen species; ZG, zona glomerulosa.

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secondary hyperparathyroidism causes myocardial fibrosis and disturbed bone metabolism; and (2) direct effects of aldosterone on parathyroid cells via binding to the MR. This adverse sequence is interrupted by mineralocorticoid receptor blockade and adrenalectomy. Hyperaldosteronism due to klotho deficiency results in vascular calcification, which can be mitigated by spironolactone treatment.

In view of the documented reciprocal interaction between aldosterone and PTH as well as the potentially ensuing target organ damage, studies are needed to evaluate diagnostic and therapeutic strategies to address this increasingly recognized pathophysiological phenomenon.

1. Introduction

Atherosclerotic cardiovascular disease (CV(D)) is globally the most important cause of premature death [1]. Endocrine systems directly impact on CV function and structure and indirectly contribute to the pathogenesis of arterial hypertension, obesity, dyslipidemia and diabetes.

Several studies demonstrated a strong link between dysregulation of the aldosterone and parathyroid hormone (PTH) axes on the one hand and CV pathology on the other hand. Such evidence documents clinically relevant interactions between aldosterone and PTH and a resulting impact on CV health [2].

This review provides an up to date overview discussing the mechanisms and the clinical relevance underlying the interactions between aldosterone and PTH.

2. Aldosterone

The classical view that aldosterone acts exclusively on the electrolyte transport in epithelial cells has been broadened after the mineralocorticoid receptor (MR) has been identified in non-epithelial cells as well, e.g. vascular smooth muscle cells and cardiomyocytes. Apart from classical genomic effects, non-genomic aldosterone mediated effects have been identified in various tissues and organs outside of the kidneys and colon, e.g. inner ear, choroid plexus, endothelial cells and cardiomyocytes [3,4].

In the past it had been documented that primary aldosteronism (PA; absolute aldosterone excess) contributed to the development of CVD [5–8]. Several studies suggested, however, that "absolute aldosterone excess" is only the tip of the iceberg leading to the concept of "relative aldosterone excess" [9]. Several large cross-sectional and prospective studies demonstrated a consistent relationship between circulating aldosterone levels, CV risk factors and mortality risk [10–16]. Such recent studies also document that even circulating aldosterone concentrations in the "normal" range may result in inappropriate aldosterone–MR interaction which may be reversed by MR blockade [17,18].

3. Parathyroid hormone

The identification of PTH receptors within the CV system e.g. in cardiomyocytes, vascular smooth muscle, and endothelial cells, indicates that inappropriate PTH secretion may impact on the CV health beyond the dysregulation of calcium and phosphate homeostasis.

Application of PTH after myocardial infarction attenuates ischaemic cardiomyopathy by increasing migration of bone marrow-derived stem cells to the ischaemic myocardium [19]. On the other hand the PTH excess in primary hyperparathyroidism (pHPT) is linked in the long-term to a spectrum of adverse effects e.g. bone loss and increased fracture risk, coronary microvascular dysfunction, derangement of lipid and glucose metabolism, subclinical aortic valve calcification, increased aortic stiffness, endothelial dysfunction and arterial hypertension [20–27]. Along this line, patients with pHPT have a remarkably higher risk to die from CV causes compared with the general population [28,29]. Various observational studies including population-based investigations linked higher levels of PTH even in the absence of pHPT to an increased risk of CV morbidity and mortality [30–36]. Elevated PTH levels in patients with a declining kidney function have been related to soft tissue calcifications and subsequent adverse CVD outcome [37].

4. Interactions between vitamin D, klotho and aldosterone

Increased activity of systemic or local renin–angiotensin systems (RAS) is linked to increased target organ damage [38]. The organ- and tissue protective effects of vitamin D have in part been explained by vitamin D induced modulation of RAS activity [39,40].

In landmark experiments Li et al. documented markedly elevated renin mRNA expression in the juxtaglomerular apparatus of vitamin D receptor (VDR) knock-out mice compared to wild type mice [41]. Furthermore, 1,25-dihydroxy vitamin D ($1,25(OH_2)D_3$) modulated renin gene transcription and renin synthesis and this was independent of serum calcium, PTH and angiotensin 2 [42]. Angiotensin 2 in turn reduces renal klotho expression resulting in modulations of FGF-23-signaling and of 1-α hydroxylase activity [39]. Klotho is a membrane (and circulating) protein which is highly expressed in the kidney and modulates the inhibitory effects of FGF-23 on calcitriol formation; klotho contributes to the regulation of renal tubular calcium and phosphate reabsorption [43]. The modulatory effects of vitamin D on the RAS might result in a lower risk of development and progression of CV morbidity and mortality [40,44]. Recently, Forman et al. documented in a placebo controlled double blind trial that vitamin D3 (cholecalciferol) supplementation significantly lowered systolic blood pressure levels in vitamin D deficient