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ALDOSTERONE: A CARDIOVASCULAR RISK FACTOR?

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ABSTRACT

The hormone aldosterone has a well-recognized physiological role in epithelial fluid and electrolyte homeostasis, and more recently defined pathophysiological roles in the cardiovascular system. The term ‘risk factor’ implies an active role in pathophysiology, with levels lower (e.g. HDL) or higher (e.g. LDL, BP) than normal contributing to an increased likelihood of morbidity and/or mortality. In this regard, primary aldosteronism represents a classic illustration of aldosterone as a cardiovascular risk factor. In this syndrome of (relatively) autonomous aldosterone secretion, the effects of elevated hormone levels are on a range of organs and tissues – the heart, blood vessels and brain, inter alia. In other cardiovascular disorders (e.g. CCF, EH) while an elevation of aldosterone levels is often regarded as a risk factor, it is more correctly a response to the severity of disease (or to treatment intervention), rather than necessarily a risk factor with a primary role in disease progression. An enduring enigma relevant to any discussion of aldosterone as a risk factor is that very high levels of aldosterone in response to chronic sodium deficiency have homeostatic (and protective of cardiovascular) functions, while the considerably lower levels commonly seen in primary aldosteronism are incontrovertibly damaging. A final section of the paper will thus propose a mechanism which might solve this enigma, based on the commonalities - and a single crucial difference - in the factors stimulating the secretion of aldosterone and endogenous ouabain from the zona glomerulosa of the adrenal gland.

INTRODUCTION : ALDOSTERONE

The hormone aldosterone was isolated and characterized in 1953 [1, 2] and the syndrome of primary aldosteronism described soon afterwards [3, 4]. Initially the hormone was termed electrocortin, reflecting its mineralocorticoid action on transepithelial electrolyte transport [5], but soon afterwards by its current name, when its structure was shown to contain a unique (and highly reactive) aldehyde (CHO) group instead of the customary methyl (CH₃) group, at carbon 18 of the steroid skeleton. In the adrenal gland aldosterone is synthesized uniquely in the external layer of the cortex, the zona glomerulosa; ectopic sites of aldosterone biosynthesis (heart, blood vessels, brain) have been both reported and disputed [6-11]. The primary stimuli to aldosterone secretion are angiotensin II, following the release of renin in response to stress (e.g. hypovolemia) and posture; equally importantly but often relegated to second place as a secretagogue, is plasma [K⁺] in chronic Na⁺ deficiency or K⁺ loading [12, 13]. The homeostatic response to elevation of aldosterone secretion is restoration of the status quo – sodium and water retention in hypovolemia and Na⁺ deficiency, kaliuresis in potassium loading, etc. In primary aldosteronism secretion of the hormone is relatively autonomous, in that although it may remain sensitive to angiotensin II or potassium status, the turn-off limb of the feedback loop is deficient, resulting in inappropriate levels for the patient's fluid and electrolyte status.

Aldosterone acts physiologically at epithelia via intracellular mineralocorticoid receptors, members of the 49 member (in humans) steroid/thyroid/retinoid/lipid/orphan receptor superfamily, and of a closely related subfamily with glucocorticoid receptors, progesterone receptors and androgen

receptors [14]. Early studies on mineralocorticoid receptors showed two puzzling features. First, they were distributed across a range of extraepithelial tissues, such as brain [15] and heart [16]. Secondly, they showed equivalently high affinity for aldosterone – which circulates at very low levels – and the glucocorticoids cortisol and corticosterone [15, 17], and in addition for progesterone [18], the potential implications of which are yet to be established. In epithelia aldosterone-selectivity of mineralocorticoid receptor activation is procured by co-expression of the enzyme 11 β -hydroxysteroid dehydrogenase [19], which is also expressed in certain non-epithelial tissues (vascular wall, placenta, nucleus tractus solitarius), making them similarly physiological aldosterone target tissues. It was initially thought [19], and is still commonly taught, that 11 β -hydroxysteroid dehydrogenase operates by excluding glucocorticoids from protected mineralocorticoid receptors via conversion to receptor-inactive 11-keto congeners (e.g. cortisol to cortisone). It has been subsequently shown that under normal conditions most epithelial mineralocorticoid receptors are occupied (~ 90%) but not activated by normal levels of endogenous glucocorticoids [20]. Mineralocorticoid receptor-glucocorticoid complexes are presumably held inactive under normal conditions by the obligate co-generation of high levels of NADH, shown to be an inhibitor of transcription by co-repressor activation in other transcriptional systems [21]. Under conditions of tissue damage, reactive oxygen species generation and intracellular redox change, cortisol becomes a mineralocorticoid receptor agonist, in the vessel wall [22] and heart [23], mimicking the deleterious effects of elevated aldosterone inappropriate for salt status.

PRIMARY ALDOSTERONISM

For forty years after the first report of primary aldosteronism, it was considered to be a rare (< 1% of hypertensives) and relatively benign condition, characterized by hypokalaemia, with adrenal mass(es) visible on imaging or scintigraphy treated by open unilateral adrenalectomy, and in the absence of lateralization by spironolactone. Currently primary aldosteronism is recognised as neither rare nor benign. In terms of prevalence estimates vary considerably, often reflecting patient referral patterns; a consensus figure is 8-13% of all hypertensives (and perhaps ~ 3% of unselected normotensives). Hypokalaemia is in fact uncommon, being seen in under half of patients subsequently shown to have an adrenal adenoma, and under 20% of those with autonomous aldosterone secretion from bilateral hyperplasia. Current guidelines [24] base case detection on an elevated plasma aldosterone to renin ratio, with the diagnosis confirmed or excluded on the basis of any one of at least four different testing procedures. Of the ~ 10% of hypertensives with primary aldosteronism diagnosed this way, 3-4% will normally have unilateral hypersecretion upon lateralization by bilateral adrenal venous sampling, and the remaining 6-7% bilateral overproduction. In addition to this ~ 10%, there is a cohort of patients who show 'resistant hypertension', with blood pressure remaining high despite 3 or more antihypertensives including a conventional diuretic. Such patients commonly respond to mineralocorticoid receptor blockade with major (~ 30mm SBP) falls in blood pressure. It has long been suspected that those patients may constitute a 'pre-primary aldosteronism' group, perhaps progressing to frank primary aldosteronism over time. An alternative possibility is that such patients in fact do have autonomous aldosterone secretion, but are missed reflecting the current lack of definition in terms of assay variability, arbitrary cut-off levels, and the conservative interpretation of

confirmatory/exclusion tests. Such patients may also be overlooked on screening, due to the confounding effects on plasma levels of renin and aldosterone of antihypertensive medications which the patient or physician is unwilling to withdraw in severe hypertension.

In terms of aldosterone as a risk factor in primary aldosteronism, it is important to say at the outset that the cardiovascular sequelae are not merely a reflection of raised blood pressure (while they may indeed be a consequence of increased sodium retention: *vide infra*). There have been a number of studies examining aldosterone as a cardiovascular risk factor in primary aldosteronism: two will be cited in extenso, as representing the opposite poles of aldosterone excess. Stowasser et al [25] compared 8 patients with familial hyperaldosteronism type 1 (FHI: glucocorticoid remediable hyperaldosteronism) in whom blood pressure was not yet elevated above normal with 24 age-, sex- and blood pressure-matched controls, and showed clear evidence of cardiovascular damage in the patients with very modestly elevated aldosterone levels. Milliez et al [26] examined patients at the other end of the spectrum, with established primary aldosteronism and clearly elevated blood pressure. Again compared with age-, sex- and blood pressure-matched essential hypertensives, the primary aldosteronism patients showed a twelve-fold higher incidence of atrial fibrillation, a six-fold higher incidence of myocardial infarction, and a four-fold higher incidence of stroke. In this study 124 patients with primary aldosteronism were compared with 465 essential hypertensives; aldosterone levels were 2-3-fold higher in the primary aldosteronism group, and active plasma renin and plasma potassium significantly lower, as might be expected.

The unexpected finding in the Milliez et al study was a highly significantly different level in total cholesterol, with a value of 5.4 ± 0.9 mmol/l in primary aldosteronism and 5.9 ± 1.1 in essential hypertension; serum glucose, in contrast, was equivalent between the two groups (6.0 ± 1.3 , 5.9 ± 1.9 mmol/l). These two values would thus not support a role for elevated levels of aldosterone per se in the metabolic syndrome; subsequent studies have demonstrated an association, although whether the hyperaldosteronism in these subjects with manifestations of the metabolic syndrome is autochthonous as well as autonomous (in terms of the classic stimuli to aldosterone secretion) is uncertain. Krug and Ehrhart-Bornstein [27], for example, postulate that hypersecretion of trophic factors from abdominal adipocytes results in aldosterone secretion, outside the normal renin/angiotensin/sodium/potassium feed back loop, leading to hypertension and cardiovascular disease, and possibly to dyslipidaemia and altered glucose homeostasis.

This postulate follows a range of population-based studies in which aldosterone and the metabolic syndrome have been associated. In an early study on subjects of African origin in the Seychelles, Bochud et al [28] showed aldosterone levels to be positively correlated with the metabolic syndrome, with blood pressure elevation in older individuals, and with waist circumference in men: a negative correlation between aldosterone levels and those of HDL-C was also found. Kidambi et al [29], in a cross-sectional study on African Americans, similarly showed that in subjects with the metabolic syndrome aldosterone levels were higher and were positively correlated with blood pressure, waist circumference and insulin resistance. In a third cross-sectional study, Colussi et al [30] showed a direct relationship between

aldosterone levels, insulin resistance and hyperinsulinaemia in a cohort of Caucasian subjects.

In these three cross-sectional studies subject numbers were respectively 356, 397 and 458; in a longitudinal study of 2,292 subjects from the Framingham cohort, Ingelsson et al [31] again reported aldosterone to be positively associated with an increase over time in blood pressure, and inversely with HDL-C levels. In addition, they reported that higher circulating aldosterone levels were associated with the development of the metabolic syndrome, and longitudinal change in its component pathologies, consistent with a causative rather than a collateral role in aetiology.

Currently, two large studies (total n = 6300) in Germany are tracking the relationship between aldosterone and the metabolic syndrome, SHIP (Study of Health in Pomerania) in north-eastern Germany and KORA (Kooperative Gesundheitsforschung in der Region Augsburg) in Bavaria. The results for women are quite different between the two locales, but those for men less so. The assays for both studies were performed centrally, and the reason(s) for the differences are presently unclear. What SHIP and KORA do, however, is to sound a note of caution re extrapolating from one study alone to the population as a whole.

In a more recent case control study [32], patients from the German Conn's Registry were age-, sex-, BMI- and blood pressure-matched with hypertensive controls from the KORA study in Bavaria. The prevalence of diabetes in the patients with primary aldosteronism was > 50% higher than in the control hypertensive group, across all patients and in those with a BMI < 30. Similar results, however, had not been seen in

previous cross-sectional studies [33-35]. In the first of these, Widimsky et al [33] reported prevalence rates of diabetes mellitus (20%/14%) and of impaired glucose tolerance (18%/10%) to be higher in primary aldosteronism than essential hypertension, without reaching statistical significance, probably reflecting the small number of patients studied (36 vs 21). Catena et al [34] compared 47 patients with primary aldosteronism with 247 with essential hypertension, and found no difference in area under the curves for glucose and insulin. Matrazova et al [35], in a much larger study, compared 460 patients with primary aldosteronism with 1363 essential hypertensives, and found no difference in incidence of diabetes (17% vs 14%), and a counterintuitive increase in impaired glucose tolerance in the essential hypertensives (26%/33%); again, the differences in statistically significant findings between studies sound a note of caution.

The mechanisms whereby aldosterone might play a causative role in impaired glucose tolerance/insulin resistance/diabetes remain lightly explored. Giachetti et al [36] have suggested that a variety of effects may be in play – that aldosterone excess may reduce both the expression and affinity of insulin receptors in adipocytes, as well as down regulating adipocyte glucose transporters, a process abetted by the effect of hypokalaemia to lower insulin secretion from the pancreas, and possible deleterious effects of aldosterone-induced fibrosis in both pancreas and adipocytes. The adipocyte effects are extrapolated from single in vitro studies, and the extent to which similar mechanisms may operate in vivo remains to be determined.

ALDOSTERONE AND THE BRAIN

It has been relatively recently recognized that mental illnesses, particularly anxiety disorder and depression, constitute a major cardiovascular risk factor. Major depression, for example, is associated with twice the chance of myocardial infarction, and twice the chance of a fatal outcome [37]. In this context there have been a number of reports of an association between plasma aldosterone concentration and depression. Over 30 years ago Malinov et al [38] reported that episodes of depression led to the diagnosis of primary aldosteronism, an observation subsequently confirmed by others [39, 40]; recently, Sonino et al [41] reported the increased incidence of anxiety disorders in patients with primary aldosteronism. In parallel, a range of studies [42, 43] have reported increased plasma aldosterone levels in depressed patients, compared with the range seen in healthy controls. Most recently, Stowasser et al [44] in a small study on 22 patients reported that patients with confirmed adrenal adenoma scored low in the SF-36 questionnaire (a self-perception index of quality of life), with significant improvement across a range of parameters at both 3 and 6 months post-adrenalectomy. Taken together, those studies suggest a possibly important association of aldosterone and depression in depressed patients, and in addition a significant association of increased anxiety, depression and somatic symptoms in primary aldosteronism, relieved by adrenalectomy. The extent to which successful alleviation of depression is reflected in normalization of plasma aldosterone levels is yet to be systematically explored. Similarly, whether the increased aldosterone levels are causative of or collateral with the increased cardiovascular risk in mental illness remains to be established.

ESSENTIAL HYPERTENSION AND HEART FAILURE

In neither essential hypertension nor heart failure is increased aldosterone secretion autonomous, and there are no data that would support aldosterone as a primary driver in either condition. In both conditions although raised aldosterone levels are often regarded as a risk factor, such an elevation is more correctly a response to the severity of the disease or to treatment intervention, rather than a risk factor with a primary role in disease progression. In essential hypertension there is clear evidence that mineralocorticoid receptor blockade can substantially lower blood pressure in ~ 80% of patients [45], as there is for the beneficial effects of mineralocorticoid receptor blockade in heart failure [46, 47]. The undisputed effectiveness of mineralocorticoid receptor blockade in these conditions is commonly translated as evidence for a deleterious effect of aldosterone rather than of mineralocorticoid receptor activation. The clinical study cited above [45] clearly distinguished the anti-hypertensive and electrolyte effects of mineralocorticoid receptor blockade, over a range of antagonist doses, and very recently Mihailidou et al [23] have shown that in experimental myocardial infarction low levels of cortisol mimic aldosterone in activating cardiomyocyte mineralocorticoid receptors and aggravating tissue damage.

Recent clinical studies would similarly suggest caution in ascribing risk factor status to aldosterone per se in progressive heart failure. Guder et al [48], in a prospective cohort study of 294 consecutive patients with progressive heart failure and 27% mortality at a median follow-up of 803 days, showed that both aldosterone and cortisol levels were independent predictors of increased mortality. The hazard ratio for the highest versus the lowest tertile for cortisol was 2.72 (95% CL 1.38-5.36, $p <$

0.004) and for aldosterone 2.19 (95% CL 1.23–3.93, $p < 0.008$). In a subsequent study on a similar sized cohort (319), Yamaji et al [49] showed – in patients with a lower event rate (9%) at a mean of 33 months – that serum cortisol levels were an independent predictor of cardiac events, but those of aldosterone were not. Again, the studies addressed different populations with different outcomes in terms of mortality, but in each cortisol would appear to be a better predictor of outcome – and possibly thus more of a risk factor – than aldosterone.

ALDOSTERONE, THE ENIGMA

Put simply, the enigma is this: In chronic sodium deficiency, plasma aldosterone levels reach very high levels, capable of reducing urinary sodium excretion to 2-3 meq/day. In such subjects available epithelial mineralocorticoid receptors are fully aldosterone-occupied and -activated, and in non-epithelial tissues (e.g. cardiomyocytes) to presumably a considerably higher percentage than the normal ~ 1% occupancy when levels of aldosterone and cortisol are in the normal range. Despite such high levels subjects have neither blood pressure elevation nor any signs of cardiovascular damage: the elevated levels of aldosterone are thus homeostatic in the context of sodium deficiency, and when sodium status is appropriate such levels are not a cardiovascular risk. Contrast this with primary aldosteronism, where hormone levels may be considerably lower, but result in cardiovascular damage. In both epithelial and nonepithelial tissues a lower number of mineralocorticoid receptors will be occupied and activated than in chronic sodium deficiency, but the effects seen are much more pronounced.

The answer at one level has been known for decades to be sodium status. In mineralocorticoid/salt models of hypertension, administration of aldosterone or deoxycorticosterone to animals on a very low sodium intake neither raises blood pressure nor causes cardiac damage. In animals systematically administered aldosterone but with their blood pressure clamped to normal levels by the intracerebroventricular administration of the mineralocorticoid receptor antagonist RU28318, the extent of cardiovascular damage is the same as in aldosterone/salt animals infused ICV with vehicle – i.e. the cardiovascular damage represents a direct mineralocorticoid/salt interaction, not one mediated via elevation of blood pressure [50].

One possible scenario yoking aldosterone and sodium status into cardiovascular damage mode (including blood pressure elevation) is the secretion of endogenous ouabain from the adrenal zona glomerulosa [51]. Whereas aldosterone secretion rates are very low, those of endogenous ouabain are an order of magnitude lower. The biosynthetic pathway for aldosterone production is well-characterized, although the recent study on Cry null mice [52] would appear to add 3 β hydroxysteroid dehydrogenase to side chain cleavage enzyme and aldosterone synthase as rate-limiting enzymes: the biosynthetic pathway for endogenous ouabain synthesis is much less well established. For aldosterone ACTH is a stimulus independent of fluid and electrolyte status, responsible for its circadian variation; for endogenous ouabain ACTH is a major stimulus, and ACTH-induced hypertension can be blocked by subtle mutation in the ouabain binding site on the α 2 subunit of the sodium/potassium ATPase, or by infusion into wild-type mice of the blocking antibody digibind [53]. Angiotensin is a primary stimulus for aldosterone secretion, acting via AT1 receptors;

angiotensin also regulates the secretion of endogenous ouabain, but via the 10-fold lower affinity AT₂ receptors [54]. Where the two products are polar opposites is in their response to sodium status. Aldosterone secretion is raised in response to sodium deficiency: secretion of endogenous ouabain is raised in response to sodium loading [55]. The physiological role of aldosterone is to retain sodium in the face of chronic deficiency; that of endogenous ouabain presumably to dump sodium, via a pressure natriuresis, in sodium loading.

Given the documented effects of endogenous ouabain to raise blood pressure, it is possible that the blood pressure elevating effects of aldosterone reflect not only direct effects on the vessel wall but also sodium retention with the resultant elevation of endogenous ouabain secretion. This may be seen as a gloss on the current teaching that aldosterone raises blood pressure via increasing circulatory volume, resulting in increased cardiac output followed by reflex vasoconstriction to normalise cardiac output. In fact it is not, in that it introduces a second hormone of adrenal cortical origin as a key mediator of the response to inappropriate aldosterone levels for sodium status, rather than a cascade of mechanical/neural responses.

The combined elevation of aldosterone and endogenous ouabain levels in response to salt/mineralocorticoid imbalance may thus be an explanation of the hypertension produced; as noted previously, however, in both primary aldosteronism and mineralocorticoid/salt experimental models excess aldosterone produces cardiovascular sequelae over and above those due to elevated blood pressure alone. Given that this is the case, any contribution of endogenous ouabain to the status of aldosterone as a marker of cardiovascular risk requires demonstration of at least

additive effects in terms of vascular contractility or cardiac cell damage. Such studies are yet to be attempted.

ENVOI

Aldosterone is clearly a cardiovascular risk factor in primary aldosteronism. Given that aldosterone levels are incompletely suppressed by chronic high salt intake, it may be that even low normal levels are a hidden risk factor in cardiovascular disease. In both these situations aldosterone levels are inappropriate for sodium status. The extension of risk factor status to aldosterone in cardiovascular disease to essential hypertension and heart failure is primarily based on the efficacy of mineralocorticoid receptor blockade in these conditions. Evidence, both experimental and clinical, is building that in these circumstances it is cortisol which activates mineralocorticoid receptors, in the context of tissue damage, to aggravate the extent of the tissue damage and accelerate the progression of functional decline: mineralocorticoid receptor activation, not aldosterone, is the risk factor.

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