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Review

Aldosterone and mineralocorticoid receptors: A personal reflection

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ABSTRACT

Since the isolation and characterization of aldosterone in 1953, subsequent developments in the field can be neatly considered over three time spans, each of two decades. In the first aldosterone itself was the primary focus; from 1973, for two decades the mineralocorticoid receptor (MR) was the front runner; since 1993 the focus has been on both, with aldosterone being discovered by cardiologists, and distinguished within their panoply of neurohumoral factors.

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1. Introduction

Since the isolation and characterization of aldosterone in 1953, subsequent developments in the field can be neatly considered over three time spans, each of two decades. In the first aldosterone itself was the primary focus; from 1973, for two decades the mineralocorticoid receptor (MR) was the front runner; since 1993 the focus has been on both, with aldosterone being discovered by cardiologists, and distinguished within their panoply of neurohumoral factors.

2. The first two decades: 1953–1973

It is worth recalling the disciplines of the people who were initially responsible for the isolation and characterization of aldosterone. Ian Bush – the pioneer of systematic separation of steroids by chromatography – was crucial, as his systems allowed aldosterone (from 500 kg of beef adrenals) to be distinguished from other steroids, as a spot on chromatography paper. The husband and wife team of Jim Tait and Sylvia Simpson – she the physiologist, he a biophysicist – were responsible for the initial demonstration, using ^{22}Na, that aldosterone was a mineralocorticoid, *the* mineralocorticoid, in that it promoted electrolyte flux across epithelia – thus the original name of 'electrocortin'. In Basel the Swiss chemists Wettstein and Reichstein were able to solve the structure of aldosterone, showing it to contain a unique aldehyde group at C18, rather than the customary methyl group – and so the name changed quickly to aldosterone.

The clinicians were not far behind – in fact, a long unrecognized Polish clinician cured a patient of hypokalemia and hypertension in 1951 by unilateral adrenalectomy, but published the result locally rather than internationally. In the post-1953 era, however, credit goes appropriately to Jerome Conn, who in 1954 reported a similar outcome for adrenalectomy in a patient with an adrenal adenoma on imaging, and spent the next twenty years making substantial further contributions to the field of primary aldosteronism (PA), still known eponymously as Conn's Syndrome.

Over the 20 years from 1953 aldosterone was explored by physiologists, internists, endocrinologists and nephrologists, a new specialty recently hived off from endocrinology. Most of those working in the field had significant interests in hypertension, and much more than is currently the case, were physician-scientists.

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This was the period when the epithelial biology of aldosterone was charted – its secretion in response to sodium deficiency and volume depletion, in action on the distal tubule to retain sodium and excrete potassium, and with sodium to retain water. Angiotensin II, in response to volume lowering, was shown to be a potent stimulus to aldosterone secretion, as subsequently was plasma potassium concentration. By today's standards, many of the tools were quaint – to study the control of secretion the autotransplanted adrenal gland of the Merino sheep in the neck, in a pouch with four loops, hooked up to the carotid and jugular, enabling close intra-arterial infusion and uniquely adrenal venous sampling. Studies on aldosterone action were not so different: toad bladders mounted on Ussing chambers, and the Kagawa bioassay in adrenalectomized rats.

These preparations notwithstanding, by the end of the period we had learned a lot about aldosterone, experimentally and clinically (Tait et al., 2004). Tedious as it was to measure in plasma, we knew the normal range of circulating levels; that the metabolic clearance rate was equivalent to hepatic blood flow; that it did not bind to CBG, with ~50% circulating free, the remainder bound to albumin; and that in solution it was ~99% cyclized, to 11-18 and 11-18-20 acetal forms. And finally, we had spironolactone from 1960, decades before any other steroid hormone antagonist, and still in use today, over 50 years later.

From studies on the toad bladder, aldosterone was the first mammalian steroid hormone to be shown to act via DNA-directed, RNA-mediated protein synthesis. Evidence for its genomic action included a ~45 min lag time in onset of action in contrast with its immediate action when preapplied for an hour to substrate-deprived toad bladders, when pyruvate (a substrate for Na^+ transport) was reintroduced; the case was finally proven by studies using actinomycin D and puromycin. Some things that were accepted wisdom then we now know not to be true – that PA was a rare (<1%) and benign form of hypertension; that patients with cardiac failure had elevated aldosterone levels (which they may, but only in response to diuretics, and terminally to ACTH); that all aldosterone action was via genomic mechanisms; and that angiotensin II is the predominant physiologic stimulus to aldosterone production (which is only the case for postural change).

3. The second period: 1973–1993

Although the foundations had been laid for exploring aldosterone action, it was not until 1973 that the first studies on MR (in whole cells, necessary for receptor survival), were published. MR were found and described in classical epithelial tissues – kidney, colon, salivary gland – but also, surprisingly in non-epithelial tissues, presaging later studies on non-epithelial actions of aldosterone. Ron De Kloet and Bruce McEwen described two classes of glucocorticoid receptor in the central nervous system, the first of which bound tritiated dexamethasone ([^{3}H]DM) with high affinity in the pituitary and in the areas of the hypothalamus outside the blood-brain barrier. The second class was found in the brain, particularly in the hippocampus, and in vivo bound tritiated corticosterone ([^{3}H]B) but not [^{3}H]DM); these were dubbed corticosterone-preferring receptors, and subsequently shown on a variety of criteria to be indistinguishable from renal MR (Krozowski and Funder, 1983).

By the end of this period all the steroid receptors had been cloned and sequenced, and the MR in many senses had become the Cinderella of the six, for at least three reasons. First, it was very fragile in broken cell systems, and difficult to maintain intact even in specially designed buffers. Secondly, despite its nonepithelial locations, its physiology appeared – or more realistically, was assumed – to be complete. Third, as previously noted, spironolactone had been released and patented in 1960, and the other steroid receptors were the focus for the development of antagonists, partial and tissue-selective, as therapeutic agents.

Of the six steroid receptors, four (MR, GR, AR, PR) were shown to belong to a highly related subfamily, with the estrogen receptor (ER) and the vitamin D receptor (VDR) much more distantly related. What the cloning of the human MR (Arriza et al., 1987) threw into stark relief was something long suspected from animal studies, the question of how aldosterone was able to selectively activate epithelial MR, given that its affinity for the physiologic glucocorticoids (cortisol, corticosterone) is equal to that for aldosterone, and the circulating glucocorticoid concentrations ~1000-fold higher. The glucocorticoids are ~95% bound to plasma protein, whereas aldosterone is only ~50% bound, so that the ratio of free glucocorticoid to free aldosterone is 'only' 100:1. Shortly after the cloning of the human mineralocorticoid receptor the crucial selectivity conferring role of the enzyme 11βHSD2 in epithelia was recognized: the initial interpretation of this finding was that the enzyme, which is expressed at high levels in epithelial cells, converts cortisol/corticosterone to their receptor-inactive 11-keto congeners, thus allowing aldosterone (in which the 11-hydroxyl group is protected by cyclization with the aldehyde group on carbon 18) to occupy and activate MR (Funder et al., 1988; Edwards et al., 1988).

4. The here and now: 1993–2013

In the last of our time-frames, there have been advances in our knowledge and understanding across the board. Arguably the two most significant are the recognition of primary aldosteronism as much more common than was previously thought and taught, and a refocussing on the cardiovascular sequelae of inappropriate non-epithelial MR activation, first described by Hans Selye in studies on DOCA/salt rats more than 10 years before the isolation of aldosterone. There have been other signal advances – from the evolution of the MR (well before that of aldosterone: Kassahn et al. (2011)), to the discovery of SGK-1 (serum and glucocorticoid activated kinase-1) and its role in the subcellular mechanism of aldosterone-induced sodium transport (Pearce, 2003), to the recent description of mutations in the potassium channel KCNJ5 as responsible for ~40% of adrenal aldosterone-producing adenomas (Choi et al., 2011). The game-changes, however, have been primary aldosteronism and the non-epithelial effects of inappropriate MR activation.

Historically, primary aldosteronism was considered rare (<1% of all essential hypertension), relatively benign and entailing hypokalemia. Physiologically renin is a much more sensitive index of sodium status than levels of aldosterone itself, so that the aldosterone/renin ratio (ARR) has come into widespread use as a screening test for possible PA. It is mathematically susceptible to very raised values if renin is highly suppressed, so that false positives are relatively common: in most instances, therefore, an aldosterone level at least in the upper normal range plus an elevated ARR is needed to proceed to one of a variety of confirmatory/exclusion tests. In unselected hypertensives from a variety of centres around the world the prevalence of PA thus established is in the range of 8–13%, a substantial minority given the prevalence of hypertension in developed countries of 15–20%. Ideally lateralization is established (or excluded) by bilateral adrenal venous sampling: if the source of autonomous aldosterone secretion is unilateral it is treated by laparoscopic adrenalectomy; if bilateral by mineralocorticoid receptor antagonists, and in the future possibly by selective aldosterone synthase inhibitors.

Though surgery clearly has more rapid effects on potassium levels and blood pressure than MR antagonists, there are data that