The neuroendocrine-immune interface gone awry in aldosteronism

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See article by Lal et al. (pages 437–447) in this issue.

Congestive heart failure (CHF), a clinical syndrome with characteristic signs and symptoms, is a salt-avid state whose origins are rooted in neurohormonal activation, including the circulating renin-angiotensin-aldosterone system (RAAS). A systemic illness accompanies CHF and contributes to a progressive downhill clinical course and poor prognosis. Features include: (a) oxi/nitrosative stress in such diverse tissues as skin, skeletal muscle, heart, lymphocytes and monocytes; (b) a proinflammatory phenotype involving multiple tissues and blood and expressed as elevated levels of chemokines and such cytokines as IL-6 and TNF-α; and (c) a catabolic state with loss of lean tissue, fat and bone that eventuates in a wasting syndrome termed cardiac cachexia.

The pathophysiology of CHF includes a neuroendocrine-immune interface gone awry. This brief commentary, prepared in response to the study from the Leenen laboratory [1], focuses on this interface in aldosteronism. Apologies are extended for the limited discussion and literature citations dictated by space constraints.

1. The neuroendocrine-immune interface

The body’s trillions of cells are organized into specialized tissues (e.g., epi- and endothelium, lymphoid cells of respiratory and gastrointestinal mucosae) and organs. Together, they serve as functional units integral to preserving homeostasis, such as the regulation of respiratory gas exchange, the composition and osmotic balance of the internal environment, or extracellular fluid, and the immune system.

The neuroendocrine and immune systems are linked together because they share ligands and receptors. This common “chemical language” promotes their bidirectional communication and integrative physiology [2]. Neurotransmitters, neuropeptides and hormones, for example, regulate the immune system; conversely, lymphohemopoietic cytokines regulate the behavior of the neuroendocrine system. Several examples of this cross-talk are listed in the Table 1. Additionally, there exists a common “molecular network” with hormones and cytokines sharing intracellular signaling substrates and having common biological actions [3].

2. Aldosteronism and the immune system

Circulating aldosterone (ALDO), the adrenal’s most potent mineralocorticoid hormone, has well-known endocrine properties, expressed by binding to its cytosolic receptor in epithelial cells of the kidneys, colon, sweat and salivary glands. It is also active in nonclassic tissues, such as the choroid plexus, brain and nervous system, and contributes to the behavior of the immune system (vide infra).

Aldosteronism, defined as inappropriate (relative to dietary Na+) elevations in plasma ALDO, such as seen in CHF, is accompanied by an activation of immune cells. Using rats receiving 1% dietary NaCl and ALDO (by minipump), to raise its plasma levels to those found in human CHF while suppressing circulating angiotensin (Ang) II, an early activation of lymphocytes precedes their invasion of the cardiovasculature. This immunostimulatory state is abrogated by co-treatment with spironolactone (Spi), an ALDO receptor antagonist. It is induced by iterations in lymphocyte cytosolic-free [Mg2+], and [Ca2+]; and trans-
Lymphocyte divalent cations occur as a direct response to proinflammatory phenotype [5]. Whether these iterations in NADPH production is regulated by K⁺, AngII, aldosterone, and mineralocorticoid receptor together with its guardian redox-sensitive transcription factor, NFκB, proinflammatory genes and mediated by activation of a second messenger in the transcriptional regulation of 11β-hydroxysteroid dehydrogenase, and the elaboration of aldosterone synthase, a mineralocorticoid receptor with its guardian redox-sensitive transcription factor, NFκB, an antioxidant (e.g., N-acetylcysteine) prevents the appearance of this proinflammatory phenotype [5]. Whether these iterations in lymphocyte divalent cations occur as a direct response to aldosterone administration or indirectly via a yet-to-be-defined pathophysiological response that accompanies aldosteronism remains unclear.

In recent years the expression of aldosterone synthase, a mineralocorticoid receptor with its guardian enzyme, 11β-hydroxysteroid dehydrogenase, and the elaboration of aldosterone have each been demonstrated in extra-adrenal tissues that include the vasculature, heart and brain, where aldosterone production is regulated by K⁺, angiotensin II, renin, and corticotropin and cortisol [6–8]. Locally produced aldosterone is upregulated following injury, such as myocardial infarction (MI) [7], where it may contribute to tissue repair. Low- and high-dose spironolactone each attenuate fibrous tissue formation in noninfarcted myocardium while the combination of spironolactone and losartan prevents fibrosis to an even greater extent implicating angiotensin II in the regulation of tissue aldosterone and repair [7].

### 3. Aldosteronism and the Central Nervous System (CNS)

#### 3.1. Hypertension

Chronic mineralocorticoid excess leads to a fall in both plasma and cerebrospinal fluid K⁺ and is accompanied by arterial hypertension [9,10]. To eliminate the contribution of hypokalemia to this response, an intracerebroventricular (icv) infusion of a mineralocorticoid, alone in small dosage, or together with either K⁺ or a receptor antagonist, prevent the rise in arterial pressure. The role of endogenous ouabain, a Na⁺/K⁺ ATPase inhibitor released from central and/or adrenal origins during mineralocorticoid excess [11,12], may contribute to this response. Na⁺ and water retention, however, are not contributory.

#### 3.2. Heart failure

Ligation of the rat left coronary artery to induce MI has been used to address an interplay between aldosteronism, the heart and CNS. However, a persistent elevation of RAAS effector hormones following MI is not a consistent finding in these pronates. Nonetheless, neuronal recordings from the paraventricular nucleus (PVN), a component of the HPA axis involved in regulating sympathetic nerve activity [13], are increased at wk 4 post-MI and can be reduced via an intracarotid infusion of spironolactone [14]. Further evidence of long-term neuronal activation post-MI is provided by immunohistochemical detection of fos-related antigen expression, a transcription factor, in the supraoptic nucleus and magnocellular divisions of the PVN [15]. Renal sympathetic nerve activity is enhanced while baroreflex regulation of heart rate and arterial pressure is blunted at week 4 after MI [16]. These aberrations in neuronal control of autonomic function are improved by either icv or intraperitoneal infusion of spironolactone [17]. Collectively, these findings link aldosteronism and/or tissue aldosterone with these pathophysiologic responses of the autonomic nervous system that appear following MI.

Relative to the proinflammatory heart failure phenotype and neuroendocrine-immune interface, plasma TNF-α levels rise progressively during the weeks following MI, a response attenuated and even normalized by icv infusion of spironolactone [18]. Francis et al. [19] have further shown the source of this rise in plasma TNF-α includes its increased synthesis in both the hypothalamus and infarcted and noninfarcted myocardium. This and other proinflammatory cytokines can adversely influence the structure and function of the infarcted heart.

In this context, Lal et al. [1] report their important findings in this issue of *Cardiovascular Research*. When given within days after MI, as either a small icv dose or a large oral dose, spironolactone improved ventricular function and reduced the adverse geometric and structural remodeling of the infarcted heart seen at wk 6 post-MI. This included: improved indices of systolic and diastolic function; prevention of ventricular dilatation; and attenuation of the adverse perivascular and interstitial accumulation of fibrillar collagen in myocardium remote to the infarct. The authors therefore conclude central aldosterone receptor binding, by ligand generated systemically and/or within the CNS, leads to adverse effects in the infarcted heart. Responsible mechanisms remain to be more fully elucidated. Given that fibroblast-mediated fibrous tissue accumulation mandates cell–cell signaling with invading inflammatory cells (vis-à-vis the absence of fibrosis following apoptotic cell death, where inflammatory cells do not appear), one might speculate aldosterone receptor antagonism post-MI would also attenuate this proinflammatory aspect of tissue repair.
4. Summary

In summary, evidence gathered to date would indicate the involvement of aldosteronism in the neuroendocrine-immune interface gone awry in CHF. This includes: an activation of circulating lymphocytes; regulation of the brain that influences plasma levels of TNF-\(\alpha\) and leads to adverse cardiac remodeling post-MI; and the sensory function of the immune system operative at sites of injury and inflammation. Aldosteronism contributes to the systemic illness that accompanies CHF and, as such, ALDO receptor antagonism has proven efficacious in this setting.

References


