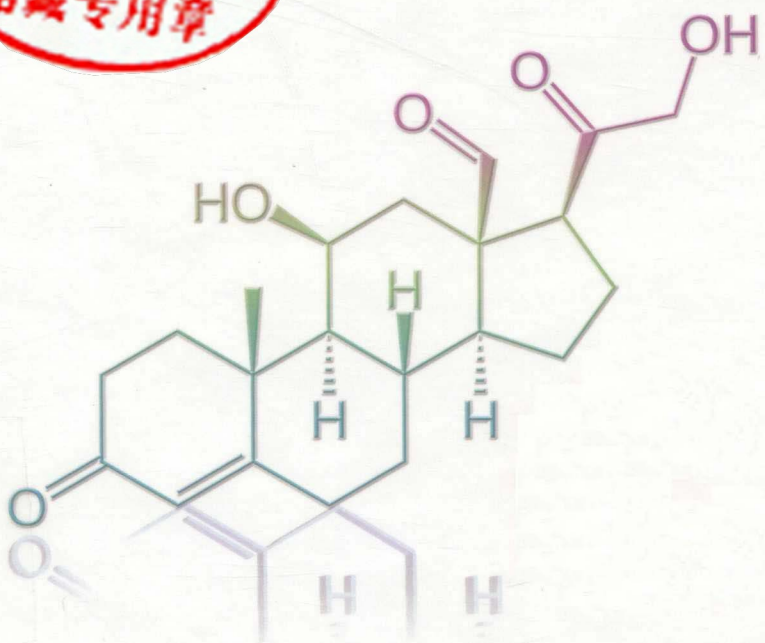
ENDOCRINOLOGY RESEARCH AND CLINICAL DEVELOPMENTS

Aldosterone

Regulation, Function and Research Insights



Jacqueline Miller
Editor

NOVA

Nova Biomedical

ENDOCRINOLOGY RESEARCH AND CLINICAL DEVELOPMENTS

ALDOSTERONE

REGULATION, FUNCTION AND RESEARCH INSIGHTS

JACQUELINE MILLER
EDITOR

nova
biomedical
New York

NOTICE TO THE READER

Library of Congress Cataloging-in-Publication Data

ISBN: 978-1-53611-043-2

Published by Nova Science Publishers, Inc. † New York

ENDOCRINOLOGY RESEARCH AND CLINICAL DEVELOPMENTS

ALDOSTERONE

REGULATION, FUNCTION AND RESEARCH INSIGHTS

ENDOCRINOLOGY RESEARCH AND CLINICAL DEVELOPMENTS

Additional books in this series can be found on Nova's website under the Series tab.

Additional e-books in this series can be found on Nova's website under the eBooks tab.

PREFACE

This book focuses on the regulation, function and further research insights on aldosterone. Chapter One discusses the role of aldosterone in the causation of cardiac oedema and highlights areas for potential future research. Chapter Two reviews secondary arterial hypertension due to primary hyperaldosteronism. Chapter Three summarizes the present knowledge about the role of aldosterone in stress adaptation with special emphasize to age-dependent changes. Chapter Four presents an overview of the effects of aldosterone, focusing on nongenomic actions in the kidney.

Chapter 1 – The syndrome of chronic heart failure is complex and relates to the compensatory mechanisms utilized by the human physiology in an attempt to maintain normal blood pressure and cardiac output. The compensatory response, which is essentially neurohumoral, is dominated by activation of both the sympathetic nervous system and the renin-angiotensin-aldosterone axis (RAAS). Aldosterone levels remain elevated in chronic heart failure despite "upstream" blockade of the RAAS by ACE inhibition and angiotensin receptor blockade; a phenomenon known as "aldosterone escape." Although aldosterone antagonists (MRAs) have been shown to improve survival and clinical outcome in a series of landmark clinical trials, uptake in real world clinical practice is relatively low. Furthermore, the evidence base in heart failure with preserved ejection is less well established. The causal relation between aldosterone blockade and improved survival is incompletely understood but potassium conservation is likely to be a key factor. Other potential mechanisms are discussed in detail. Paradoxically, the risk of serious hyperkalaemia is probably the main factor limiting their more widespread use in clinical practice. The role of aldosterone in the causation of cardiac oedema is discussed and areas for potential future research are highlighted throughout.

Chapter 2 – Primary hyperaldosteronism is a syndrome due to the excess of secretion of mineralocorticoids and it is the first cause of secondary arterial hypertension (5% of the cases in not selected population and up to 20% in patients suffering from severe and refractory hypertension). Several causes can provoke it: 60% are due to bilateral idiopatic hyperplasia, 35% are provoked by aldosterone producing adenoma, also named Conn syndrome, inilateral adrenal hyperplasia is responsible for 2% of cases, type I familial hyperaldosteronism generates 1% of all primary hyperaldosteronisms, type II familial hyperaldosteronism provokes 2% of cases, adrenocortical adenocarcinoma generates 1% and there is an aldosterone ectopic production in 0,1% of the patients. Correct diagnosis of primary hyperaldosteronism is essential in order to optimize the control of the blood pressure and to avoid the damage that aldosterone causes in vessels and heart. The authors should suspect the presence of this syndrome in every patient who suffers from arterial hypertension belonging to one of these groups of higher risk: spontaneuos or secondary to diuretics hypokalemia, resistant hypertension, hypertension with suprarrenal mass, hypertension in young patients (less than 20 years old) who have family record of arterial hypertension or hemorrhagic stroke in young people (less than 40 years old), mayor hypertension or suspicion of secondary hypertension. In these patients they should determine: plasmatic aldosterone, plasmatic renine activity and the aldosterone/plasmatic renine activity ratio. When aldosterone levels are >15ng/dL, plasmatic renine activity >1ng/ml/h and the ratio >20-25, the authors should suspect the existence of a primary hyperaldosteronism and make confirmation tests, such us the cateterización of the adrenal veins, which is the most sensitive and specific one, since it can locate mycroadenoms after confirming the lateralisation of the aldosterone secretion. A differential diagnosis should be made, in order to search other causes of secondary hypertension, like: renovascular disease, diuretics, Cushing syndrome, excessive ingestion of licorice, congenital adrenal hyperplasia, Liddle/Bartter syndrome (blood pression is normal) or renine secretory tumors. It is important to establish an etiological diagnosis, which makes possible the prescription of a specific treatment and the genetic advice.

Chapter 3 – Stress is an important pathogenic factor in many disorders and the hypothalamic-pituitary-adrenocortical axis is one of the main components of stress-adaptation. The endhormones of the axis are glucocorticoids, however, the pituitary component of the axis, adrenocorticotropin is a potent regulator of mineralocorticoid secretion as well. The primary role of mineralocorticoids is the regulation of salt-water homeostasis, which function

can be a key element of stress-adaptation. In this respect the perinatal period seems to be especially important, as the water content of a newborn is even higher than that of an adult. Therefore its regulated maintenance seems to be utmost important. Moreover, positive developmental impact of low stressor-induced glucocorticoid levels in early development has been also recognized for a long time. Indeed, our studies using early postnatal rats confirmed that at this age-group animals react to stressors with higher mineralo- (aldosterone) than glucocorticoid (corticosterone) elevation. However, this reactivity type changes with age. Namely, in adults the same stressor triggered higher corticosterone and lower aldosterone secretion. In this review the authors aim to summarize the present knowledge about the role of aldosterone in stress adaptation with special emphasize to age-dependent changes.

Chapter 4 – The steroid hormone aldosterone plays an important role in the kidney to regulate water, electrolytes, and acid-base homeostasis. The classical role of aldosterone operates through a genomic mechanism. The aldosterone-mineralocorticoid receptor (MR) complex binds to its hormone-responsive elements within the nucleus and initiates the expression of target genes. To date, many studies have provided extensive evidence for the nongenomic actions of aldosterone that present a rapid onset (≤30 minutes). These are insensitive to inhibitors of transcription and translation. Most studies in this regard have been performed in cell culture models, and *in vivo* examinations are rare. Kidney cell line experiments have demonstrated that aldosterone nongenomically modulates various rapid cellular alterations. Several available pieces of evidence have clearly documented a crucial role of epidermal growth factor receptor (EGFR) in the response to aldosterone. It has been demonstrated that aldosterone rapidly induces EGFR transactivation and then generates intermediate components and signal transduction cascades that act as downstream signals via the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway. Aldosterone also nongenomically stimulates some upstream mediators that initiate EGFR transactivation. These signals include the heat shock protein 90 (Hsp90) family and cytosolic tyrosine kinase of Src (c-Src), which are enhanced by aldosterone. Both Hsp90 and c-Src reside in MR complexes that are released upon aldosterone binding and then activate EGFR. This mini-review presents an overview of the effects of aldosterone, focusing on nongenomic actions in the kidney. Previous *in vitro* and our first *in vivo* examinations will be discussed, including EGFR transactivation, intermediate components of upstream (Hsp90, c-Src) and downstream signals (MAPK/ERK), and some rapid cellular responses (protein kinases, enzymes,

and ion transporters). Investigations performed in animal models could elaborate the underlying molecular mechanisms of rapid aldosterone-induced cellular dysfunctions that may validate the clinical implications. Future perspective studies in these regards can reveal insights into the nongenomic effects of aldosterone *in vivo*.

CONTENTS

In: Aldosterone
Editor: Jacqueline Miller
ISBN: 978-1-53611-043-2

Chapter 1

THE ROLE OF ALDOSTERONE AND ALDOSTERONE ANTAGONISTS IN CHRONIC HEART FAILURE: A CLINICAL PERSPECTIVE

Robert Stevenson*
Consultant Cardiologist, Huddersfield Royal Infirmary,
Huddersfield, England, UK

ABSTRACT

The syndrome of chronic heart failure is complex and relates to the compensatory mechanisms utilized by the human physiology in an attempt to maintain normal blood pressure and cardiac output. The compensatory response, which is essentially neurohumoral, is dominated by activation of both the sympathetic nervous system and the renin-angiotensin- aldosterone axis (RAAS). Aldosterone levels remain elevated in chronic heart failure despite "upstream" blockade of the RAAS by ACE inhibition and angiotensin receptor blockade; a phenomenon known as "aldosterone escape." Although aldosterone antagonists (MRAs) have been shown to improve survival and clinical outcome in a series of landmark clinical trials, uptake in real world clinical practice is relatively low. Furthermore, the evidence base in heart failure with preserved ejection is less well established. The causal relation between aldosterone blockade and improved survival is incompletely understood but potassium conservation is likely to be a key factor. Other

*E mail: robert.stevenson@cht.nhs.uk; or: robertnstevenson@btinternet.com.

potential mechanisms are discussed in detail. Paradoxically, the risk of serious hyperkalaemia is probably the main factor limiting their more widespread use in clinical practice. The role of aldosterone in the causation of cardiac oedema is discussed and areas for potential future research are highlighted throughout.

INTRODUCTION

Heart failure is amongst the commonest of chronic medical conditions particularly in the Western World. The prevalence varies according to definition but is approximately 1-2% of the adult population in developed countries. The prevalence increases with age and is set to rise steadily as the population ages. In the U.K. National Heart Failure Audit, the mean age at first hospital presentation was 76 years for men and 80 years for women. Substantially more than half of the audit population was aged 75 or above [1].

Whilst there is no current universally accepted definition, heart failure is a complex clinical syndrome of symptoms and signs that suggest inability of the heart as a pump to support a normal physiological circulation. The most recent guidelines from the European Society of Cardiology define heart failure as a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intra-cardiac pressures at rest or during stress [2].

Heart failure should be considered as an abnormal physiological state rather than a diagnosis per se and the precise mechanism and aetiology should be sought for the individual patient. Some conditions which lead to heart failure may be potentially reversible such as primary heart valve disease, alcohol related cardiomyopathy and severe uncontrolled hypertension. It is clearly essential that these conditions are identified and managed appropriately e.g., valve replacement surgery for heart valve disease.

The content of this chapter refers specifically to the medical management of patients with heart failure caused by impaired left ventricular function focusing primarily on the role of aldosterone and aldosterone antagonists.

Traditionally the term left ventricular dysfunction has been used synonymously with the terms *left ventricular systolic dysfunction (LVSD)* or *systolic heart failure*. Systolic function essentially describes the pumping

ability of the heart or *myocardial contractility*. More recently, however, it has become evident that almost half of patients with heart failure have relatively preserved left ventricular systolic function and cardiac function is compromised primarily by abnormal diastolic function. Diastolic function essentially refers to the ability of the heart to actively relax and refill between contractions. This is a complex and active process and when impaired leads to a reduction in cardiac output and elevated filling pressure despite apparently normal or near normal myocardial contractility [3]. The term *heart failure with preserved ejection fraction (HFpEF)* is used to describe this condition in order to distinguish it from systolic heart failure which is now referred to as *heart failure reduced ejection fraction (HFrEF).*

The left ventricular ejection fraction (LVEF) is the standard measure of contractility and refers to the percentage of blood pumped from the heart with each contraction. The normal value for a healthy heart is at least 60% at rest whereas in heart failure caused by left ventricular systolic dysfunction the ejection fraction is reduced usually to 40% and below. Although there is not currently a universally accepted cut-off point, the ejection fraction is usually greater the 50% in patients with HFpEF. In practice, heart failure secondary to left ventricular dysfunction may best be considered as a spectrum of abnormal physiology comprising varying degrees of diastolic and systolic abnormality and this is reflected in the most recent European Society of Cardiology Heart Failure guidelines which suggest the term *heart failure with intermediate ejection fraction* to describe patients who have an ejection fraction between 40% and 50% [2].

The symptoms and clinical signs of heart failure are broadly similar in patients with either *reduced* or *preserved* ejection fraction and reflect the common end product of reduced cardiac output in association with elevated filling pressure. Survival and prognosis is also broadly similar [4], though patients with HFPEF tend to be more elderly and have a higher incidence of hypertension, atrial fibrillation and diabetes [5].

Heart failure may be caused by a multitude of conditions, the commonest denominators being coronary (ischaemic) heart disease and chronic hypertension. The term non- ischaemic cardiomyopathy refers to a number of conditions of varied aetiology including genetic, infective (usually viral), chemical (alcohol most commonly) and hormonal factors.

PATHOPHYSIOLOGY OF HEART FAILURE

The pathophysiology of acute heart failure, following an acute myocardial infarction for example, relates directly to the haemodynamic consequences of an abrupt reduction in cardiac contractility. Symptoms and signs can be explained in terms of a reduced cardiac output accompanied by an acutely elevated left ventricular filling pressure. The latter accounts for the acute breathlessness associated with pulmonary oedema and this is usually readily relieved by the administration of diuretics. In contrast, the syndrome of chronic heart failure is more complex and relates more to the compensatory mechanisms utilized by the human physiology in an attempt to maintain normal blood pressure and cardiac output. The compensatory response, which is essentially neurohumoral, is dominated by activation of both the sympathetic nervous system and the renin-angiotensin- aldosterone axis and to a lesser extent antidiuretic hormone (ADH) and the natriuretic peptides. Numerous other vasoactive substances have been variously implicated in the process including nitrous oxide, endothelin, bradykinin and various cytokines but these will not be considered further in this discussion. This neurohumoral cascade is essentially an evolutionary response to low blood pressure and failing cardiac output which in the context of primary cardiac pump failure is ultimately maladaptive [6].

Thus, whilst sympathetic activation initially maintains cardiac contractility, chronic beta receptor stimulation ultimately leads to progressive myocardial dysfunction and cardiomyocyte aptosois (cell death). Moreover, increase in heart rate may provoke coronary ischaemia and compromises left ventricular filling by shortening time in diastole. Increased sympathetic activity also increases afterload on the failing ventricle by increasing systemic vasoconstriction directly and via stimulation of renin production.

The renin-angiotensin-aldosterone system (RAAS) is activated through a variety of pathways but mainly via renin release in response to reduction in stretch of the afferent arterioles of the renal glomerulus and reduction in chloride delivery to the macula densa, as well as beta adrenergic receptor stimulation. Activation of RAAS is also maladaptive and leads to angiotensin mediated systemic vasoconstriction and aldosterone mediated salt and water retention.

Angiotensin may also have adverse effects on cardiomyocytes similar to those of norepinephrine and may be synthesized locally in the myocardium as well as other tissues.

Antidiuretic hormone (ADH), released in response to baroreceptor activation, stimulates thirst and promotes water reabsorption in the collecting ducts of the kidney. Excessive ADH production contributes to the dilution related hyponatraemia seen frequently in the advanced stages of heart failure.

Atrial and brain natriuretic peptides are released from atria and ventricles in response to stretch. In heart failure, natriuretic peptides produced in response to elevated cardiac filling pressure, promote sodium and water loss through a direct action on the kidney (natriuretic effect). This potentially beneficial effect, along with a modest vasodilator action, is usually insufficient to counter the adverse effects of neurohumoral activation in general. However, brain natriuretic peptide (BNP) and its derivatives have a valuable diagnostic role primarily as a "rule out test" for the initial diagnosis of heart failure. Whilst low levels virtually rule out heart failure, serial assays can also be employed to guide treatment and monitor prognosis in patients with an established diagnosis.

The summary effect of neurohumoral activation is ultimately maladaptive and results in increased afterload on the left ventricle, elevation of diastolic filling pressure and volume expansion through salt and water retention. These changes not only account for the clinical syndrome of heart failure but also create a "vicious cycle" of worsening cardiac function and inappropriate neurohumoral activation.

PHARMACOTHERAPY

Whilst being an oversimplification, this account of the pathophysiology of heart failure serves to explain the rational for our current therapeutic approach to the treatment of chronic heart failure.

Diuretics are indicated for all forms of heart failure in order to relieve fluid congestion. Loop diuretics are used most commonly and are highly effective at relieving both pulmonary congestion and peripheral oedema. Their primary mode of action is to block chloride and sodium reabsorption in the loop of Henle. In cases of resistant oedema, loop diuretics may be combined synergistically with thiazide (or thiazide type) diuretics which attenuate the compensatory reabsorption of sodium in the distal tubule of the kidney. The clinical effectiveness of diuretics was established long before the era of randomized controlled clinical trials, and consequently there are limited published data to substantiate any prognostic benefit. Furthermore, diuretics

tend to potentiate neurohumoral activation by removing fluid from the circulation with resultant central volume depletion.

The introduction of angiotensin converting enzyme (ACE) inhibitors in the late 1980s revolutionised the treatment of chronic heart failure [7]. In contrast to the earlier generation of vasodilator drugs, ACE inhibitors directly block the maladaptive effects of RAAS activation and effectively break the "vicious cycle" that leads to progressive decline in cardiac function. A series of large randomised placebo controlled trials of ACE inhibition in patients with heart failure and reduced ejection fraction have consistently demonstrated substantial symptomatic and prognostic benefit including highly significant reductions in mortality. A meta-analysis comprising over 12,000 patients demonstrated a 28% reduction in the composite end-point of death, myocardial infarction and hospital admission for heart failure [8]. The greatest reduction was observed amongst patients with the lowest ejection fractions. Cough is a common unwanted effect and is a result of the action of ACE inhibition on bradykinin breakdown. Although bradykinin may contribute usefully to the vasodilator effect of ACE inhibition, heightened levels of bradykinin can trigger a troublesome cough or even angioedema in susceptible individuals. Angiotensin receptor blockers (ARBs), which were developed after the introduction of ACE inhibitors, act by blocking the angiotensin II receptor directly and do not therefore interact with bradykinin production. Although a very useful alternative for patients who are intolerant of ACE inhibitors, ARBs are generally considered second line as the evidence base for prognostic benefit is less well established. A meta-analysis of all the randomised heart failure trials involving ARBs concluded that although there was a trend towards a treatment benefit when compared with placebo, ARBs were less effective when compared directly with ACE inhibitors [9]. In the U.K. approximately 90% of patients aged <75yrs discharged from hospital with a diagnosis HFrEF were prescribed an ACE inhibitor and/or an ARB with ACE inhibitors being the preferred choice (79% prescribed an ACE inhibitor vs 18% prescribed an ARB) [1]. However, the recent introduction of the first and only angiotensin receptor blocker (ARB) and neprilysin inhibitor combination, sacubitril/valsartan, is likely to change clinical practice. This novel drug which combines angiotensin receptor blockade with BNP enhancement (through inhibition of BNP breakdown) was shown to be superior to the ACE inhibitor enalapril in the landmark PARADIGM-HF trial and has been widely approved for use as an alternative to a standard ARB or ACE inhibitor [10].

Although historically, beta receptor antagonist (beta blockers) were considered to be contraindicated in heart failure, the realisation that

sympathetic activation was a key component of the neurohumoral response led to a series of landmark clinical trials [11]. A large meta-analysis of all the randomised trials of beta blockers in chronic heart failure confirmed the benefits in terms of mortality reduction to be unequivocal estimating 3.8 lives saved and 4 fewer hospitalisations per 100 patients treated in the first year [12].

It is important to recognise the clinical trial evidence base relates only to patients with heart failure associated with a reduced ejection fraction (generally <40%). Whilst professional guidelines universally recommend treatment with both an ACE inhibitor (or an ARB if ACEI intolerant) and a beta blocker in this group of patients to improve symptoms and survival, the guidance does not apply to those with heart failure associated with a preserved ejection fraction.

ROLE OF ALDOSTERONE IN HEART FAILURE

The role of aldosterone in the pathophysiology of heart failure was recognised as long ago as 1965 [13]. As the end product of the renin-angiotensin–aldosterone pathway aldosterone levels are elevated as much as twenty fold in untreated patients with congestive cardiac failure compared to normal controls, and serum levels have been shown to correlate with mortality [14]. In elderly female nursing home residents high circulating aldosterone levels were related to increased mortality and aldosterone related mortality was associated with the presence of advanced heart failure [15].

The most obvious consequence of excessive aldosterone production is of course promotion of salt and water retention though its well established action on the distal tubule of the kidney. In addition, by exchanging sodium for potassium, aldosterone promotes hypokalaemia accompanied by hypomagnesaemia with likely deleterious consequences in terms of sensitizing the myocardium to ventricular arrhythmia. There are, however, a number of other potential mechanisms through which aldosterone may contribute to the pathophysiology of chronic heart failure though the evidence for these is largely from small studies in humans and animal models. These have been reviewed in detail by *Struthers* [16, 17] and include effects on endothelial function, baroreceptor sensitivity and promotion of myocardial fibrosis through stimulation of mineralocorticoid receptors located in the heart. In turn, myocardial fibrosis is likely to lead to a reduction in both myocardial contractility and relaxation thereby contributing to both systolic and diastolic