CARDIO NEWS 6

CEVA ANIMAL HEALTH | AT THE HEART OF INNOVATION

First Human and Veterinary Crossover Symposium on Aldosterone

Minutes n°1: Aldosterone receptor antagonists - how cardiovascular actions explain their beneficial effects in heart failure

SUMMARY:

Keywords: Aldosterone, Cardiac fibrosis, Glucocorticoid, Mineralocorticoid Receptor antagonists, Profibrotic state, Remodelling of blood vessels.

The first 'human-veterinary crossover' cardiology symposium was held on 16-18 October in Bordeaux, France. The programme included well-known cardiology researchers, both from the human and veterinary fields. Organised by CEVA Santé Animale, the symposium focused on the role of aldosterone in human and canine heart disease, and on how health can be improved by the use of aldosterone antagonists. Over 60 invited specialists in veterinary cardiology from 12 countries attended this unique event.

The next 3 CardioNews issues will report on this research data, mixing state-of-the-art science with the most recent clinical developments in man and animals. The key questions raised by the delegates are also presented at the end.

LECTURERS:

Nicolette Farman
MD, PhD- Research Director (Senior Investigator) INSERM (French National Institute of Health and Medical Research), Paris, France.

Frédéric Jaisser
MD, PhD- Research Director INSERM Paris, France.

Johann Bauersachs
MD- Associate Professor, Consultant Cardiology and Critical Care Department of Medicine I, University Hospital, Würzburg, Germany.

Introduction

Cardiologists' interest in aldosterone was initially stimulated by the fact that the aldosterone antagonists, spironolactone and eplerenone, substantially reduce the risk of cardiovascular mortality in humans.[1,2]

These benefits are not related to any diuretic or blood pressure effect of aldosterone blockade, but appear to be a consequence of blocking the mineralocorticoid receptors (MR) in the heart and blood vessels that mediate cardiovascular remodelling and fibrosis. Scientific understanding of the role of aldosterone and its receptors in the heart was the subject of the symposium's first two presentations, which were given by Dr Nicolette Farman and Dr Frédéric Jaisser from the French National Institute of Health and Medical research (INSERM) in Paris. The science linking experimental MR studies with clinical benefits was further explored by Dr Johann Bauersachs from the University Hospital in Würzburg, Germany ■

I - Aldosterone: a key role in heart failure

1 - Aldosterone and its receptor: how it works

Dr Farman began her presentation by outlining the pathway by which the hormone aldosterone stimulates reabsorption of sodium and excretion of potassium within the kidneys, highlighting the role of mineralocorticoid receptors (MR). Aldosterone is synthesised in the adrenal cortex following activation of the renin-angiotensin system in response to lowering of blood pressure and, or, extracellular sodium within the kidney. Aldosterone binds to MR within the cytoplasm of cells in the distal portion of the nephron, triggering an increase in the number and activity of sodium transporters and channels. This results in increased reabsorption of sodium and the retention of water.

Mineralocorticoid receptors and glucocorticoid receptors can bind to, and be activated by, both aldosterone and glucocorticoids (such as cortisol and corticosterone). Over-activation of the MR in renal cells by glucocorticoids, which is 100-1000 fold more abundant than aldosterone, is prevented by a so-called MR protector enzyme (11 β-hydroxysteroid dehydrogenase; HSD2).[3] This enzyme is co-expressed alongside the MR in the distal nephron and degrades glucocorticoids, thus ensuring that only aldosterone binds to the MR. As well as the kidney, cardiac myocytes and arterial smooth muscle cells also contain MR but have little HSD2, meaning that both aldosterone and glucocorticoids bind to these receptors. Blocking the MR with spironolactone could therefore decrease both aldosterone and glucocorticoids activity within these tissues. This could help to explain why spironolactone reduces the risk of mortality in patients with heart failure, especially in light of recent evidence in man linking better survival times with low plasma concentrations of aldosterone and glucocorticoids.[4] ■

2 - Spironolactone: a drug with an exciting future

In addition to its beneficial role in heart failure, Dr Farman highlighted other possible future applications of MR angatonists, which are the subject of current research.

"Studies in rats and man have shown that chronic hyperaldosteronism is deleterious for the kidneys, and therefore MR antagonists may help to protect the kidneys." Spironolactone has been shown to protect against the development of glomerulonephritis in experimental models of renal failure in rats, and to reduce proteinuria and collagen excretion in humans with chronic renal disease.[5]

As well as in the kidneys, heart and blood vessels, MR receptors have also been identified in the eye, brain, adipocytes and keratinocytes, although their exact function in these tissues is still being discovered. It is known, however, that excessive MR activation may play a pathologic role in atherosclerosis and other vascular diseases, stroke, diabetes mellitus and metabolic syndromes.

Over-expression of MR has also been associated with anxiety-like behaviour and alopecia in animal models, raising the possibility of benefits from MR antagonism in skin and neurologic diseases.[6,7]

Dr Farman concluded by suggesting where future research into MR may take basic and clinical scientists. She was excited by the potential for spironolactone to improve animal health and looked forward to the prospect of new tissue-specific MR antagonists being developed as well as unravelling the roles of aldosterone and MR in other body tissues.

"I have been working on aldosterone for 30 years, but research on the topic is far from finished – it's constantly being renewed", she concluded ■

II - Aldosterone: profibrotic

1 - Aldosterone and cardiovascular diseases

Dr Jaisser examined the pathological consequences of chronic mineralocorticoid receptor (MR) activation in the heart as well as the kidney. He began by comparing the effects of MR activation to Janus - the Roman god that had two heads facing in opposite directions - with its positive influence on blood pressure and body fluid composition being opposed by chronic pathological effects that include hypertension and a profibrotic state (see Figure 1).

Research over the past decade has identified that MR is expressed in cardiomyocytes and in endothelial and smooth muscle cells in coronary blood vessels, the aorta and resistance arteries. Although its function in these tissues remains poorly understood, there is increasing evidence that chronic MR activation leads to endothelial dysfunction and vascular wall remodelling.[8]

Evidence of the role of MR activation in cardiovascular disease comes from a number of clinical and experimental studies, which were briefly described by Dr Jaisser. The RALES and EPHESUS clinical trials, which demonstrated that the MR antagonists spironolactone and eplerenone markedly reduce overall and cardiovascular mortality in humans with heart failure, provide the most convincing proof.[1,2] Animal studies have also shown that MR antagonists reduce cardiac fibrosis and remodelling of the blood vessels, and improve vascular function.

Dr Jaisser's presentation focused on the role of MR in the heart and blood vessels. Aldosterone was shown to have a profibrotic effect in the early 1990s, inducing interstitial remodelling of the left and right ventricles in animals that was unrelated to changes in blood pressure. Administration of low doses of spironolactone prevented this cardiac and vascular remodelling, as well as local inflammation, independent of any effect on blood pressure, thereby confirming that the deleterious effect of aldosterone was due to local, rather than renal, MR activation.[9]

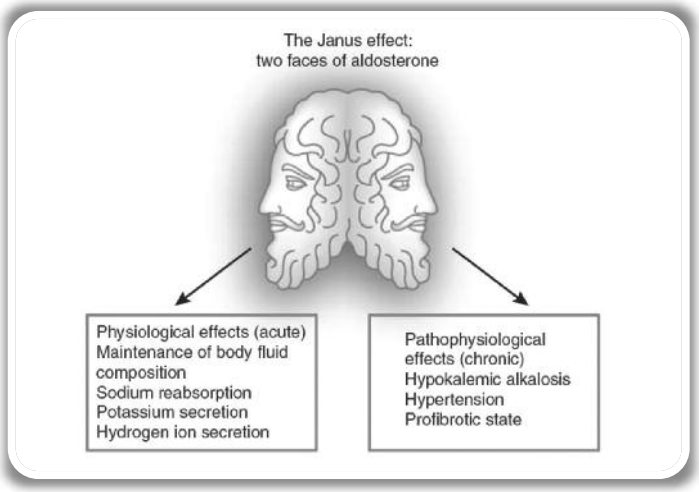

Figure 1:
The "two faces" of aldosterone presented by Frédéric Jaisser during his lecture.

2 - Transgenic mouse models: a clue to understand specific roles of MR in the heart and vessels

Research in this area has been pursued through the development of transgenic mouse models that have allowed Dr Jaisser's team to better understand the role of MR and glucocorticoid receptors (GR) in specific body tissues. One of their key findings has been that cardiac over-expression of MR leads to major electrocardiographic abnormalities, with prolonged ventricular repolarisation and ventricular arrhythmias. Affected mice suffered high mortality rates that were reduced by administration of spironolactone. The question of the specificity of the effects observed in mice with cardiac over-expression of MR has been answered by the development of mice that over-express GR in the heart. Such mice also suffer conduction defects, but these are different in nature (atrioventricular block) to those associated with cardiac MR over-expression indicating that MR and GR regulate distinct pathways in the heart.[10,11] ■

III - Aldosterone antagonists: how experimental evidence supports their clinical benefit

The science underlying the therapeutic benefits of mineralocorticoid receptor (MR) blockade in cardiovascular disease was reviewed by Dr Bauersachs. He began by outlining that aldosterone induces myocardial fibrosis and that high circulating levels impair cardiac and vascular function, and confer a greater risk of mortality in humans suffering acute myocardial infarction or congestive heart failure. The higher incidence of myocardial infarction and stroke in patients with primary hyperaldosteronism, together with the fact that MR blockade reduces mortality in heart failure, are further testament to the direct effects of this hormone on the cardiovascular system (See Figure 2).

Understanding the role of aldosterone is complicated by the fact that MR antagonists are clinically effective in patients that do not have high plasma aldosterone concentrations. Indeed plasma aldosterone concentrations do not correlate with clinical response to MR antagonists. One explanation for this conundrum is provided by Dr Bauersachs' own research, which showed that cardiac MR expression is increased in heart failure following myocardial infarction. This would explain why deleterious effects of aldosterone on cardiomyocytes, cardiac fibroblasts, endothelial and smooth muscle cells – leading to cardiac hypertrophy, fibrosis and vascular injury – are seen in the absence of high aldosterone levels. Other explanations include local production of aldosterone, which acts locally , and the possibility that MR antagonists are blocking the harmful effects of corticosteroids, rather than aldosterone, on the cardiac MR.[12]

Dr Bauersachs then reviewed evidence from dogs with chronic heart failure induced by microembolism, showing how the MR antagonist eplerenone prevents

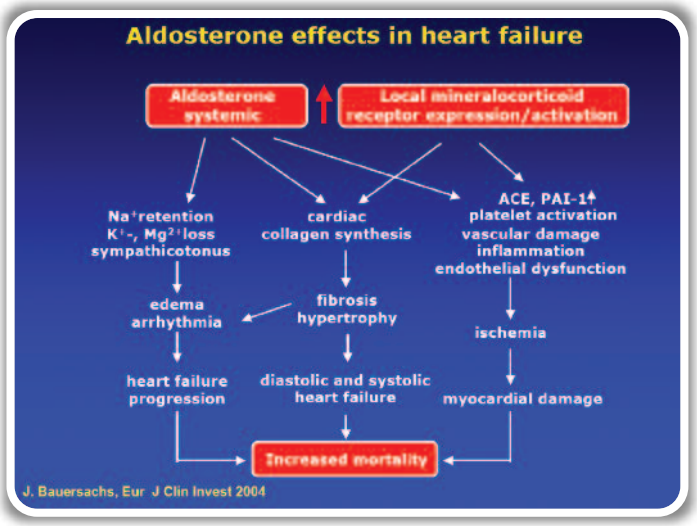

Figure 2:
Harmful effects of aldosterone in heart failure (from Bauersachs, Eur J Clin Invest. 2004).[13]

progressive left ventricular dysfunction and associated remodelling (dilatation, hypertrophy and fibrosis). Similar effects are seen with spironolactone in dogs with heart failure induced by rapid pacing, reducing atrial fibrosis and the frequency and duration of episodes of atrial fibrillation.[14] These findings are supported by rodent and organ bath experiments, which also highlight additive effects of treatment with MR antagonists and angiotensin converting enzyme (ACE) inhibitors.[15] Combination treatment significantly improved cardiac function, reversed changes in collagen formation and myocardial remodelling, normalised endothelial function, blocked platelet activation and reduced oxidative stress. The development of mice lacking the cardiomyocyte MR gene has provided further evidence that the clinical benefits of MR antagonists are mediated, at least in part, via direct effects on cardiomyocytes. In chronic heart failure, these mice showed reduced left ventricular dilatation and hypertrophy, decreased fibrosis and reduced oxidative stress ■

Question session

Sessions were organised with 30 minute lectures and 15 minute questions and answers to allow debates between delegates and speakers on the different subjects dealt with during the symposium. For the 3 lectures presented in this edition of CardioNews, Professor Jonathan Elliott, Vice Principal – Research Professor of Veterinary Clinical Pharmacology from the Royal Veterinary College in London (see Photo 1) chaired the question sessions. Here below a selection of some of the questions which were asked during these sessions.

Question 1 (Delegate) - How much do we know about MR in fibroblasts? Does activation have an effect on the amount of collagen, or the cross-linking or quality of the collagen?

Answer (FJaisser) - High doses of aldosterone have been shown to induce collagen synthesis in fibroblasts in vitro, but it is not know if MR is expressed in fibroblasts in vivo. Aldosterone has been shown to bind to glucocorticoid receptors (GR) in many studies and high doses of MR antagonists appear to block GR activity. This could, therefore, explain how aldosterone induces collagen synthesis. Current consensus is, however, that other factors, e.g. oxidative stress induced by aldosterone, may cause secondary remodelling and vascular changes.

Question 2 (Delegate)- Can we assume that all dog breeds would have the same MR expression in cardiomyocytes? After all there is evidence in rats that different levels of MR expression occur between breeds.

Answer (NFarman) - In principle it is possible that the expression of MR in the hearts of dogs would mimic that seen in other species. It is not difficult to do the research to find out.

Comment (JElliott) - Pharmacogenomics is an important area and one in which veterinary medicine lags behind human medicine. This could be very important in dogs since there is a wide range of breeds produced by genetic selection with differences in their susceptibility to heart disease - no one has really studied whether they differ in their response to treatment and whether genetics explain any differences.

Question 3 (Delegate)- Do you believe that the mechanism by which heart failure occurs is important in determining the response to therapy? Does the mechanism of induction determine the response to treatment?

Answer (JBauersachs) - There appears to be no clinical distinction in terms of symptoms despite the different underlying pathologies, but the effects of drugs are important and different. The best treatments are those that work in multiple models of heart failure. Spironolactone, for example, does work in multiple models.

Photo 1:
Fifteen minutes were dedicated to questions during the symposium to allow exchanges between human and veterinary specialists. From left: Jonathan Elliott, Johann Bauersachs.

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