CARDIO NEWS 3

CEVA SANTE ANIMALE | AT THE HEART OF INNOVATION

Aldosterone: From the kidney to the heart

For this third edition of Cardionews, the renowned human cardionephrologist Dr Nicolette Farman explains how the harmful cardiovascular effects of aldosterone were discovered. She then explores the clinical benefits of using the aldosterone antagonist spironolactone in heart failure therapy and discusses recent discoveries and on-going studies relating to this active area of research.

AUTHOR

Cardionews (CN): Dr Farman, tell us about your very first encounter with aldosterone and its specific mineralocorticoid receptor (MR) …

Dr N. Farman: During my residency in Medicine, I went away to work for 2 years in the United States in the department of Professor Isidore Edelman, the leading authority on aldosterone at the time, and I studied the effects of aldosterone on the toad bladder there. When I came back to France, I finished my residency in the cardiology department of Professor Hatt, a cardiologist and researcher at the Inserm, who has trained many renowned cardiologists. Our team started working on regulation of sodium reabsorption in the kidney as part of studies on arterial hypertension, notably involving aldosterone.

CN: What was the discovery that had a major impact on your work in the 1980s?

Dr N. F.: The 1980s saw the emergence of molecular biology and its new tools for studying proteins. In 1987, the American team of Ron Evans published the nucleotide sequence of the aldosterone receptor known as the mineralocorticoid receptor. Thanks to this, its properties could be studied, and it could be located in the tissues.

CN: Was it when the receptor was discovered in tissues other than in the kidney that you came to suppose that aldosterone could have effects other than diuretic ones?

Dr N. F.: Exactly! The receptor could be located by mRNA in histological sections. Ron Evans' group was the first to pinpoint the presence of mineralocorticoid receptors in the brain. Meanwhile, we were working under Dr Bonvalet on the cardiovascular system, and demonstrated the presence of the receptors in the heart and blood vessels in rabbits, then in the human heart in 1995. These discoveries raised a new question: *"If mineralocorticoid receptors are present in other organs than the kidney, what is their role in these organs, and in particular in the heart?*
In 1991, we organised the first International Symposium on aldosterone. A lot of research teams started working on aldosterone and its receptor, notably in Europe and in the United States. Karl Weber and Christian Brilla were the first to mention the harmful role of activation of this receptor in cardiovascular pathologies in rats. We were in regular contact with these teams and kept track of their work and publications, stimulated by a healthy spirit of competition.

"Mineralocorticoid (aldosterone) receptors were discovered in the heart and blood vessels raising the question *what is their role in these organs?*"

AUTHOR

After serving as a Resident in Paris Hospitals and a Post Doctorate in San Francisco from 1974 to 1976 in the laboratory of Professor Isidore Edelman, Nicolette Farman joined the Inserm (French National Institute of Health and Medical Research) in 1978 (Inserm U2, Limeil Brévannes Hospital) and did a PhD Thesis in Sciences in 1981.

As a full-time Inserm personnel, she worked for 10 years at the CEA, then for 15 years at Bichat Medical School, working from the outset on the role of the hormone, aldosterone, and its specific receptor, the mineralocorticoid receptor (MR). Dr Farman was therefore one of the pioneers in discovering the cardio-vascular effects of this hormone, and she is now one of the leading experts on the subject.

Nicolette Farman is currently working alongside Dr Frédéric Jaisser at Unit 772 of the Inserm, a research unit based on the premises of the Collège de France. It was there that she met us, in this world-renowned multidisciplinary research institution created in the 16th century.

Inner courtyard of the Collège de France.

CN: A lot of teams around the world have worked, like you, on the role of aldosterone in heart failure and on the beneficial effects of spironolactone. Could you tell us about the work that led to the set-up of the RALES (Randomised Aldactone Evaluation Study) in 1999?

Dr N. F.: To get to know the role of the receptors in the heart, the US team of Dr Weber and Dr Brilla studied a specific animal model in which the MR was hyperstimulated. This model induced arterial hypertension, which is associated with cardiac fibrosis. Treatment with spironolactone, an aldosterone receptor antagonist, prevented the appearance of arterial hypertension and cardiac fibrosis. Large-scale clinical trials then confirmed the interest of spironolactone in the treatment of heart-failure patients. The RALES study showed the benefits of adding spironolactone to the standard treatment on survival of heart failure patients (reduction of 31% in mortality of cardiac origin when compared to the standard treatment given alone).

CN: What recent discoveries has your research unit made?

Dr N. F.: We are continuing to study the role of the aldosterone receptor in the heart, notably by using genetically-modified animal models. We have created a transgenic mouse model in which the receptor is overexpressed only in the heart. In adult mice, ventricular rhythm problems are observed (ventricular extrasystoles, torsades de pointe and repolarisation anomalies), as well as high arrhythmia-related mortality rates. Spironolactone can prevent these rhythm problems in transgenic mice, resulting in reduced mortality.

CN: What work is currently underway on aldosterone and its receptor?

Dr N.F.: Laboratories working on aldosterone have also diversified their research into the efficacy of spironolactone in a variety of pathological conditions, and some research teams are now studying the role of spironolactone in kidney failure and diabetes. There are regular publications on these subjects.
The future therapeutic prospects are many, and one lifetime will not be enough to discover the full potential of this receptor.

“Large-scale clinical trials have confirmed the interest of spironolactone in the treatment of heart failure patients”

CN: 10 years on from publication of the RALES study, what conclusions do you draw from the results of the clinical trials carried out by CEVA Santé Animale?

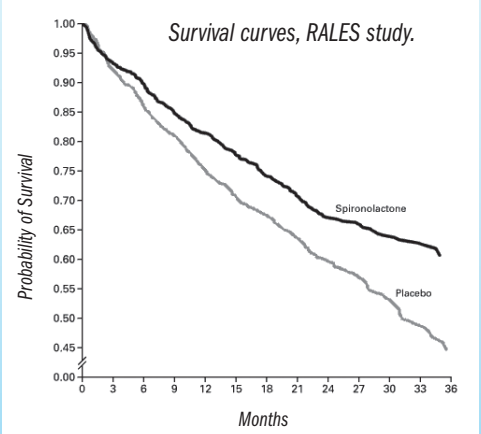
Dr N. F.: These results are spectacular and show the interest of exchanges between research teams in human and veterinary medicine. It is always important to meet up with people from different backgrounds, share ideas and adapt to new developments. There is no such thing as absolute truth. Making sure we keep all our curiosity intact allows new ideas to emerge and interesting collaborations to be established.

CN: In your opinion, what is the key idea researchers and practitioners retain from all the work carried out on aldosterone, its receptor and spironolactone?

Dr N. F.: I think it is generally acknowledged today that administration of spironolactone protects against the harmful effects of aldosterone in humans and animals alike. In particular, it can reduce cardiac fibrosis and therefore mortality in heart failure patients. More and more often, doctors have the heart in mind when they prescribe spironolactone.

THE RALES STUDY

The RALES study was a large-scale clinical trial published in the New England Journal of Medicine in 1999. This randomised, double blind, placebo-controlled trial included 1,663 patients with heart failure treated with an angiotensin conversion enzyme (ACE) inhibitor and a loop diuretic. This study demonstrated that adding spironolactone to this standard treatment resulted in a 31% reduction in cardiac mortality risk. This major improvement in survival rates resulted in the trial being suspended one year prior to the date initially scheduled for ethical reasons. A complementary analysis of this study showed that the increase in cardiac collagen markers is associated with an increased mortality rate. **Spironolactone enables a significant reduction in these markers and therefore in fibrosis, when compared to the placebo group. It is via this action on myocardial and vascular fibrosis that spironolactone enables the mortality risk to be reduced.**



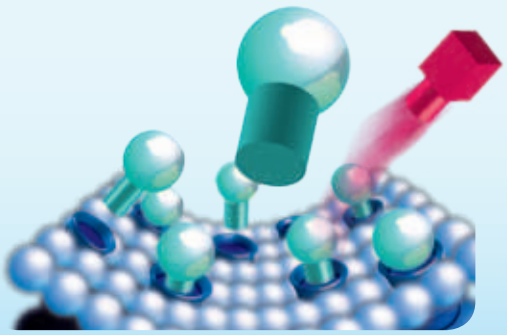
ABOUT ALDOSTERONE AND ITS RECEPTORS

Aldosterone is a mineralocorticoid hormone belonging to the family of steroid hormones, such as cortisol, oestrogen, testosterone or progesterone. Aldosterone exerts its biological effects by binding onto specific receptors, the mineralocorticoid receptors (MR). These receptors are present in the heart, blood vessels, central nervous system and epidermis, as well as in the cells of the renal collecting tubule and distal tubule of the nephron. Spironolactone is a competitive aldosterone antagonist: by binding onto the MR in the place of aldosterone, spironolactone inhibits the effects of aldosterone.


Spironolactone


Aldosterone


Mineralocorticoid receptor


Competitive binding to a MR in the place of aldosterone.

"More and more often, doctors have the heart in mind when they prescribe spironolactone"

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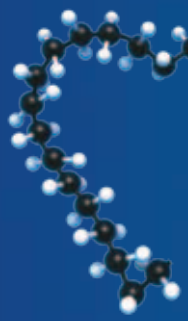

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