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Mini Review

Effects of aldosterone and mineralocorticoid receptor antagonism on cardiac ion channels in the view of upstream therapy of atrial fibrillation

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Abstract. Atrial fibrillation (AF) is the most common sustained arrhythmia in man. Over the past years, importance of the renin-angiotensin-aldosterone system in AF pathophysiology has been recognized. Lately, the role of aldosterone in AF pathophysiology and mineralocorticoid receptor (MR) antagonism in "upstream" AF treatment is discussed with special regards concerning the effects on AF-induced structural remodeling. However, there is more and more evidence that MR antagonism also influences atrial electrophysiology and, respectively, AF-induced electrical remodeling, whereas the molecular mechanisms are almost unknown.

The aim of this mini-review is to give an overview about the role of aldosterone in AF pathophysiology in principle and to summarize current available data concerning affection of cardiac ion channels by aldosterone and MR antagonism. Finally, as modulation of oxidative stress is discussed as one main therapy principle of "upstream" treatment of AF, potential mechanisms how modulation of oxidative stress by aldosterone and accordingly MR antagonism might alter atrial ion currents are delineated.

Summarized, publications concerning potential mechanisms of aldosterone- and MR antagonism-modulated cardiac ion channels in various experimental settings are almost exclusively limited to the ventricular level and, partly, they are also contradictorily. Translation of these data to the atria is problematic because atrial and ventricular electrophysiology exhibit remarkable differences. It can be concluded that further research on the "atrial level" is needed in order to clarify the potential impact of the affection of atrial ion channels by aldosterone and accordingly MR antagonism in "upstream" therapy of AF.

Key words: Atrial fibrillation — Atrial remodeling — Aldosterone — Mineralocorticoid receptor antagonism — Upstream therapy

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in man (Fuster et al. 2006). It is characterized by a variety of electrophysiological, mechanical and structural changes caused by the arrhythmia itself. This process termed "atrial remodeling in atrial fibrillation" is a time-dependent adaptive regulation mechanism promoting maintenance of cell homeostasis after arrhythmia onset (Wijffels et al. 1995; Allessie et al. 2002). Progressive shortening, reduced rate-adaption and increased heterogeneity of atrial effective refractory period are characteristic features of *in vivo* electrophysiological alterations in AF which have been studied extensively in several animal models and humans (Workman et al. 2008). Many of these observations can be explained by influence of AF on atrial ion channels and their regulative mechanisms (Nattel et al. 2008). For example, a reduced amplitude of the L-type calcium current ($I_{Ca,L}$) amplitude can be observed (Allessie et al. 2002). Atrial remodeling begins within a few hours after arrhythmia onset (Bosch et al. 2003; Laszlo et al. 2008). Over the past years, importance of the renin-angiotensin-aldosterone system (RAAS) in AF

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pathophysiology has been recognized (Heusch and Schulz 2006) and provides a basis for the so-called "upstream" therapy of AF by targeting signalling pathways involved in AF pathophysiology. For example, RAAS-blockage with angiotensin-converting-enzyme-inhibitors or angiotensin-II type 1 receptor antagonists seems to be useful in AF treatment (Krishnamoorthy and Lip 2009). Lately, the role of aldosterone in AF pathophysiology and accordingly mineralocorticoid receptor (MR) antagonism as a new therapeutic principle in AF treatment are discussed with special regards concerning the effects on AF-induced structural remodeling (Goette et al. 2007). However, there is also some evidence that MR antagonism influences atrial electrophysiology and, respectively, AF-induced electrical remodeling (Shroff et al. 2006) whereas the molecular mechanisms are unknown to a large extent.

Theoretically, the influence of aldosterone or MR antagonism on structural remodeling might also have indirect electrophysiological consequences: for example atrial conduction velocity also depends on the degree of atrial fibrosis (Workman et al. 2008).

A significant proportion of the effect of aldosterone and accordingly of MR antagonism on atrial electrophysiology might be mediated by another potential mechanism – the affection of atrial ion channels or their regulative mechanisms, as a balanced interaction of a variety of ion currents is the molecular basis of atrial or ventricular electrophysiology as a whole (Nerbonne and Kass 2005). Basal current density of each ion channel is mediated by a complex interaction between various signalling cascades changing ion channel expression in the cell membrane and/or influencing biophysical channel properties. In turn, these signalling cascades can be altered due to the impact of aldosterone or MR antagonism on various endogenous states (for example cellular redox state (Wagner et al. 2008)) or, respectively, local and systemic regulatory systems (e.g. RAAS (Lemarie et al. 2008), cardiac ryanodine receptor activity (Gomez et al. 2009), blood pressure, blood potassium levels or acid-base homeostasis (Zannad 1991; Wehling et al. 1998; Stier et al. 2002; Struthers and MacDonald 2004; McManus et al. 2008; Ovaert et al. 2010)).

The aim of this mini-review is to give a short overview about the role of aldosterone in AF pathophysiology in principle and to summarize current available data concerning the affection of cardiac ion channels by aldosterone and MR antagonism in various experimental settings. Finally, since modulation of oxidative stress is discussed as one main therapy principle of "upstream" treatment of AF with MR antagonists (Pitt et al. 2003b; Chai and Danser 2006; Cachofeiro et al. 2008), we delineate potential mechanisms how modulation of oxidative stress by aldosterone and accordingly MR antagonism might also alter atrial ion currents.

Potential role of aldosterone in AF pathophysiology

Serum aldosterone levels are elevated in patients with persistent AF (Goette et al. 2001) and there is a positive correlation between the fall in aldosterone concentration 24 hours after successful cardioversion and maintenance of sinus rhythm during 30 days of observation (Wozakowska-Kaplon et al. 2010). Compared to age-, gender- and blood pressure-matched control persons with essential hypertension, patients with primary hyperaldosteronism show a 12-fold greater risk of AF (Milliez et al. 2005). A polymorphism of aldosterone synthase gene associated with increased aldosterone activity seems to predispose to clinical AF in patients with congestive heart failure (CHF) (Amir et al. 2008). A small study in 25 patients suggested an up-regulation of mineralocorticoid receptors and 11-β-hydroxysteroid dehydrogenase type 2 (which mediates selectivity of aldosterone binding to mineralocorticoid receptor (Chai and Danser 2006)) in human atrial fibrillation (Pei et al. 2007). In CHF, aldosterone production is increased due to RAAS activation.

Firstly, aldosterone seems to promote inflammation and oxidative stress (Chai and Danser 2006), processes that have been also implicated in atrial remodeling in AF (Korantzopoulos et al. 2003; Issac et al. 2007). Secondly, on ventricular level, increased aldosterone concentration seems to result in myocardial and vascular fibrosis in terms of an adverse ventricular structural remodeling (Struthers et al. 2004). Thus, mineralocorticoid receptor stimulation might be also involved in structural remodeling of the AF substrate associated with CHF (Li et al. 2001). Even independent from CHF, in an experimental study by Zhao et al. (2010), spironolactone treatment prevented myocardial apoptosis, myolysis, atrial fibrosis and dilatation in a dog model of long-term (6 weeks) rapid atrial pacing-induced structural remodeling.

Acting on the assumption of a beneficial effect of aldosterone receptor antagonism on ventricular electrophysiology particularly in congestive heart failure (Pitt et al. 1999, 2003a), effects of a selective MR blockade with eplerenone on inducibility of atrial tachycardias were studied by Shroff et al. (2006) in a canine model of CHF induced by rapid ventricular pacing. As a main result, eplerenone suppressed the inducibility of sustained atrial tachyarrhythmias. In addition, direct impact of eplerenone on atrial electrophysiology was demonstrated for the first time; eplerenone prolonged effective refractory period in some regions of the atrium remodeled by CHF (but not in normal atrium).

Effects of aldosterone and mineralocorticoid receptor antagonism on cardiac ion channels

In principle, it is important to differentiate between genomic and non-genomic actions when discussing effects of aldoster-

one mediated *via* MR (Chai and Danser 2006). Non-genomic effects such as direct pharmacological interaction with ion channels can be observed shortly after drug exposure; for example intravenous administration of aldosterone led to a lengthening of monophasic atrial action potentials in patients with supraventricular arrhythmias within 4–6 minutes (Tillmann et al. 2002). Potentially mediated by direct block of repolarizing potassium currents by spironolactone or its main metabolite canrenoic acid (Caballero et al. 2003; Gomez et al. 2005), spironolactone also prolonged action potential duration in rabbit and rat multicellular preparations (Briggs and Holland 1959; Coraboeuf and Deroubaix 1974). Finally, acute application of canrenoic acid reduced L-type calcium current $I_{Ca,L}$ in ventricular myocytes of male Wistar rats (Costa et al. 2009). Table 1 summarizes the non-genomic effects of aldosterone and MR antagonism on cardiac electrophysiology.

Genomic effects on the ventricular level

In contrast to the non-genomic effects, genomic effects are due to alterations of protein synthesis and can be initially observed after hours. Chronic aldosterone exposition of ventricular myocytes resulted in a prolongation of action potential in mice (Boixel et al. 2006) and rats (Martin-Fernandez et al. 2009). In a transgenic mouse model with conditional cardiac-specific overexpression of human mineralocorticoid receptor, mice exhibited a high rate of death due to life-threatening ventricular arrhythmias. In turn, these arrhythmias were prevented by spironolactone treatment (Ouvrard-Pascaud et al. 2005). Mediated *via* MR, aldosterone induced an upregulation of $I_{Ca,L}$ with no concomitant alterations of its biophysical properties through a specific genomic pathway in cultured adult rat ventricular myocytes (Benitah and Vassort 1999). Furthermore, non-genomic effects of aldosterone on $I_{Ca,L}$ were excluded and co-incubation with spironolactone blunted upregulation of $I_{Ca,L}$, possible effects of spironolactone on the channel´s biophysical properties were not described. Similar effects of aldosterone on current density and, respectively, the missing effect on biophysical properties of $I_{Ca,L}$ were obtained in ventricular neonatal rat cardiomyocytes (Lalevee et al. 2005). Correlation of $I_{Ca,L}$ current density and plasma level of aldosterone was demonstrated

Table 1. Non-genomic effects of aldosterone or MR antagonism on cardiac electrophysiology in various experimental settings

	Atrium	Ventricle	*In vitro*
Briggs et al. 1959	Spironolactone prolongs action potential duration in isolated rabbit atrium.		
Coraboeuf et al. 1974		Spironolactone derivative sodium canrenoic acid prolongs action potential duration in isolated rat ventricle.	
Tillmann et al. 2002	Intravenous administration of aldosterone leads to a lengthening of monophasic action potential in humans.		
Caballero et al. 2003		Aldosterone and canrenoic acid block native $I_{K,r}$ in guinea-pig ventricular myocytes.	Spironolactone and its main metabolite canrenoic acid block human ether-a-go-go-related gene channels in stably transfected Chinese hamster ovary cells.
Gomez et al. 2005			Spironolactone and its main metabolite canrenoic acid block hKv1.5 in stably transfected mouse fibroblasts and, respectively, Kv4.3 and Kv7.1+minK channels in transiently transfected Chinese hamster ovary cells.
Costa et al. 2009		Acute application of canrenoic acid reduces $I_{Ca,L}$ in male Wistar rats ventricular myocytes.	

in a transgenic mouse model *in vivo* (Perrier et al. 2005). In a rat model of hyperaldosteronism of another group, treatment with aldosterone for three weeks also resulted in an upregulation of $I_{Ca,L}$ without changes of the channel's biophysics (Martin-Fernandez et al. 2009). Contrary to these results, a physiological increase in serum aldosterone concentration in response to restriction in sodium intake did not affect $I_{Ca,L}$ in the rat left ventricle *in vivo* (Wagner et al. 2008). Finally, in a rat model of myocardial infarction, long-term (3 weeks) MR antagonism prevented electrical remodeling that precedes cellular hypertrophy after myocardial infarction (Perrier et al. 2004).

Concerning transient outward potassium current I_{to}, aldosterone exposition of ventricular rat myocytes resulted in a reduction of I_{to} without concomitant alterations of its biophysical properties. Aldosterone-induced reduction of I_{to} was prevented by specific MR antagonism, sole effect of MR antagonism on I_{to} was not examined in this study (Benitah et al. 2001). In contrast, the same authors who also reported that a physiological increase in serum aldosterone concentration in response to restriction in sodium intake does not affect $I_{Ca,L}$ also found no alterations of I_{to} (Wagner et al. 2008). Even more complicated seems to be a gender-relation and sex-hormone dependence of I_{to} alteration by aldosterone or MR antagonism: in streptozotocin-induced diabetic rat heart, spironolactone augmented I_{to} in diabetic males (with a concomitant shortening of action potential duration) but had no effect in diabetic female animals. Effects of spironolactone were restored in ovariectomized diabetic females and abolished in orchidectomized diabetic males (Shimoni et al. 2008). Boixel et al. (2006) showed that incubation of isolated adult mouse ventricular myocytes with aldosterone resulted in a significant increase of cardiac sodium current I_{Na} (without alterations of the biophysical properties) which was prevented by co-incubation with spironolactone.

Finally, "funny" current I_f was transcriptionally upregulated *via* MR activation by aldosterone in physiological concentrations in cultured neonatal rat ventricular myocytes resulting in an increase of the rate of spontaneous beating, whereas the effect on I_f was abolished by MR antagonists (Muto et al. 2007).

Genomic effects on the atrial level

In contrast to the comprehensive data on the ventricular level, there are only a few publications on the effect of aldosterone or MR antagonism on the atrial level: besides some *in vitro* data concerning the inhibitory effects of spironolactone and its main metabolite canrenoic acid on human ether-a-go-go-related gene channels (Caballero et al. 2003) or hKv1.5, Kv4.3 and Kv7.1+minK channels (Gomez et al. 2005), the lacking effect of aldosterone exposition on $I_{Ca,L}$ in atrial neonatal rat myocytes (in contrast to effects on ventricular myocytes in the same model) was described (Lalevee et al. 2005). Furthermore, our group showed recently that in a rabbit model of rapid atrial pacing, selective MR antagonism with eplerenone alone does not alter I_{to} but reduces $I_{Ca,L}$ and accordingly expected tachycardia-induced downregulation of $I_{Ca,L}$ does not occur after eplerenone treatment whereas pacing-induced alterations of I_{to} cannot be prevented by this treatment (Laszlo et al. 2010).

Genomic effects of aldosterone and MR antagonism on atrial and ventricular electrophysiology are summarized in Table 2.

Effects of the modulation of oxidative stress by aldosterone or mineralocorticoid receptor antagonism on cardiac ion currents

Recent studies report an association between AF and various endogenous states including oxidative stress and inflammation (Kim et al. 2003; Korantzopoulos et al. 2003, 2007; Lin et al. 2003; Neuman et al. 2007; Van Wagoner 2008). Oxidative stress refers to a situation when formation and bonding of reactive oxygen species is imbalanced. By reacting with macromolecules like lipids, nucleic acids and proteins including ion channels, free radicals provoke fibrosis and inflammation (Korantzopoulos et al. 2007). Aldosterone seems to promote inflammation and oxidative stress (Pitt et al. 2003b; Chai et al. 2006; Cachofeiro et al. 2008) where as in turn, MR antagonism seems to reduce oxidative stress (Korantzopoulos et al. 2004; Shimoni et al. 2008; Lendeckel et al. 2010). Both of these pathophysiological states can affect ion channels, therefore anti-inflammatory effects of MR antagonism or, respectively, its impact on oxidative stress might also alter atrial electrophysiology: reduction of oxidative stress is attended by a reduced activity /expression of NAD(P)H oxidase (Cai et al. 2003) resulting in diminished atrial superoxide concentrations (Takemoto et al. 2001). In turn, this lowers the amount of the oxidized form of glutathione and increases the reduced form. Thus, this shift of cellular redox state might finally alter important cardiac ion currents like transients I_{to} (Rozanski and Xu 2002), $I_{Ca,L}$ (Hool 2008) or I_{Na} (Qu et al. 1994). However, these theoretical considerations have to be confirmed *in vivo*, not only as Wagner et al. (2008) provided evidence that the activation of the MR *per se* depends on the intracellular redox state of cardiac myocytes.

Summary and Conclusion

MR antagonism has been introduced as a new therapeutic principle in "upstream" treatment of AF. Besides

Table 2. Genomic effects of aldosterone or MR antagonism on cardiac electrophysiology in various experimental settings

	Atrium	Ventricle
Benitah et al. 1999		Incubation of adult rat cardiomyocytes with aldosterone upregulates $I_{Ca,L.}$
Benitah et al. 2001		Incubation of rat ventricular myocytes with aldosterone (48 hours) reduces I_{to}, co-incubation with a selective MR antagonist prevents the reduction.
Perrier et al. 2004		In a rat model of myocardial infarction, long term (3 weeks) MR antagonism prevented electrical remodeling that precedes cellular hypertrophy after myocardial infarction.
Lalevee et al. 2005	*In-vitro* stimulation of cultured atrial neonatal rat ventricular cardiomyocytes with aldosterone (24 hours) does not alter $I_{Ca,L}$.	*In-vitro* stimulation of cultured ventricular neonatal rat ventricular cardiomyocytes with aldosterone (24 hours) leads to a substantial increase of $I_{Ca,L}$ (and $I_{Ca,T}$).
Perrier et al. 2005		Blood concentration of aldosterone exerts chronic regulation of $I_{Ca,L}$ in mouse ventricular cardiomyocytes.
Shroff et al. 2006	Selective MR antagonism (5 weeks) prolongs effective refractory period in some regions of the atrium remodeled by CHF but not in normal atrium (canine model of congestive heart failure).	
Boixel et al. 2006		Incubation of adult mice ventricular myocytes with aldosterone (24 hours) prolongs action potential duration and results in a significant increase of I_{Na} (without alterations of the biophysical properties) which in turn is prevented by co-incubation with spironolactone.
Muto et al. 2007		In cultured neonatal rat ventricular myocytes, aldosterone in physiological concentrations increases I_f channel gene expression and the rate of spontaneous beating *via* MR activation. Increase of I_f can be abolished by MR antagonists.
Wagner et al. 2008		Incubation of rat left ventricular myocytes with aldosterone (24 hours) increases $I_{Ca,L}$ *in vitro*. A physiological increase in serum aldosterone concentration in response to restriction in sodium intake does not affect $I_{Ca,L}$, I_{to} and action potential duration in the rat left ventricle *in vivo*.
Shimoni et al. 2008		In streptozotocin-induced diabetic rat heart, spironolactone augments I_{to} in diabetic males (with a concomitant shortening of action potential duration) but has no effect in diabetic female animals.
Martin-Fernandez et al. 2009		Chronic (3 weeks) aldosterone exposition of ventricular myocytes increases $I_{Ca,L}$ and prolongs action potential duration (rat model of hyperaldosteronism).
Laszlo et al. 2010	In a rabbit model of rapid atrial pacing, selective MR antagonism with eplerenone alone does not alter I_{to} but reduces $I_{Ca,L}$ and accordingly expected tachycardia-induced downregulation of $I_{Ca,L}$ does not occur after eplerenone treatment whereas pacing-induced alterations of I_{to} cannot be prevented by this treatment.	

positive effects on structural remodeling, effects of MR antagonism on atrial electrophysiology were described whereas the molecular mechanisms are currently unknown to a large extent. We delineated that the effect of aldosterone and accordingly of MR antagonism on atrial electrophysiology might be mediated, at least partly, by the affection of atrial ion channels or their regulative mechanisms. Summarized, publications concerning

potential mechanisms of modulation of cardiac ion channels by aldosterone and MR antagonism in various experimental settings are almost exclusively limited to the ventricular level and partly, they are also contradictorily. However, translation of data obtained in ventricular myocytes to the atria is problematic because atrial and ventricular electrophysiology in general and, respectively, molecular composition or pharmacological properties of ion channels exhibit remarkable differences (Nattel et al. 2000; Schram et al. 2002; Lalevee et al. 2005; Hatano et al. 2006). Therefore it can be concluded that further research on the "atrial level" is needed in order to clarify the potential impact of the affection of atrial ion channels by aldosterone and accordingly MR antagonism in upstream therapy of AF.

Disclosure information

No potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence this work is being declared.

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