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Decreased sarcolipin protein expression and enhanced sarco(endo)plasmic reticulum Ca^{2+} uptake in human atrial fibrillation

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Abstract

Sarcolipin (SLN), a key regulator of cardiac sarco(endo)plasmic reticulum (SR) Ca^{2+} ATPase, is predominantly expressed in atria and mediates β-adrenergic responses. Studies have shown that SLN mRNA expression is decreased in human chronic atrial fibrillation (AF) and in aortic banded mouse atria; however, SLN protein expression in human atrial pathology and its role in atrial SR Ca^{2+} uptake are not yet elucidated. In the present study, we determined the expression of major SR Ca^{2+} handling proteins in atria of human AF patients and in human and in a mouse model of heart failure (HF). We found that the expression of SR Ca^{2+} uptake and Ca^{2+} release channel proteins are significantly decreased in atria but not in the ventricles of pressure-overload induced HF in mice. In human AF and HF, the expression of SLN protein was significantly decreased; whereas the expressions of other major SR Ca^{2+} handling proteins were not altered. Further, we found that the SR Ca^{2+} uptake was significantly increased in human AF. The selective downregulation of sarcolipin and enhanced SR Ca^{2+} uptake in human AF suggest that SLN downregulation could play an important role in abnormal intracellular Ca^{2+} cycling in atrial pathology.

Keywords

Atrial Fibrillation; Calcium; Heart failure; Sarcolipin; SERCA

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1. Introduction

Sarcolipin (SLN), a 31 amino acid sarco(endo)plasmic reticulum (SR) membrane protein is expressed predominantly in atria [1,2]. Overexpression of SLN in the adult rat ventricular myocytes [3] or in the mouse ventricles [4,5,6] demonstrates that SLN is an inhibitor of cardiac sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA). The inhibitory effect of SLN is independent of phospholamban (PLN) and relieved upon isoproterenol treatment [4,5,6]. Recently, using adenoviral mediated gene expression in adult rat ventricular myocytes; it has been shown that the conserved threonine 5 at the N-terminus of SLN critically regulates SLN function and mediates β-adrenergic responses [7]. Together, these studies suggest that SLN is a key regulator of cardiac SERCA pump and a mediator of β-adrenergic responses.

The expression of SLN both at mRNA and protein levels are shown to be altered in the diseased atrial myocardium [1,8,9]. SLN protein level was found to be increased in atria of canine heart failure (HF) and decreased in atria of ischemic dog hearts [1]. Sarcolipin mRNA levels are decreased in atria of patients with chronic atrial fibrillation (AF) [9] and in pressure-overload mouse models of cardiac hypertrophy [8]. The functional significance of SLN downregulation in atrial Ca^{2+} homeostasis was demonstrated using a gene knockout mouse model [10]. Ablation of SLN selectively increases the atrial SERCA pump activity [10], SR Ca^{2+} load and Ca^{2+} transients, but results in structural and electrical remodeling [11] suggesting that loss of SLN function can cause abnormal intracellular Ca^{2+} cycling and atrial remodeling. However, altered SLN protein expression and its role in atrial Ca^{2+} handling in human atrial pathology are yet to be reported. The present study is, therefore, aimed to determine the SLN protein expression in human AF and HF and how it affects the SR Ca^{2+} uptake in human AF.

2. Materials and Methods

We examined right atrial biopsies obtained from three patients with normal sinus rhythm, three patients with AF and three patients with normal sinus rhythm with HF. All protocols for obtaining human cardiac tissue were approved by the Ethical Committee of the Institut Hospitalier Jacques Cartier, France and were conducted in accordance with the Declaration of Helsinki principles. Informed consent was obtained before cardiac surgery from each patient.

Animals used in this study were 3-4 months old C57/BL6 mice. All animal procedures were performed with the approval of Institute Animal Care and Use Committee (IACUC) in the UMDNJ-Newark campus in accordance with the provision of the animal welfare act, the PHS policy on Human Care and Use of Laboratory Animals.

2.1. Western blot analysis

Total protein extracts from atria and ventricles were used for Western blot analyses using protein-specific antibodies as described earlier [12]. Signals detected by Super Signal WestDura substrate (Pierce) were quantitated by densitometry and then normalized to calsequestrin (CSQ) or sarcomeric α-actin levels.

2.2. SR Ca^{2+} uptake assays

The SR Ca^{2+} uptake was measured by the Millipore filtration technique as described earlier [12]. The rate of SR Ca^{2+} uptake and the Ca^{2+} concentration required for half maximal velocity of Ca^{2+} uptake (EC_{50}) were determined by non-linear curve fitting analysis using Graph Pad PRISM 5.0 software.

2.3. Aortic banding

Pressure-overload in mice was induced by transverse aortic constriction against a 28G needle as described previously [12]. Corresponding sham-operated animals were used as controls. The echocardiography was performed after three weeks of aortic banding as described earlier [12]. The pressures in left ventricle and abdominal aorta were measured simultaneously using two separate 1.4F Millar catheters and the pressure gradients were calculated.

2.4. Statistical Analysis

All data reported as mean± SEM of at least three independent experiments. Statistical analysis was performed with two-tailed ANOVA or Student's *t* test. Significance was assigned at $P<0.05$.

3. Results

3.1. Selective downregulation of SLN in atria from AF and HF patients

Table 1 shows the clinical parameters of three groups of patients (sinus rhythm, AF and HF) studied. Mean age values were not significantly different in all three groups. Data obtained from atrial tissues of patients with normal sinus rhythm (NSR) without HF were used as control and compared to data obtained from AF and HF patients.

To determine the protein expression of various SR Ca^{2+} handling proteins, total protein prepared from atria of patients in NSR, AF and HF was studied by quantitative Western blot analysis. Results shown in Figure 1 point out that the level of SLN protein is significantly decreased both in AF (NSR: 100.0±5.5% *vs.* AF: 53.1±6.5%; P= 0.0053) and in HF (25.1±5.5%; P= 0.0006) atrial tissues compared to NSR patients. The protein levels of SERCA2a, PLN, ryanodine receptor (RyR), calsequestrin (CSQ) and triadin were not significantly different between all three groups of patients. Although PLN protein levels were not altered, PLN phosphorylation at Ser16 was significantly decreased in the atrial tissues of patients with AF (NSR: 100.0±1.0% *vs.* AF: 25.0±%) and HF (11.6±6.0%) compared to NSR controls.

3.2. The SR Ca^{2+} uptake is increased in atria of patients with AF

We next determined the rate as well as the maximum velocity (V_{max}) of SR Ca^{2+} uptake in atria of patients with AF. The rates of Ca^{2+}-dependent Ca^{2+} uptake was significantly increased in atria of patients with AF compared to the samples from NSR controls (Fig. 2). The EC_{50} value for Ca^{2+} uptake was significantly decreased in AF (NSR: 159±10 *vs.* AF: 129±9 nmol/L; $P < 0.05$) indicating an increased Ca^{2+} affinity of the SERCA pump. The V_{max} of Ca^{2+} uptake was also significantly increased (NSR: 135±15 *vs.* AF: 204±8 nmol of Ca^{2+} per mg·min^{-} 1; $P < 0.05$).

3.3. Decreased expression of SR Ca^{2+} handling proteins in atria of mouse model of HF

To determine the expression of SR Ca^{2+} handling proteins in animal models of HF, we studied the expression of major SR Ca^{2+} handling proteins in atria and in the ventricles of pressure-overloaded mice hearts. Pressure-overload was imposed on the mouse heart by transverse aortic banding. After 3 weeks of aortic banding, the left ventricular ejection fraction decreased significantly compared to sham operated control mice (from 75±0.01% to 44±0.02%; N=4; P<0.05) indicating a cardiac dysfunction. The increased ratio of left ventricle (LV) weight to tibia length (from 3.0±0.2 to 4.7±0.6; P<0.05), and lung weight to body weight ratio (from 3.8±0.2 to 10.6±2.6; P<0.05) further confirmed that 3 weeks of aortic banding induced cardiac hypertrophy/heart failure. The left (LA) and right atrial (RA)

weights were also significantly increased in the aortic banded mice (LA: from 4.9±0.7 to 10.8±1.3 mg; RA: from 4.0±0.4 to 8.0±1.5 mg; $P<0.05$)

To determine the expression levels of SR Ca^{2+} handling proteins, we quantitated SERCA2a, SLN, PLN, RyR, CSQ and triadin protein levels in atria and in the ventricles of aortic banded mice. Results in Fig. 3A and 3B show that the expression of all the SR Ca^{2+} handling proteins analyzed were significantly decreased in atria of aortic banded mice. However in the LV of aortic banded mice, the expression of these proteins were not altered compared to the sham-operated controls (Fig. 3C).

4. Discussion

The key findings of the present study are: (i) sarcolipin protein expression is specifically decreased in human atria from AF and HF patients; (ii) the Ca^{2+} sensitivity as well as the V_{max} of SR Ca^{2+} uptake are significantly increased in human atria from AF patients; and (iii) the expression of SR Ca^{2+} handling proteins is significantly decreased in atria but not in the ventricles of mouse models of HF.

Our studies demonstrate that SLN protein expression is selectively downregulated and the SR Ca^{2+} uptake is increased in the atria of AF patients. Our data corroborate the decreased SLN mRNA levels reported in atria of patients with chronic AF [9]. Studies using transgenic mouse models have suggested that unlike PLN, SLN can affect the V_{max} of SR Ca^{2+} uptake. Transgenic overexpression of SLN in the mouse heart has been shown to decrease the V_{max} of SR Ca^{2+} uptake [4]. Whereas, loss of SLN function in atria is associated with an increased Ca^{2+} sensitivity and an increased V_{max} of SR Ca^{2+} uptake [10]. Thus, the increased Ca^{2+} sensitivity and V_{max} of SR Ca^{2+} uptake in human AF could be due to the downregulation of SLN protein. The decreased basal level of PLN phosphorylation in AF and HF may be a compensatory alteration for the loss of SLN function.

Several studies have suggested abnormal Ca^{2+} handling as one of the major causes of atrial remodeling and arrhythmogenesis [13,14,15,16,17,18,19,20,21,22,23,24,25]. The atrial tachycardia remodeling which promotes AF in a goat model causes contractile dysfunction, mainly via Ca^{2+} handling abnormalities [23]. The reduced SR Ca^{2+} load and diastolic Ca^{2+} levels are suggested to cause atrial dilatation and AF in this model [16,20]. Studies from congestive HF dog model susceptible to sustained AF suggest that the increased SR Ca^{2+} load can contribute to the generation of delayed afterdepolarizations (DAD) and triggered activities in atrial myocytes [18]. Similarly, atrial arrhythmias observed during acidosis are associated with an increase in SR Ca^{2+} load [13]. Using a SLN knockout mouse model, we have shown that loss of SLN in atria is associated with increased SR Ca^{2+} load and atrial remodeling [10,11]. Thus, the increased SR Ca^{2+} uptake can cause an increased atrial SR Ca^{2+} load in AF patients. Altogether, these studies suggest that SLN is a key regulator of atrial SERCA pump and its downregulation in AF could lead to an increased SR Ca^{2+} load and contribute to abnormal intracellular Ca^{2+} handling and associated atrial remodeling.

Our studies also demonstrate that the expression pattern of SLN and other SR Ca^{2+} handling proteins in atria of human HF patients is similar to that of AF patients. These data suggest that the selective downregulation of SLN can enhance the SERCA activity and SR Ca^{2+} uptake in atria in HF as observed in AF. On the other hand, in mouse models of cardiac hypertrophy/heart failure, the expression level of all major SR Ca^{2+} handling proteins tested was significantly decreased in atria but not in ventricles. This is in contrast to studies showing a decrease in SERCA levels and SR Ca^{2+} uptake in hypertrophic ventricles [26,27]. Although the reason for this discrepancy is unknown, this could be due to the greater atrial structural remodeling including fibrosis and decreased muscle content in aortic banded mice.

The supportive evidence also came from a recent study which reported that atrial fibroblasts are consistently more reactive than the ventricular fibroblasts and contribute to increased atrial fibrosis during HF [28]. These studies along with our data showing atrial dilatation in aortic banded mice suggest that atria may be more sensitive to pressure-overload than ventricles.

In conclusion, the present study is the first report to demonstrate the decreased levels of SLN protein and its effect on SR Ca^{2+} uptake in human atria of AF patients. Our studies suggest that the specific downregulation of SLN in AF and HF could contribute for the abnormal Ca^{2+} handling and atrial remodeling.

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Abbreviations

AF	atrial fibrillation
CSQ	calsequestrin
HF	heart failure
LV	left ventricle
NSR	normal sinus rhythm
PLN	phospholamban
RA	right atrium
RyR	ryanodine receptor
SERCA	sarco(endo)plasmic reticulum Ca^{2+} ATPase
SLN	sarcolipin
SR	sarco(endo)plasmic reticulum

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Highlights

- Sarcolipin, a key regulator of atrial SERCA pump, is specifically downregulated in human atrial fibrillation and heart failure
- The SR Ca^{2+} uptake is significantly increased in human atria from atrial fibrillation patients
- The expression of SR Ca^{2+} handling proteins is decreased in atria but not in the ventricles of aortic banded mice

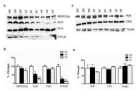

Fig. 1.

Western blot analysis of SR Ca^{2+} uptake (A) and SR Ca^{2+} release (B) proteins in atria of human NSR, AF and HF patients. The fold change in expression levels of these proteins are shown in panel B and D; *n*=3 for each group. The expression level of CSQ was used as a loading control. Asterisks (*) indicate statistically significant differences in SLN levels or PLN phosphorylation in AF or HF samples compared to NSR controls; # from AF. P<0.05.

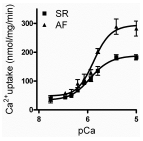

Fig. 2.

SR Ca^{2+} uptake. Ca^{2+}-dependent SR Ca^{2+} uptake assays were performed by using total homogenates from atria of human AF and NSR patients. *n*=3 for each group. The V_{max} of Ca^{2+} uptake was obtained at pCa 6.0.

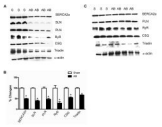

Fig. 3.

Western blot analysis of SR Ca^{2+} handling proteins in atria (Panel A) and in the ventricles (Panel C) of 3 weeks aortic banded and sham-operated control mice. Panel B shows the quantitative analysis of SR Ca^{2+} handling protein levels in atria of 3 weeks aortic banded and sham-operated control mice. The expression level of sarcomeric α-actin was used as control. Asterisks (*) indicate statistically significant differences from sham-operated controls. S-sham-operated; AB- aortic banded. n=4; $P<0.05$.

Table 1

Clinical characteristics of patients

Patient	Cardiac frequency (min^{-1})	Rhythm	RA Size	LA Size	RV Size	LV Size	EF %	Age, Sex	Diagnosis	Kind of surgery	Treatment
NSR	60	SR	Normal	Normal	Normal	Normal	60	72, M		AVS, CABG	
NSR	75	SR	Normal	Normal	Normal	Normal	70	77, M	Aortic stenosis	AVS, CABG	ACE Inhibitors; Diuretics; Statines
NSR	55	SR	Normal	Normal	Normal	Normal-hypertrophic	49-53	86, M	Light mitral insufficiency	CABG	β blockers; Statines
AF	83	cAF	Normal	Dilated	Normal	Normal-hypertrophic	55	75, M	Aortic insufficiency, CAR	AVS, CABG	ACE Inhibitors; Diuretics; β blockers
AF	90	cAF	Normal	Dilated	Normal	Normal-hypertrophic	80	84, M		AVS	Diuretics Digoxine
AF	69	AF	Normal	Normal	Normal	Normal	60	75, M	Light mitral insufficiency	AVS, CABG	β blockers; Statines
HF	67	SR	Normal	Normal	Normal	Normal-hypertrophic	48	77, M	HF, AHT, CAR	AVS, CABG	Diuretics
HF	80	SR	Normal	Normal	Normal	Normal	35-40	61, M	Moderate-grave mitral insufficiency	CABG	β blockers; Statines
HF		SR	Normal	Normal	Normal	Dilated	30	79, M		CABG	Antiarrhythmics

AF, atrial fibrillation; AHT, arterial hypertension; AVS, Aortic valve surgery; CABG, coronary artery bypass graft; cAF, chronic AF; CAR, coronary artery revascularization; EF, ejection fraction; LA, left atrium; LV, left ventricle; NSR, normal sinus rhythm; RA, right atrium; RV, right ventricle.

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