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Ca^{2+} transport and heat production in vesicles derived from the sarcoplasmic reticulum terminal cisternae: Regulation by K^+ ☆

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ABSTRACT

In this work, we compared the effect of K^+ on vesicles derived from the longitudinal (LSR) and terminal cisternae (HSR) of rabbit white muscle. In HSR, K^+ was found to inhibit both the Ca^{2+} accumulation and the heat released during ATP hydrolysis by the Ca^{2+}-ATPase (SERCA1). This was not observed in LSR. Valinomycin abolished the HSR Ca^{2+}-uptake inhibition promoted by physiological K^+ concentrations, but it did not modify the thermogenic activity of the Ca^{2+} pump. The results with HSR are difficult to interpret, assuming that a single K^+ is binding to either the ryanodine channel or to the Ca^{2+}-ATPase. It is suggested that an increase of K^+ in the assay medium alters the interactions among the various proteins found in HSR, thus modifying the properties of both the ryanodine channel and SERCA1.

1. Introduction

In skeletal muscle, the sarcoplasmic reticulum (SR) is the main intracellular Ca^{2+} reservoir. The Ca^{2+} retention in the reticulum is sustained by the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA), an enzyme that pumps Ca^{2+} from the cytosol into the SR lumen using the energy derived from ATP hydrolysis. The SR has two morphologically and functionally distinct regions, the longitudinal tubule and the terminal cisternae. These regions are isolated by differential centrifugation and correspond to the light fraction (LSR) and the heavy fraction (HSR), respectively. The LSR is enriched in Ca^{2+}-ATPase and is derived from the network of membranes that are spread along the myofibrils. The HSR vesicles are derived from the enlarged portion of the reticulum, which is in direct contact with the muscle T-tubules. In addition to the Ca^{2+}-ATPase, HSR contains several intrinsic proteins such as calsequestrin and the ryanodine Ca^{2+} channel [1–7]. The muscle contraction–relaxation cycle is controlled by changes in the sarcoplasmic Ca^{2+} concentration. During depolarization of the cell membrane (action potential), Ca^{2+} is released from HSR through the ryanodine Ca^{2+} channel, thus triggering muscle contraction. At the end of a contraction onset, the SR Ca^{2+}-ATPase drains the Ca^{2+} that was released during excitation back into the reticulum, thus promoting muscle relaxation [3].

The different SERCA isoforms are able to convert the chemical energy released during ATP hydrolysis into either osmotic energy (Ca^{2+} transport) or heat production (thermogenesis). The amount of heat released per mol of ATP cleaved varies depending on the SERCA isoform. The SERCA 1 isoform produces more heat during ATP hydrolysis than the other SERCA isoforms tested so far. SERCA 1 is predominantly found in white skeletal muscle and in brown adipose tissue (BAT). This isoform can hydrolyze ATP through two different catalytic routes, one coupled and the other uncoupled from Ca^{2+} transport. In the coupled route, part of the energy derived from ATP hydrolysis is used for Ca^{2+} translocation across the membrane, and the other part is dissipated as heat. In the uncoupled catalytic route, also known as slippage, there is no Ca^{2+} transport, and all the energy derived from ATP hydrolysis is converted into heat [8–14]. The two routes are represented in the reaction sequence shown in Fig. 1. The uncoupled route is an important source of heat production in both large mammals and adult humans. In hyperthyroidism and cold exposure, two conditions known to affect thermogenesis, SERCA 1 expression is upregulated [12–17].

Several reports have shown that K^+ affects different intermediate steps of the SERCA 1 catalytic cycle [18,19]. In this report, we explore the effect of K^+ on SERCA 1 thermogenic activity. A surprising new finding was that the effect of K^+ varies

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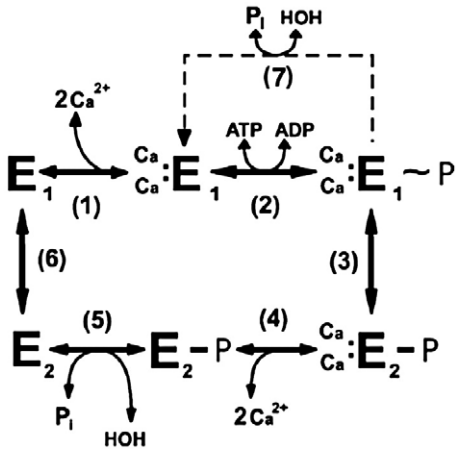

Fig. 1. The catalytic cycle of the Ca^{2+}-ATPase. The sequence includes two distinct enzyme conformations, E_1 and E_2. In the E_1 form, the Ca^{2+} binding sites face the external side of the vesicle, and the enzyme has a high affinity for Ca^{2+} ($K_a = 10^{-6}$ M at pH 7). In the E_2 form, the Ca^{2+} binding sites face the vesicle lumen and have a low affinity for Ca^{2+} ($K_a = 10^{-3}$ M at pH 7). The Ca^{2+} transport involves the phosphorylation by ATP of an aspartyl residue located in the catalytic site to form an acyl phosphate residue of high-energy (reactions 1 to 3) [3]. The translocation of Ca^{2+} across the membrane occurs simultaneously with the conversion of the acyl phosphate from a high- to a low-energy state (reactions 4 to 6) [3]. The increase of Ca^{2+} accumulation in the vesicle lumen promotes reversal of reaction 3, accumulation of the high-energy phosphoenzyme 2Ca:E_1~P, and a decrease in the ATP hydrolysis rate. The inhibition promoted by high intravesicular Ca^{2+} concentration is called "back inhibition." The rise of the intraluminal Ca^{2+} concentration leads to an enhancement of the steady-state level of the acyl phosphate of high-energy (2Ca:E_1~P), which is cleaved before its conversion into low-energy (reaction 7) and thus, before the Ca^{2+} translocation. This reaction is named uncoupled ATPase activity or slippage [8–10,24]. The change of the energy level occurring in reaction 3, i.e., conversion of 2Ca:E_1~P into 2Ca:E_2~P, is promoted by the change of water activity at the catalytic site of the enzyme and of the acyl phosphate residue solvation [10].

depending on the reticulum region in which the enzyme is inserted.

2. Materials and methods

2.1. Preparation of light and heavy SR vesicles

Rabbit hind limb white muscles were dissected from white male rabbits. Vesicles derived from light and heavy sarcoplasmic reticulum were prepared as described in previous reports [20]. Prior to use, vesicles were diluted in a medium containing 50 mM MOPS/Tris buffer, 100 mM KCl, 10 mM P_i, 0.1 mM $CaCl_2$ and 0.1 mM of EGTA to give 4 μM free Ca^{2+}.

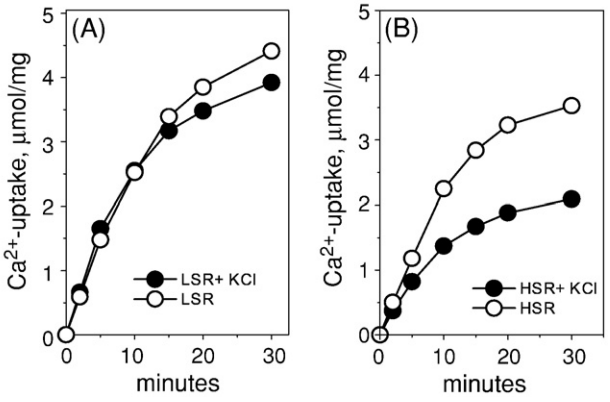

Fig. 2. Effect of KCl (100 mM) on Ca^{2+} uptake. Ca^{2+} uptake in vesicles derived from LSR (A) and HSR fractions (B). The assay medium composition was 50 mM Mops/Tris buffer (pH 7.0), 1 mM ATP, 2 mM $MgCl_2$, 0.1 mM $CaCl_2$, 0.1 mM EGTA, 10 mM Pi, 5 mM NaN_3 and trace amounts of ^{45}Ca. The reaction was performed at 35 °C and was started by the addition of vesicles (5 μg protein/ml). The calculated free Ca^{2+} concentration in the medium was 4 μM. The figures show a representative experiment.

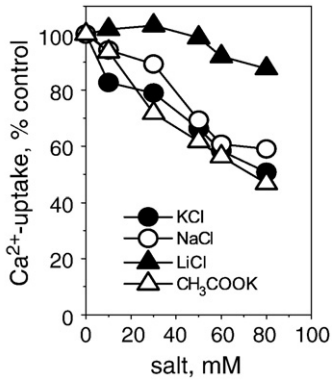

Fig. 3. Effects of LiCl, KCl, NaCl and CH_3COOK on HSR Ca^{2+} uptake. The assay medium composition was the same as the one described in Fig. 2. The incubation time was 20 min at 35 °C. The figure shows a representative experiment.

2.2. Ca^{2+} uptake

Trace amounts of ^{45}Ca were included in the assay medium. The reaction was arrested by filtering samples of the assay medium through Millipore filters [21]. After filtration, the filters were washed 5 times with 5 ml of 3 mM $La(NO_3)_3$, and the radioactivity remaining on the filters was counted using a liquid scintillation counter. The assay medium contained 50 mM MOPS-Tris (pH 7.0), 2 mM $MgCl_2$, 10 mM P_i, 0.1 mM $CaCl_2$, 0.1 mM EGTA, 1 mM ATP, 5 mM NaN_3 and 5–10 μg vesicle protein/ml. The free Ca^{2+} concentration in all experiments was 4 μM. For efflux experiments the vesicles were pre-loaded with calcium, and, after the steady-state was reached, KCl was added at the time indicated by the arrow.

2.3. ATPase activity

ATPase activity was assayed by measuring the release of $^{32}P_i$ from [γ-^{32}P]ATP. The reaction was arrested with trichloroacetic acid (final concentration 5% w/v). The [γ-^{32}P]ATP that was not hydrolyzed during the reaction was extracted with activated charcoal as previously described [22]. Two different ATPase activities can be distinguished in sarcoplasmic reticulum vesicles [3,23]. The Mg^{2+}-dependent activity requires only Mg^{2+} for its activation and is measured in the presence of 5 mM EGTA to remove contaminant Ca^{2+} from the medium. The Ca^{2+}-dependent ATPase activity, which is

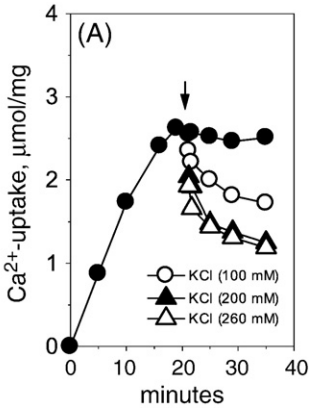

Fig. 4. Modulation of HSR Ca^{2+} efflux by KCl. (A) Effect of increasing KCl concentrations on Ca^{2+}-uptake. KCl was added 20 min after the reaction started (arrow). The assay medium composition was that described in Fig. 2. The figure shows a representative experiment.

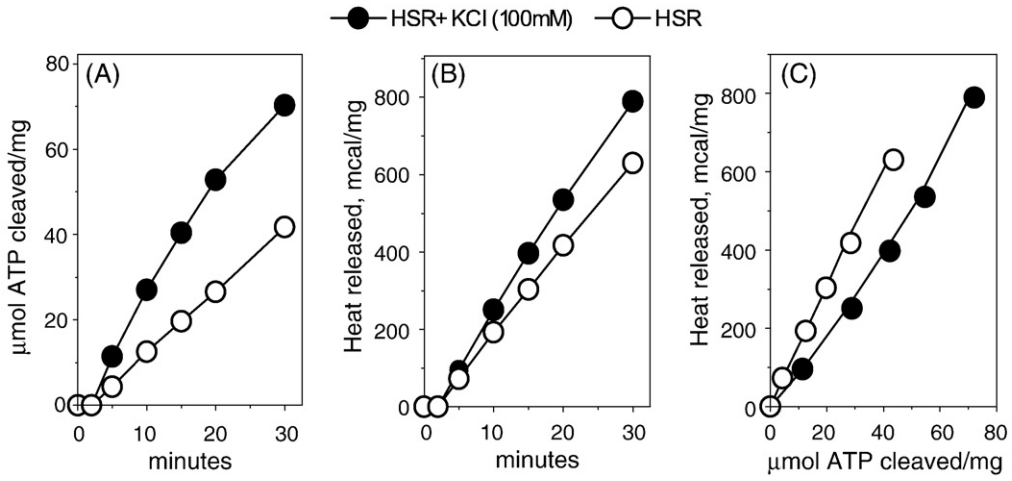

Fig. 5. ATPase activity (A), heat released (B) and correlation between ATPase activity and heat released (C) by HSR. The assay medium composition was that described in Fig. 2. The figures show a representative experiment.

correlated with Ca^{2+} transport, is determined by subtracting the Mg^{2+}-dependent activity from the activity measured in the presence of both Mg^{2+} and Ca^{2+}. In both LSR and HSR, the Mg^{2+} dependent ATPase represents only 5% of the total ATPase activity. In all experiments described in this work, we show the Ca^{2+}-dependent ATPase activity. In order to measure the Ca^{2+}-ATPase activity in permeabilized vesicles A23187 (4 µM) was added to the assay medium.

2.4. Heat of reaction

The heat of reaction was measured using an OMEGA Isothermal Titration Calorimeter from Microcal, Inc. (Northampton, MA). The calorimeter sample cell (1.5 ml) was filled with reaction medium, and the reference cell was filled with Milli-Q water. After equilibration at 35 °C, the reaction was started by injecting vesicles into the sample cell, and the heat change was recorded for 30 min. The volume of vesicle suspension injected into the sample cell varied between 0.02 and 0.03 ml. The heat change measured during the initial 2 min after vesicle injection was discarded in order to avoid artifacts. Such artifacts may include heat derived from the dilution of the vesicle suspension in the reaction medium or binding of ions to the vesicles. The duration of these events is less than one min [8–11]. Calorimetric enthalpy (ΔH^{cal}) was calculated by dividing the amount of heat released by the amount of ATP hydrolyzed. The units used are moles for substrate hydrolyzed and kcal for heat released. Negative values indicate that the reaction was exothermic, and positive values indicate that it was endothermic.

2.5. Experimental procedure

All experiments were performed at 35 °C. In a typical experiment, the assay medium was divided into three samples that were used for the simultaneous measurement of Ca^{2+} uptake, ATP hydrolysis and heat release. The syringe of the calorimeter was filled with vesicles, and the temperature of the syringe was allowed to equilibrate with that of the reaction cell of the calorimeter, a process that usually took between 8 and 12 min. During this time, the vesicles used for measurements of Ca^{2+} uptake and ATP hydrolysis were kept at the same temperature and the same protein dilution as the vesicles in the calorimeter syringe. These different measurements were started simultaneously by adding vesicles to a final concentration of 5 to 10 µg protein/ml. NaN_3 (5 mM), an inhibitor of mitochondrial ATP synthase, was added to the assay medium in order to avoid interference from possible contamination of the sarcoplasmic reticulum vesicles with this enzyme. The free Ca^{2+} concentration in the medium was calculated as previously described [24,25].

3. Results

3.1. Effects of KCl on the SERCA 1 Ca^{2+} uptake

In a recent report [20], we have shown that, in the presence of KCl, white skeletal muscle HSR vesicles accumulated less Ca^{2+} than LSR vesicles. This is confirmed in Fig. 2. We now show that the difference between LSR and HSR vesicles is related to the presence of KCl in the medium. In accordance with previous reports [26,27] using LSR vesicles, both the initial rate of Ca^{2+} uptake and the amount of Ca^{2+} accumulated at steady-state are practically the same in the presence and absence of a physiological (100 mM KCl) monovalent salt concentration (Fig. 2A). However, in HSR, the rate of Ca^{2+} uptake is maximal in the absence of KCl and decreased in the presence of 100 mM KCl (Fig. 2B). Typical experiments are shown in Fig. 2, and the average values of several different experiments are shown in Table 1.

Next we tested if the effect observed was related to the cation (K^+) or the anion (Cl^-) and whether or not the effect of K^+ could be observed with other monovalent cations. KCl and CH_3COOK equally inhibited HSR Ca^{2+} uptake (Fig. 3). Therefore, the inhibition seems to be promoted by the cation and not by the anion. The inhibitory activities of KCl and NaCl were practically the same, whereas LiCl, a non-physiological salt, in concentrations up to 80 mM, did not modify the rate of HSR Ca^{2+} transport (Fig. 3).

3.2. Effect of KCl in Ca^{2+} efflux

The rate of Ca^{2+} accumulation depends on both the rates of Ca^{2+} pumping and Ca^{2+} efflux [10]. Steady-state is reached when the velocity of pumping equals the rate of efflux. Addition of KCl to a HSR suspension promoted a decrease of the steady-state level of Ca^{2+} accumulation (Fig. 4). This decrease was not accompanied by an inhibition of the Ca^{2+}-dependent ATPase activity (Table 1). Surprisingly, the Ca^{2+}-dependent ATPase activity was increased (Table 1) thus indicating that K^+ enhanced the Ca^{2+} efflux without decreasing the ATPase activity.

3.3. Correlation between the rates of ATP hydrolysis and heat production

The thermogenic activity of the Ca^{2+}-ATPase can be evaluated by the ΔH^{cal} of ATP hydrolysis. This is estimated by measuring the amount of heat released during the hydrolysis of each ATP molecule

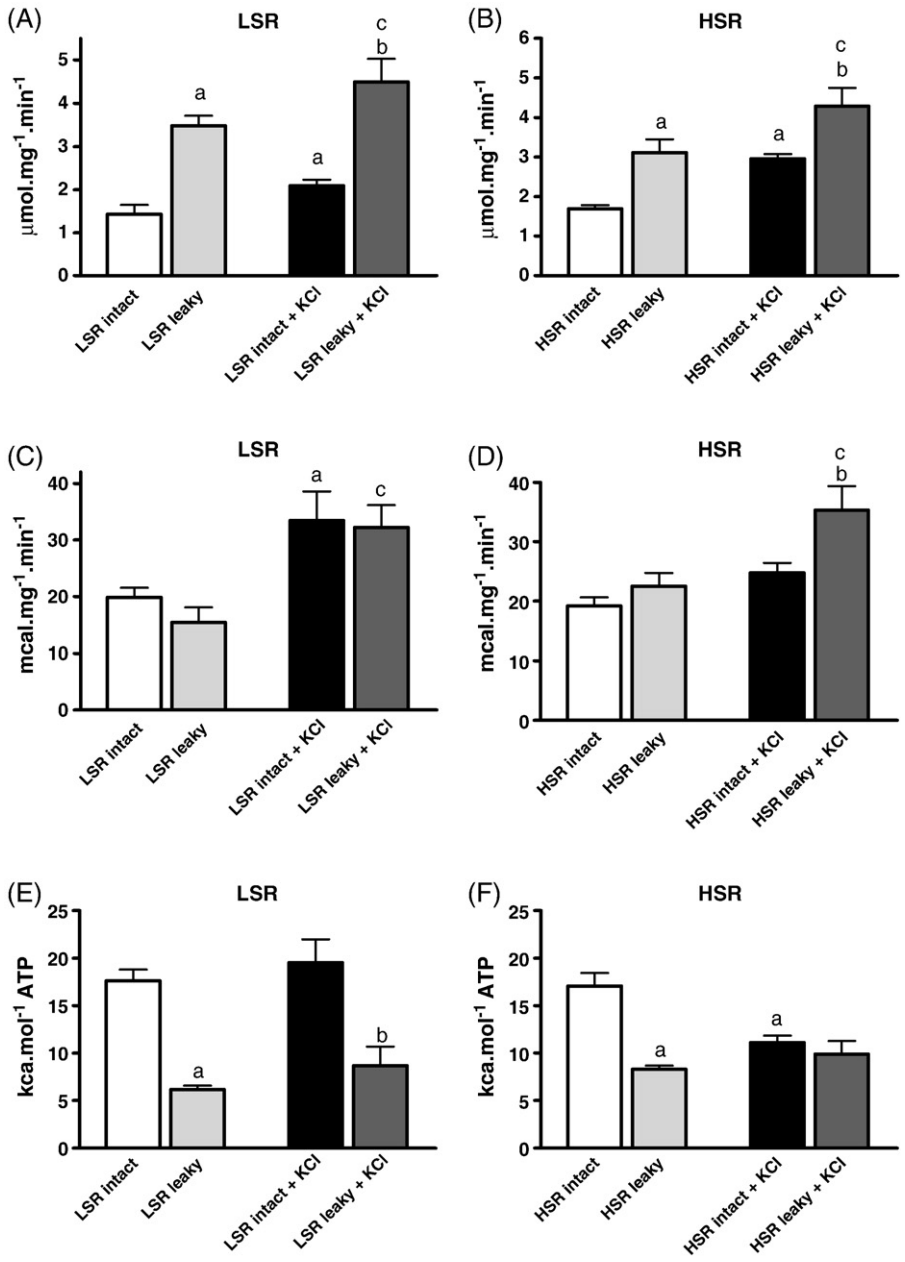

Fig. 6. ATPase activity (A and B), heat released (C and D) and ΔH^{cal} of ATP hydrolysis (E and F) by LSR and HSR. The assay medium composition was that described in Fig. 2; *t*-test $^{a}p<0.05$ compared with intact; $^{b}p<0.05$ compared with intact + KCl; $^{c}p<0.05$ compared with leaky.

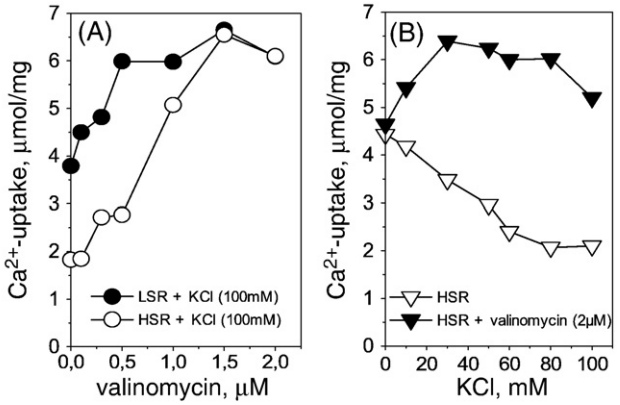

Fig. 7. Effects of valinomycin (2 µM) (A) and KCl (100 mM) (B) on LSR and HSR Ca^{2+} uptake. The assay medium composition was that described in Fig. 2. The incubation time was 20 min at 35 °C. The figures show a representative experiment.

[10]. In early reports, it was shown that: *i*) in leaky LSR vesicles that are not able to accumulate Ca^{2+} during ATP hydrolysis, the amount of heat released per mol of ATP cleaved is about 50% lower than the amount of heat released by intact vesicles that accumulate Ca^{2+} [8] and *ii*) in contrast to LSR, in HSR, the ΔH^{cal} of ATP hydrolysis is not changed by Ca^{2+} accumulation, i.e., it was the same in intact and leaky vesicles [20]. This is confirmed in Table 2. These measurements were all performed in an assay medium containing 100 mM KCl. We now show that, in LSR, the ΔH^{cal} is the same in the presence and absence of KCl. However, in HSR, the removal of K^{+} enhances the thermogenic activity of the Ca^{2+}-ATPase and the ΔH^{cal} reaches the same values as that of LSR (Table 2 and Fig. 5). In HSR, both the rates of ATP hydrolysis (Fig. 5A) and of heat release (Fig. 5B) were decreased when K^{+} was omitted from the assay medium, but the decrease of heat was smaller than the decrease involved in ATP cleavage. As a result, the heat released for each ATP molecule cleaved was enhanced (Table 2 and Fig. 5C), reaching practically the same level as that measured with LSR.

Table 1
Effects of KCl on the rates of Ca^{2+} uptake and ATP hydrolysis.

	ATP hydrolysis (μmol mg^{-1} min^{-1})		Ca^{2+}-uptake (μmol mg^{-1} min^{-1})	
	LSR	HSR	LSR	HSR
100 mM KCl	2.09 ± 0.14 (9)	2.55 ± 0.16[c] (11)	3.77 ± 0.21 (12)	1.94 ± 0.17[d] (20)
Without KCl	1.43 ± 0.22[a] (7)	1.36 ± 0.08[b] (11)	4.09 ± 0.25 (12)	3.33 ± 0.28[b,c] (20)

Assay medium and experimental conditions were as described in Fig. 2. For ATP hydrolysis trace amounts of ^{32}ATP were added instead of ^{45}Ca. Values are means ± SE. The numbers of experiments are in parentheses; *t*-test [a]$p<0.05$ compared with 100 mM KCl; [b]$p<0.001$ compared with 100 mM KCl; [c]$p<0.05$ compared with LSR vesicles; [d]$p<0.001$ compared with LSR vesicles.

This was only observed in vesicles that were able to accumulate Ca^{2+}. In leaky HSR vesicles, the ΔH^{cal} of ATP hydrolysis was not modified by KCl (Table 2). A comparative analysis of the K^+ effect in LSR and HSR vesicles is shown in Fig. 6.

3.4. The effects of valinomycin on Ca^{2+} uptake and heat production

In order to explore whether or not the different responses of LSR and HSR were related to a difference in K^+ permeability of the two vesicles preparations, we tested the effect of the K^+ ionophore valinomycin. Fig. 7A shows that valinomycin enhances the Ca^{2+} accumulation of both LSR and HSR but that the effect is much more pronounced in HSR than in LSR. With 1.5 to 2.0 μM valinomycin, the difference in Ca^{2+} uptake between LSR and HSR was abolished. Fig. 7B shows that valinomycin abolished the Ca^{2+} accumulation inhibition promoted by K^+ in HSR. In three experiments, we measured the ΔH^{cal} of ATP hydrolysis in the presence of 100 mM KCl, with or without 2 μM valinomycin. In HSR, the values found in the presence vs. absence of valinomycin were −11.4 ± 1.5 and −12.9 ± 0.4 kcal/mol ATP cleaved, respectively (Table 3). This result shows that although valinomycin abolished the inhibition of Ca^{2+} uptake, it did not alter the decrease of HSR thermogenic activity that was observed in the presence of 100 mM KCl.

4. Discussion

Ryanodine channels interact with the dihydropyridine receptors (DHPR) and this physical interaction seems to be necessary to the excitation–contraction (E–C) coupling in mammalian skeletal muscles. During the depolarization of the T-tubule, a conformational change in DHPR leads to activation of RyR channel [28]. While the action potential propagates through the T-tubule membrane there is also a change of K^+ and Na^+ concentrations in the narrow tubule T-SR gap junction. The ryanodine channel is located in the SR membrane facing this gap and senses the ionic change just before increasing its Ca^{2+} permeability [29]. Therefore, the variation of Na^+ and K^+ concentration in this region could be important to increase Ca^{2+} efflux trough the terminal cisternae. The ability of K^+ to trigger Ca^{2+} efflux from the HSR was already described in previous studies, but the mechanism by which it occurs is still debated. Different studies have shown that K^+ and Na^+ interact with the ryanodine receptor, enhancing its Ca^{2+} permeability [29,30]. Because the ryanodine receptors are predominantly found in the HSR [20], the K^+ effects on Ca^{2+} efflux could be ascribed to the binding of K^+ to the ryanodine receptor. This, however, does not account for the difference in the thermogenic activity found between the HSR and LSR vesicles. Different reports have shown that K^+ binds to the Ca^{2+}-ATPase and modifies the rate constant of different catalytic cycle intermediary steps [18,19]. In fact, Fig. 6 and Table 1 show that K^+ enhances the ATPase activity of both LSR and HSR. Valinomycin was able to abolish the inhibition of Ca^{2+} uptake promoted by K^+, but it did not change the ΔH^{cal} as observed with the simple addition of K^+. These observations suggest that the effects of K^+ are probably not limited to a single K^+ interaction with either the ryanodine channel or with the Ca^{2+}-ATPase.

In addition to the ryanodine channels and the Ca^{2+}-ATPase, there are several other proteins in HSR vesicles such as calsequestrin, as well as triadin and junctin, two proteins that connect calsequestrin to the ryanodine channel [1–7]. The decrease of both Ca^{2+} uptake and thermogenic activity noted in the HSR may indicate that the rise of K^+ in the assay medium can modify the interaction of the different proteins found in the HSR, and, as a consequence, it can simultaneously modify the properties of both the ryanodine channel and the Ca^{2+}-ATPase.

Finally, the K^+ effects measured do not seem to be related to the K^+ channels because the effects are found to be equally distributed in both HSR and LSR [31].

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Table 2
LSR and HSR: ΔH^{cal} of ATP hydrolysis.

	LSR ΔH^{cal} (kcal mol^{-1})		HSR ΔH^{cal} (kcal mol^{-1})	
	Intact vesicles	Permeabilized vesicles	Intact vesicles	Permeabilized vesicles
100 mM KCl	−19.52 ± 2.47 (6)	−8.68 ± 2.00[a] (4)	−11.11 ± 0.71 (12)	−9.89 ± 1.36 (5)
Without KCl	−17.63 ± 1.15 (5)	−6.16 ± 0.44[b] (4)	−17.08 ± 1.35[c] (15)	−8.28 ± 0.40[a] (6)

Assay medium and experimental conditions were as described in Table 1. Permeabilized vesicles means in the presence of 4 μM of A23187. Values are means ± SE. The number of experiments is shown in parentheses; *t*-test [a]$p<0.02$ compared with intact vesicles; [b]$p<0.001$ compared with intact vesicles; [c]$p<0.001$ compared with 100 mM KCl.

Table 3
Effects of valinomycin on the rates of ATP hydrolysis and Heat Production.

	Heat production mcal mg^{-1} min^{-1}		ATP hydrolysis μmol Pi mg^{-1} min^{-1}		ΔH^{cal} kcal mol^{-1}	
	LSR	HSR	LSR	HSR	LSR	HSR
100 mM KCl	−47.20 ± 2.44 (3)	−33.03 ± 1.55[a,b] (3)	2.30 ± 0.21 (3)	2.61 ± 0.19 (3)	−20.3 ± 1.00 (3)	−12.9 ± 0.40[a] (3)
100 mM KCl + 2 μM valinomycin	−38.90 (2)	−21.65 ± 2.08 (3)	1.96 ± 0.11 (3)	1.92 ± 0.08 (3)	−19.7 (2)	−11.4 ± 1.5 (3)

Assay medium and experimental conditions were as described in Table 1. Values are means ± SE. The number of experiments is shown in parentheses; *t*-test [a]$p<0.01$ compared with LSR; [b]$p<0.01$ compared with HSR in the presence of valinomycin.

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