Stimulation of Na\(^+\)-Ca\(^{2+}\) Exchange in Cardiac Sarcolemmal Vesicles by Phospholipase D*

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Treatment of canine cardiac sarcolemmal vesicles with phospholipase D resulted in a large stimulation (up to 400\%) of Na\(^+\)-Ca\(^{2+}\) exchange activity. The phospholipase D treatment decreased the apparent \(K_{m}\) (Ca\(^{2+}\)) for the initial rate of Na\(^+\)-dependent Ca\(^{2+}\) uptake from 18.2 ± 2.6 to 6.3 ± 0.3 \(\mu\)M. The \(V_{max}\) increased from 18.0 ± 3.6 to 31.5 ± 3.6 nmol of Ca\(^{2+}\)/mg of protein/s. The effect was specific for Na\(^+\)-Ca\(^{2+}\) exchange; other sarcolemmal transport enzymes ((Na\(^+,K\(^{+}\)))-ATPase; ATP-dependent Ca\(^{2+}\) transport) were inhibited by incubation with phospholipase D. Phospholipase D had little effect on the passive Ca\(^{2+}\) permeability of the sarcolemmal vesicles. After treatment with 0.4 unit/ml of phospholipase D (20 min, 37°C), the sarcolemmal content of phosphatidic acid rose from 0.9 ± 0.2 to 8.9 ± 0.4%; simultaneously, Na\(^+\)-Ca\(^{2+}\) exchange activity increased 327 ± 87%. It is probable that the elevated phosphatidic acid level is responsible for the enhanced Na\(^+\)-Ca\(^{2+}\) exchange activity. In a previous study (Philipson, K. D., Frank, J. S., and Nishimoto, A. Y. (1983) J. Biol. Chem. 258, 5905–5910), we hypothesized that negatively charged phospholipids were important in Na\(^+\)-Ca\(^{2+}\) exchange, and the present results are consistent with this hypothesis. Stimulation of Na\(^+\)-Ca\(^{2+}\) exchange by phosphatidic acid may be important in explaining the Ca\(^{2+}\) influx which accompanies the phosphatidylinositol turnover response which occurs in a wide variety of tissues.

A highly active, electrogenic Na\(^+\)-Ca\(^{2+}\) exchange mechanism is present in sarcolemmal vesicles from cardiac muscle (e.g. Refs. 1–9). This Ca\(^{2+}\) transport system may be important in regulating the trans-sarcolemmal fluxes of Ca\(^{2+}\) which accompany each heart beat. Sarcolemmal Na\(^+\)-Ca\(^{2+}\) exchange can be stimulated by membrane potential (2–4), high pH (5), proteinase treatment (6), or calmodulin-dependent phosphorylation (7). In a recent study (8), we found that phospholipase C treatment caused mild stimulation of Na\(^+\)-Ca\(^{2+}\) exchange. We speculated that the negatively charged phospholipids phosphatidylinositol and phosphatidylserine may be especially important in the Na\(^+\)-Ca\(^{2+}\) exchange process. In the present study, we further pursue the relationship between Na\(^+\)-Ca\(^{2+}\) exchange and negatively charged phospholipids through the use of phospholipase D which converts phospholipids to phosphatidic acid. Stiking stimulation of Na\(^+\)-Ca\(^{2+}\) exchange is observed after phospholipase D treatment.

Breakdown of phosphatidylinositol has been correlated with the influx of Ca\(^{2+}\) which accompanies stimulus-response coupling in many tissues (for reviews, see Refs. 10–12). It has been speculated that phosphatidic acid, a breakdown product of phosphatidylinositol, may be involved in the Ca\(^{2+}\) influx response. Our results provide evidence of a stimulatory role for phosphatidic acid in a well defined Ca\(^{2+}\) transport pathway.

MATERIALS AND METHODS

Sarcolemmal vesicles were prepared from canine ventricles as described previously (9). The vesicles used for most of the experiments reported here had the following sarcolemmal marker enzyme activities: K\(^{+}\)-dependent \(p\)-nitrophenyl phosphatase activity was 35.8 ± 2.7 \(\mu\)mol/mg of protein/h and was purified 76.0 ± 8.0-fold as compared with the initial tissue homogenate. The yield of this enzyme was 18.3 ± 2.7%. (Na\(^+,K\(^{+}\)))-ATPase activity was 51.0 ± 5.6 and 140.3 ± 6.2 \(\mu\)mol/mg of protein/h in the absence and presence of amethicin (12.5 \(\mu\)g/ml; donated by Dr. J. E. Grady, The Upjohn Co.), respectively. \(n = 6\) for all data. Further characterization is given in Ref. 9.

Sarcolemmal vesicles (1–3 mg of protein/ml) were treated with phospholipase D by mixing 0.014 ml of Na\(^+\)-loaded vesicles (140 mM NaCl, 10 mM Mops (pH 7.4, 37°C)) with an equal volume of phospholipase D dissolved in the identical medium. Aliquots (0.005 ml) were used directly in Ca\(^{2+}\)-transport experiments after 20 ± 1 min. The phospholipase D (Streptomyces chromofuscus, Calbiochem, La Jolla, CA) activity was 33 IU/ml and the sarcolemmal protein/phospholipase D ratio in most experiments was about 80. Proteinase contamination in the phospholipase D was assessed using a Boehringer Mannheim kit (catalogue no. 582433) which determines the ability of a sample to solubilize a fibrin film; 1.0 IU of phospholipase D had less than 0.004 IU of proteinase activity using trypsin as a standard.

Na\(^+\)-Ca\(^{2+}\) exchange was measured as the initial rate of Na\(^+\)-dependent Ca\(^{2+}\) uptake as described in detail previously (5, 6, 8, 9). Briefly, 0.005 ml of Na\(^+\)-loaded (140 mM NaCl, 10 mM Mops (pH 7.4, 37°C)) sarcolemmal vesicles was rapidly diluted into 0.25 ml of Ca\(^{2+}\) uptake medium containing 140 mM KCl, variable CaC\(_2\), 1.25 \(\mu\)Ci of \(^{45}\)CaCl\(_2\), 0.4 \(\mu\)M valinomycin, 10 mM Mops (pH 7.4, 37°C). After 1.0 or 1.5 ± 0.5 (unless otherwise noted), the Ca\(^{2+}\) uptake was automatically quenched by addition of 0.03 ml of stopping solution. Our usual stopping solution was 140 mM KCI, 1 mM LaCl\(_3\), but we found this stopping solution resulted in unusually high blank values in experiments using phospholipase D-treated sarcolemmal vesicles. Therefore, many of the Ca\(^{2+}\) uptake experiments were quenched using 0.03 ml of 140 mM KCl, 10 mM EGTA followed by the immediate addition of 1.0 ml of ice-cold 140 mM KCl, 1 mM EGTA. The vesicles were then harvested by Millipore filtration (0.45 \(\mu\)m) and washed with two 3-ml aliquots of cold 140 mM KCl, 1 mM EGTA. Qualitatively similar results were obtained with either stoppering technique. Blank values were obtained by using Ca\(^{2+}\) uptake medium which contained 140 mM NaCl instead of KCl. Blank values were subtracted for all data points to correct for superficially bound Ca\(^{2+}\) and Na\(^+\) gradient-independent Ca\(^{2+}\) uptake.

(Na\(^+\))\(^{-}\)-ATPase activity (Fig. 1) was measured over 0.4 min as

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The abbreviations used are: Mops, 4-morpholinepropanesulfonic acid; EGTA, ethylene glycol bis(\(\alpha\)-aminoethyl ether)-N,N,N',N'-tetraacetic acid.

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Fig. 1. Effects of phospholipase D on cardiac sarcolemmal vesicles. The Na⁺-dependent Ca²⁺ influx reaction proceeded for either 1.0 or 1.5 s at [Ca²⁺] = 10 μM. Control values: Na⁺-dependent Ca²⁺ influx = 5.4 ± 0.5 nmol/mg of protein/s (n = 6); (Na⁺,K⁺)-ATPase activity = 94.9 ± 14.3 μmol of Pi/mg of protein/h (n = 4); ATP-dependent Ca²⁺ uptake = 8.6 nmol of Ca²⁺/mg of protein/min (n = 3).

described previously (13). ATP-dependent Ca²⁺ uptake was measured at 37 °C by adding KCl-loaded sarcolemmal vesicles (0.005 ml) to 0.25 ml of medium containing KCl (140 mM), Tris-ATP (1.2 mM), MgCl₂ (1.5 mM), and labeled CaCl₂ (5 μM), and the reaction was stopped at 1 min by Millipore filtration. Blank values obtained in the absence of MgCl₂ and Tris-ATP were subtracted. If the external NaCl was raised to 70 mM after 1 min of ATP-dependent Ca²⁺ uptake, about 85% of the Ca²⁺ would be released over a 1-min period by Na⁺-Ca²⁺ exchange. This property distinguishes the sarcolemmal and sarcoplasmic reticular ATP-dependent Ca²⁺ pumps. Phospholipid analyses were performed as described previously (8). A solvent system containing chloroform:methanol:acetic acid:water (80:13:8:0.3) was used to separate phosphatidic acid (14).

The endogenous Ca²⁺ level in the Ca²⁺ uptake solutions was about 2 μM as determined by a Ca²⁺-selective electrode (Orion). The data shown in Fig. 2 have been corrected for the additional Ca²⁺.

Data are presented as mean ± S.E.

RESULTS

Fig. 1 demonstrates the stimulation of the initial rate of Na⁺-Ca²⁺ exchange activity in canine cardiac sarcolemmal vesicles after phospholipase D pretreatment. In all experiments, Na⁺-Ca²⁺ exchange is measured as Na⁺-dependent Ca²⁺ uptake. At the higher phospholipase D concentrations Na⁺-Ca²⁺ exchange is 4-fold higher than the initial level. The stimulation by phospholipase D is specific for Na⁺-Ca²⁺ exchange. Two other sarcolemmal transport activities, (Na⁺,K⁺)-ATPase and the ATP-dependent Ca²⁺ pump, show moderate or large inhibitions, respectively, after phospholipase D treatment (Fig. 1). The source of the phospholipase D was S. chromofuscus; this enzyme (15) does not require the low pH or high Ca²⁺ concentration required of the more commonly used phospholipase D from peanut or cabbage.

The dependence of Na⁺-Ca²⁺ exchange activity on [Ca²⁺] is changed after exposure of the sarcolemmal vesicles to phospholipase D. Fig. 2 shows a representative experiment in which both the capacity and apparent affinity for Ca²⁺ are increased after enzyme treatment. In a series of five experiments, the Vₘₐₓ of Na⁺-Ca²⁺ exchange was elevated from 18.0 ± 3.6 to 31.5 ± 3.6 nmol of Ca²⁺/mg of protein/s while the apparent Kₐₐᵢₜ for Ca²⁺ decreased from 18.2 ± 2.6 to 6.3 ± 0.3 μM.

The enhanced Na⁺-dependent Ca²⁺ uptake reflects Na⁺-Ca²⁺ exchange activity and is not due to effects of phospholipase D on other transport pathways. The Ca²⁺ taken up by phospholipase D-treated vesicles could be readily released by the addition of the Ca²⁺ ionophore A23187 (0.75 μM). In 1.0 min, 92% of the Ca²⁺ was released by ionophore addition. This indicates that Ca²⁺ had been accumulated against a concentration gradient (using the energy of the Na⁺ gradient) and that phosphatidic acid was not acting primarily as a Ca²⁺ ionophore to enhance passive Ca²⁺ influx. Likewise, if monensin (2 μM) was used to dissipate the Na⁺ gradient obtained by diluting Na⁺-loaded vesicles into KCl medium, the Na⁺-dependent Ca²⁺ uptake activity could be eliminated (in both control and phospholipase D-treated vesicles). This demonstrates that the observed Ca²⁺ transport activity was dependent upon the presence of an outwardly directed Na⁺ gradient. In all Na⁺-Ca²⁺ exchange experiments, valinomycin (0.4 μM) was included in the Ca²⁺ uptake medium to maintain an inside-positive membrane potential for maximal Na⁺-dependent Ca²⁺ uptake activity (4). Thus, the effects of phospholipase D were due to direct stimulation of Na⁺-Ca²⁺ exchange and were not due to effects on sarcolemmal membrane potential. In fact, the stimulatory effects of phospholipase D on Na⁺-Ca²⁺ exchange were evident even in the absence of valinomycin or if sucrose or choline chloride were used in the Ca²⁺ uptake medium instead of KCl.

In the experiments described above, sarcolemmal vesicles were preincubated with phospholipase D and this mixture was then used directly in Na⁺-Ca²⁺ exchange experiments (see "Materials and Methods"). Thus, the phospholipase D and any soluble hydrolysis products were present during the brief period of the Ca²⁺ uptake reaction and may have affected the measurement. Since the vesicles are diluted 50-fold to initiate
the Ca\(^{2+}\) transport, the concentrations of these substances would be very low in the final uptake medium. Control experiments were run in which control and phospholipase D-treated (0.4 unit/ml) vesicles were diluted and pelleted by centrifugation to remove the phospholipase D. After resuspension, the vesicles which had been exposed to phospholipase D had Na\(^{+}\)-Ca\(^{2+}\) exchange activity which was 325% of control levels. This demonstrates that the stimulated exchange was due to a membrane-bound product of phospholipase D hydrolysis.

The preparation of cardiac sarcolemmal vesicles contains a mixture of inside-out and right-side-out vesicles (9). We tested whether the phospholipase D treatment was preferentially stimulating the Na\(^{+}\)-Ca\(^{2+}\) exchange of one type of sarcolemmal vesicle using our published technique (9) for examining the exchange of inside-out vesicles only. We found (not shown) that the inside-out vesicles and the total population (inside-out plus right-side-out vesicles) were stimulated to equal extents by phospholipase D treatment. Apparently, both the inside-out and right-side-out sarcolemmal vesicles are susceptible to and responsive to phospholipase D treatment.

Since phosphatidic acid has been reported to act as a Ca\(^{2+}\) ionophore (16-23), we examined the effects of phospholipase D treatment on the passive Ca\(^{2+}\) permeability of the sarcolemmal vesicles. Control or phospholipase D-treated vesicles were first loaded with Ca\(^{2+}\) by Na\(^{+}\)-dependent Ca\(^{2+}\) uptake. EGTA was added after 30 s to inhibit further Ca\(^{2+}\) uptake and the slow loss of Ca\(^{2+}\) from the vesicles was a measure of the passive Ca\(^{2+}\) permeability. As shown in Fig. 3, there was little change in passive Ca\(^{2+}\) flux after phospholipase D treatment.

We observe a large stimulation of Na\(^{+}\)-Ca\(^{2+}\) exchange activity when the initial rate of Na\(^{+}\)-dependent Ca\(^{2+}\) uptake is measured over 1.0 or 1.5 s (Figs. 1 and 2). The magnitude of the stimulation decreases with time and after 30 s of Ca\(^{2+}\) uptake only a moderate stimulation is noted. This explains why the Ca\(^{2+}\) content of the phospholipase D-treated vesicles (loaded with Ca\(^{2+}\) by 30 s of Na\(^{+}\)-Ca\(^{2+}\) exchange) in Fig. 3 is only about 50% above the level of the control vesicles.

We analyzed the sarcolemmal membrane by thin layer chromatography using a solvent system which separated the phospholipids into three spots representing phosphatidic acid, phosphatidylethanolamine, and a combination of the other sarcolemmal phospholipids (phosphatidylinositol, phosphatidylserine, and sphingomyelin). After phospholipase D treatment (0.4 unit/ml), the vesicle phosphatidic acid level increased from 0.9 ± 0.2 to 8.9 ± 0.4% (n = 4) of the total phospholipid content. In these same sarcolemmal samples, the initial rate of Na\(^{+}\)-Ca\(^{2+}\) exchange rose 327 ± 78% after enzyme treatment. The phospholipid contents of both of the two other phospholipid spots decreased by about equal percentages. The normal phospholipid composition of the vesicles is given in Ref. 8. One incidental finding was that the sarcolemmal membranes apparently possess a phosphatidic acid phosphatase activity. After phospholipase D treatment, the total phospholipid content of vesicles was slightly diminished. This decrease could be largely accounted for by the appearance of inorganic phosphate. Evidently, some of the phosphatidic acid produced by the phospholipase D was being hydrolyzed by the sarcolemma to diacylglycerol. If exogenous phosphatidic acid was added to sarcolemmal vesicles, inorganic phosphate would rapidly appear in the medium consistent with this interpretation. Plasma membrane phosphatidic acid phosphatase has been described in other systems (24) and will be the object of a separate study.

Thin section electron microscopy (courtesy of Dr. J. S. Frank, Department of Medicine, UCLA) of phospholipase D (0.4 unit/ml)-treated vesicles did not reveal morphological damage such as that seen after phospholipase C treatment (8).

**DISCUSSION**

We have demonstrated that phospholipase D pretreatment causes a large stimulation in the initial rate of Na\(^{+}\)-Ca\(^{2+}\) exchange in cardiac sarcolemmal vesicles. The stimulation is specific for Na\(^{+}\)-Ca\(^{2+}\) exchange; we observe no stimulation of other sarcolemmal ion transport enzymes (Fig. 1). The phospholipase D increases both the capacity and Ca\(^{2+}\) affinity of the exchange mechanism (Fig. 2). The enhanced Ca\(^{2+}\) uptake is Na\(^{+}\) gradient-dependent and results in the formation of an outwardly directed Ca\(^{2+}\) gradient. This eliminates the possibility that the phospholipase D-induced increase in Ca\(^{2+}\) uptake is due to an ionophoretic action (16-23) of phosphatidic acid. Although a small increase in passive Ca\(^{2+}\) flux may be occurring (Fig. 3), this is not the dominant effect of phospholipase D in our system.

It is most likely that the phosphatidic acid produced by phospholipase D is responsible for the stimulation of the Na\(^{+}\)-Ca\(^{2+}\) exchange. Stimulation persists after soluble hydrolysis products are removed by centrifugation. Large stimulation of Na\(^{+}\)-Ca\(^{2+}\) exchange is apparent when about 8% of the sarcolemmal phospholipid is phosphatidic acid.

In a recent study (8), we found that phospholipase C (which produces diacylglycerol) caused moderate stimulation (20-80%) of sarcolemmal Na\(^{+}\)-Ca\(^{2+}\) exchange. Since the negatively charged phospholipids phosphatidylserine and phosphatidylinositol were little affected by this enzyme, their relative sarcolemmal content (per cent of total phospholipid) increased after phospholipase C treatment. We speculated that negatively charged phospholipids could enhance Na\(^{+}\)-Ca\(^{2+}\) exchange activity. The present results demonstrate in a much more direct manner the stimulation of Na\(^{+}\)-Ca\(^{2+}\) exchange by a negatively charged phospholipid. Perhaps phosphatidic acid associates with the Na\(^{+}\)-Ca\(^{2+}\) exchange protein and increases

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**Fig. 3. Passive efflux of Ca\(^{2+}\) from control and phospholipase D-treated sarcolemmal vesicles.** NaCl-loaded vesicles were first preincubated for 20 min at 37 °C in the presence and absence of phospholipase D (0.4 unit/ml). To load the vesicles with Ca\(^{2+}\), Na\(^{+}\)-dependent Ca\(^{2+}\) uptake, 0.005 ml of this mixture were diluted to 0.25 ml with KCl (or NaCl for blanks) medium containing 10 mM 46Ca and 0.4 mM valinomycin. To initiate passive Ca\(^{2+}\) efflux, the vesicles were diluted a second time after 30 s by the addition of 0.75 ml of 140 mM KCl, 10 mM Mops (pH 7.4, 37 °C) containing 0.1 mM EGTA. At the times indicated, 1.0 ml of ice cold 140 mM KCl, 1.0 mM EGTA was added, and the vesicles were immediately filtered.
the availability of Ca\(^{2+}\) for exchange. 

Increased turnover of plasma membrane phosphatidylinositol is associated with a large number of stimulus-response coupling mechanisms involving receptors which control Ca\(^{2+}\) influx (for reviews, see Refs. 10–12). A prevalent finding is that the phosphatidylinositol is hydrolyzed to diacylglycerol which is phosphorylated to phosphatidic acid. It has been hypothesized that it is the phosphatidic acid which is responsible for the Ca\(^{2+}\) influx. The hypothesis is primarily based on results which show that phosphatidic acid can act as a Ca\(^{2+}\) ionophore in model systems (16, 22, 23). Evidence has also accrued that phosphatidate can increase Ca\(^{2+}\) influx into intact cells from several tissues (18–21). The implication in the cellular systems is that, by analogy, the phosphatidic acid is again acting as a Ca\(^{2+}\) ionophore. There is no strong evidence, however, to support this assertion. An alternative explanation is that phosphatidate mobilizes cellular Ca\(^{2+}\) influx by activation of plasma membrane Na\(^{+}\)-Ca\(^{2+}\) exchange. 

Na\(^{+}\)-Ca\(^{2+}\) exchange activity has been reported in plasma membrane vesicles from an increasing number of tissues and may be widespread (e.g. Refs. 25–28). Electrogenic Na\(^{+}\)-Ca\(^{2+}\) exchange can transport Ca\(^{2+}\) in both directions across the plasma membrane. Whether stimulation of Na\(^{+}\)-Ca\(^{2+}\) exchange will result in a net influx or efflux of Ca\(^{2+}\) will be a function of the intracellular Na\(^{+}\) and Ca\(^{2+}\) levels and of the membrane potential. Thus, another possibility is that phosphatidate-stimulated Na\(^{+}\)-Ca\(^{2+}\) exchange may be important in returning elevated cellular Ca\(^{2+}\) to its normal level following the "phosphatidylinositol response."

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