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Drug-induced calcium release from heavy sarcoplasmic reticulum of skeletal muscle

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Calcium release from isolated heavy sarcoplasmic reticulum of rabbit skeletal muscle by several calmodulin antagonistic drugs was measured spectrophotometrically with arsenazo III and compared with the properties of the caffeine-induced calcium release. Trifluoperazine and W7 (about 500 μM) released all actively accumulated calcium (half-maximum release at 129 μM and 98 μM, respectively) in the presence 0.5 mM $MgCl_2$ and 1 mg/ml sarcoplasmic reticulum protein; calmidazolium (100 μM) and compound 48/80 (70 μg/ml) released maximally 30–40% calcium, whilst bepridil (100 μM) and felodipin (50 μM) with calmodulin antagonistic strength similar to trifluoperazine (determined by inhibition of the calcium, calmodulin-dependent protein kinase of cardiac sarcoplasmic reticulum) did not cause a detectable calcium release, indicating that this drug-induced calcium release is not due to the calmodulin antagonistic properties of the tested drugs. Calcium release of trifluoperazine, W7 and compound 48/80 and that of caffeine was inhibited by similar concentrations of magnesium (half-inhibition 1.4–4.2 mM compared with 0.97 mM for caffeine) and ruthenium red (half-inhibition for trifluoperazine, W7 and compound 48/80 was 0.22 μM, 0.08 μM and 0.63 μg/ml, respectively, compared with 0.13 μM for caffeine), suggesting that this drug-induced calcium release occurs via the calcium-gated calcium channel of sarcoplasmic reticulum stimulated by caffeine or channels with similar properties.

Introduction

Calcium release from sarcoplasmic reticulum has been observed with a variety of drugs [1] such as quinidine [2], local anesthetics [3,4], tetraphenylboron [5,6], quercetin [7,8], ryanodine [9–13] and also by drugs with calmodulin antagonistic properties such as trifluoperazine [14,15], compound 48/80 [14,15], calmidazolium [15,16] and W7 [17].

Since it was recently reported that calmodulin inhibits the rate of the calcium-induced calcium release and calcium release induced by the ATP analog p[CH_2]ppA [16], which both occur via the calcium-gated calcium channel of heavy sarcoplasmic reticulum [7,10,18–21] we have investigated whether the calcium release induced by various drugs with calmodulin antagonistic properties might be due to their effect on calmodulin and/or on the calcium release channel of heavy sarcoplasmic reticulum. The relative calmodulin antagonistic potency of the tested drugs was examined for convenience by measuring the inhibition

Abbreviations: W7, *N*-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide; p[CH_2]ppA, adenosine 5′-[β,γ-methylene]triphosphate.

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of phospholamban phosphorylation of cardiac sarcoplasmic reticulum [22,23].

Caffeine-induced calcium release [24–28] or choline influx [29,30] occur via the identical calcium release channel as the calcium-induced calcium release [18,29,30], due to an increase in calcium affinity at the calcium receptor site of the channel [26]. For this reason calcium release from heavy sarcoplasmic reticulum of skeletal muscle by calmodulin antagonists was compared with the known properties of the caffeine-induced calcium release.

Materials and Methods

Reagents

Arsenazo III, ATP, Mops, caffeine, compound 48/80, W7, procaine, ruthenium red, ATP were purchased from Sigma Chemical Co. (St. Louis); calmidazolium was purchased from Janssen Pharmaceutica (Beerse), bepridil from Thiemann GmbH (Luenen), trifluoperazine was a gift from Smith & Kline French (Vienna), felodipin was a gift from Hässle AB (Stockholm).

Preparation of sacroplasmic reticulum and calmodulin

Heavy sarcoplasmic reticulum vesicles from rabbit skeletal muscle were prepared according to Kasai et al. [18]. Briefly, white back and leg muscle (fast twitch muscle) were put through a meat grinder and homogenized in a Waring blender for 3 min in a medium containing 5 mM histidine buffer (pH 7.0), 5 mM NaN_3, 100 mM NaCl, and centrifuged for 30 min at $4000 \times g$. The supernatant was filtered through cheese cloth and centrifuged for 30 min at $10000 \times g$. The pellet was resuspended in 5 mM histidine buffer (pH 7.0), 5 mM NaN_3, 0.6 M KCl and centrifuged for 30 min at $100000 \times g$. The pellet was washed once in the same medium, except that the concentration of KCl was 0.1 M, centrifuged again for 30 min at $100000 \times g$, resuspended in 5 mM histidine buffer (pH 7.0), 5 mM NaN_3, 0.1 M KCl and stored at $-70\,^{\circ}C$.

Sarcoplasmic reticulum vesicles from hearts of mongrel dogs were prepared as described previously [31].

Calmodulin from bovine brain (obtained from the slaughter-house) was prepared by Phenyl-Sepharose affinity chromatography [32] as described previously [33].

Analyses

Calcium uptake and drug-induced calcium release. Calcium uptake was carried out in a medium containing 20 mM Mops-Tris (pH 7.0), 5 mM NaN_3, 10 mM sucrose, 40 mM KCl, 100 μM arsenazo III, 20 μM added $CaCl_2$, 4 mM phospho*enol*pyruvate, 40 μg/ml pyruvate kinase, 0.25–10 mM $MgCl_2$, 0.25 mM ATP and 0.25–3 mg/ml sarcoplasmic reticulum protein. Calcium uptake was started by addition of ATP. Calcium release was started by injection of the drug into the cuvette (1×1 cm) by a Hamilton syringe in a volume ranging from 1 to maximally 5% of the uptake medium. All reactions were performed at $25\,^{\circ}C$, pH 7.0. Ruthenium red was added 3 min, and drugs 5 min after starting calcium uptake with ATP. Alterations in absorption were monitored by a dual-wavelength spectrophotometer (Sigma ZWS II) at wavelength pairs of 675 nm and 685 nm [34], as described previously [23].

Rates of calcium release were determined by stopped-flow with the Sigma ZWS II spectrophotometer at the same wavelength pairs. Syringes I and II: 20 mM Mops-Tris (pH 7.0), 5 mM NaN_3, 10 mM sucrose, 40 mM KCl, 100 μM arsenazo III, 4 mM phospho*enol*pyruvate, 40 μg/ml pyruvate kinase, 0.5 mM $MgCl_2$; Syringe I contained in addition 40 μM added $CaCl_2$, 0.5 mM ATP, 2 mg/ml sarcoplasmic reticulum; Syringe II contained the drugs in addition. The contents of syringes I and II were mixed in the ratio 1 : 1. The drug-induced release was started 3 min after starting the uptake with ATP.

The contaminating calcium in the medium with or without sarcoplasmic reticulum was determined by titration in the presence of arsenazo III, calibrated by addition of known amounts of calcium plus chelation of calcium by EGTA. Contaminating calcium amounted to 5–6 μM in the complete medium without protein and to about 15 μM in the presence of 1 mg/ml sarcoplasmic reticulum. The total calcium in the calcium uptake medium with 1 mg/ml sarcoplasmic reticulum was therefore about 35 μM (20 μM calcium added plus 15 μM calcium as contaminant).

Calcium-, calmodulin-dependent phosphorylation of cardiac sarcoplasmic reticulum was carried out as described previously [23,35,36] for 3 min in a medium containing 182 mM Mops, 5 mM NaN_3, 10 mM NaF, 2 mM $CaCl_2$, 2 mM EGTA, 2.04 mM $MgCl_2$, 1.07 mM [^{32}P]ATP, 20 μM calmodulin, 0.2 mg/ml sarcoplasmic reticulum protein (25 °C; pH 7.0) without or with various concentrations of the tested drugs. Drugs were dissolved in dimethylsulfoxide (final concentration in the incubation medium was 2% with or without drugs).

Protein was measured by the Folin method [37] standardized against bovine serum albumin.

Calculations

The theoretical curves of the stopped-flow experiments were calculated by fitting one- or two-exponential functions to the experimental data using an interative, non-linear least-squares procedure as described elsewhere [38].

Results

Drug-induced calcium release

Fig. 1 shows typical experiments on calcium uptake by sarcoplasmic reticulum vesicles (measured with arsenazo III in the presence of 0.5 mM magnesium, 0.25 mM ATP, phospho*enol*pyruvate plus pyruvate kinase as an ATP regenerating system, 1 mg sarcoplasmic reticulum/ml and release of calcium by the calmodulin antagonists trifluoperazine, W7, calmidazolium and compound 48/80. Maximum calcium uptake is obtained in about 2–2.5 min and the release of calcium was started at 3 min by injection of the drugs into the cuvette with a Hamilton syringe under vigorous stirring.

Trifluoperazine and W7 released the actively accumulated calcium completely at high drug concentrations and low magnesium concentration (0.5 mM), and half maximum calcium release was obtained at 129 and 98 μM with trifluoperazine and W7, respectively (Fig. 2). The maximum calcium release obtained in the presence of 0.5 mM magnesium was less with calmidazolium (approx. 40% at 100 μM) and compound 48/80 (approx. 30% at 70 μg/ml) than with trifluoperazine or W7 (Figs. 1 and 2). Higher concentrations of calmidazolium

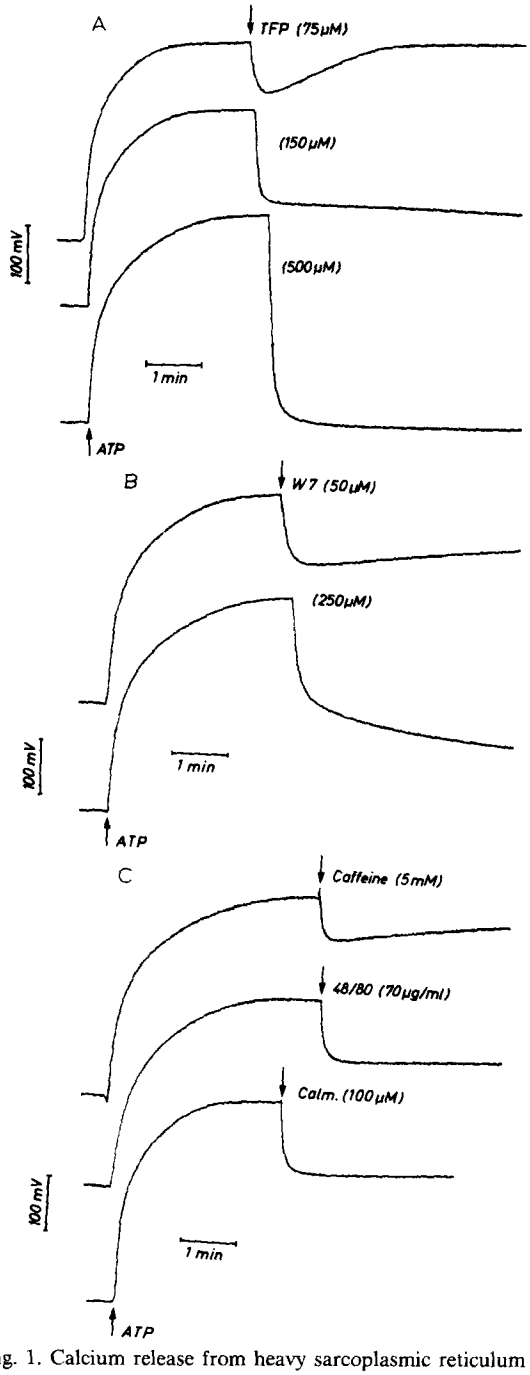

Fig. 1. Calcium release from heavy sarcoplasmic reticulum by trifluoperazine, W7, compound 48/80, calmidazolium and caffeine. Calcium uptake: 20 mM Mops-Tris (pH 7.0), 5 mM NaN_3, 10 mM sucrose, 40 mM KCl, 4 mM phospho*enol*pyruvate, 40 μg/ml pyruvate kinase, 0.5 mM $MgCl_2$, 0.25 mM ATP, 1.0 mg/ml sarcoplasmic reticulum, 100 μM arsenazo III, 35 μM total calcium (20 μM added plus about 15 μM present as contaminant); 25 °C. Calcium release was started by addition of the drugs at concentrations indicated.

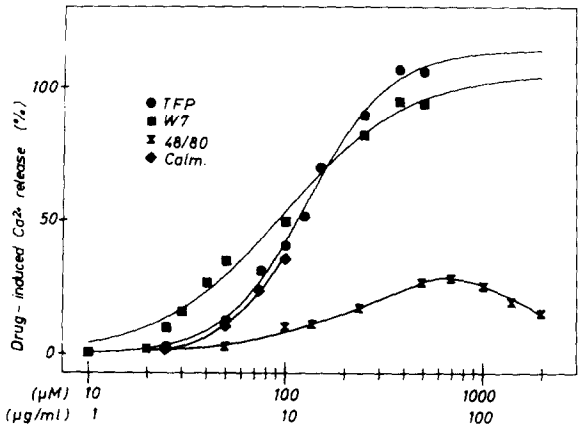

Fig. 2. Concentration dependence of drug-induced calcium release from heavy sarcoplasmic reticulum. Calcium uptake was carried out as given in Fig. 1. Drugs were added 2.5–3.5 min after the uptake was started with ATP at the indicated concentrations (μM: trifluoperazine, W7, calmidazolium (calm.); μg/ml: compound 48/80). The Hill equation was fitted to the trifluoperazine and W7 data. Curves for compound 48/80 and calmidazolium (calm.) were fitted by eye. Values are means of two experiments with different sarcoplasmic reticulum preparations.

could not be tested because of the low solubility of the drug in an aqueous medium; concentrations of compound 48/80 higher than 80–100 μg/ml led to a decrease in the amount of released calcium (Fig. 2).

The drug concentration required to release calcium depends not only on the magnesium concentration in the medium, but also essentially on the sarcoplasmic reticulum protein concentration used in the release experiments. 125 μM trifluoperazine, which release about 50% of accumulated calcium in the presence of 1 mg/ml sarcoplasmic reticulum protein and 0.5 mM magnesium, released 75–80% of the load at 0.25 mg/ml sarcoplasmic reticulum, but almost zero at 3 mg/ml sarcoplasmic reticulum; similarly, 100 μM calmidazolium released about 80% of the calcium load at a low protein concentration of 0.25 mg/ml compared with about 40–50% at 1 mg/ml. This finding indicates that the lipophilic drugs are unspecifically bound to the sarcoplasmic reticulum membranes.

Calcium release from sarcoplasmic reticulum by other drugs with calmodulin-antagonistic properties was small or absent when carried out under conditions given in Fig. 1, i.e. in the presence of 0.5 mM magnesium: A single injection of prenylamine (250 μM) released less than 10% of the calcium load. Felodipin (50 μM) and bepridil (100 μM) failed to release calcium at concentrations which were soluble in 0.5–2% (v/v) DMSO (final concentration).

Repeated addition of felodipin (50 μM and twice 100 μM at 1 min intervals after completion of calcium uptake) in the presence of 0.5 or 0.25 mM magnesium gave a small release which was less than 10% of the calcium load; repeated addition of bepridil (three times 100 μM at approximately 1 min intervals after completion of calcium uptake) gave a small release, which was also less than 10% of the calcium load.

The above results apply to sarcoplasmic reticulum vesicles stored at −70 °C and thawed only once. No alteration in drug-induced calcium release was observed over a period of weeks. On the other hand, when vesicles kept initially at −70 °C were stored for 24 h at −20 °C drug-induced release was obtained at considerably lower trifluoperazine and W7 concentrations, demonstrating that storage conditions affect the drug-induced calcium release.

The rate of calcium release by trifluoperazine, W7 and caffeine was determined by stopped-flow measurements with arsenazo III and in the presence of 0.5 mM magnesium (Fig. 3). Calcium uptake was carried out for 3 min in Syringe 1 and calcium release was started by mixing with the drug from the second syringe. A transient release of calcium was obtained at low drug concentrations. High concentrations of trifluoperazine and W7 (500 μM) resulted in a biphasic calcium release, which was not complete within the 50 s sampling time. The apparent rates for the two phases of calcium release with 500 μM trifluoperazine were 0.73 s^{-1} and 0.03 s^{-1}; and 0.71 and 0.07 s^{-1}, respectively, with 500 μM W7. When 500 μM trifluoperazine or W7 was added to the medium before ATP no calcium accumulation was observed. Calcium uptake and calcium dependent ATPase should be nearly completely inhibited by this high trifluoperazine concentrations [39]. 0.1 mM chlorpromazine inhibits calcium uptake and Ca^{2+}-ATPase 70–75% [40]. The rate of calcium release by trifluoperazine under these conditions

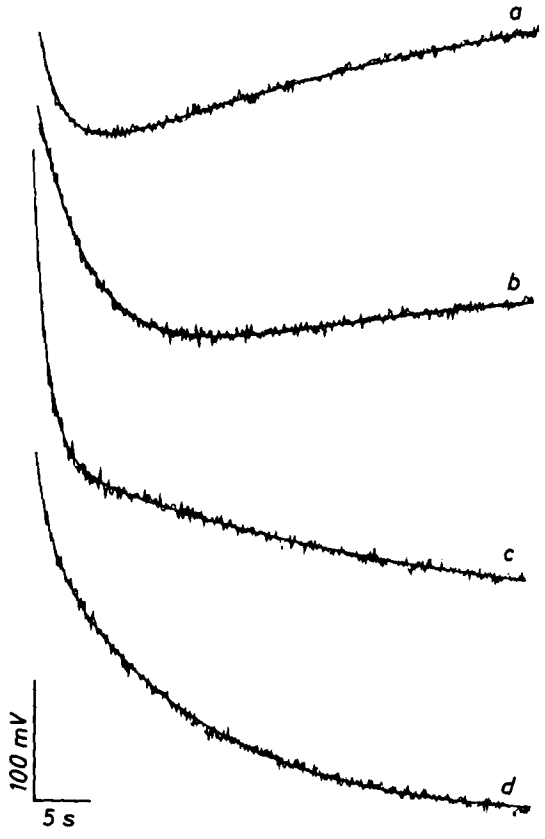

Fig. 3. Rates of calcium release by trifluoperazine, W7 and caffeine from heavy sarcoplasmic reticulum measured by stopped-flow spectrophotometry. Conditions are given in Materials and Methods. (a) 5 mM caffeine; (b) 125 μM trifluoperazine; (c) 500 μM trifluoperazine; (d) 500 μM W7 (final concentrations).

should, therefore, be close to the 'true' rate of release and not influenced by calcium uptake.

At low concentrations only a monophasic release was observed. The k_{obs} were 0.2 s^{-1} with 125 μM trifluoperazine, 0.5 s^{-1} with 100 μM W7 and 0.2–0.3 s^{-1} with 70 μg/ml compound 48/80. These apparent rates are similar to those obtained with 5 mM caffeine (k_{obs} 0.41 s^{-1}).

Inhibition of drug-induced calcium release by magnesium or ruthenium red

The drug-induced calcium release depends greatly on the selected magnesium concentration used in the release medium, since the drug-induced calcium release is progressively inhibited by increasing magnesium concentrations.

Magnesium dependence of the drug-induced calcium release was tested at fixed drug concentrations of 100 μM trifluoperazine, 100 μM W7, 100 μM calmidazolium and 70 μg/ml compound 48/80 and compared with magnesium inhibition of the caffeine-induced (5 mM) calcium release. Half-maximum inhibition of calcium release by trifluoperazine, W7, calmidazolium and 48/80 was obtained at 1.4 mM, 3.9 mM, 3.0 mM and 4.2 mM, respectively. Calcium release by prenylamine (250 μM) was completely inhibited by 3 mM magnesium. Half maximum inhibition of caffeine-induced calcium release (5 mM) was obtained at 0.97 mM magnesium chloride (Fig. 4; Table I).

The effect of ruthenium red on the drug-induced calcium release was tested in the presence of 0.5 M magnesium and 1 mg/ml sarcoplasmic reticulum protein. Ruthenium red proved to be a potent inhibitor of drug-induced calcium release. At drug concentrations giving about half-maximum calcium release, i.e. 125 μM trifluoperazine, 100 μM W7 or 70 μg/ml compound 48/80, half

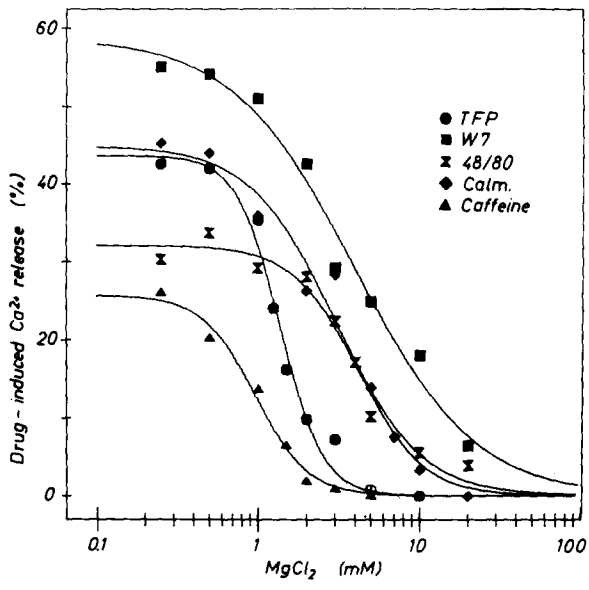

Fig. 4. Inhibition of drug-induced calcium release from heavy sarcoplasmic reticulum by $MgCl_2$. Conditions for calcium uptake and calcium release are given in Fig. 1, except that $MgCl_2$ was varied from 0.25 to 20 mM. The fixed drug concentrations were: 100 μM trifluoperazine, W7, calmidazolium; 70 μg/ml compound 48/80; 5 mM caffeine. Values are means of two experiments with different sarcoplasmic reticulum preparations.

TABLE I

HALF-MAXIMUM INHIBITION OF DRUG-INDUCED CALCIUM RELEASE BY $MgCl_2$ AND RUTHENIUM RED

Conditions as in Figs. 4 and 5; values are means of two experiments.

		IC_{50}	
		$MgCl_2$ (mM)	Ruthenium red (μM)
Trifluoperazine	(100–125 μM)	1.37	0.22
W7	(100 μM)	3.91	0.08
Calmidazolium	(100 μM)	3.01	-
Compound 48/80	(70 μg/ml)	4.20	0.63
Caffeine	(5 mM)	0.97	0.13

maximum inhibition of calcium release by ruthenium red was obtained at concentrations of 0.22 μM, 0.08 μM and 0.63 μM, respectively. By comparison, half-maximum inhibition of the caffeine-induced calcium release by ruthenium red occurs at 0.13 μM (Fig. 5; Table I).

On the other hand, the release at drug concentrations giving maximum calcium release (500 μM trifluoperazine or W7) was only partially inhibited at concentrations as high as 20 μM ruthenium red.

Inhibition of calmodulin-dependent phosphorylation by calmodulin antagonistic drugs

The relative calmodulin antagonistic potency of calmodulin antagonists used in the calcium release experiments was tested by measuring the inhibition of calmodulin-dependent phosphorylation of cardiac sarcoplasmic reticulum, carried out in the presence of 0.2 mg/ml sarcoplasmic reticulum (Fig. 6; Table II). Calmidazolium was the most potent drug and showed a biphasic inhibition with an IC_{50} of 62 nM and 2.96 μM (Table II; only the latter phase is shown in Fig. 6). Trifluoperazine, bepridil, felodipin and prenylamine were similarly effective, and W7 a little less effective, with IC_{50} values ranging from 22 to 61 μM (Table II).

The degree of inhibition depends also on the sarcoplasmic reticulum protein concentration and is shifted to lower or higher drug concentrations at 4–5-times lower or higher protein concentrations (assayed at 0.04 mg/ml and 1 mg/ml, respec-

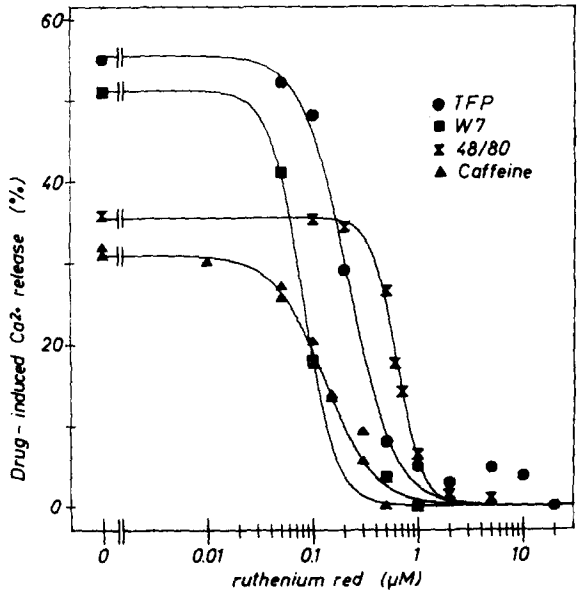

Fig. 5. Inhibition of drug-induced calcium release from heavy sarcoplasmic reticulum by ruthenium red. Conditions for calcium uptake and calcium release are given in Fig. 1. Ruthenium red was added 3 min after starting the uptake with ATP at the indicated concentrations, the drugs were added 2 min later. Trifluoperazine, 125 μM; W7, 100 μM; compound 48/80, 70 μg/ml; caffeine, 5 mM.

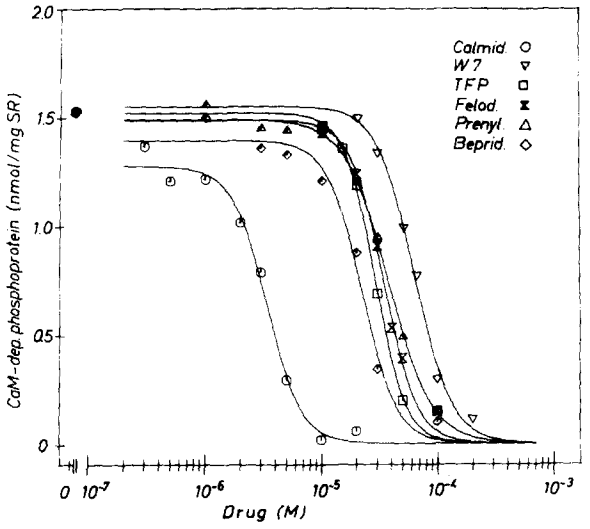

Fig. 6. Inhibition of calmodulin-dependent phosphorylation of cardiac sarcoplasmic reticulum by calmodulin antagonists. Conditions are given in Material and Methods. More than 90% of the phosphoester formation is due to phosphorylation of phospholamban [23,33,34]. ●, Control; ○, calmidazolium; ▽, W7; □, trifluoperazine; ⧗, felodipin; △, prenylamine; ◇, bepridil.

TABLE II

HALF-MAXIMUM INHIBITION OF CALMODULIN-DEPENDENT PHOSPHORYLATION OF CARDIAC SARCOPLASMIC RETICULUM BY CALMODULIN ANTAGONISTS

Conditions are given in Material and Methods. Values are means of three experiments.

	IC_{50} (μM)
Trifluoperazine	28
W7	63
Calmidazolium	2.3 (0.062)
Bepridil	22
Felodipin	34
Prenylamine	37
Compound 48/80 (μg/ml)	3.3

tively). These findings are in agreement with the data of Campbell and MacLennan [39], who demonstrated a 15-fold increase in the concentration of trifluoperazine required for half-inhibition of calmodulin-dependent phosphorylation of a 60 kDa protein of skeletal muscle sarcoplasmic reticulum when the protein concentration was increased 50-fold. The protein-dependence of the drug effect indicates that a considerable amount of the drugs is unspecifically bound by sarcoplasmic reticulum membranes.

Discussion

The present study demonstrates calcium release from heavy sarcoplasmic reticulum of skeletal muscle by several calmodulin antagonists such as trifluoperazine, W7, calmidazolium and compound 48/80. The main finding is the fact that this drug-induced calcium release possesses similar properties to the caffeine-induced calcium release [24–28]. This postulate is inferred from the findings that this drug-induced calcium release is strongly inhibited by magnesium (Fig. 4) and ruthenium red (Fig. 5). Half-maximum inhibition by magnesium and ruthenium red occurs at concentrations similar to that required for inhibition of the caffeine-induced calcium release (Table I). Furthermore, the drug-induced calcium release is transient at low drug concentrations–which could be due to inactivation of channels assuming a simple three-state model of the calcium release channel (closed, open and inactivated [10])–and the released calcium is taken up again by the calcium pump of the membranes.

These findings together indicate that the above drugs release calcium via a channel, possibly via the calcium release channel of sarcoplasmic reticulum as in the case of caffeine. Alternatively release could occur via a different channel with properties similar to the caffeine-affected calcium release channel.

The biphasic calcium release at high drug concentrations with an initially fast phase followed by a sustained slow release (Fig. 3) could be due to several reasons: (a) a fast calcium release through a rapid inactivating channel plus a slow calcium efflux, independent of the drug-activated channel; the slow efflux become apparent only with marked inhibition of the calcium pump and, therefore, inhibition of re-uptake; (b) an unspecific effect due to membrane damage at high drug concentrations; (c) more complexly a fast and slow rate of inactivation of identical channels or two types of channel with different opening and/or inactivation kinetics.

All drugs tested for their ability to induce calcium release from heavy sarcoplasmic reticulum have calmodulin antagonistic properties, which were separately tested on cardiac sarcoplasmic reticulum by measuring inhibition of the endogenous calmodulin-dependent protein kinase [22]. On the other hand, several lines of indirect evidence point to the fact that this drug induced calcium release is not due to inhibition of a calmodulin-mediated processes.

(a) Both drug-induced calcium release from skeletal muscle sarcoplasmic reticulum and inhibition of calmodulin-dependent activity of heart sarcoplasmic reticulum protein kinase by drugs depend on the sarcoplasmic reticulum protein concentration. But calcium release requires higher drug concentrations as inhibition of phosphorylation at comparable protein concentrations.

(b) Bepridil or felodipin which both have strong calmodulin-antagonistic effects comparable to trifluoperazine (Fig. 6; Table II) did not release calcium (100 or 50 μM, respectively) at low magnesium concentrations of 0.25–0.5 mM, indicating that calcium release by trifluoperazine is not due to its calmodulin-antagonistic effect.

(c) Calmodulin itself does not fully block the calcium release channel of sarcoplasmic reticulum, but only modifies the rate of release. Meissner [16] has recently demonstrated that exogenous calmodulin causes a maximally 2.5-fold reduction in the rate of calcium-induced calcium release and the rate of p[CH_2]ppA-induced calcium release from passively loaded heavy sarcoplasmic reticulum vesicles; endogenous calmodulin apparently had no effect on calcium release [16]. Plank et al. [41] have also shown that exogenous calmodulin inhibits the rate of calcium-, caffeine- and AMP-induced calcium release from passively loaded heavy sarcoplasmic reticulum of skeletal muscle about 2-fold.

For this reason it is not be expected that blockade of endogenous calmodulin by calmodulin antagonists would induce the rapid transient calcium release oberserved. Calcium release by trifluoperazine, W7, compound 48/80 and calmidazolium could be induced by binding to the calcium release channel or a regulatory structure of the channel of sarcoplasmic reticulum, quite independently of their effect on calmodulin.

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