The Role of a Ryanodine-Sensitive Ca^{2+}-Store in the Regulation of Smooth Muscle Tone of the Cat Gastric Fundus

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Abstract. The smooth muscle of the gastric fundus maintains spontaneous tone, but the mechanism underlying this activity is not fully understood. The aim of the present study was to examine whether Ca^{2+} release from the sarcoplasmic reticulum (SR) could play a role in the maintenance of the spontaneous smooth muscle tone of the cat gastric fundus. The effects on the contractile activity of SR Ca^{2+} release activators ryanodine and caffeine and of the inhibitor ruthenium red were studied. The contractile activity of isolated muscle strips was recorded under isometric conditions using organ baths.

Ryanodine concentration-dependently (10^{-7}–3.10^{-5} mol/l) increased the tone of the fundus strips. In the presence of nifedipine (10^{-5} mol/l), ryanodine induced a nifedipine-resistant tonic contraction. The tonic contraction induced after inhibition of the SR Ca^{2+}-pump by cyclopiazonic acid was potentiated by ryanodine (10^{-5} mol/l). In strips precontracted with supramaximal concentration of acetylcholine (10^{-5} mol/l), ryanodine (3.10^{-5} mol/l) further potentiated the tone. Caffeine (10^{-4}–10^{-2} mol/l) decreased and even completely inhibited the tone, suggesting some other effects of caffeine. Ruthenium red concentration-dependently (10^{-6}–10^{-4} mol/l) decreased the tone.

The present data provide evidence for the role of Ca^{2+} release from a SR ryanodine-sensitive Ca^{2+} store in the maintenance of the muscle tone of the cat gastric fundus.

Key words: Ca^{2+} release — Sarcoplasmic reticulum — Ryanodine — Smooth muscle — Gastric fundus

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Introduction

Smooth muscle contractions are associated with an increase of intracellular Ca^{2+} concentration, which could result either from Ca^{2+} influx into the cell from the extracellular space or from Ca^{2+} release from the sarcoplasmic reticulum (SR), considered to be the intracellular Ca^{2+} store (Van Breemen and Saida 1989).

The circular muscle of the cat gastric fundus has a spontaneous tone, but the mechanism underlying this activity is still unclear. The spontaneous tone of the gastric fundus consists of two components: a Ca^{2+} antagonist-sensitive and a Ca^{2+} antagonist-resistant (Boev et al. 1976). It is possible that intracellular Ca^{2+} release from the SR is involved in the maintenance of the spontaneous tone.

In our previous studies we have found that both the spontaneous and agonist-induced tone of the gastric fundus muscle depends on the activity of SR Ca^{2+}-ATPase and Ca^{2+} accumulation in the SR (Petkov and Boev 1996a, b). The present work was aimed at understanding whether the activators of SR Ca^{2+} release ryanodine and caffeine, and the inhibitor ruthenium red, could modulate the spontaneous tone of the cat gastric fundus. Ryanodine, a plant alkaloid, has been shown to unlock the SR Ca^{2+} release channels in an open state, thereby resulting in depletion of the SR Ca^{2+} stores (Iino et al. 1988; Ganitkevich and Isenberg 1993). Caffeine's ability to potentiate SR Ca^{2+} release is well documented (Iino 1989; Watanabe et al. 1992; Burdyga et al. 1995; Chowdhury et al. 1995). Ruthenium red has been reported to inhibit the Ca^{2+} release channels (Zhang et al. 1993).

Materials and Methods

Male adult cats weighing 2.5–4.5 kg were anaesthesized with alpha-chloralose (80 $mg.kg^{-1}$ i.p.). Through a midline incision in the abdomen, the entire stomach was removed and immediately placed in a modified Ca^{2+}-containing physiological Krebs solution (composition in mmol/l: 137.5 Na^+; 5.9 K^+; 2.5 Ca^{2+}; 1.2 Mg^{2+}; 134.2 Cl^-; 15.5 HCO_3^-; 1.2 $H_2PO_4^-$; 11.5 glucose) at room temperature (23–25°C). After opening along the longitudinal axis of the greater curvature, the stomach was pinned flat in a Petri dish with the muscle side up and stretched to its *in vivo* length. It was carefully scraped free of fat and connective tissue.

Circular smooth muscle strips (2 mm wide and 10 mm long) were cut out from the fundus region of the stomach, removing the mucosal layer. The strips were then suspended vertically in 10 ml organ baths (two strips per bath). One end of each strip was anchored to the bottom of the bath and the other was connected to a force-displacement transducer (UL type) coupled to a pen recorder for isometric tension recording. The strips were suspended under a 10 mN tension. These procedures were carried out in a Ca^{2+}-free Krebs solution, which was prepared as Ca^{2+}-containing solution (see above) by substituting Na^+ for Ca^{2+}. Ten

minutes later the bath solution was substituted by a Ca^{2+}-containing physiological Krebs solution to initiate contractions. The bath solutions were thermostatically controlled (37 °C) and continuously bubbled with a mixture of 95% O_2 and 5% CO_2 to achieve pH 7.4. There was a 90–120 min equilibration period. During this period the bath solution was changed every 15 min.

Dose-response curves for the effect of ryanodine and ruthenium red were obtained by cumulative application of the drugs. Tetrodotoxin and atropine were added to the bath for at least 20 min before test drug application.

The drugs tested were: acetylcholine, atropine, caffeine, cyclopiazonic acid, nifedipine, tetrodotoxin (Sigma, St. Louis, USA); ryanodine (Calbiochem, Luzern, Switzerland); ruthenium red (Merck, Darmstadt, Germany). All other compounds were of analytical grade quality. Stock solution of cyclopiazonic acid in dimethylsulfoxide was prepared to yield 10^{-2} mol/l. Ryanodine and nifedipine were dissolved in ethanol. Dimethylsulfoxide and ethanol in the concentrations used had no permanent effect on the contractility of the cat gastric smooth muscles.

All the responses are expressed in percentages as mean ± S.E.M. for n, the number of preparations ($n/2$ = the number of animals). The amplitude of the spontaneous tone was assumed to be 100%. The data were assessed for statistical significance using Student's t-test at $P < 0.05$.

Results

Effect of ryanodine on the spontaneous tone of the cat gastric fundus

To evaluate the role of Ca^{2+} release from the SR in the maintenance of the spontaneous tone of the cat gastric fundus, we investigated the effect of ryanodine. Ryanodine applied at concentrations above 3.10^{-8} mol/l concentration-dependently increased the tone (Fig. 1), without provoking phasic contractions (Fig. 2*A*). The maximal response to ryanodine was elicited by a concentration of 3.10^{-5} mol/l within 10–15 min after the administration (Fig. 2*A*). This contraction was sustained and persisted for hours (at least 4 hours) until ryanodine was washed out.

As ryanodine can also activate intracellular Ca^{2+} release in enteric neurons, thus affecting neurotransmission, tetrodotoxin and atropine were used in control experiments to study the possible involvement of nervous structures in the contractile effect of ryanodine. The dose-response curve for the effect of ryanodine in the presence of 10^{-6} mol/l tetrodotoxin did not differ significantly ($P > 0.05$) from the dose-response curve obtained under control conditions (Fig. 1). In the presence of 10^{-6} mol/l atropine, the response to ryanodine was not significantly ($P > 0.05$) changed either (data not shown). All this suggests that the effect of ryanodine is not mediated by the release of a neurotransmitter and that the effect should be considered a myogenic one.

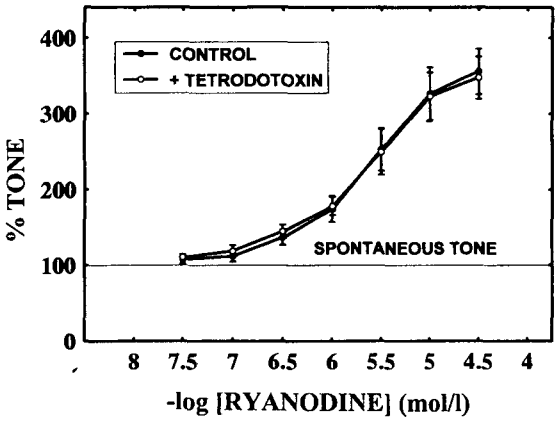

Figure 1. Cumulative dose-response curves for the contractile effect of ryanodine in cat gastric fundus strips Control response, $n = 10$, in the presence of 10^{-6} mol/l tetrodotoxin, $n = 6$, $P > 0\ 05$ The spontaneous tone was taken as 100% Values are means ± S E M

The role of extracellular Ca^{2+} in the effect of ryanodine

Experiments were performed in Ca^{2+}-free solution to determine whether ryanodine mobilizes only Ca^{2+} from intracellular stores or whether the ryanodine-induced contraction also requires Ca^{2+} influx through the plasma membrane Exposure of the strips to ryanodine ($3\ 10^{-5}$ mol/l) in Ca^{2+}-free solution caused no contraction at all ($n = 8$, Fig 2*B*) However, Ca^{2+} (2 5 mmol/l) added to the bath induced a very strong and rapid contraction (an increase within 2–3 min), whose amplitude was much higher than that of the spontaneous tone (Fig 2*B*) These results suggest the obligatory role of extracellular Ca^{2+} in the effect of ryanodine

Nifedipine was used to study the contribution to contraction induced by ryanodine of Ca^{2+} entry through the L-type Ca^{2+} channels Nifedipine (10^{-5} mol/l) partly suppressed the ryanodine-induced tone ($n = 8$, Fig 2*A*) As most likely the Ca^{2+} antagonist-resistant component of the spontaneous tone of the cat gastric fundus (Boev et al 1976) is due to SR Ca^{2+} release, we investigated the effect of ryanodine in the presence of nifedipine After 10^{-5} mol/l nifedipine, ryanodine ($3\ 10^{-5}$ mol/l) elicited a nifedipine-resistant tonic contraction (Fig 2*C*) The development of this contraction was slow and stable response was observed after more than 25–30 min ($n = 8$, Fig 2*C*) As shown in Figure 2, contraction induced by ryanodine in Ca^{2+}-containing solution (Fig 2*A*) differed from that induced by ryanodine in Ca^{2+}-free solution after the addition of 2 5 mmol/l Ca^{2+} (a fast increase in the tone, Fig 2*B*) and from nifedipine-resistant contraction provoked by ryanodine (Fig 2*C*)

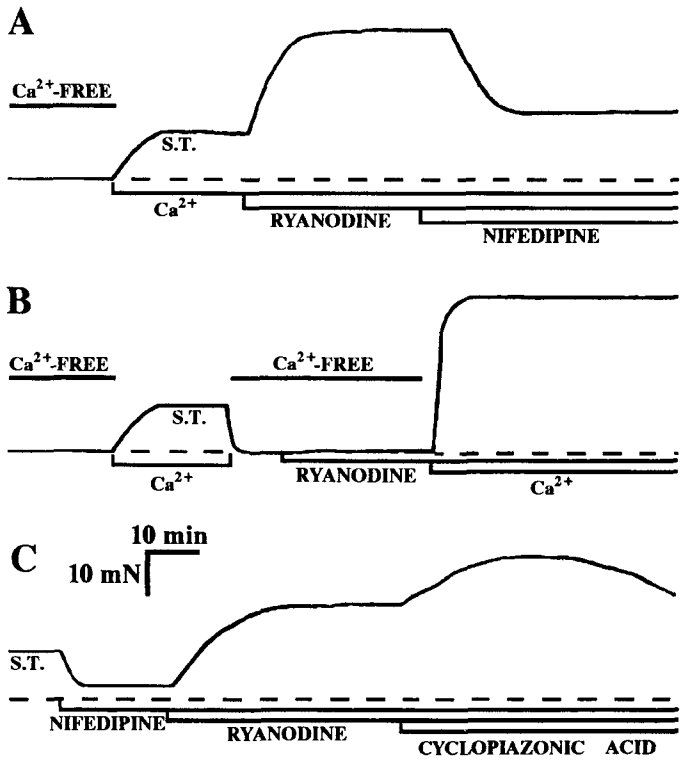

Figure 2. Recordings of changes in tension of cat gastric fundus strips, induced by 3 10^{-5} mol/l ryanodine **A**) Appearance of spontaneous tone (S T) after the addition of 2 5 mmol/l Ca^{2+} and a typical contraction caused by ryanodine The contraction was partially abolished by 10^{-5} mol/l nifedipine **B**) The lack of contractile effect of ryanodine in Ca^{2+}-free solution and the appearance of a rapid and strong contraction after addition of 2 5 mmol/l Ca^{2+} **C**) A typical contraction induced by ryanodine in the presence of 10^{-5} mol/l nifedipine and the additional effect of 10^{-5} mol/l cyclopiazonic acid The lines indicate the presence of the drugs throughout the experiment

Effects of ryanodine and cyclopiazonic acid

The role of SR Ca^{2+} stores in contractile activity of the gastric fundus could be evaluated after complete Ca^{2+} depletion, i.e. simultaneous activation of SR Ca^{2+} release and inhibition of Ca^{2+} uptake.

Unlike ryanodine, cyclopiazonic acid inhibits SR function by blocking SR Ca^{2+}-ATPase (Seidler et al. 1989). In earlier studies (Petkov and Boev 1996a, b) we have found that cyclopiazonic acid causes a stable increase in the tone of guinea-pig and cat gastric fundus (Fig 3*A*) due to the disruption of the "buffer

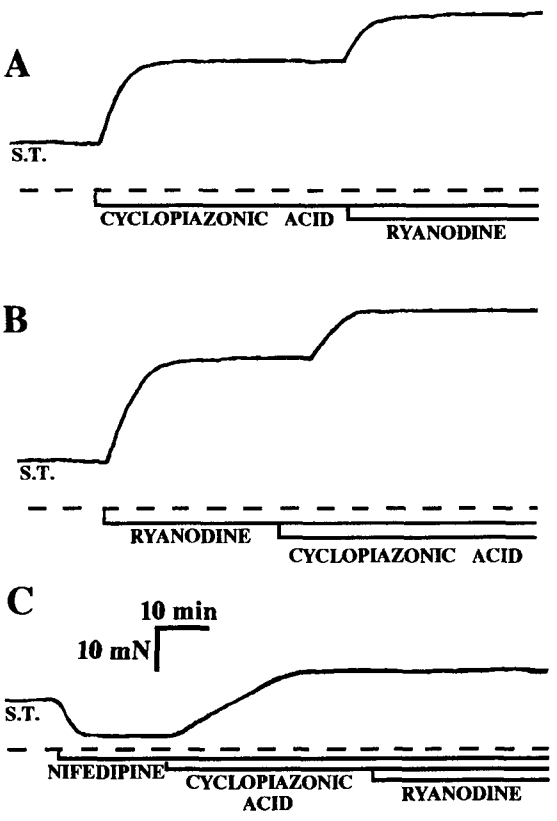

Figure 3. Recordings of changes in tension of cat gastric fundus strips, induced by 3 10^{-5} mol/l ryanodine and 10^{-5} mol/l cyclopiazonic acid **A**) Effect of 10^{-5} mol/l cyclopiazonic acid on the spontaneous tone (S T) and the additional contractile effect of 3 10^{-5} mol/l ryanodine **B**) Effect of 3 10^{-5} mol/l ryanodine on the spontaneous tone (S T) and the additional contractile effect of 10^{-5} mol/l cyclopiazonic acid **C**) The lack of contractile effect of ryanodine in the presence of 10^{-5} mol/l nifedipine and 10^{-5} mol/l cyclopiazonic acid The lines indicate the presence of the drugs throughout the experiment

barrier" function of the SR (Van Breemen et al. 1995). This effect was also observed in the presence of nifedipine (Fig. 3*C*).

In these experiments, we investigated the effects of combinations of ryanodine and cyclopiazonic acid. In the presence of cyclopiazonic acid (10^{-5} mol/l), ryanodine (3.10^{-5} mol/l) further increased the tone ($n = 6$; Fig. 3*A*). In the presence of 3 10^{-5} mol/l ryanodine, cyclopiazonic acid (10^{-5} mol/l) was also able to increase the tone ($n = 6$; Fig. 3*B*). In Figure 4, the increase of the tone induced by 3.10^{-5} mol/l ryanodine is compared to the increase induced by both 3.10^{-5} mol/l ryan-

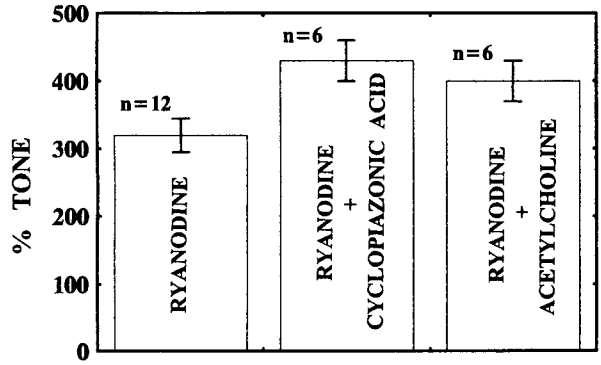

Figure 4. Quantative data showing the contractile effect of ryanodine ($3\ 10^{-5}$ mol/l), ryanodine ($3\ 10^{-5}$ mol/l) plus cyclopiazonic acid (10^{-5} mol/l), ryanodine ($3\ 10^{-5}$ mol/l) plus acetylcholine (10^{-5} mol/l) on cat gastric fundus strips The spontaneous tone was taken as 100% Values are means ± S E.M

odine and 10^{-5} mol/l cyclopiazonic acid. These results suggest additive effects of ryanodine and cyclopiazonic acid on the SR Ca^{2+} stores in the cat gastric fundus.

In the presence of nifedipine (10^{-5} mol/l) and ryanodine (3.10^{-5} mol/l), cyclopiazonic acid (10^{-5} mol/l) increased the tone ($n = 6$; Fig. 2*C*). However, ryanodine lost its ability to induce tone in the presence of 10^{-5} mol/l nifedipine and 10^{-5} mol/l cyclopiazonic acid ($n = 12$; Fig. 3*C*). It is possible that the simultaneous blockade of Ca^{2+} influx through the L-type Ca^{2+} channels and intracellular Ca^{2+} uptake results in a rapid depletion of SR Ca^{2+} stores and thus in a lack of the ryanodine effect.

Effects of ryanodine and acetylcholine

In order to understand whether ryanodine could modulate contractions after acetylcholine which activates Ca^{2+} influx from the extracellular space and releases Ca^{2+} from the intracellular stores in the gastric fundus, we evaluated the effect of ryanodine on acetylcholine-induced tone. Unlike ryanodine, acetylcholine activates SR Ca^{2+} release through inositol 1,4,5-trisphosphate sensitive Ca^{2+} channels.

In strips precontracted with supramaximal concentration of acetylcholine (10^{-5} mol/l), ryanodine (3.10^{-5} mol/l) further potentiated the tone ($n = 6$). In the presence of 3.10^{-5} mol/l ryanodine, acetylcholine (10^{-6} mol/l) was also able to induce tonic contraction ($n = 4$). In Figure 4, the increase of the tone induced by 3.10^{-5} mol/l ryanodine is compared to that induced by both 3.10^{-5} mol/l ryanodine and 10^{-5} mol/l acetylcholine. These results suggest additive effects of ryanodine and acetylcholine in the cat gastric fundus.

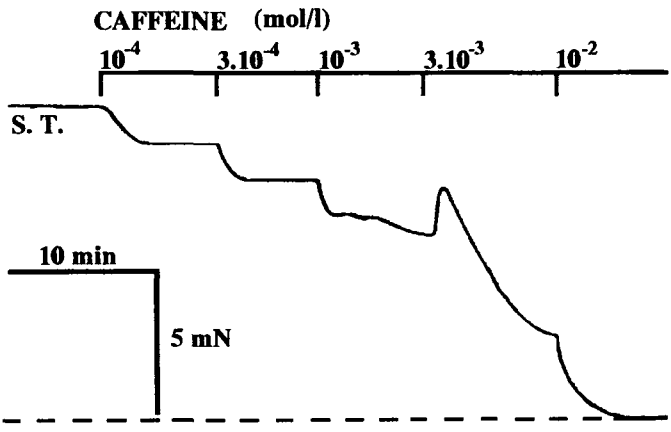

Figure 5. Recording of changes in tension of a cat gastric fundus strip showing the inhibitory effect of caffeine (10^{-4}–10^{-2} mol/l) on the spontaneous tone (S.T.). The line indicates the administration of different concentrations of caffeine throughout the experiment.

Effect of caffeine

Caffeine like ryanodine also activates SR Ca^{2+} release channels in some types of smooth muscle (Iino 1989). This prompted us to examine, in comparative experiments, the effects of caffeine on the spontaneous tone. Unlike ryanodine, caffeine caused a concentration-dependent (10^{-4}–10^{-2} mol/l) decrease, and at concentrations higher than 10^{-2} mol/l completely inhibited the spontaneous tone ($n = 6$; Fig. 5). In some of the strips caffeine administered at concentrations of 10^{-3}–3.10^{-3} mol/l caused a transient tonic contraction followed by sustained relaxation (Fig. 5).

Caffeine concentration-dependently (10^{-3}–3.10^{-2} mol/l) inhibited ryanodine (3.10^{-5} mol/l)-induced ($n = 6$) and cyclopiazonic acid (10^{-5} mol/l)-induced tone ($n = 8$). The relaxant effect of caffeine also occurred in the presence of both ryanodine (3.10^{-5} mol/l) and cyclopiazonic acid (10^{-5} mol/l), as complete inhibition of the tone was achieved at 5.10^{-2} mol/l caffeine.

The data suggest the lack of the effect of caffeine as activator of SR Ca^{2+} release in the cat gastric fundus with its relaxant effects predominating.

Effect of ruthenium red

Ruthenium red was used to block the SR Ca^{2+} release channels. Administered cumulatively (10^{-6}–10^{-4} mol/l), ruthenium red suppressed the spontaneous tone in a concentration-dependent manner ($n = 6$; Fig. 6). In two out of six strips ruthenium red (3.10^{-5}–10^{-4} mol/l) caused a transient tonic contraction followed

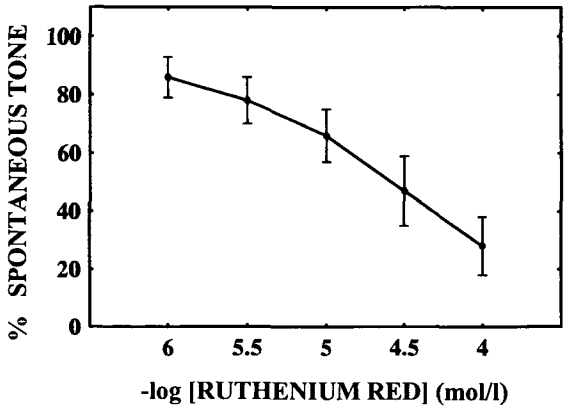

Figure 6. Cumulative dose-response curve for the inhibitory effect of ruthenium red in cat gastric fundus strips (n = 6). The spontaneous tone was taken as 100%. Values are means ± S.E.M.

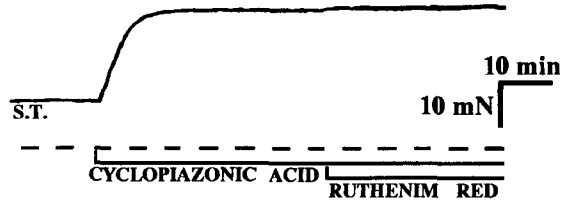

Figure 7. Recording of changes in tension of a cat gastric fundus strip showing the lack of effect of ruthenium red (3.10^{-5} mol/l) in the presence of 10^{-5} mol/l cyclopiazonic acid. The lines indicate the presence of the drugs throughout the experiment.

by sustained relaxation. The inhibitory effect of ruthenium red was not significantly affected by the presence of 10^{-6} mol/l tetrodotoxin, suggesting the myogenic action of the drug.

In order to block the SR Ca^{2+} release and Ca^{2+} uptake, we used cyclopiazonic acid and ruthenium red. In the presence of 10^{-5} mol/l cyclopiazonic acid, ruthenium red (10^{-6}–10^{-3} mol/l) did not exert any effect on the tone (n = 4; Fig. 7). Thus, the simultaneous blockade of SR Ca^{2+} uptake and Ca^{2+} release led to "disruption of the SR buffer-barrier to Ca^{2+} entry" (Van Breemen et al. 1995) in the cat gastric fundus and to inability of SR to control the smooth muscle tone.

Discussion

Effect of ryanodine

Ryanodine has been widely used to assess the role of intracellular Ca^{2+} release in the contractile activity of various types of smooth muscle (Iino et al 1988), including guinea-pig gastric antrum (Chowdhury et al 1995) and rat gastric fundus (Cox and Cohen 1995) The present study showed that incubation of cat gastric fundus in solution containing Ca^{2+} and ryanodine resulted in a significant increase in the muscle tone, which persisted as long as ryanodine and extracellular Ca^{2+} remained in the solution Incubation of cat gastric fundus strips in Ca^{2+}-free solution completely suppressed the ability of ryanodine to contract the muscle

According to the so-called "Capacitative Ca^{2+} entry" model (Putney 1990) depletion of the intracellular Ca^{2+} stores provides, somehow, a signal for activation of Ca^{2+} entry across the plasma membrane Thus, it can be predicted from the "capacitative Ca^{2+} entry" model that ryanodine should activate a Ca^{2+} influx pathway through the extracellular space In the present experiments, however, no clear evidence for such a pathway was obtained

According to the "superficial buffer barrier" hypothesis (Van Breemen et al 1995), part of the Ca^{2+} entering the smooth muscle cell through the plasma membrane is actively taken up into SR Ca^{2+} stores, before it can reach the contractile myofilaments and activate contraction Activation of the SR Ca^{2+} release would interrupt this process leading to an enhanced contractile response Confirming this view is the remarkable persistence of the ryanodine-induced contraction observed in this study

Effect of caffeine

Iino (1989) was the first to show that a Ca^{2+}-induced Ca^{2+} release mechanism operates in the caffeine releasable SR Ca^{2+} store in the intestinal smooth muscle The present results, however, showed an essential difference between the effects of ryanodine and caffeine one contractile and the other one relaxant The difference could be due either to the fact that the ability of caffeine to affect the Ca^{2+} store in the cat gastric fundus is not sufficiently expressed or to a different action of caffeine and ryanodine in this tissue Although caffeine has several possible actions, in many types of smooth muscles it is able to release Ca^{2+} from the SR The cat gastric fundus thus resembles the rat myometrium (Savineau and Mironneau 1990) and the rat ureter (Burdyga et al 1995), which do not either contract in response to caffeine The relaxant effect of caffeine in cat gastric fundus may be related to an increase of intracellular cyclic AMP It has been shown that in some smooth muscles caffeine increases cyclic AMP levels due to phosphodiesterase inhibition (Watanabe et al 1992) It is also possible that some SR ryanodine-receptor of type

III, which has been shown to be sensitive to ryanodine but not to caffeine (Giannini et al. 1992), exists in the cat gastric fundus.

Does SR Ca^{2+} release play a role in the maintaining of the tone?

The Ca^{2+}-induced Ca^{2+} release has been demonstrated in spike-generating smooth muscles, e.g. ileum and taenia caeci (Iino 1989). In these smooth muscles SR Ca^{2+} release is triggered by Ca^{2+} entry during the spike action potential. In gastric antrum smooth muscles, Ca^{2+} antagonists inhibit spontaneous and acetylcholine-induced phasic contractions (Boev et al. 1976; Ozaki et al. 1993). However, Ca^{2+} antagonists are unable to completely suppress the spontaneous and acetylcholine-induced tone of the cat (Boev et al. 1976) and guinea-pig (Duridanova et al. 1995) fundus. The mechanism of the acetylcholine-induced contractions in the gastric smooth muscles involves activation of an atropine-sensitive nonselective cation channel and release of Ca^{2+} from the internal store (Sims 1992). The present results showed that ryanodine increased the maximal contraction after acetylcholine administration to fundus strips. Ryanodine also potentiated the tonic contraction occurring after blockade of the SR Ca^{2+}-ATPase by its selective inhibitor cyclopiazonic acid. Since the Ca^{2+}-induced Ca^{2+} release depends on the intracellular Ca^{2+} concentration (Iino 1989) acceleration of the Ca^{2+} release in the presence of acetylcholine or cyclopiazonic acid could be due to increased Ca^{2+} levels in the cytoplasm

In the presence of Ca^{2+} and nifedipine, the increase in muscle tone caused by ryanodine was delayed, suggesting the important role of the L-type Ca^{2+} channels in the effect of ryanodine on one hand, and the existence of a nifedipine-resistant part of the ryanodine-induced contraction, on the other one. This fact supports the assumption that the Ca^{2+} antagonist-resistant component of the tone is partly due to the release of Ca^{2+} from a ryanodine-sensitive store. Furthermore, ruthenium red used in our experiments as an inhibitor of the SR Ca^{2+} release channels, led to a significant inhibition of the spontaneous tone.

The intracellular Ca^{2+} stores function as an important regulatory factor for the membrane ionic currents. According to Iino (1989), the Ca^{2+}-induced Ca^{2+} release cannot play a primary role in triggering a physiological contraction, but it is important as a modulating factor for the Ca^{2+}-activated K^+ channel opening. Indeed, our earlier study has shown that the Ca^{2+}-induced Ca^{2+} release can activate K^+ currents in smooth muscle cells from guinea-pig gastric fundus (Duridanova et al. 1996). However, the present study showed that the SR Ca^{2+} release from a ryanodine-sensitive Ca^{2+} store could directly contribute to the maintenance of spontaneous and agonist-induced tone of the cat gastric fundus.

In conclusion, all the above results provide evidence for the existence of ryanodine-sensitive SR Ca^{2+} store in the cat gastric fundus, and suggest the role of SR Ca^{2+} release in the maintenance of spontaneous smooth muscle tone in this tissue.

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References

Boev K , Golenhofen K , Lukanow J (1976) Selective suppression of phasic and tonic activation mechanisms in stomach smooth muscle In Physiology of Smooth Muscle (Eds E Bulbring and M F Shuba) pp 203—208, Raven Press, New York

Burdyga T V , Taggart M J , Wray S (1995) Major difference between rat and guinea-pig ureter in the ability of agonists and caffeine to release Ca^{2+} and influence force J Physiol (London) **489**, 327—335

Chowdhury J U , Pang Y W , Huang S M , Tsugeno M , Tomita T (1995) Sustained contraction produced by caffeine after ryanodine treatment in the circular muscle of the guinea-pig gastric antrum and rabbit portal vein Brit J Pharmacol **114**, 1414—1418

Cox D A , Cohen M L (1995) 5-Hydroxytryptamine(2B) receptor signaling in rat stomach fundus Role of voltage-dependent calcium channels, intracellular calcium release and protein kinase C J Pharmacol Exp Ther **272**, 143—150

Duridanova D , Gagov H , Petkov G , Shkodrov G , Boev K (1995) Cyclic GMP activation of potassium currents by sarcoplasmic reticulum Ca^{2+} pump-dependent mechanism Gen Physiol Biophys **14**, 139—151

Duridanova B D , Gagov H S , Boev K K (1996) Ca^{2+}-induced Ca^{2+} release activates potassium currents by cyclic GMP-dependent mechanism in single gastric smooth muscle cells Eur J Pharmacol **298**, 159—163

Ganitkevich V Ya , Isenberg G (1993) Ca^{2+} entry through Na^{+}-Ca^{2+} exchange can trigger Ca^{2+} release from Ca^{2+} stores in Na^{+}-loaded guinea-pig coronary myocytes J Physiol (London) **468**, 225—243

Giannini G , Clementi E , Ceci R , Marziali G , Sorrentino V (1992) Expression of a ryanodine receptor-Ca^{2+} channel that is regulated by TGF-beta Science **257**, 91—94

Iino M (1989) Calcium-induced calcium release mechanism in guinea pig teania caeci J Gen Physiol **94**, 363—383

Iino M , Kobayashi T , Endo M (1988) Use of ryanodine for functional removal of the calcium store in smooth muscle cells of the guinea-pig Biochem Biophys Res Commun **152**, 417—422

Ozaki H , Gerthoffer W T , Hori M , Karaki H , Sanders K M , Publicover N G (1993) Ca^{2+} regulation of the contractile apparatus in canine smooth muscle J Physiol (London) **460**, 33—50

Petkov G V , Boev K K (1996a) Cyclopiazonic acid-induced changes in contractile activity of smooth muscle strips isolated from cat and guinea-pig stomach Eur J Pharmacol **318**, 109—115

Petkov G V , Boev K K (1996b) The role of sarcoplasmic reticulum and sarcoplasmic reticulum Ca^{2+}-ATPase in the smooth muscle tone of the cat gastric fundus Pflugers Arch **431**, 928—935

Putney Jr J W (1990) Capacitative calcium entry revisited Cell Calcium **11**, 611—624

Savineau J P , Mironneau J (1990) Caffeine acting on pregnant rat myometrium analysis of its relaxant action and its failure to release Ca^{2+} from intracellular stores Brit J Pharmacol **99**, 261—266

Seidler N W , Jona I , Vegh M , Martonosi A (1989) Cyclopiazonic acid is a specific inhibitor of the Ca^{2+}-ATPase of sarcoplasmic reticulum J Biol Chem **264**, 17816—17823

Sims S M (1992) Cholinergic activation of a non-selective cation current in canine gastric smooth muscle is associated with contraction J Physiol (London) **449**, 377—398

Van Breemen C , Chen Q , Laher I (1995) Superficial buffer barrier function of smooth muscle sarcoplasmic reticulum Trends Pharmacol Sci **16**, 98—105

Van Breemen C , Saida K (1989) Cellular mechanisms regulating $[Ca^{2+}]_i$ smooth muscle Annu Rev Physiol **51**, 315—329

Watanabe C , Yammamoto H , Hirano K , Kobayashi S , Kanaide H (1992) Mechanism of caffeine-induced contraction and relaxation of rat aortic smooth muscle J Physiol (London) **456**, 193—213

Zhang Z D , Kwan C Y , Daniel E E (1993) Subcellular-membrane characterization of [^{3}H]ryanodine-binding sites in smooth muscle Biochem J **290**, 259—266

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