A Xestospongin C-sensitive Ca\(^{2+}\) Store Is Required for cAMP-induced Ca\(^{2+}\) Influx and cAMP Oscillations in Dictyostelium*

Ralph Schaloske, Christina Schlatterer, and Dieter Malchow†

From the Faculty of Biology, University of Konstanz, Postfach 55 60, 78457 Konstanz, Germany

Xestospongin C (XeC) is known to bind to the inositol 1,4,5-trisphosphate (IP\(_3\))-sensitive store in mammalian cells and to inhibit IP\(_3\) and thapsigargin-induced Ca\(^{2+}\) release. In this study we show that this is also true for Dictyostelium. In addition, XeC inhibited Ca\(^{2+}\) uptake into purified vesicle fractions and induced Ca\(^{2+}\) release. This suggests that, in the case of Dictyostelium, XeC opens rather than plugs the IP\(_3\) receptor channel as was proposed for mammalian cells (Gafni, J., Munsch, J. A., Lam, T. H., Catlin, M. C., Costa, L. G., Molinski, T. F., and Pessah, I. N. (1997) Neuron 19, 723–733). In order to elucidate the function of the XeC-sensitive Ca\(^{2+}\) store in Dictyostelium during differentiation, we applied XeC to the cells and found that it caused a time-dependent increase of basal [Ca\(^{2+}\)]\(_i\), and inhibited cAMP-induced Ca\(^{2+}\) influx in single cells as well as in cell suspensions. Moreover, XeC blocked light scattering spikes and pulsatile cAMP signaling.

Early development of Dictyostelium requires the pulsatile release of cAMP that binds to the cAMP receptor (CAR1) and attracts neighboring cells to migrate to the cAMP source (for review, see Refs. 1–3). This pulsatile release of cAMP underlies spike-like light scattering oscillations of Dictyostelium cells (4).

Oscillations in cAMP are thought to arise due to a positive extracellular feedback loop of cAMP (5–7). Extracellular binding of cAMP to CAR1 transiently activates adenyl cyclase (ACA). This leads to an increase in cytosolic cAMP. One portion of cAMP is secreted and restimulates CAR1. The CAMP remaining in the cytosol activates protein kinase A (PKA) (for review, see Ref. 9). A negative feedback loop thereafter by extracellular phosphodiesterases (for review, see Refs. 1–3). This pulsatile release of cAMP underlies oscillatory regulation of cAMP.

EXPERIMENTAL PROCEDURES

Materials—Xestospongin C, inositol 1,4,5-trisphosphate, microcystin LR and thapsigargin were purchased from Calbiochem (Bad Soden, Germany). Fura-2 and fura-2-dextran were obtained from MobiTec (Göttingen, Germany) and 2,5-di-(tert-butyl)-1,4-hydroquinone (BHQ) from Aldrich (Steinheim, Germany).

Culture of Cells and Induction of Differentiation—The axenic strain Ax2 was grown in shaking culture as described (18). Differentiation was induced by washing cells free of medium twice in ice-cold Sørensen phosphate buffer (17 mM KH\(_2\)PO\(_4\), pH 6.0). Cells were shaken on a rotary shaker at 23 °C, 150 rpm at 2 × 10\(^{6}\) cells/ml until use.

Preparation of Vesicles—30 ml of a cell suspension differentiated for 1–2 h were washed once in ice-cold 20 mM Hepes buffer, pH 7.2, resuspended at 2 × 10\(^6\) cells/ml, and lysed by passage through nucleopor filters. Immediately, 3% sucrose, 50 mM KCl, 1 mM MgCl\(_2\), 20 µM leupeptin, 1 µM aprotinin, 2.5 mM dihithiothreitol, and 1 µM microcystin LR were added (final concentrations). After centrifugation for 5 min at 3000 × g, the supernatant was further fractionated by centrifugation for 20 min at 12,000 × g. The sediment (P1) was resuspended in 1 ml of the above buffer yielding a protein concentration of about 2 mg/ml. P1 contained the IP\(_3\)-sensitive Ca\(^{2+}\) store and part of the acidic vesicle fraction. For further purification, 1 ml of P1 (from 45 ml of cell suspension preincubated for 2 h in 5 mM EGTA) was centrifuged on a 30% Percoll gradient (10 ml) for 30 min at 40,000 × g at 4 °C. Ca\(^{2+}\) Transport—Ca\(^{2+}\) transport was measured as described (15). In brief, about 70 µl of P1 was added to 10 mM Hepes, pH 7.2, 50 mM KCl, 3% sucrose, 6 µg/ml antimycin A, 6 µg/ml oligomycin A, 100 µM NaN\(_3\), 2 mM MgCl\(_2\), and about 6 µM fura-2 in a total volume of 1 ml. After preincubation for 3–10 min at 23 °C in the absence or presence of drugs, 1 mM ATP was added to activate Ca\(^{2+}\) uptake. Fura-2 fluorescence was monitored at 355 and 380 nm excitation and 508 nm emission with a double wavelength fluorimeter (Sigma ZWS11, Sigma Instrumente, Berlin, Germany).

Determination of [Ca\(^{2+}\)]\(_i\) was determined as described (15). Cells were electroporated at 2–3 h after induction of differentiation with fura-2-dextran, and [Ca\(^{2+}\)]\(_i\) imaging was carried out at 5–7 h of differentiation. 10 min before [Ca\(^{2+}\)]\(_i\) recording buffer covering the cells was replaced by 90 µl of fresh buffer (5 mM Hepes, 5 mM KCl, pH 7.0) containing 1 mM Ca\(^{2+}\). [Ca\(^{2+}\)]\(_i\) imaging was performed with an Axiovert T100 microscope (Zeiss, Jena, Germany). The cells were viewed with a 100× Fluor objective (numeric aperture, 1.3); 340 and 380 nm excitation was performed with a mercury lamp and a rotating filter wheel. Images of the cells were recorded with an ICCD camera (HL-A, Prox-
subsequent experiments to analyze the mechanism of XeC action. IP3 was added where indicated. Ca2+ concentrations were determined with fura-2 as described under "Experimental Procedures." Bars indicate extravesicular [Ca2+]. One out of three independent experiments is shown.

**Chemotaxis and Cell Shape Recording**—200 μl of 5 × 104 cells/ml in Sørensen phosphate buffer were placed on a coverslip, and a borosilicate glass capillary filled with 100 μM cAMP was inserted at time zero. Cells were viewed with a 16× or 25× objective using an inverted Zeiss IM microscope. Cell movement was recorded using a CCD camera and a digital video recorder (Sony).

**Other Measurements—Ca2+ influx was determined with a Ca2+-sensitive electrode (14), and light scattering oscillations were recorded as described (18).** Protein concentrations were determined with the Coomassie protein assay reagent (Pierce) using bovine serum albumin as standard. The amount of cAMP (intracellular and extracellular) uptake was measured as described under "Experimental Procedures." cAMP-induced Ca2+ uptake in each of three independent experiments (by 19.7%); 3) XeC- and Tg-induced Ca2+ release activity distributed similarly on a Percoll gradient; 4) after Ca2+ had been liberated from fraction 2 by Tg and IP3, XeC-induced Ca2+ release was inhibited by 92 ± 12% (n = 3). Therefore, we conclude that the IP3-sensitive store is indeed the target of XeC action in Dictyostelium. We then aimed to elucidate the function of the IP3-sensitive store in early development of Dictyostelium.

**RESULTS**

**Vesicular Uptake and IP3-induced Ca2+ Release**—When Dictyostelium extracts were centrifuged for 20 min at 12,000 × g, the supernatant (S1) and the pellet (P1) contained about equal amounts of Ca2+ transport activity. The rate of Ca2+ uptake for S1 was 1.25 ± 0.61 nmol/min × 10^8 cells and 1.24 ± 0.67 nmol/min × 10^9 cells for P1 (± S.D. n = 9). We found that XeC induced Ca2+ release (see below). This effect was larger in P1 (71 ± 3%; n = 3) than in S1. Therefore, we used P1 in the subsequent experiments to analyze the mechanism of XeC action. We first tested whether XeC inhibited Ca2+ uptake into IP3-sensitive Ca2+ stores of Dictyostelium.

ATP-induced Ca2+ uptake into the microsomal fraction P1 in the presence of mitochondrial inhibitors. Addition of IP3 caused a slow but steady release of Ca2+ from the store (Fig. 1B). In the presence of 20 μM XeC, Ca2+ transport was strongly reduced and IP3-mediated Ca2+ release was virtually absent (Fig. 1A). In Table I we compared the potency of XeC with that of the Ca2+-ATPase blocker BHQ. BHQ was shown to inhibit Ca2+ uptake into the IP3-sensitive store at about 100 μM concentration and into the acidic vesicles at 200 μM concentration (11, 12). Table I demonstrates that 20–30 μM XeC was as potent as 100 μM BHQ to block Ca2+ uptake and IP3-induced Ca2+ release.

A Thapsigargin-sensitive Ca2+ Store Is Inhibited by XeC—Thapsigargin is another specific blocker of the Ca2+-pump of the IP3-sensitive store in mammalian cells. Inhibition of the pump results in leakage of Ca2+ from storage compartments (20). To investigate whether Tg- and XeC-sensitive vesicles distribute similarly on a density gradient, we purified the microsomal fraction P1 on a 30% Percoll gradient (Fig. 2). Protein was distributed over two peaks, whereas Ca2+ uptake activity was present predominantly in one peak at the top of the gradient. Under these conditions mitochondrial porin was found in fractions 6–8 (data not shown). Thapsigargin and XeC elicited Ca2+ release mainly in fractions 1 and 2 at the top of the gradient (Fig. 2, A and B). The amount of Ca2+ released by XeC or Tg from the same fraction (fraction 2 of Fig. 2A) was in the same range (29 nmol/mg protein and 34 nmol/mg protein for XeC and Tg, respectively). This suggests that XeC acts on the same store as Tg. We therefore analyzed whether XeC blocks the Tg-sensitive store. Fig. 3 shows that 30 μM XeC inhibited Tg-induced Ca2+ release to a greater extent (68%) than Ca2+ uptake (50%).

In Dictyostelium the target of XeC seems to be the IP3-sensitive store as in mammalian cells for the following reasons. 1) XeC inhibited IP3-induced Ca2+ release and Ca2+ uptake to a similar extent as BHQ; 2) XeC inhibited Tg-induced Ca2+ release to a greater extent than Ca2+ uptake in each of three independent experiments (by 19.7 ± 7%); 3) XeC- and Tg-induced Ca2+ release activity distributed similarly on a Percoll gradient; 4) after Ca2+ had been liberated from fraction 2 by Tg and IP3, XeC-induced Ca2+ release was inhibited by 92 ± 12% (n = 3). Therefore, we conclude that the IP3-sensitive store is indeed the target of XeC action in Dictyostelium. We then aimed to elucidate the function of the IP3-sensitive store in early development of Dictyostelium.

**cAMP-induced Ca2+ influx**—Indirect evidence had pointed to the necessity of the IP3-sensitive store for cAMP-induced Ca2+ influx (13, 14). Previously, we have shown that an active phospholipase A2 is required for cAMP-induced Ca2+ influx (14). Free fatty acids like arachidonic acid cause Ca2+ release from the acidic vesicles, the second Ca2+ store in Dictyostelium besides the IP3-sensitive Ca2+ store (15). We reasoned that the increase in cytosolic Ca2+ then either activates phospholipase C or IP3 phosphatase. Both events lead to IP3 formation and subsequent release of Ca2+ from the IP3-sensitive store that in turn elicits capacitative Ca2+ entry (21).

Here we used XeC to address the question of whether the IP3-sensitive store was indeed required for capacitative Ca2+ entry. cAMP-induced Ca2+ influx was reduced immediately after XeC application, and maximal inhibition occurred within 25 min. 36 μM XeC caused nearly complete inhibition of cAMP-induced Ca2+ influx, demonstrating that the IP3-sensitive store is required to induce capacitative Ca2+ entry (Table II).

**Spiked-shaped Oscillations and Chemotaxis**—Spikedlike light scattering oscillation start spontaneously in Dictyostelium cell suspensions after about 4 h of differentiation (21). In the pres-
FIG. 2. Percoll gradient fractionation of Ca\(^{2+}\) uptake activity and Ca\(^{2+}\) release by XeC (A) or Tg (B). P1 was separated on a 30% Percoll gradient. The fractions were assayed for ATP-activated Ca\(^{2+}\) uptake ( ), Ca\(^{2+}\) release induced by XeC (A, 10 \(\mu\)M, \(\nabla\)) or Tg (B, 40 \(\mu\)M, \(\nabla\)), respectively, and for protein content ( ). The top of the gradient is to the left. One out of two experiments is shown in A and one out of three experiments in B. A and B are from separate experiments.

FIG. 3. XeC blocks Tg-induced Ca\(^{2+}\) release. ATP-induced Ca\(^{2+}\) uptake into fraction 2 of the Percoll gradient of Fig. 2B was measured in the absence (B) or presence of 30 \(\mu\)M XeC (A). 40 \(\mu\)M Tg was added where indicated. One out of three independent experiments is shown.

FIG. 4. Light scattering spikes are attenuated by XeC. Light scattering was measured as described under “Experimental Procedures.” To a cell suspension displaying free running spikes 28 \(\mu\)M XeC was added as indicated. One out of three independent experiments is shown. Control cells continued spiking when spikes were abolished in XeC-treated suspensions. The solvent ethanol did not significantly affect spike amplitude in controls.

XeC affected the morphology of the amoebae. Aggregation-competent control cells displayed an elongated, polarized cell shape with many protrusions at the front and laterally (Fig. 5A). In the presence of 8 \(\mu\)M XeC, cells rounded up. After about 30 min they began to extend pseudopods at one end, thereby forming pointed ends in the direction of migration. Little or no pseudopods were observed along their sides (Fig. 5B). Within 60 min these cells recovered to control cell behavior (data not shown). Cells treated with 15–20 \(\mu\)M XeC behaved in the same way, except that extension of pseudopods and migration of the cells began about 90 min later.

As soon as the migration stage was reached, XeC-treated cells were able to orient and to migrate to a cAMP-source (Fig. 6). In contrast to control cells, which exhibited multiple pseudopods at the front and laterally (Fig. 6A), XeC-treated cells predominantly extended pseudopods at the front (Fig. 6B). Only in rare cases were pseudopods formed along their sides. We conclude that formation of lateral protrusions is suppressed transiently in XeC-treated cells.

Basal [Ca\(^{2+}\)]\(_i\), Increases during XeC Treatment—Determination of [Ca\(^{2+}\)]\(_i\) in single cells in the presence of 20 \(\mu\)M XeC revealed a time-dependent increase in the cytosolic Ca\(^{2+}\) concentration (Fig. 7). The basal concentration of 56 ± 9 nM (65 cells) increased within 30 min to 230 ± 11 nM (15 cells). Concomitantly, the percentage of cells that exhibited a cAMP-dependent transient [Ca\(^{2+}\)]\(_i\) increase dropped to zero. In five experiments basal cytosolic Ca\(^{2+}\) increased 3-fold to 188 ± 58 nM in the presence of 15–20 \(\mu\)M XeC, whereas the percentage of responding cells decreased to 12 ± 8%.

cAMP Oscillations—Although we found that spike formation was attenuated in the presence of XeC, periodic cAMP synthesis could still occur. Therefore, we measured cAMP concentrations during free running spikes before and after XeC addition. Fig. 8 shows that the cAMP concentration periodically in-

Table II

| Compound                  | Ca\(^{2+}\) influx pmol/10\(^7\) cells | Inhibition % |
|---------------------------|--------------------------------------|-------------|
| I. Control                | 306                                  |             |
| 20 \(\mu\)M xestospongin C| 158                                  | 48          |
| II. Control               | 306                                  |             |
| 36 \(\mu\)M xestospongin C| 0                                   | 100         |
| III. Control              | 173                                  |             |
| 36 \(\mu\)M xestospongin C| 40                                  | 77          |

| XeC | 
|-----|
| 100 s | 
| ATP | 
| Tg | 
| 6.4 min | 

A cell suspension of 5 × 10^7 cells/ml, 5 h following induction of differentiation, was treated with 20–36 \(\mu\)M XeC. Ca\(^{2+}\)-induced influx was measured as described under “Experimental Procedures” with a Ca\(^{2+}\)-sensitive electrode. Three independent experiments are shown.

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creased beneath the spikes before and after XeC addition, but finally dropped to basal levels when light scattering oscillations had completely stopped. The rather long time required for inhibition of cAMP oscillations may indicate that a threshold concentration of \([\text{Ca}^{2+}]_i\) controls cAMP synthesis. Inspection of Fig. 7 reveals a steep 2-fold \([\text{Ca}^{2+}]_i\) increase about 20 min after addition of XeC.

**DISCUSSION**

In the first part of this study we have shown that XeC is an efficient inhibitor of the IP$_3$-sensitive Ca$^{2+}$ store in *Dictyostelium*. XeC had a similar potency in *Dictyostelium* as compared with PC12 cells or primary astrocytes, where 20 \(\mu M\) XeC was used to block bradykinin-induced Ca$^{2+}$ release or Ca$^{2+}$ oscillations, respectively. By contrast, we found that the IP$_3$-sensitive store displayed a low affinity for Tg in *Dictyostelium* as opposed to mammalian cells.\(^2\) Previously, Tg-induced Ca$^{2+}$ release from internal stores of this organism escaped detection (12, 23). Only recently, a \([\text{Ca}^{2+}]_i\) increase in response to Tg was reported for aequorin-expressing cells (24).

The site of XeC binding to the IP$_3$-sensitive store is not known, only that \(^{3}H\)IP$_3$ binding was not antagonized by XeC (17). The authors suggested that XeC binds to the Ca$^{2+}$ release channel and blocks the channel because of its rod-shaped structure. However, we found that XeC not only inhibited Ca$^{2+}$ release by Tg and IP$_3$, but also was a potent inhibitor of Ca$^{2+}$ uptake into the IP$_3$-sensitive store. Moreover, XeC by itself induced Ca$^{2+}$ release. This indicates that in *Dictyostelium* XeC does not act as a plug of the Ca$^{2+}$ release channel as suggested previously (17). It seems instead to open the channel counter-acting Ca$^{2+}$ uptake. In agreement with this assumption, basal \([\text{Ca}^{2+}]_i\) increased 4-fold during the course of incubation with XeC for 30 min.

In the second part, the use of XeC allowed us to examine the role of the IP$_3$-sensitive store in cell motility and cellular oscillations. Incubation of cells with XeC had a profound effect on

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\(^2\) D. Malchow, manuscript in preparation.
cell motility and cell shape. It is known that in *Dictyostelium* the Ca$^{2+}$-dependent actin-binding proteins $\alpha$-actinin and sev-
erin are involved in cytoskeletal rearrangements (25, 26). Fur-
thermore, the time of the maximal rate of Ca$^{2+}$ influx, 20 s
after stimulation with cAMP, corresponds to the association of
myosin II with the plasma membrane (27) and to the cringing
response, where the cell adopts a rounded shape and contracts
(28). A small artificial elevation of [Ca$^{2+}$], by calmidazolium
causes an extension of pseudopods over the whole cell’s circum-
ference, whereas a larger [Ca$^{2+}$], elevation induces full contrac-
tion (19). In the presence of XeC, the cells first assumed a
round, contracted state. Afterward the cells resumed migration,
where visible extensions were largely confined to the front.
This altered type of behavior can be explained by (a) the
increased [Ca$^{2+}$], of XeC-treated cells and (b) a Ca$^{2+}$ gradient
with the maximum at the rear end reported for amoeboid
movement (29, 30). As long as the [Ca$^{2+}$], remains high, the
cells display a contracted round shape. As soon as the Ca$^{2+}$
concentration drops below a critical level at a particular site,
pseudopod extensions become possible and a front end is gener-
s. Since the front displays the lowest Ca$^{2+}$ concentration,
pseudopods occur predominantly at the front. The rear remains
inactive due to the still elevated Ca$^{2+}$-level. Our results show
that the IP$_3$-sensitive store is crucially involved in the gener-
ation of Ca$^{2+}$ fluxes required to regulate cell shape and motility.

A principal event during early differentiation is the periodic
synthesis and release of cAMP. However, it is still an open
question how cAMP oscillations evolve during differentiation.
Spicule-shaped and sinuosoidal light scattering oscillations exist
(22), but only the former are accompanied by cAMP oscillations
(31). Do cAMP oscillations arise independently, or are they
coupled to a cellular oscillator? Phase shift experiments have
shown that light scattering spikes and cAMP oscillations are
coupled (18). However, Wurster and Mohn described a mutant,
agp 43, that displayed spicule-shaped light scattering oscillations
without elevation of the cAMP concentration. This result indicated
that, despite the coupling of both oscillations, cAMP is
not the pacemaker for cellular oscillations (32). We found
that light scattering oscillations were attenuated in the pres-
ence of XeC. Therefore, we conclude that the IP$_3$-sensitive
Ca$^{2+}$ store is part of this unknown pacemaker.

The finding that periodic cAMP pulses also were inhibited by
XeC could result from (i) the requirement of the pacemaker for
cAMP oscillations or (ii) suppression of cAMP-production by
the cytosolic Ca$^{2+}$ elevation. The first possibility becomes plau-
sible if we assume that store-operated Ca$^{2+}$ oscillations serve
as a pacemaker. In the presence of XeC, Ca$^{2+}$ uptake by the
IP$_3$-sensitive store was inhibited and basal [Ca$^{2+}$], increased.
Therefore, ongoing Ca$^{2+}$ oscillations should be perturbed. With
respect to the second possibility, an inhibition of the increase of
the concentration of cAMP by Ca$^{2+}$ under various conditions has
been shown (18, 33, 34). It is unknown, however, whether
adenyl cyclase activity is inhibited or hydrolysis of cAMP is
activated by Ca$^{2+}$. Schaup and co-workers (35) reported a 47%
inhibition of adenyl cyclase activity in *Dictyostelium* homoge-

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