In NIH 3T3 cells, treatment with phorbol 12-myristate 13-acetate (PMA) reduced the release of Ca\(^{2+}\) by thapsigargin, but did not activate Ca\(^{2+}\) entry; Ca\(^{2+}\) influx was triggered after the residual pool was emptied by thapsigargin, and this Ca\(^{2+}\) influx was similar to that induced by thapsigargin in control cells. The effect of PMA was due to decreased Ca\(^{2+}\) storage because 1) Ca\(^{2+}\) release by ionomycin was similarly affected by PMA, and in both control and PMA-treated cells, ionomycin did not release Ca\(^{2+}\) following thapsigargin treatment; 2) PMA reduced \(^{45}\)Ca\(^{2+}\) accumulation; and 3) studies with Ca\(^{2+}\) indicator compartmentalized into the endoplasmic reticulum indicated that stored Ca\(^{2+}\) was reduced by PMA. Although PMA did not itself activate Ca\(^{2+}\) entry, PMA potentiated Ca\(^{2+}\) entry with low concentrations of cyclopiazonic acid. With a somewhat higher concentration of cyclopiazonic acid, PMA had no effect on calcium entry. Thus, protein kinase C has two apparent actions on calcium signaling in NIH 3T3 cells: 1) reduced intracellular Ca\(^{2+}\) storage capacity and 2) augmented calcium entry with submaximal intracellular Ca\(^{2+}\) pool depletion. These actions indicate a complex and potentially important role for the protein kinase C system in calcium homeostasis in this cell type.
**FIG. 1.** PMA significantly reduces the apparent size of the thapsigargin-sensitive Ca\(^{2+}\) pool without activating capacitative Ca\(^{2+}\) influx. NIH 3T3 cells grown on coverslips were treated with Me\(_2\)SO (control; solid lines) or 1.6 \(\mu\)M PMA (dashed lines) for 1 h, and [Ca\(^{2+}\)]\(_i\) was measured as described under “Materials and Methods.” Except where indicated, experiments were performed in nominally Ca\(^{2+}\)-free HPSS medium. The concentration of thapsigargin used in all experiments was 2 \(\mu\)M. A, despite the substantial depletion of Ca\(^{2+}\) stores by PMA, Ca\(^{2+}\) entry was not detected when 1.8 mM Ca\(^{2+}\) was added to the Ca\(^{2+}\)-deficient buffer. However, after thapsigargin released the residual Ca\(^{2+}\)-pool, Ca\(^{2+}\) influx was detected upon restoration of 1.8 mM Ca\(^{2+}\) to the extracellular medium, and this entry was not different in PMA-treated cells compared with controls. B, the PMA effect did not result from redistribution of Ca\(^{2+}\) since following thapsigargin addition to control or PMA-treated cells, addition of 10 \(\mu\)M ionomycin (Iono.) + 200 \(\mu\)M EGTA did not mobilize additional Ca\(^{2+}\).

**RESULTS**

NIH 3T3 fibroblasts were exposed to either 1.6 \(\mu\)M PMA or vehicle (0.1% [v/v] Me\(_2\)SO) for 1 h at 37 °C. The cells were loaded with furan-2, and [Ca\(^{2+}\)]\(_i\) was measured before and after addition of 2 \(\mu\)M thapsigargin (Fig. 1). In PMA-treated cells kept in nominally Ca\(^{2+}\)-free HPSS buffer, the thapsigargin-induced Ca\(^{2+}\) peak was diminished in comparison with control cells; however, although this might be taken as indicative of depletion of Ca\(^{2+}\) stores by PMA, addition of 1.8 mM Ca\(^{2+}\) prior to thapsigargin did not evoke Ca\(^{2+}\) influx in PMA-treated or control cells (Fig. 1A). Substantial Ca\(^{2+}\) entry was seen only after the residual stored Ca\(^{2+}\) was depleted with thapsigargin. Neither the magnitude nor the rate of the [Ca\(^{2+}\)]\(_i\) rise associated with influx was significantly different from that in control cells (Fig. 1A; data not shown). The action of PMA to produce an apparent reduction in releasable Ca\(^{2+}\) did not result from redistribution of Ca\(^{2+}\) to other sites because, in PMA-treated cells, addition of 10 \(\mu\)M ionomycin (in the presence of 200 \(\mu\)M EGTA) after thapsigargin did not induce any further Ca\(^{2+}\) mobilization (Fig. 1B). Furthermore, PMA-dependent reduction in stored Ca\(^{2+}\) was also observed when 10 \(\mu\)M ionomycin (in the presence of 200 \(\mu\)M EGTA) was used, instead of thapsigargin, to assess stored Ca\(^{2+}\) (data not shown; see Fig. 1B). Thus, in NIH 3T3 cells, PMA significantly reduces the amount of sequestered Ca\(^{2+}\) without any accompanying activation of Ca\(^{2+}\) entry.

**Fig. 2.** The effect of PMA on the thapsigargin-sensitive Ca\(^{2+}\) pool is concentration-, time-, and temperature-dependent. \(\gamma\) axis values denote the peak [Ca\(^{2+}\)]\(_i\), level in response to 2 \(\mu\)M thapsigargin in Ca\(^{2+}\)-deficient buffer following the different treatments. In A, the time of PMA incubation and the temperature of the incubation were varied, while in B, all treatments were for 60 min at 37 °C. A, the action of PMA was time- and temperature-dependent, as it was observed when the cells were incubated with 1.6 \(\mu\)M phorbol ester at 37 °C, but not at 25 °C. B, the depletion of the Ca\(^{2+}\) stores by PMA depended on the concentration used. *, significantly different from \(t = 0\) (A) or no PMA (B) (\(p < 0.05\)).
Fig. 3. The PMA-induced depletion of the thapsigargin-sensitive Ca\(^{2+}\) pool is reproduced by other activators of PKC. y axis values denote the peak [Ca\(^{2+}\)] level in response to 2 \(\mu M\) thapsigargin in Ca\(^{2+}\)-deficient buffer following the different treatments. A, the PKC activator oleoylacylglycerol (OAG) mimicked the PMA action in a concentration-dependent fashion and was not additive with PMA. B, similarly, activation of PKC by phorbol dibutyrate (PDBu) reproduced the PMA effect in a concentration-dependent way. No depletion occurred with the inactive 4\(\alpha\)-PMA (data not shown). Oleoylacylglycerol and phorbol esters were applied for 1 h at 37 °C.

rapid and was maximal by 60 min. The effect of PMA on thapsigargin-released Ca\(^{2+}\) was also dependent on PMA concentration (Fig. 2B); in cells incubated with the phorbol ester for 60 min at 37 °C, half-maximal inhibition of the thapsigargin release of stored Ca\(^{2+}\) required 16 nm PMA (thapsigargin-induced release was 114 ± 5 and 83 ± 7 nm in control and 16 nm PMA-treated cells, respectively).

In the experiments shown in Fig. 2A, prior to and following addition of thapsigargin, 1.8 nm Ca\(^{2+}\) was restored to the medium to assess calcium entry. Again, despite the time-dependent effects of PMA on Ca\(^{2+}\)-store capacity, Ca\(^{2+}\)-entry was never activated until thapsigargin was added; as discussed above for Fig. 1A, following the complete depletion of stores with thapsigargin, the extent of Ca\(^{2+}\)-entry was statistically indistinguishable in control and PMA-treated cells (control, 229 ± 30 nm; 15-min PMA treatment, 192 ± 21 nm; 45-min PMA treatment, 260 ± 19 nm; and 90-min PMA treatment, 206 ± 27 nm; p > 0.05).

To confirm that the reduction in Ca\(^{2+}\)-storage caused by PMA resulted from activation of PKC, cells were treated under the same conditions used for PMA with oleoylacylglycerol (Fig. 3A). Oleoylacylglycerol mimicked the effect of PMA in a concentration-dependent manner and was not additive with PMA, suggesting that both compounds acted via activation of PKC to promote Ca\(^{2+}\)-pool depletion. A similar result was achieved with the less potent phorbol ester phorbol dibutyrate (Fig. 3B). The effects of PMA were at least partially reversed by the specific protein kinase C inhibitor chelerythrine chloride (thapsigargin-induced release, percent increase over base line: control, 142.3 ± 21.4%; 16 nm PMA, 41.3 ± 17.9%; and 16 nm PMA + 1 \(\mu M\) chelerythrine chloride, 100.4 ± 13.2%). Finally, treatment with the inactive 4\(\alpha\)-phorbol did not promote any loss of stored Ca\(^{2+}\), consistent with the involvement of PKC in this phenomenon (thapsigargin-induced release, percent increase over base line: control, 147.1 ± 12.7%; and 1.5 \(\mu M\) 4\(\alpha\)-PMA, 161.4 ± 19.8%; p > 0.05).

That PMA induces a net loss of sequestered Ca\(^{2+}\) was confirmed by measurement of \(^{45}\text{Ca}^{2+}\) uptake. Fig. 4 shows that steady-state \(^{45}\text{Ca}^{2+}\) accumulation in attached NIH 3T3 cells was significantly diminished by incubation with PMA. However, the initial rate of uptake and the rate of efflux after removal of \(^{45}\text{Ca}^{2+}\) from the medium appeared to be unaffected by phorbol ester treatment.

We next carried out experiments to assess differences in the levels of stored calcium by using a Ca\(^{2+}\)-sensitive fluorescent indicator compartmentalized in the endoplasmic reticulum. Fura-2 was used in these experiments because its \(K_d\) for Ca\(^{2+}\) is 25 \(\mu M\) (13), in the range expected in the lumen of the endoplasmic reticulum. The prolonged incubation time with fura-F/AM at 37 °C encourages compartmentalization of the dye into intracellular organelles (18). The signal from cytoplasmic noncompartmentalized dye was reduced or eliminated by addition of 20 mm MnCl\(_2\) to the cells; this caused an increase in the fluorescence ratio as the relative contribution of dye sequestered in Mn\(^{2+}\)-inaccessible compartments with elevated [Ca\(^{2+}\)] was increased (Fig. 5). This elevated fluorescence ratio results in large part from Ca\(^{2+}\) in the endoplasmic reticulum because addition of thapsigargin reduces the ratio as Ca\(^{2+}\) is released from endoplasmic reticulum stores. As shown in Fig. 5, in cells pretreated with either PMA or a 1 \(\mu M\) concentration of the reversible Ca\(^{2+}\)-ATPase inhibitor cyclopiazonic acid, the increase in ratio on addition of Mn\(^{2+}\) and the decrease in ratio on addition of thapsigargin were substantially diminished as compared with control cells. These data suggest (but do not prove) that the average endoplasmic reticulum luminal [Ca\(^{2+}\)] is lower in cells treated with either PMA or cyclopiazonic acid. In each case, this could result from a reduction in the volume of the Ca\(^{2+}\)-storing compartment relative to other sites of dye sequestration, from partial loss of Ca\(^{2+}\) from all of the endoplasmic reticulum, or from a complete loss of Ca\(^{2+}\) from a fraction of the total endoplasmic reticulum.

In NIH 3T3 cells, virtually all of the sequestered Ca\(^{2+}\) appears to be stored in a thapsigargin-sensitive compartment because once Ca\(^{2+}\) is released by thapsigargin, no further release of Ca\(^{2+}\) by ionomycin is observed. However, because it appears that this Ca\(^{2+}\)-pool can be substantially reduced without affecting the entry of Ca\(^{2+}\), we next sought to determine whether the entire thapsigargin-sensitive Ca\(^{2+}\)-pool is homogeneously sensitive to IP\(_3\). As shown in Fig. 6, cells were microinjected with a 1 \(nm\) concentration (pipette concentration) of the nonhydrolyzable IP\(_3\) analog (2,4,5)IP\(_3\) in the absence of external Ca\(^{2+}\) and treated subsequently with 2 \(\mu M\) thapsigargin; (2,4,5)IP\(_3\) appeared to cause the release of total stored Ca\(^{2+}\) because application of 2 \(\mu M\) thapsigargin was without any additional effect. Next, IP\(_3\) was generated from activation of phospholipase C-\(\gamma\) by a maximal concentration (100 ng/ml) of platelet-derived growth factor (PDGF) in control and PMA-treated cells (Fig. 7). In control cells, addition of PDGF in the absence of external Ca\(^{2+}\) increased [Ca\(^{2+}\)], and following the return of [Ca\(^{2+}\)], to baseline levels, additional Ca\(^{2+}\) was
mobilized by subsequent application of 2 μM thapsigargin. This indicates that the quantity of IP₃ produced in PDGF-stimulated cells is insufficient to empty the entire thapsigargin- and IP₃-sensitive Ca²⁺ store. In cells pretreated with PMA, PDGF-induced Ca²⁺ release was significantly diminished, while the subsequent thapsigargin response was almost completely blunted (Fig. 7). (Note that there was always a substantial and highly variable delay preceding the rise in [Ca²⁺], following PDGF treatment, but this delay was not affected by treatment with PMA.) Together, the results from Figs. 6 and 7 suggest that PMA treatment does not selectively alter Ca²⁺ storage in agonist- or IP₃-insensitive pools and that all of the thapsigargin-sensitive stores are also sensitive to IP₃.

Because the reduction in stored Ca²⁺ by PMA treatment required up to 1 h for maximal effect, we considered the possibility that the total ER content of the cells may have diminished. Therefore, total homogenates from control or PMA-treated cells were subjected to Western blots for two ER markers, the IP₃ receptor and calreticulin, an ER resident protein. As shown in Fig. 8, the PMA treatment did not affect the density of either marker, suggesting that the Ca²⁺ pool depletion elicited by PMA was not a consequence of loss of ER membrane.

Activation of PKC by phorbol esters is known to induce morphological changes due to cytoskeleton rearrangement in different cell types (19–21). To determine if the activation of PKC by PMA promoted any significant alterations in cell morphology, control and PMA-treated cells were visualized by differential interference contrast microscopy (Fig. 9, A and B, respectively). The flattened, planar aspect of control cells, characteristic of naive fibroblasts, was changed to a rounded shape after a 60-min incubation with 1.6 μM PMA, agreeing with previous observations that activation of PKC alters NIH 3T3 cell structure (22). To determine if the morphology of the ER was affected by the PMA treatment, control and PMA-treated cells were stained with the fluorescent dye rhodamine 6G to label the ER and were examined by confocal fluorescence microscopy (Fig. 9, C and D, respectively). In control cells, the fluorescent staining was spread, and a tubular network of organelles resembling the normal structure of stacks of ER was observed; on the other hand, in PMA-treated cells, the spread fluorescent labeling was lost and became punctate.

One possible explanation for the inability of PMA to activate calcium influx despite its ability to cause an apparent depletion of Ca²⁺ stores would be that the extent of depletion by PMA was beneath some critical threshold amount of depletion required to activate influx. Alternatively, because PMA is known to inhibit capacitative calcium influx in some systems (10, 11,
Fig. 10A illustrates the protocol; the upper and lower tracings are representative experiments in which 10 and 0.1 μM cyclopiazonic acid were used, respectively. As shown in Fig. 10B, each of three concentrations of cyclopiazonic acid (0.5, 1.0, and 2.5 μM) induced a graded (but nonlinear), submaximal (as compared with 2 μM thapsigargin) depletion of intracellular stores, as indicated by a graded diminution in residual ionomycin-releasable Ca²⁺; at all three concentrations of cyclopiazonic acid, this depletion was greater in the PMA-treated cells. Fig. 10C shows the data for Ca²⁺ entry from these same experiments. Again, the three concentrations of cyclopiazonic acid induced a graded increase in Ca²⁺ entry, and PMA did not inhibit Ca²⁺ entry under any of the conditions examined. Rather, PMA significantly augmented Ca²⁺ entry at the two lowest cyclopiazonic acid concentrations (0.5 and 1.0 μM). This effect of PMA was not obtained with the inactive stereoisomer 4α-PMA (with 0.5 μM cyclopiazonic acid; control entry, 30 ± 12 nM, n = 4; entry in cells treated with 1.5 μM 4α-PMA, 27 ± 9 nM, n = 4; p > 0.05). PMA treatment did not augment Ca²⁺ entry due to 2.5 μM cyclopiazonic acid, despite the fact that, at this concentration of cyclopiazonic acid, both Ca²⁺ store depletion and Ca²⁺ entry were submaximal, and Ca²⁺ store depletion was significantly greater in the PMA-treated cells. Note that
PMA treatment induced an apparent greater depletion of Ca\(^{2+}\) stores than did 0.5 or 1.0 \(\mu\)M cyclopiazonic acid, despite the fact that these concentrations of cyclopiazonic acid induced significant influx of Ca\(^{2+}\), while PMA did not.

These results indicate two effects of PMA on calcium homeostasis in NIH 3T3 cells. Minimal depletion of intracellular stores by cyclopiazonic acid activated significant Ca\(^{2+}\) entry, while an apparently greater depletion by PMA alone did not. This indicates that the failure of PMA to activate entry is not simply due to an inability to release Ca\(^{2+}\) to some threshold level. Also, PMA did not inhibit cyclopiazonic acid-induced Ca\(^{2+}\) entry at any of the concentrations examined. Rather, in a restricted range of cyclopiazonic acid concentrations, entry was actually augmented by PMA. Therefore, we conclude that the effects of PMA on Ca\(^{2+}\) storage are decidedly unlike those of the Ca\(^{2+}\)-ATPase inhibitors. In addition, the ability of PMA to augment Ca\(^{2+}\) entry in a specific range of pool depletion appears to indicate an action of protein kinase C on calcium entry that is independent of the action of PMA on intracellular Ca\(^{2+}\) storage.

**DISCUSSION**

This study demonstrates that PMA treatment of NIH 3T3 cells results in a substantial loss of Ca\(^{2+}\) from thapsigargin- and IP\(_3\)-sensitive Ca\(^{2+}\) pools, but this apparent depletion of stored Ca\(^{2+}\) does not lead to activation of capacitative Ca\(^{2+}\) entry (Fig. 1). The effect of PMA on sequestered Ca\(^{2+}\) is concentration-, time-, and temperature-dependent (Fig. 2) and appears to be mediated by PKC (Fig. 3); however, it may result from the activation of a temperature-dependent pathway initiated or regulated by PKC rather than from a direct action of PKC since activation of PKC by PMA has been observed at 25 °C in several systems.

We have also found that PMA treatment reduces stored Ca\(^{2+}\) in an epidermal cell line (A431) as well as in freshly isolated lacrimal cells (data not shown), suggesting that this phenomenon may be a general one. This suggestion is further supported by two recent reports on glioma C6 cells (24) and platelets (25), where it was shown that PMA treatment decreased thapsigargin-dependent Ca\(^{2+}\) release, in agreement with our results. However, those data differ from our data in that the phorbol ester treatment also inhibited thapsigargin-activated Ca\(^{2+}\) influx, no experiments were carried out to determine if Ca\(^{2+}\) storage was affected, and the authors concluded that the effects on release and entry were in some way related (i.e., by increased Ca\(^{2+}\) extrusion, for example). While our findings may not be directly applicable to these other systems, they may indicate that the effects of PMA on release of Ca\(^{2+}\) and on entry are in fact not related. Thus, with the results of our work included, there now exist cell types in which PMA induces an inhibition of entry, with no effect on the size of the stores, an inhibition of entry as well as a diminution in stored Ca\(^{2+}\), and now a diminution in store Ca\(^{2+}\) with no effect on entry.

The mechanism underlying the action of PKC on Ca\(^{2+}\) storage in NIH 3T3 cells is not known. Possible Ca\(^{2+}\) transport systems that could be modulated by the activated enzyme are the ER Ca\(^{2+}\)-ATPase, the ER leak channel, the ER IP\(_3\) receptor, or the plasma membrane Ca\(^{2+}\)-ATPase. Although their activities have not been directly measured in this study, the initial unidirectional rates of \(^{45}\)Ca\(^{2+}\) uptake in intact cells (Fig. 4), a primary function of Ca\(^{2+}\)-ATPase-dependent Ca\(^{2+}\) sequestration, are not different in control versus PMA-treated fibroblasts; these data suggest that the activity of this Ca\(^{2+}\) transporter is not regulated by PKC and thus cannot mediate the PMA action. The \(^{45}\)Ca\(^{2+}\) efflux rates (Fig. 4), a result of the combined activities of the leak channel and the plasma membrane Ca\(^{2+}\)-ATPase, are the same in control and PMA-treated cells, suggesting that these Ca\(^{2+}\) transport systems are not affected by PKC activation either. One possibility consistent with these observations is that a subtraction of the ER that is specifically PKC-sensitive is so completely emptied by PMA treatment that it does not contribute to the measured kinetics. Modulation of IP\(_3\) receptor function may be a possibility to account for the ER Ca\(^{2+}\) loss, but probably not though changes in IP\(_3\) levels since phospholipase C activity is inhibited by PKC activation in these cells. Since the IP\(_3\) receptor has been suggested to interact with ankyrin, a cytoskeletal protein (26, 27), it is possible that PKC activation increases the permeability of this Ca\(^{2+}\) channel through a cytoskeletal modulation resulting in Ca\(^{2+}\) loss.

Our data suggest that activation of PKC in NIH 3T3 cells induces profound changes in the architecture of the ER, perhaps a fragmentation of that organelle (Fig. 9) without net loss of its membrane (Fig. 8). These results are supported by a
recent report on the effects of phorbol ester on cell morphology and localization of overexpressed PKC isoforms in NIH 3T3 fibroblasts (22); after a 15-min treatment with 100 nM PMA, PKC-α localized in the cell periphery and accumulated in cell margins, but a portion of the activated PKC-α concentrated in punctate regions in the cytoplasm, near the nucleus, and the punctate labeling was confirmed by double staining to be in the ER. Interestingly, colocalization of PKC-α and ER proteins was seen even in the absence of PKC activation (22). Since PKC-α is expressed in wild-type NIH 3T3 cells (22, 28), we can speculate that activation of this PKC isoform and its association with components of the ER are somehow causally related to the loss of sequestered Ca^{2+}. These results raise an important question: Are these modifications in ER structure a result or a cause of the Ca^{2+} pool depletion promoted by PMA? An earlier study in starfish oocytes reported that sperm-induced fertilization or microinjection of IP3, maneuvers that deplete the ER of Ca^{2+}, transiently fragmented the ER (29). Furthermore, it was suggested that, since the period when the ER was fragmented temporally correlated with the time when [Ca^{2+}] was high, the fragmentation may have been caused by loss of Ca^{2+} from the ER (29). Our findings suggesting that activation of PKC degrades Ca^{2+} and causes ER fragmentation are in good agreement with that report, but the temporal relationship between these events remains to be established in NIH 3T3 cells.

Recent studies have suggested that activation of PKC may affect capacitative Ca^{2+} entry by either stimulating or inhibiting its activity depending on the cell type (rat thyroid cells (8), human neutrophils (23), Xenopus oocytes (11), pancreatic cells (12), and RBL-2H3 cells (10)). Our data indicate that, in NIH 3T3 cells, PKC does not inhibit but rather augments capacitative calcium entry. Curiously, this augmentation only occurs with a minimal degree of calcium store depletion, as obtained with 0.5 and 1.0 μM cyclopiazonic acid. While the depletion of Ca^{2+} stores by PMA might be expected to contribute to capacitative Ca^{2+} entry, this does not appear to be the mechanism by which PMA augments entry in this situation. PMA induces an apparent Ca^{2+} store depletion that is greater than that due to 0.5 μM cyclopiazonic acid, but does not activate entry, and with 2.5 μM cyclopiazonic acid, there is a substantial increase in intracellular store depletion in the PMA-treated cells, but no additional Ca^{2+} entry. Thus, the ability of PMA to deplete Ca^{2+} stores and the ability of PMA to potentiate Ca^{2+} entry are not well correlated, and it appears likely that the effect on Ca^{2+} entry results from an additional site of action of PMA somewhere in the pathway signaling capacitative Ca^{2+} entry.

In summary, this study provides a number of novel and potentially important insights regarding the regulation of Ca^{2+} homeostasis and Ca^{2+} signaling by protein kinase C. The data clearly establish that, in a variety of cell types, activation of the protein kinase C pathway has profound effects on cellular Ca^{2+} storage. Yet, these changes in Ca^{2+} storage do not impact in a major way on the ability of ER calcium stores to regulate capacitative calcium entry. Further research is necessary to understand the molecular and subcellular actions of protein kinase C in regulating Ca^{2+} storage in NIH 3T3 and other cell types.

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