How different extracellular stimuli can evoke different spatiotemporal Ca\(^{2+}\) signals is uncertain. We have elucidated a novel paradigm whereby different agonists use different Ca\(^{2+}\)-storing organelles ("organelle selection") to evoke unique responses. Some agonists select the endoplasmic reticulum (ER), and others select lysosome-related (acidic) organelles, evoking spatial Ca\(^{2+}\) responses that mirror the organelar distribution. In pancreatic acinar cells, acetylcholine and bombesin exclusively select the ER Ca\(^{2+}\) store, whereas cholecystokinin additionally recruits a lysosome-related organelle. Similarly, in a pancreatic β cell line MIN6, acetylcholine selects only the ER, whereas glucose mobilizes Ca\(^{2+}\) from a lysosome-related organelle. We also show that the key to organelle selection is the agonist-specific coupling messenger(s) such that the ER is selected by recruitment of inositol 1,4,5-trisphosphate (or cADP-ribose), whereas lysosome-related organelles are selected by NAADP.

Increases in the Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_i\)) represent a ubiquitous transduction mechanism in response to stimuli as diverse as fertilization, neurotransmitters, hormones, and blood glucose (1). In turn, Ca\(^{2+}\)-binding proteins responsible for decoding these Ca\(^{2+}\) signals promote an array of cellular responses from cell division to cell death, notably including secretion (1). However, what remains perplexing is that not all stimuli that increase Ca\(^{2+}\) elicit the same physiological response, implying differences in their [Ca\(^{2+}\)]\(_i\) handling. Some early indications arose from single cell and subcellular [Ca\(^{2+}\)]\(_i\) studies which revealed that each stimulus evoked its own unique Ca\(^{2+}\) response in time and space (exemplified by agonist-specific "Ca\(^{2+}\) signatures") (2). But the mechanism(s) underlying stimulus-specific Ca\(^{2+}\) signaling is poorly understood.

It has become clear that a primary factor governing agonist specificity is the release of Ca\(^{2+}\) from intracellular stores, a process that encompasses multiple channel families regulated by the second messengers inositol 1,4,5-trisphosphate (IP\(_3\)), cyclic ADP-ribose (cADPR), and nicotinic acid adenine dinucleotide phosphate (NAADP). By differential recruitment of second messenger complements, different agonists could, in principle, elicit different Ca\(^{2+}\) signals, and several cellular systems have indeed been shown to exploit messenger diversity, e.g. pancreatic acinar cells (3).

However, the use of different messengers per se is not sufficient to evoke different signals; only if these systems are non-equivalent and differ in their properties, regulation, or spatial distribution will this hold. In spatial terms, IP\(_3\) and cADPR mobilize the endoplasmic reticulal (ER) Ca\(^{2+}\) store in nearly all cell types (1, 4), although an outstanding issue has been the identity and location of the NAADP-sensitive store. Only recently has this been characterized in sea urchin eggs as a lysosome-related organelle (5), with its mammalian counterpart remaining elusive beyond an isolated report that secretory vesicles support NAADP-induced Ca\(^{2+}\) release in permeabilized cells (6).

Given the uncertainties surrounding the role and properties of different potential Ca\(^{2+}\) stores, we therefore show for the first time that different agonists generate their specific signals by signaling through Ca\(^{2+}\) mobilization from different intracellular stores (organelle selection). This is determined by their second messenger complements, with NAADP-linked agonists coupling to lysosome-related organelles in mammalian cells and those linked to IP\(_3\)/cADPR coupling to ER pools.

**EXPERIMENTAL PROCEDURES**

**Cell Preparation**—To obtain pancreatic acinar cells, pancreata were excised from male CD1 mice 8–10 weeks old, and small clusters of pancreatic acinar cells were prepared by collagenase digestion as described previously (7). MIN6 cells were cultured in Dulbecco’s modified Eagle’s medium (25 mM glucose) supplemented with 10% fetal calf serum, 2 mM glutamine, 100 units/ml penicillin, 100 µg/ml streptomycin, and 50 µM β-mercaptoethanol equilibrated with 5% CO\(_2\) and 95% air at 37 °C. Twenty hours before each experiment, cells were placed in low glucose Dulbecco’s modified Eagle’s medium (5 mM glucose).

**Ca\(^{2+}\) Imaging**—Both acinar and MIN6 cells were seeded onto polylysine-coated number 1 glass coverslips and loaded with 1–5 µM fura-2 acetoxymethyl ester (fura-2/AM) for 60 min at room temperature. Acinar and MIN6 cells were maintained in buffer of the following compositions: for acinar cells (in mM), 140 NaCl, 4.7 KCl, 1.1 MgCl\(_2\), 1 CaCl\(_2\), 10 Hepes, 10 glucose, pH 7.2; for MIN6 cells (in mM), 119 NaCl, 4.75 KCl, 1.2 NaHCO\(_3\), 1.2 MgSO\(_4\), 1.18 KH\(_2\)PO\(_4\), 20 Hepes, 2.54 CaCl\(_2\), and 2.8 glucose, pH 7.4. After the loading period, cells were washed and imaged immediately. Coverslips were mounted in a static chamber (Harvard Apparatus), on an inverted Zeiss 35 Axiosvert microscope, and imaged with a conventional epifluorescence system, using Metaflou
software (Universal Imaging). Cells were excited alternately with 340 and 380 nm light (emission 510 nm), and ratio images of clusters were recorded every 4–5 s, using a 12-bit CCD camera (MicroMax, Princeton Instruments). All experiments were conducted at room temperature for acinar cells and at 37 °C for MIN6 cells.

**Imaging Lysosomes**—Acidic organelles in both cell types were labeled by incubating cells with 50 nM Lysotracker Red for 20 min at room temperature. Labeling was visualized after 20–40 min of removing excess dye using a Leica TCS NT laser scanning confocal microscope (excitation 568 nm, emission /590 nm).

**Flash Photolysis**—Acinar cells and MIN6 cells were pressure-microinjected (Femtojet, Eppendorf) with Oregon Green BAPTA-1 dextran (OGBD, final concentration of 20 and 5 μM, respectively) with caged compounds. In acinar cells the Ca2+-sensitive dye was imaged (excitation 490 nm, emission 530 nm) as mentioned, and the caged compounds were photolysed with an XF-10 arc lamp (HI-TECH Scientific, the ultraviolet flash efficiency was 0.5–1%). On the other hand, MIN6 cells were imaged by laser-scanning confocal microscopy (Leica TCS NT), and caged compounds were photolysed with an ultraviolet laser (efficiency of uncaging of ~50%). Images were processed using Metamorph software (Universal Imaging). Ca2+ concentration is given as the ratio F/F0 where F0 is the fluorescence before stimulation, and F the fluorescence at a given time. Changes in Ca2+ concentration are given as increases in the mentioned ratio (ΔF/F0).

**Statistical Analysis**—Data are presented as means ± S.E. Statistical significance were evaluated by paired Student's t test and, for multiple comparisons, analysis of variance followed by Fisher's Least Significant Difference test (Statview, Abacus Concepts).

**Materials**—Caged IP3 was from Calbiochem. Caged cADPR, Fura-2/AM, OGBD, and Lysotracker Red were from Molecular Probes, and collagenase was from Worthington. Caged NAADP was synthesized essentially as described previously (8). All other reagents were from Sigma.
The EN, on the other hand, is the established Ca$^{2+}$ reservoir for many G protein-coupled receptors, including those for acetylcholine and bombesin. In pancreatic acinar cells, these stimuli are well documented to release Ca$^{2+}$ from the ER using both IP$_3$ and ryanodine receptors (12, 13). Furthermore, cholecystokinin-induced Ca$^{2+}$ signals were also confirmed to derive from the ER as evidenced by the marked inhibition by thapsigargin (Fig. 1n). Together, the evidence supports cholecystokinin recruiting both lysosomes and ER, whereas acetylcholine and bombesin only target the ER in order to generate [Ca$^{2+}$], signals.

An obvious issue is whether this differential organelar recruitment is specific to acinar cells or a universal blueprint for other mammalian cell types and stimuli. In choosing another model, the pancreatic β cell, we opted for a system with very different properties from the acinar cell, the new one being an excitable cell in which Ca$^{2+}$ signals are elicited by nutrients as well as by G protein-coupled agonists (14, 15). In the β cell line, MIN6 (16), we compared three different stimuli, glucose, acetylcholine, and K$^+$, with regard to their relative sensitivities to bafilomycin A1 or thapsigargin. Mechanistically, glucose metabolism generates intracellular signals that culminate in a complex interplay between Ca$^{2+}$ influx and Ca$^{2+}$ release from intracellular stores (17); muscarinic acetylcholine receptors are G protein-coupled to phospholipase C (15), whereas high K$^+$ depolarizes the plasma membrane to induce voltage-operated Ca$^{2+}$ entry (18, 19).

In MIN6 cells, the sensitivity of Ca$^{2+}$ responses to bafilomycin A1 was, like acinar cells, highly dependent upon the stimulus. Remarkably, glucose responses were profoundly inhibited by a preincubation with bafilomycin A1 (Fig. 2, a and b), whereas neither acetylcholine nor K$^+$ stimulation was affected (Fig. 2, d and e and g and h). That the acidic stores of the glucose response were lysosome-related was confirmed by the inhibition by GPN (data not shown). Moreover, these results confirm the specificity of bafilomycin and GPN because neither inhibition by GPN (data not shown). Moreover, these results confirm the specificity of bafilomycin and GPN because neither interacts with the IP$_3$-calcium release pathway (acetylcholine) nor calcium influx (K$^+$). Remarkably, the effects of interfering with ER stores with thapsigargin were almost the mirror of those with bafilomycin A1. Glucose-induced Ca$^{2+}$ signals were not inhibited by ER depletion (Fig. 2c) but rather appeared to be potentiated because thapsigargin greatly reduced the lag phase and eliminated the initial fall in basal [Ca$^{2+}$]. Similarly, responses induced by K$^+$ were also slightly potentiated (Fig. 2i), attesting to the role of the ER as a Ca$^{2+}$ sink in β cells (20). On the other hand, the ER appeared to play a major role during acetylcholine-induced Ca$^{2+}$ mobilization because responses were completely eliminated by thapsigargin (Fig. 2g). Taken together, the data in this cell type support a model of the reciprocal recruitment of different organelles where metabolic activation is heavily reliant upon lysosome-related Ca$^{2+}$ stores, contrasting with an exclusive ER role in response to neurotransmitter.

Next we provide a mechanism to couple particular extracellular stimuli to specific intracellular organelles with the appropriate fidelity. Interestingly, our data show an absolute correlation between those stimuli that recruit lysosome-related organelles and those known to utilize NAADP as a Ca$^{2+}$-mobilizing messenger (21), i.e. cholecystokinin in pancreatic acinar cells (22) and glucose in β cells (16). The agonists that fail to require acidic stores are well known to couple to IP$_3$ and/or ryanodine receptors that mobilize ER Ca$^{2+}$ stores (13, 23, 24). We therefore tested whether NAADP was the unique link to acidic stores, with IP$_3$ and/or CADPR showing a preference for non-acidic (ER) stores.

First, in pancreatic acinar cells, photorelease of IP$_3$ or...
cADPR from their caged precursors evoked robust, monotonic Ca\(^{2+}\) transients in control cells (Fig. 3, a and b) comparable in magnitude to the subsequent response to acetylcholine. Elimination of lysosomal Ca\(^{2+}\) storage by preincubation with GPN had no effect upon the magnitude of the [Ca\(^{2+}\)], rise in response to either IP\(_3\) or cADPR (or the following acetylcholine responses) (Fig. 3, d and e). By contrast, GPN profoundly inhibited the Ca\(^{2+}\) oscillations following uncaging of NAADP (Fig. 3, c and f). Note that the NAADP-induced Ca\(^{2+}\) spikes are initially small and became progressively amplified by Ca\(^{2+}\)-induced Ca\(^{2+}\) release mechanism through the recruitment of IP\(_3\) and ryanodine receptors (3, 22, 25–27). In agreement with the effects of GPN, bafilomycin A1 displayed an identical and selective block of NAADP-induced over IP\(_3\)-induced responses (data not shown, n = 4). The very fact that the Ca\(^{2+}\) responses to second messengers alone are inhibited strongly suggests that bafilomycin A1 and GPN are working downstream of NAADP, and not at an upstream element of the signaling cascade initiated by agonist. We conclude that only NAADP couples to the lysosome-related Ca\(^{2+}\) store in acinar cells, whereas cADPR and IP\(_3\) couple to the ER.

Our hypothesis is also supported in experiments with the β cell system; in these cells NAADP-dependent Ca\(^{2+}\) release occurs via specific binding sites (16). Just as glucose and acetylcholine manifest a reciprocal dependence upon lysosomes and ER, so NAADP and IP\(_3\) displayed this mutually exclusive pattern. NAADP photorelease stimulated a Ca\(^{2+}\) increase that was inhibited by bafilomycin A1 but not by thapsigargin (Fig. 4, a, c and e), whereas the converse occurred when photoreleasing IP\(_3\) (Fig. 4, b, d, and f). Thapsigargin-induced depletion of stores profoundly inhibited IP\(_3\) transients, which were otherwise insensitive to bafilomycin A1. Once again, NAADP selects lysosome-related stores, whereas IP\(_3\) predominantly selects the ER. Hence, the data suggest that lysosome-related stores couple via NAADP to particular extracellular stimuli (16), cholecystokinin and glucose, respectively. Furthermore, by recruiting NAADP, agonists select a novel Ca\(^{2+}\) store with distinct properties, distribution, and ramifications from the ER (primarily the domain of IP\(_3\) and cADPR).

To confirm that the distribution of lysosomal Ca\(^{2+}\) stores indeed has a bearing upon the spatial profile of the Ca\(^{2+}\) response, we compared NAADP-mediated Ca\(^{2+}\) release with the distribution of the organelle in live cells. Lysotracker Red labeling was markedly polarized and confined to the apical region of pancreatic acinar cells reminiscent of secretory vesicle staining (Fig. 5, a and b) (28), which are highly related if not overlapping organelles (29). The observed pattern with Lysotracker Red faithfully reflected lysosomal staining as confirmed by the elimination of the punctate fluorescence by treatment with either GPN (Fig. 5a) or bafilomycin A1 (Fig. 5b). Interestingly, the organelle distribution coincided with the ensuing NAADP-evoked small Ca\(^{2+}\) oscillations, which do not fully recruit Ca\(^{2+}\)-induced Ca\(^{2+}\) release (22, 30) and were confined to the apical pole in acinar cells (Fig. 5c). In contrast, in β cells Lysotracker Red comprised staining of bright punctate bodies, albeit superimposed on a diffuse fluorescent background. This punctate staining was uniformly dispersed throughout the cytoplasm but excluded from the nucleus (Fig. 6, a–c). As in acinar cells, the Lysotracker Red granular staining was eliminated by GPN (Fig. 6a) or bafilomycin A1 (Fig. 6b) but not by thapsigargin (Fig. 6c). Moreover, in MIN6 cells, the response to NAADP in β cells was essentially global (Fig. 6d). Specifically, the close spatial correlation of Ca\(^{2+}\) release and the
acridic store distribution strongly imply that there is a substantive rationale for using different Ca\(^{2+}\)-storing organelles.

**DISCUSSION**

In this present report we provide evidence for a novel mechanism that explains how agonists evoke their own characteristic Ca\(^{2+}\) response, that of organelle selection (Fig. 7). According to this model, different agonists (even within the same cell) mobilize Ca\(^{2+}\) in different ways in time and space by coupling to (selecting) different Ca\(^{2+}\)-storing organelles with their own unique properties and distribution. Moreover, we reveal that a given organelle couples via a particular second messenger, such that an agonist selects organelles by recruiting the appropriate messenger complement. Although our recent results in sea urchin egg (5) provided a framework (that different messengers mobilize Ca\(^{2+}\) from different organelles), the differential recruitment of these organelles by different agonists has never been shown.

In essence, irrespective of cell type, agonists can be divided into those that recruit lysosome-related organelles (cholecystokinin and glucose) and those that do not (acetylcholine and bombesin). Such a conclusion is drawn from pharmacological studies using two mechanistically and chemically distinct inhibitors of lysosomal function, bafilomycin A1 and GPN. Whether added before or during Ca\(^{2+}\) oscillations, these agents selectively inhibited responses to the former pair of agonists, while having little or no effect upon the latter. We are confident that these agents act specifically upon acidic Ca\(^{2+}\) stores because of the following: (a) they did not indiscriminately inhibit all agonists, as evidenced by their lack of effect upon the ER-coupled acetylcholine and bombesin; (b) their site of action is likely downstream of second messengers themselves as indicated by photolysis studies (see below) and therefore not an upstream signal; (c) they do not block depolarization-induced Ca\(^{2+}\) entry; and (d) they eliminate Lysotracker Red staining.

We have proceeded to show that cell surface receptors couple to an intracellular store type by virtue of a characteristic selecting messenger, i.e. NAADP was unique in coupling to lysosome-related organelles, whereas IP\(_3\)/cADPR coupled to the ER. Not only does the published messenger profiles of the agonists support our hypothesis (3, 15), but the sensitivity of the second messengers themselves to various store inhibitors showed an absolute agreement. Therefore, sea urchin eggs are not anomalous in having acidic stores sensitive to NAADP but rather are vindicated as an excellent model system to study mammalian Ca\(^{2+}\) signaling. Moreover, our data are of interest in the light of a previous study (6) in permeabilized MIN6 cells suggesting that NAADP releases Ca\(^{2+}\) from secretory vesicles, themselves an acidic organelle. It should be noted that our data differ from that by Mitchell et al. (6) because (a) we have used intact cells; (b) we show agonist (glucose) coupling to acidic stores via NAADP; and (c) in our hands NAADP predominantly releases Ca\(^{2+}\) from a bafilomycin A1-sensitive and lysosomal-related store.

At first sight, it might appear contradictory that selective elimination of acidic Ca\(^{2+}\) stores has such a marked effect upon cholecystokinin when clearly there is an additional ER component (Fig. 1) (22). More surprisingly, glucose-stimulated Ca\(^{2+}\) signals in β cells also manifest a profound sensitivity to acidic store blockade when there ought to be a substantial residual Ca\(^{2+}\) entry component (17, 18) (and perhaps an ER component) (31). Although there is currently no complete mechanistic explanation for this absolute dependence, it has been empirically determined that desensitization of the NAADP receptor by its own ligand ablates both the cholecystokinin- as well as the glucose-induced Ca\(^{2+}\) signals (16, 22). Therefore, the effects of bafilomycin A1 and GPN remain entirely consistent with the blockade of the NAADP store. For the acinar cells, it has been suggested that the ER is essential to amplify NAADP-induced Ca\(^{2+}\) release via Ca\(^{2+}\)-induced Ca\(^{2+}\) release at the IP\(_3\) or ryanodine receptors (3, 25). It is currently less clear how NAADP might affect Ca\(^{2+}\) entry in β cells, but in sea urchin eggs a link between NAADP signaling and voltage-gated Ca\(^{2+}\) channels has been suggested (32).

The agonist-specific recruitment of different organelles also has ramifications in the spatial domain. It has been clearly shown that the apical pole of pancreatic acinar cells has a high density of zymogen granules (33), with only small fingers of ER penetrating into this region, and that the ER is highly concentrated in the basolateral part of the cell (34). The distribution of acidic vesicles may display a more cell-specific pattern; certainly for pancreatic acinar cells, intense Lysotracker Red staining was confined to the apical pole, whereas MIN6 cells appeared to display a more uniform staining. Supporting our model that these are Ca\(^{2+}\) stores, this pattern mirrored the subsequent Ca\(^{2+}\) responses that were evoked upon uncaging NAADP; in pancreatic acinar cells the region of highest NAADP sensitivity was confirmed as the apical pole (30), whereas the MIN6 response was essentially uniform. It should be noted, however, that a previous study in permeabilized cells...
FIG. 5. Comparison of lysosome-related store distribution and NAADP-induced Ca\textsuperscript{2+} signals in acinar cells. Micrographs showing vital fluorescence staining of pancreatic acinar cells labeled with 50 nm Lysotracker Red (a and b, left side) plus corresponding bright field images of pancreatic acinar cells (a and b, left side, lower panels). The predominantly apical fluorescence was dramatically reduced by pretreatment with 50 \mu M GPN (a, right-hand upper panel, \(n = 4\)) or 3 \mu M bafilomycin A1 (b, right-hand upper panel, \(n = 3\)). Cells were arbitrarily treated for 25–40 min but fluorescence began to fall immediately upon their application. The local Ca\textsuperscript{2+} response to photolysis of caged NAADP in a single acinar cell is also confined to the apical pole (c, blue trace), but not to the basal pole (c, red trace) (\(n = 8\)).

FIG. 6. Comparison of lysosome-related store distribution and NAADP-induced Ca\textsuperscript{2+} signals in \(\beta\) cells. The distribution of 50 nm Lysotracker Red fluorescence in pancreatic \(\beta\) cells was detected throughout the cells (except nucleus) (a–c, left panels) and eliminated by 50 \mu M GPN (a, \(n = 6\)) and 2 \mu M bafilomycin (b, \(n = 4\)) but not by thapsigargin (c, \(n = 4\)). Photolysis of caged NAADP in \(\beta\) cells induced a global Ca\textsuperscript{2+} response, and identical localized responses are obtained all over the cell (d, \(n = 58\)).
described the basolateral pole as the region of highest NAADP sensitivity (35). We cannot currently rationalize this apparent discrepancy, but we suggest methodological differences (e.g. permeabilization, uneven distribution of compartmentalized Ca\(^{2+}\) content of acidic stores) may affect processes such as secretory vesicle fusion (39), membrane repair (29), and proteolysis (40). Furthermore, if the NAADP-sensitive Ca\(^{2+}\) store is indeed an acidic secretory vesicle (6) or secretory lysosome (29), Ca\(^{2+}\) is delivered precisely where required to evoke exocytosis of zymogens (41), ATP (28), or insulin (6, 42), depending upon cell type, and provides another potential target for treatment of diabetes.

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