Characteristics of the Histamine-sensitive Calcium Store in Vascular Smooth Muscle

COMPARISON WITH NOREPINEPHRINE- OR CAFFEINE-SENSITIVE STORES*

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Using the microfluorometry of an intracellularly trapped calcium indicator dye, quin2, characteristics of intracellular Ca2+ store sites sensitive to histamine, norepinephrine, or caffeine were investigated using rat vascular smooth muscle cells in primary culture at 25 °C. With similar time courses, both histamine- and norepinephrine-sensitive Ca2+ store sites were readily depleted in Ca2+-free medium and almost completely replenished by loading the cells with 1.0 mM Ca2+ solution for 3 min, while the caffeine-sensitive Ca2+ store site was little affected. In the absence of extracellular Ca2+, transient elevations of cytosolic Ca2+ repeatedly appeared in response to repetitive applications of histamine, norepinephrine, or caffeine, with progressive reductions in peak levels. Histamine released Ca2+ from the norepinephrine-sensitive store site and norepinephrine released Ca2+ from the histamine-sensitive one. On the other hand, caffeine had released Ca2+ from the norepinephrine-sensitive store with progressive reductions in peak levels. Histamine and norepinephrine released Ca2+ from the histamine-sensitive store site, compared it with the norepinephrine-sensitive 

EXPERIMENTAL PROCEDURES

Cell Culture—VSMCs were cultured from the aortic media of male Wistar rats weighing 300-350 g, as described (22). Briefly, the aortic media were dispersed into single cells by incubation with collagenase (1 mg/ml) and elastase (10 units/ml), and seeded on Lux chamber slides in Dulbecco’s modified Eagle’s medium (GIBCO) containing 10% heat-inactivated fetal bovine serum (GIBCO) and antibiotics. The growth medium was changed every 2 days. We used only primary cell cultures for all experiments. Electron microscopic observations and direct staining with fluorescein isothiocyanate-labeled antibodies against native smooth muscle actin and myosin revealed that these cultured cells had little or no contamination with fibroblasts and endothelial cells (16, 22, 23). High cell viability (>95%) was maintained during the course of each experimental procedure, using the trypan blue exclusion test, as described (22).

Microfluorometry of Quin2—On days 5 to 6, just before reaching confluence, the cultured cells on Lux chamber slides were loaded with quin2 by incubating with 50 μM quin2/AM (acetoxymethyl ester) for 60 min at 37 °C (16-18). The cells were then washed three times with physiological saline solution (PSS) at 25 °C to remove the dye in the extracellular space and were then incubated with normal PSS for at least 30 min before the optical measurements (24). Unless otherwise indicated, the experiments were performed in normal PSS at 25 °C to prevent leakage of quin2 (25). As reported previously (18), there was no significant leak of quin2 from the cells, and the concentration of quin2 was stable in the cytosol, under the present experimental conditions. There was no morphological change in the cells throughout the experiment, as determined by phase contrast microscopy at ×400, thereby indicating that loading VSMCs with quin2 may not

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1 The abbreviations used are: [Ca2+]i, cytosolic Ca2+ concentration; VSMCs, vascular smooth muscle cells; PSS, physiological saline solution; HEPES, N-2-hydroxyethylpiperazine-N’-2-ethanesulfonic acid; EGTA, (ethylenebis(oxyethylenenitrilo))tetraacetic acid.
**RESULTS**

**Ca**²⁺ Release Induced by Histamine—Fig. 1A shows the responses of fluorescence change observed when VSMCs were exposed to 10⁻⁵ M histamine in Ca²⁺-free PSS. When VSMCs were incubated in Ca²⁺-free PSS containing 2 mM EGTA, the fluorescence intensity decreased gradually, reached a steady state within 6 min, and remained at this level for at least 60 min, as previously reported (16, 29) (Fig. 2). As shown in Fig. 1A, histamine induced a transient [Ca²⁺]i elevation, which reached a peak level at 1 min, then rapidly declined to the pre-exposure level within 8 min. Using the method of Tsien et al. (26), an estimate of [Ca²⁺]i, was made (23). The maximum and minimum fluorescence signals were obtained by permeabilizing the cells with 10⁻⁷ M ionomycin in the presence of excess Ca²⁺ (10⁻³ M) or very low Ca²⁺ caused by 10 mM EGTA (approximately 10⁻⁹ M), respectively. Using these values, it can be calculated that the [Ca²⁺]i of VSMCs in normal PSS, Ca²⁺-free PSS containing 2 mM EGTA for 10 min and the peak value induced by 10⁻⁵ M histamine in Ca²⁺-free PSS for 10 min were 93 ± 7, 46 ± 6, and 196 ± 25 nM, respectively (n = 4). The resting level of [Ca²⁺]i in normal PSS found here is similar to reported data (27–29). The extent of the peak levels of [Ca²⁺]i transient induced by histamine was concentration-dependent (p < 0.05 by analysis of variance), and the optimal dose of histamine was 10⁻⁵ M (Fig. 1D).

**Ca**²⁺ Release Induced by Norepinephrine—When VSMCs were exposed to norepinephrine in Ca²⁺-free PSS containing 2 mM EGTA, there was a transient elevation of [Ca²⁺]i, which reached a peak level at 2 min with a duration of 6 min. The
peak level of the [Ca^{2+}] transient was dose dependent ($p < 0.05$ by analysis of variance) and $10^{-5}$ M norepinephrine induced a maximum response (Fig. 1, B and E).

**Ca^{2+} Release Induced by Caffeine**—In Ca^{2+}-free PSS containing 2 mM EGTA, caffeine induced a transient, which reached a peak level at 30 s with a duration of 2 min, and the concentration-dependent ($p < 0.05$ by analysis of variance) elevation of [Ca^{2+}] of VSMCs and the optimal dose of caffeine was $10^{-5}$ M (Fig. 1, C and F).

**Effect of the Incubation Time in Ca^{2+}-free Medium on [Ca^{2+}]**—Elevations Induced by Histamine, Norepinephrine, or Caffeine—Fig. 2 shows the effect of duration of the exposure time to Ca^{2+}-free medium on the peak levels of [Ca^{2+}], transients induced by the first application of $10^{-5}$ M histamine, $10^{-5}$ M norepinephrine, and $10^{-5}$ M caffeine. The longer the exposure time to Ca^{2+}-free PSS containing 2 mM EGTA, the less was the extent of [Ca^{2+}], elevation induced by either histamine or norepinephrine, while the extent of caffeine-induced [Ca^{2+}], elevation was little affected by the exposure time in Ca^{2+}-free solution. The half-times for decay of the peak levels of histamine-, norepinephrine-, and caffeine-induced elevations of [Ca^{2+}] were 14, 15, and 170 min, respectively. Fig. 2 also shows the effect of re-exposure to Ca^{2+}-containing media on [Ca^{2+}], of VSMCs after Ca^{2+} depletion. When VSMCs were reincubated with 1.0 mM Ca^{2+} PSS for 3 min and then re-exposed to Ca^{2+}-free medium for 1 min prior to the application of histamine after 15 min or longer in Ca^{2+}-free solution, the extent of peak elevation of [Ca^{2+}] by histamine was as large as that observed in VSMCs not exposed to Ca^{2+}-free solution (0 min), and independent of the duration of the first incubation with Ca^{2+}-free medium, as is the case of norepinephrine (19). We suggest that the histamine- and the norepinephrine-sensitive Ca^{2+} store sites respond differently from the caffeine-sensitive one to Ca^{2+}-free media and Ca^{2+} repletion.

**Effects of Ca^{2+} Loading on Ca^{2+} Store Sites after Depletion by Repetitive Applications of Histamine, Norepinephrine, and Caffeine in Ca^{2+}-free Medium**—Fig. 3 shows the effect of Ca^{2+} loading on the histamine-, norepinephrine-, and caffeine-sensitive Ca^{2+} store sites after depletion by repetitive applications of these agonists in the absence of extracellular Ca^{2+}. When VSMCs were repeatedly exposed to $10^{-5}$ M histamine, $10^{-5}$ M norepinephrine, or $10^{-5}$ M caffeine in Ca^{2+}-free PSS containing 2 mM EGTA, there were transient [Ca^{2+}] elevations in response to each application, but the peak levels of the elevations of [Ca^{2+}] were reduced progressively by each exposure, and the third application of histamine, third application of norepinephrine, and fifth application of caffeine produced little or no response. This suggested that the stored Ca^{2+} sensitive to each stimuli was completely depleted. When the cells were reincubated with 1.0 mM Ca^{2+} PSS for 3 min after the depletion of histamine-sensitive stored Ca^{2+}, and then incubated in Ca^{2+}-free PSS for 10 min, histamine induced a near-maximal [Ca^{2+}], elevation (Fig. 3A), an event indicating an almost complete replenishment of Ca^{2+} at the histamine-sensitive store site. Also in the case of norepinephrine, the norepinephrine-sensitive Ca^{2+} store site was almost completely replenished (Fig. 3B) by incubation for 3 min with...
FIG. 4. Effects of repeated applications of $10^{-5}$ M histamine (His) on the subsequent elevation of cytosolic Ca$^{2+}$ induced by $10^{-5}$ M norepinephrine (NE) in Ca$^{2+}$-free PSS containing 2 mM EGTA. A, prior to the application of norepinephrine, histamine was not applied (a), histamine was applied once (b), twice (c), and three times, for 8 min (d). Interval between exposures was 2 min. Time on the abscissa is the incubation time in Ca$^{2+}$-free media. Broken lines indicate the time course of the peak levels of fluorescence induced by the first application of $10^{-5}$ M norepinephrine in Ca$^{2+}$-free medium, as obtained from Fig. 2. B, the relationship between the amount of Ca$^{2+}$ released by n-th application of $10^{-5}$ M histamine and the amount of Ca$^{2+}$ released by $10^{-5}$ M norepinephrine after $(n - 1)$ time applications of $10^{-5}$ M histamine. Bars indicate S.D. of four experiments. The line was obtained by linear regression analysis. There is a positive slope of 1.09 with a correlation coefficient of 0.99.

Overlap of the Histamine- and the Norepinephrine-sensitive Ca$^{2+}$ Store Sites—At 10 min in Ca$^{2+}$-free PSS containing 2 mM EGTA, the extent of the elevation of [Ca$^{2+}$]$_i$ induced by the first application of $10^{-5}$ M norepinephrine (Fig. 4Aa) was almost equal to that induced by the first application of $10^{-5}$ M histamine (Fig. 4Ab). When VSMCs were exposed to $10^{-5}$ M norepinephrine after the first application of $10^{-5}$ M histamine in Ca$^{2+}$-free PSS (Fig. 4Ac), the peak level of [Ca$^{2+}$], transient was almost equal to that observed when VSMCs were exposed to $10^{-5}$ M histamine after the first application of $10^{-5}$ M histamine (Fig. 4Ad). After the second or further applications of $10^{-5}$ M histamine, $10^{-5}$ M norepinephrine induced little or no Ca$^{2+}$ release (Fig. 4Ac and d), although $10^{-5}$ M norepinephrine did produce an elevation of [Ca$^{2+}$], at the same incubation time in Ca$^{2+}$-free solution, without the pre-treatment of histamine (Fig. 2).

To estimate the amount of Ca$^{2+}$ released with each treatment, the area bound by the fluorescence trace and the steady-state base line in Ca$^{2+}$-free media was measured using a computerized manipulator (Houston Instrument). The calculated area was expressed as "fluorescence (F) × minute (min)," indicating relative amounts of Ca$^{2+}$ transiently re-
produced little or no response, thereby indicating the complete cytosolic Ca\(^{2+}\) induced by \(10^{-5}\) M pretreatments with \(10^{-5}\) M histamine (His) when VSMCs were repeatedly exposed to \(10^{-5}\) M histamine (Fig. 6A). Conversely, the relative changes in \([Ca^{2+}]_i\) induced by the first application of \(10^{-7}\) M caffeine \((A)\) and \(10^{-5}\) M histamine \((B)\) in \(Ca^{2+}\)-free medium, as obtained from Fig. 2.

![Figure 6A](http://www.jbc.org/)

**FIG. 6. A,** effects of three repetitive pretreatments with \(10^{-5}\) M histamine (His) on the subsequent elevation of cytosolic \(Ca^{2+}\) induced by \(10^{-7}\) M caffeine (CF) in \(Ca^{2+}\)-free PSS containing 2 mM EGTA. Data are means ± S.D. of four experiments. **B,** effects of five repetitive pretreatments with \(10^{-2}\) M caffeine on the subsequent elevation of cytosolic \(Ca^{2+}\) induced by \(10^{-5}\) M histamine in \(Ca^{2+}\)-free PSS containing 2 mM EGTA. Data are means ± S.D. of four experiments. **Broken lines** indicate the time course of the peak levels of fluorescence induced by the first application of \(10^{-7}\) M caffeine \((A)\) and \(10^{-5}\) M histamine \((B)\) in \(Ca^{2+}\)-free medium, as obtained from Fig. 2.

On the other hand, when VSMCs were repeatedly exposed to \(10^{-4}\) M noradrenaline in \(Ca^{2+}\)-free PSS containing 2 mM EGTA, the extent of the subsequent release of \(Ca^{2+}\) induced by histamine was progressively reduced with the increasing number of previous exposures to noradrenaline (Fig. 5, Aa-d). As shown in Fig. 5B, the relative changes in \([Ca^{2+}]_i\), induced by histamine after \((n - 1)\) time exposure \((1 < n < 3)\) to noradrenaline was almost equal to that observed during \(n\) time application of noradrenaline. Thus, the histamine-sensitive \(Ca^{2+}\) store site almost completely overlaps the noradrenaline-sensitive one.

**Histamine- and Norepinephrine-sensitive \(Ca^{2+}\) Store Sites Differ from Caffeine-sensitive Ones**—When VSMCs were repeatedly exposed to \(10^{-5}\) M histamine in \(Ca^{2+}\)-free PSS containing 2 mM EGTA, the third application produced little or no \(Ca^{2+}\) release, thereby indicating that histamine-sensitive stored \(Ca^{2+}\) was almost completely depleted. However, the subsequent application of \(10^{-5}\) M caffeine induced a transient \([Ca^{2+}]_i\) elevation and the peak level of the \([Ca^{2+}]_i\), transient was almost equal to that induced by \(10^{-5}\) M caffeine with the same incubation time (40 min, 30 s) in \(Ca^{2+}\)-free solution and without the pretreatment of histamine (Fig. 6A). Conversely, when VSMCs were repeatedly exposed to \(10^{-2}\) M caffeine in \(Ca^{2+}\)-free PSS containing 2 mM EGTA, the fifth application produced little or no response, thereby indicating the complete depletion of caffeine-sensitive stored \(Ca^{2+}\) (Fig. 6B). The subsequent application of \(10^{-5}\) M histamine produced an elevation of \([Ca^{2+}]_i\), and the extent of \([Ca^{2+}]_i\), was almost equal that observed during the first application of \(10^{-5}\) M histamine for the same duration of incubation (31 min) in \(Ca^{2+}\)-free PSS, without the pretreatment of caffeine. Thus, it is suggested that the histamine-sensitive \(Ca^{2+}\) store site differs from the caffeine-sensitive one.

In the case of norepinephrine, we obtained results similar to those seen with histamine, in comparison with caffeine and as reported (19). This would suggest that the norepinephrine-sensitive \(Ca^{2+}\) store site also differs from the caffeine-sensitive one.

**DISCUSSION**

In the present study, using the quin2-microfluorometry of intact VSMCs of rat aortic media in primary culture, we obtained evidence that \(Ca^{2+}\) in the histamine- and noradrenaline-sensitive store sites is readily depleted in \(Ca^{2+}\)-free solution and is readily replenished by loading with 1.0 mM \(Ca^{2+}\)-PSS, whereas \(Ca^{2+}\) in the caffeine-sensitive store site is little affected. Histamine induced a release of all the stored \(Ca^{2+}\) in the norepinephrine-sensitive store site, and norepinephrine released \(Ca^{2+}\) from the histamine-sensitive store. However, histamine and norepinephrine could not release \(Ca^{2+}\) from the caffeine-sensitive store site, and caffeine could not release \(Ca^{2+}\) from the histamine- and norepinephrine-sensitive \(Ca^{2+}\) store. We reported that there is a complete overlap of the caffeine- and \(K^+\) depolarization-sensitive intracellular \(Ca^{2+}\) store sites (18) and that the norepinephrine-sensitive intracellular \(Ca^{2+}\) store differs from the caffeine-sensitive one in VSMCs of rat aorta in primary culture (19). The present findings clearly show that the histamine-sensitive \(Ca^{2+}\) store site completely overlaps with the norepinephrine-sensitive one and differs from the caffeine-sensitive one in VSMCs in primary culture.

The present study shows the advantages of the quin2-microfluorometry of \([Ca^{2+}]_i\); over the estimation of \([Ca^{2+}]_i\), changes by tension measurement, when attempting to determine the characteristics of the intracellular \(Ca^{2+}\) store site in VSMCs. For example, the peak levels of \([Ca^{2+}]_i\), transients induced by the second or more applications of histamine or norepinephrine and also those induced by histamine or norepinephrine after five repetitive pretreatments of caffeine were lower than the \([Ca^{2+}]_i\), level in cells in normal PSS containing 5 mM \(K^+\) and 1 mM \(Ca^{2+}\). Thus, using quin2-microfluorometry, changes in \([Ca^{2+}]_i\), below the resting cell levels can be recorded, namely, changes in \([Ca^{2+}]_i\), in the subthreshold levels required for the contractile response.

Replicative applications of histamine and norepinephrine induced a progressive reduction in the amount of \(Ca^{2+}\) released from the intracellular store site in VSMCs in \(Ca^{2+}\)-free PSS. The possibility that desensitization to histamine and norepinephrine occurs during repetitive treatments with these agonists can be excluded by the finding that histamine and norepinephrine induced a near-maximal release of \(Ca^{2+}\) after repletion of \(Ca^{2+}\), by replacement of \(Ca^{2+}\)-free medium with 1.0 mM \(Ca^{2+}\)-PSS at 3 min after repetitive treatments with agonists in \(Ca^{2+}\)-free solution.

With regard to the source of \(Ca^{2+}\) released by norepinephrine, there is no general agreement. Grover et al. (9) suggested that the norepinephrine-sensitive stored \(Ca^{2+}\) is a component of bound \(Ca^{2+}\) on the plasma membrane of rabbit aortic smooth muscle. Daniel (5) proposed that there is a norepinephrine-sensitive \(Ca^{2+}\) store in the sarcoplasmic reticulum near the plasma membrane or at the inner aspect of the
plasma membrane. Our findings that Ca\(^{2+}\) in the histamine/norepinephrine-sensitive store is readily depleted and replenished may indicate that the site is located in close proximity to the cell surface. It is also possible that this site may have communication with extracellular milieu, and may easily lose and accumulate Ca\(^{2+}\) during depletion and repletion, respectively. Conversely, Ca\(^{2+}\) in the caffeine-sensitive store was hardly depleted and replenished during depletion and repletion of extracellular Ca\(^{2+}\), respectively suggesting that the caffeine-sensitive store might be located in the central part of the cell and/or communication with extracellular milieu may be inadequate. It is also possible that prompt Ca\(^{2+}\) depletion and repletion of histamine/norepinephrine-sensitive Ca\(^{2+}\) store may be related to their close proximity of location to cell surface rather than to their primary characteristics. By measuring the tension development of vascular smooth muscle in Ca\(^{2+}\)-free PSS containing EGTA, Guan et al. (30) found that "EGTA in Ca\(^{2+}\)-free medium may remove the superficially bound Ca\(^{2+}\) and subsequently reduce the intracellular Ca\(^{2+}\) pool via extraction of the intracellular Ca\(^{2+}\) at the cell membrane surface. This would lead to destabilization of the cell membrane and to an increased permeability to the subsequently added Ca\(^{2+}\) to refill the receptor-released intracellular Ca\(^{2+}\) pool."

Saida and van Breemen (11) noted in tension studies of the rabbit mesenteric artery that norepinephrine releases Ca\(^{2+}\) from a store near the receptor, which diffuses to the caffeine-sensitive store to release Ca\(^{2+}\) through the Ca\(^{2+}\)-induced Ca\(^{2+}\) release mechanism. This occurs when [Ca\(^{2+}\)]\(_{\text{e}}\) exceeds 2 \(\times\) 10\(^{-6}\) M (31). Using rat aortic VSMCs in primary culture, Yamamoto and van Breemen (32) noted that there was no significant decrease in the caffeine-releasable content in the range 3 \(\times\) 10\(^{-6}\) to 1 \(\times\) 10\(^{-5}\) M free Ca\(^{2+}\) concentrations and that there was a decrease in Ca\(^{2+}\) content of the sarcoplasmic reticulum at 1 \(\times\) 10\(^{-4}\) M Ca\(^{2+}\). Thus, the threshold for the (norepinephrine/histamine-released) Ca\(^{2+}\)-induced Ca\(^{2+}\) release from caffeine-sensitive Ca\(^{2+}\) store is very much higher than the Ca\(^{2+}\) concentration obtained by the application of 10 \(^{-5}\) M histamine in the absence of extracellular Ca\(^{2+}\), as it was in the present study. It may be that the Ca\(^{2+}\)-induced Ca\(^{2+}\) release is not actively involved in the mechanism of Ca\(^{2+}\) release from the sarcoplasmic reticulum in VSMCs because the threshold Ca\(^{2+}\) concentration would be too high for physiological conditions. However, since primary cultured smooth muscle cells, albeit retaining most of their original characteristics, may be modified to some extent during cultivation, no conclusions can be drawn concerning the importance of this mechanism in intact VSMCs, under physiological conditions.

On the other hand, Bond et al. (12) and Kowarski et al. (15) reported that using electron probe x-ray microanalysis, norepinephrine releases Ca\(^{2+}\) from both the junctional (near the plasma membrane) and internal (central) sarcoplasmic reticulum. With regard to the mechanism of Ca\(^{2+}\) release from the internal (central) sarcoplasmic reticulum, Somlo (4) proposed several possible mechanisms, including diffusion of Ca\(^{2+}\) from the internal to the junctional sarcoplasmic reticulum through luminal communications, the release of Ca\(^{2+}\) mediated by a chemical transmitter such as inositol 1,4,5-trisphosphate and change in Ca\(^{2+}\) permeability propagated from the junctional to the internal sarcoplasmic reticulum. In the present study, there were differences not only in the rates of Ca\(^{2+}\) depletion and replenishment but also in the mechanism of Ca\(^{2+}\) release between the histamine/norepinephrine-sensitive Ca\(^{2+}\) store site and the caffeine-sensitive Ca\(^{2+}\) store site. Histamine and norepinephrine had little effect on the caffeine-sensitive Ca\(^{2+}\) store site, and caffeine had little effect on the histamine/norepinephrine-sensitive Ca\(^{2+}\) store site, in Ca\(^{2+}\)-free medium. We reported that a GTP-binding protein, a pertussis toxin substrate, couples the \(\alpha_{1}\)-adrenoceptor and the \(H_{1}\) histamine receptor to mediate the release of intracellular Ca\(^{2+}\) and that this protein is not involved in the caffeine-induced Ca\(^{2+}\) release in VSMCs (33). These results are compatible with the idea that the mechanism of Ca\(^{2+}\) release from the histamine/norepinephrine-sensitive Ca\(^{2+}\) store site differs from that of the caffeine-sensitive one. Thus, there may be no overlap between the histamine/norepinephrine-sensitive Ca\(^{2+}\) store site and the caffeine-sensitive one. However, it has to be noted that these results were obtained in the absence of extracellular Ca\(^{2+}\) and that norepinephrine or histamine may release Ca\(^{2+}\) from the caffeine-sensitive store in an indirect manner when extracellular Ca\(^{2+}\) is present.

In conclusion, our observations suggest that the histamine and the norepinephrine-sensitive Ca\(^{2+}\) store sites completely overlapped and the histamine/norepinephrine-sensitive Ca\(^{2+}\) store site does not overlap with the caffeine-sensitive Ca\(^{2+}\) store site. These two Ca\(^{2+}\) store sites also have different properties for Ca\(^{2+}\) leakage and accumulation during Ca\(^{2+}\) depletion and repletion, respectively.

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