Am J Physiol Heart Circ Physiol 294: H1183–H1187, 2008.
First published December 21, 2007; doi:10.1152/ajpheart.01148.2007.

Role of $iPLA_2$ and store-operated channels in agonist-induced Ca^{2+} influx and constriction in cerebral, mesenteric, and carotid arteries

Kristen M. Park,[1] Mario Trucillo,[2] Nicolas Serban,[1] Richard A. Cohen,[2] and Victoria M. Bolotina[1]

[1]*Ion Channel and Calcium Signaling Unit and* [2]*Vascular Biology Unit, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts*

Submitted 3 October 2007; accepted in final form 19 December 2007

Park KM, Trucillo M, Serban N, Cohen RA, Bolotina VM. Role of $iPLA_2$ and store-operated channels in agonist-induced Ca^{2+} influx and constriction in cerebral, mesenteric, and carotid arteries. *Am J Physiol Heart Circ Physiol* 294: H1183–H1187, 2008. First published December 21, 2007; doi:10.1152/ajpheart.01148.2007.—Store-operated channels (SOC) and store-operated Ca^{2+} entry are known to play a major role in agonist-induced constriction of smooth muscle cells (SMC) in conduit vessels. In microvessels the role of SOC remains uncertain, in as much as voltage-gated L-type Ca^{2+} (Ca_L^{2+}) channels are thought to be fully responsible for agonist-induced Ca^{2+} influx and vasoconstriction. We present evidence that SOC and their activation via a Ca^{2+}-independent phospholipase A_2 ($iPLA_2$)-mediated pathway play a crucial role in agonist-induced constriction of cerebral, mesenteric, and carotid arteries. Intracellular Ca^{2+} in SMC and intraluminal diameter were measured simultaneously in intact pressurized vessels in vitro. We demonstrated that *1*) Ca^{2+} and contractile responses to phenylephrine (PE) in cerebral and carotid arteries were equally abolished by nimodipine (a Ca_L^{2+} inhibitor) and 2-aminoethyl diphenylborinate (an inhibitor of SOC), suggesting that SOC and Ca_L^{2+} channels may be involved in agonist-induced constriction of cerebral arteries, and *2*) functional inhibition of $iPLA_2\beta$ totally inhibited PE-induced Ca^{2+} influx and constriction in cerebral, mesenteric, and carotid arteries, whereas K^+-induced Ca^{2+} influx and vasoconstriction mediated by Ca_L^{2+} channels were not affected. Thus $iPLA_2$-dependent activation of SOC is crucial for agonist-induced Ca^{2+} influx and vasoconstriction in cerebral, mesenteric, and carotid arteries. We propose that, on PE-induced depletion of Ca^{2+} stores, nonselective SOC are activated via an $iPLA_2$-dependent pathway and may produce a depolarization of SMC, which could trigger a secondary activation of Ca_L^{2+} channels and lead to Ca^{2+} entry and vasoconstriction.

store-operated calcium entry; smooth muscle cells; constriction

IN CEREBRAL ARTERIES and other small-diameter vessels, voltage-gated L-type Ca^{2+} (Ca_L^{2+}) channels are known to be the primary channels responsible for agonist-induced constriction, in as much as their inhibition was shown to fully relax most microvessels (19, 20). On the other hand, depletion of intracellular Ca^{2+} stores by different agonists [or by inhibitors of sarco(endo)plasmic reticulum Ca^{2+}-ATPase] activates store-operated (SOC) channels and store-operated Ca^{2+} entry (SOCE) in isolated smooth muscle cells (SMC) (for review see Refs. 1, 3, 26). In conduit vessels, nonselective cation SOC (rather than Ca_L^{2+} channels) play a major role in agonist-induced constriction and nitric oxide-induced relaxation (8, 27), but the role of SOC in constriction of microvessels, especially in the cerebral circulation, remains unclear. In SMC of cerebral arterioles, activation of SOCE increases Ca^{2+} but fails to generate constriction (11, 12), suggesting that SOC may be mediating Ca^{2+} influx into restricted space (or cellular compartments), which may be spatially separated from the contractile apparatus. In interlobular arteries, SOC are present but do not significantly contribute to Ca^{2+} entry after agonist stimulation (10). In numerous other types of SMC, Ca^{2+} store depletion was reported to increase Ca^{2+} and cause constriction, although it was studied only using poorly selective SOC inhibitors (for review see Refs. 3 and 14). Thus the following questions remain. *1*) By what mechanism might SOC be involved in the physiological regulation of agonist-induced constriction in microvessels? *2*) How might their role be related to activation of Ca_L^{2+} channels. Because of the nonselective cation permeability of SOC in SMC, SOC activation should cause a significant membrane depolarization, which may result in cross talk between SOC and Ca_L^{2+} channels (7); this theory is supported by studies in isolated SMC from guinea pig gallbladder (18) and in the A7r5 cell line (21), but little is known about their possible cross talk in intact vessels.

Recently, the Ca^{2+}-independent phospholipase A_2 ($iPLA_2$) β (group VI) (2, 30) was found to be a crucial determinant of SOCE activation in isolated aortic SMC, but the role of $iPLA_2\beta$ in intact cerebral and other microvessels is unknown. Functional inhibition of $iPLA_2$ with its suicidal substrate bromoenol lactone (BEL) or specific antisense oligonucleotides against $iPLA_2\beta$ has been shown to produce identical impairment of SOCE in isolated SMC (24, 25), as well as astrocytes (23), keratinocytes (22), skeletal muscle (4), fibroblasts (16), prostate cancer (28), and other cell types (24, 25). The crucial role of $iPLA_2\beta$ in SOCE activation was recently confirmed in a screen of *Drosophila melanogaster* genes (29), where molecular knockdown of the CG6718 gene (a *Drosophila* homolog of human $iPLA_2\beta$) significantly affected SOCE. In isolated vascular SMC, we discovered that single-cation SOC and SOCE can be activated by lysophospholipids, which are produced by the plasma membrane-bound $iPLA_2\beta$ (24). Activation of $iPLA_2\beta$ can be physiologically achieved by Ca^{2+} influx factor, which is produced in endo(sarco)plasmic reticulum on depletion of Ca^{2+} stores (5) and is capable of displacing inhibitory calmodulin from its binding site on $iPLA_2\beta$. Thus agonist-induced depletion of the stores can activate SOC and SOCE in SMC via an $iPLA_2\beta$-dependent pathway (24).

Discovery of $iPLA_2\beta$ as a crucial component of the SOCE mechanism in SMC and development of a chiral-specific functional inhibitor of $iPLA_2\beta$ (9, 15) have opened new avenues for

Address for reprint requests and other correspondence: V. Bolotina, Ion Channel and Calcium Signaling Unit, Dept. of Medicine, Boston Univ. School of Medicine, 650 Albany St., X-704, Boston, MA 02118 (e-mail: bolotina@bu.edu).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

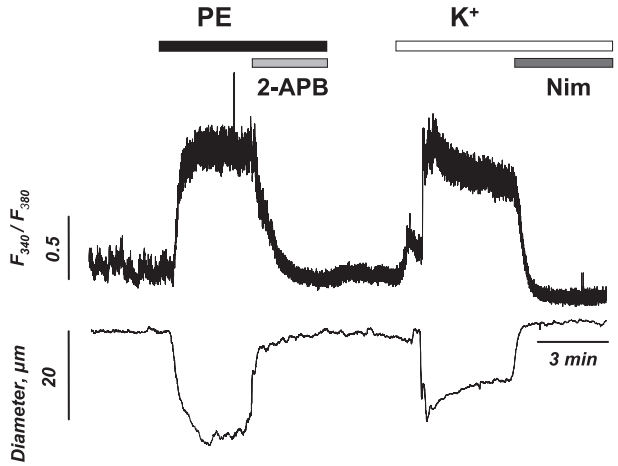

Fig. 1. Simultaneous Ca^{2+} rise in smooth muscle cells (SMC) and constriction caused by phenylephrine (PE) and high K^+ in intact cerebral artery. Representative traces show changes in intracellular Ca^{2+} [as ratio of fura 2-AM fluorescence at 340 nm to 380 nm (*top trace*)] and intraluminal diameter of intact pressurized vessel (*bottom trace*) during bath application of 10 μM PE, 75 μM 2-aminoethyl diphenylborinate (2-APB), high (60 mM) K^+, and 5 μM nimodipine (Nim). Vessel was washed for 3 min between PE and K^+ applications.

studying the role of the SOCE mechanism in vascular constriction. In the present study, we have examined the roles of SOC and Ca_L^{2+} channels in microvessels and tested the hypothesis that agonist-induced iPLA$_2$-dependent activation of SOC may be required for secondary activation of Ca_L^{2+} and Ca^{2+} entry, which trigger contractile responses in cerebral, mesenteric, and carotid arteries. Using simultaneous recording of Ca^{2+} in SMC and vessel diameter, we demonstrate that phenylephrine (PE)-induced constriction fully depends on the functional activity of iPLA$_2$β and SOC, as well as Ca_L^{2+} channels. These new findings establish the crucial role of iPLA$_2$β-dependent SOC in vascular responses to agonist stimulation and provide a new important mechanism of regulation of tone in different microvascular beds.

MATERIALS AND METHODS

Drugs and materials. Unless otherwise indicated, all drugs were purchased from Sigma. BEL was purchased from Biomol; *S*- and *R*-BEL from Cayman Chemicals; and fura 2-AM from Invitrogen. Physiological salt solution (PSS) consisting of (in mM) 119 NaCl, 4.7 KCl, 24 $NaHCO_3$, 1.2 KH_2PO_4, 1.6 $CaCl_2$, 1.2 $MgSO_4$, 0.023 EDTA, and 11 glucose was bubbled with 95% O_2-5% CO_2 to ensure pH 7.4.

Isolation of mouse cerebral and mesenteric and rabbit carotid arteries. Posterior cerebral arteries (PCA) and mesenteric arteries were obtained from male mice (C57BL/6, 8–10 wk old). First-order PCA and second-order mesenteric arteries (~120 μm diameter) were dissected free from the mesenteric arterial bed or brain and connective tissue in ice-cold PSS. Dissected arterial segments (200 μm long) were cannulated in a chamber connected to a pressure myograph (Living Systems Instrumentation, Burlington, VT) and immediately used for experiments.

Carotid arteries were obtained from male New Zealand rabbits (3.1 ± 0.4 kg body wt), cleaned of all connective tissue in cold PSS, and mounted onto a myograph (see below).

All research was performed in accordance with the American Physiological Society "Guiding Principles in the Care and Use of Animals" and with Institutional Animal Care and Use Committee approval.

Simultaneous recording of Ca^{2+} and vessel diameter. Mircovessels were maintained at 37°C throughout the experiment by superfusion with prewarmed, bubbled PSS at a rate of 5 ml/min. Before the experiments, vessels were equilibrated for 20 min at 10 mmHg, then pressure was raised to 60 mmHg; intravascular pressure was controlled by a pressure servo and peristaltic pump (Living Systems Instrumentation). The chamber with the microvessel was mounted on an Olympus microscope equipped with the IonOptix data acquisition system (IonOptix, Milton, MA), which allowed simultaneous measurement of *1*) intraluminal diameter using the Softedge Acquisition Subsystem and *2*) intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) using a ratiometric photomultiplier system. Fura 2-AM loading of SMC was accomplished by incubation of the mounted arteries in external PSS containing 5 μM fura 2-AM for 50 min at room temperature in the dark. The fura 2-AM ratio (ratio of fura 2 fluorescence at 340-nm excitation to that at 380-nm excitation, with emission at 510 nm) was recorded at a sampling rate of 5 Hz. Arterial diameter and fluorescence ratio were simultaneously recorded and plotted over time.

Isometric tension measurements. Isometric tension was measured as previously described (6, 8). Briefly, 5-mm-long rings of rabbit carotid artery segments were cleaned of connective tissue and mounted on metal stirrups in organ chambers, and isometric tension was recorded. Rings were maintained at 37°C in bubbled (95% O_2-5% CO_2) PSS. Rings were equilibrated and stretched to an optimal tension of 7 g. Pharmacological agents were added to the bath as indicated.

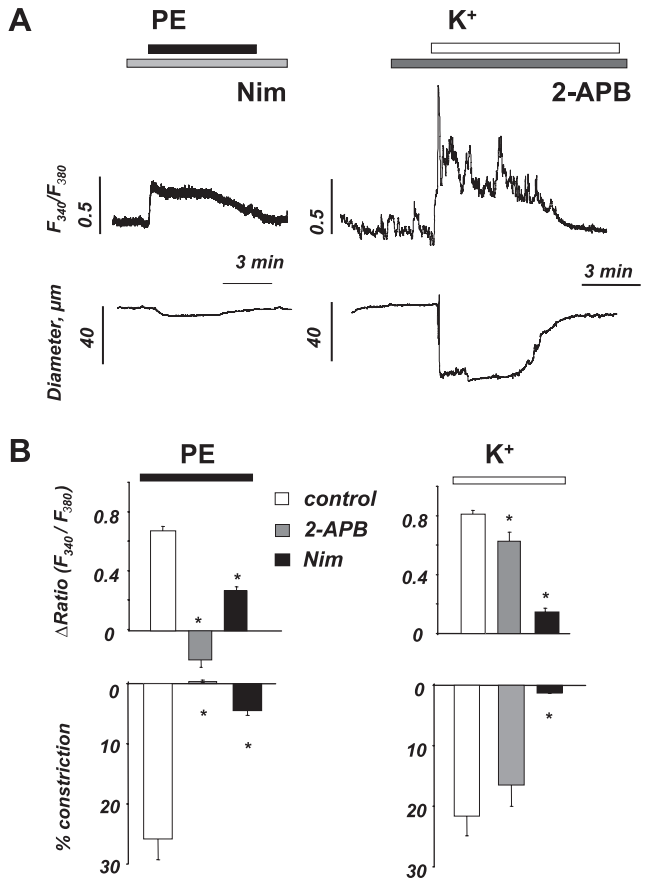

Fig. 2. Effects of 2-APB and Nim on PE- and high-K^+-induced simultaneous Ca^{2+} rise and constriction in intact cerebral arteries. *A*: changes in intracellular Ca^{2+} (*top trace*) and intraluminal diameter (*bottom trace*) during application of 10 μM PE, 5 μM Nim, 60 mM K^+, and 75 μM 2-APB. *B*: changes in Ca^{2+} (*top*) and simultaneous changes in intraluminal vessel diameter (*bottom*). Values are means ± SE from 8 experiments. *$P < 0.05$ vs. control.

Statistical analysis. Summary data are presented as means ± SE. Student's *t*-test was used to determine the statistical significance of the data. $P < 0.05$ was considered significant.

RESULTS

To investigate the role of SOC in contractile responses of microvessels, we first tested and compared the effects of 2-aminoethyl diphenylborinate (2-APB, a widely used SOC inhibitor) and nimodipine (Nim, an inhibitor of Ca_L^{2+} channels) on responses to PE or high K^+. $[Ca^{2+}]_i$ in SMC was measured simultaneously with intraluminal vessel diameter in PCA (Fig. 1). The high-K^+-induced Ca^{2+} rise and vessel constriction were inhibited by 5 μM Nim but were not affected by 75 μM 2-APB [which is known to fully inhibit SOC and SOCE in SMC (12)], consistent with the involvement of only Ca_L^{2+} channels in depolarization-induced $[Ca^{2+}]_i$ rise and vessel constriction (Figs. 1 and 2). On the other hand, PE (10 μM)-induced $[Ca^{2+}]_i$ rise and vessel constriction were inhibited by Nim and 2-APB (Figs. 1 and 2), suggesting the involvement of SOC and Ca_L^{2+} channels in agonist-induced responses.

To provide new mechanistic insights into the role of SOC activation and the iPLA$_2$-mediated SOCE pathway in microvessel constriction, the effect of functional inhibition of iPLA$_2$ on PE- and K^+-induced Ca^{2+} influx and constriction of cerebral, mesenteric, and carotid arteries was examined. Simultaneous changes in $[Ca^{2+}]_i$ and vessel diameter in response to consecutive application of K^+ (60 mM) and PE (10 μM) to a cerebral artery are shown in Fig. 3. After the responses were tested under control conditions, the vessels were treated for 30 min with 25 μM BEL, which was previously shown to irreversibly impair iPLA$_2$ function in SMC (25). After the vessels were treated with BEL and washed for 10 min, K^+ and PE were reapplied (Fig. 3), and the vessels retained a normal response to high K^+, but not PE. As shown in Fig. 4*A*, inhibition of iPLA$_2$ did not affect Ca^{2+} influx and vessel constriction induced by high K^+ (and mediated by Ca_L^{2+} channels) but dramatically impaired agonist-induced responses in cerebral arteries. Similar results in mouse mesenteric arteries (Fig. 4*B*) and rabbit carotid artery (Fig. 5) extended our findings to these additional microvascular beds as well as different types of animals. Figure 5 also demonstrates that inhibition of iPLA$_2$ not only could prevent agonist-induced constriction but also could relax the preconstricted artery.

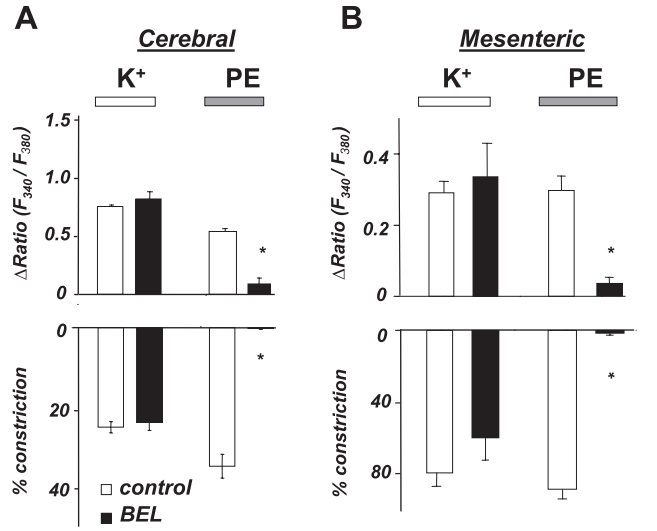

Fig. 4. Inhibition of iPLA$_2$ by BEL results in inhibition of Ca^{2+} influx and vessel constriction on stimulation by agonist, but not high K^+, in cerebral (*A*) and mesenteric (*B*) arteries. Summary data are from experiments similar to those described in Fig. 3. Values are means ± SE for 6 (*A*) and 8 (*B*) experiments. *$P < 0.05$ vs. control.

To confirm that iPLA$_2\beta$, and not iPLA$_2\gamma$, is required for agonist-induced Ca^{2+} entry and constriction in microvessels, we compared the effects of *S*-BEL and *R*-BEL [chiral enantiomers of this suicidal substrate that can discriminate these iPLA$_2$ isoforms (9, 15)] on PE-induced responses in cerebral arteries. Although vessels pretreated with *R*-BEL (which is specific to iPLA$_2\gamma$) responded normally to PE, *S*-BEL (which is specific to iPLA$_2\beta$) totally impaired PE-induced Ca^{2+} entry and constriction in the same vessels (Fig. 6).

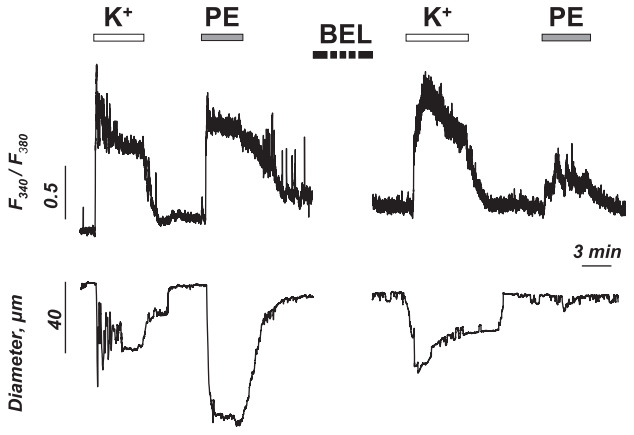

Fig. 3. Effect of irreversible Ca^{2+}-independent phospholipase A$_2$ (iPLA$_2$) inhibition by bromoenol lactone (BEL) on K^+- and PE-induced responses in intact cerebral artery. Results from a representative experiment show effects of application of high (60 mM) K^+ and 10 μM PE on Ca^{2+} (*top trace*) and vessel diameter (*bottom trace*) before and after 30 min of treatment with 25 μM BEL. Addition of PE after BEL treatment dramatically reduced intracellular Ca^{2+} rise and completely abolished constriction; K^+ did not affect Ca^{2+} or vessel diameter. Traces represent results from 4 experiments.

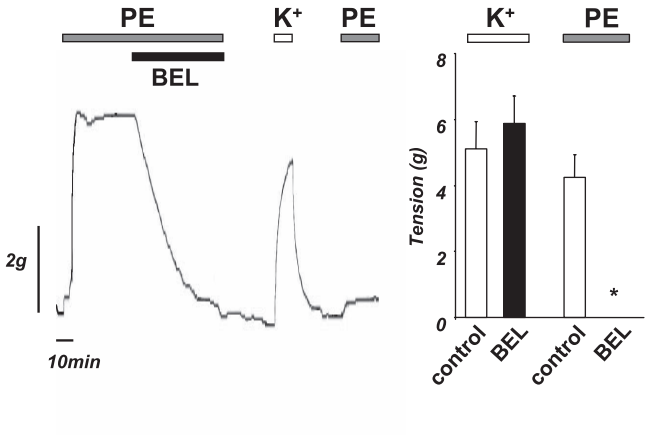

Fig. 5. Inhibition of iPLA$_2$ by BEL results in vessel relaxation and irreversible inhibition of agonist-induced, but not depolarization-induced, constriction in carotid artery SMC. Carotid artery ring was constricted with 0.1 μM PE, and 25 μM BEL was added in the continuous presence of PE. After complete vessel relaxation, PE and BEL were washed out for 20 min, and vessel was treated with high (30 mM) K^+ and then with PE. Values are means ± SE from 4 experiments. *$P < 0.05$ vs. control.

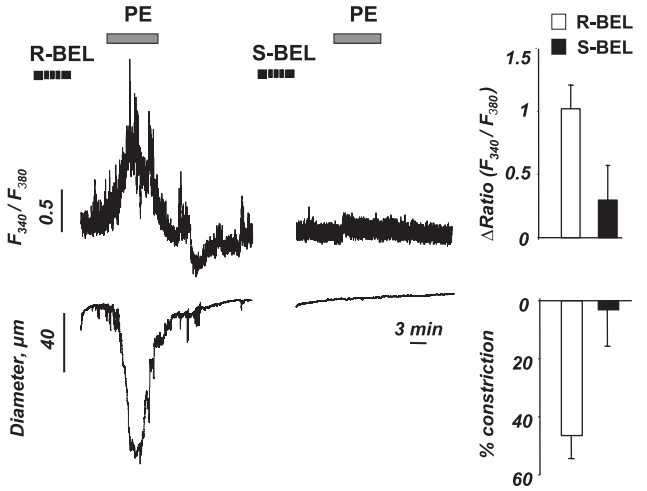

Fig. 6. Inhibition of iPLA$_2\beta$ by *S*-BEL results in inhibition of agonist-induced Ca^{2+} influx and vessel constriction, whereas inhibition of iPLA$_2\gamma$ by *R*-BEL has no effect on agonist responses. Representative traces and summary data show PE (10 μM)-induced Ca^{2+} (*top trace*) and diameter (*bottom trace*) responses of cerebral vessels after treatment with *R*-BEL (25 μM for 25 min) and then again after treatment with *S*-BEL (25 μM for 25 min).

DISCUSSION

Our data in intact cerebral, mesenteric, and carotid arteries demonstrate for the first time that iPLA$_2$-dependent activation of SOC is essential for agonist-induced Ca^{2+} entry and constriction in a wide variety of arteries, suggesting that this is a widespread phenomenon in microvessels.

To account for our finding of the equally important role of iPLA$_2\beta$, as well as SOC and Ca_L^{2+} channels, we propose a model for agonist-induced responses in microvessels (Fig. 7). On the basis of our earlier findings in isolated SMC (8, 24), we propose that agonist stimulation causes depletion of Ca^{2+} stores and activation of iPLA$_2$, which produces lysophospholipids that activate SOC. Nonselective cation SOC (27) can produce significant membrane depolarization and secondary activation of Ca_L^{2+} channels, which cause Ca^{2+} entry and, in turn, lead to vessel constriction. In this way, Ca_L^{2+} channels and SOC may be equally important for agonist-induced Ca^{2+} entry in SMC and constriction, as we found in microvessels. In contrast to smaller arteries, in the aorta we found that Ca_L^{2+} channels are not essential for agonist-induced Ca^{2+} influx and constriction (inhibition of Ca_L^{2+} has little to no effect on aortic tone) (8, 27). The difference may be explained by an ability of Ca^{2+} entering through SOC to directly cause contraction in aortic SMC and/or SOC-induced depolarization being insufficient for secondary activation of Ca_L^{2+} channels in SMC of these vessels. There is little doubt about the role of Ca_L^{2+} channels in responses of resistance vessel to agonists, in as much as selective inhibition of Ca_L^{2+} channels in all vessels tested in the present study impaired Ca^{2+} entry and constriction. This result was consistent with Ca_L^{2+} channels, not SOC, mediating Ca^{2+} entry, which triggers vessel constriction. However, SOC still plays a crucial role in agonist-induced responses, if not as a major Ca^{2+} entry path (as in aortic SMC), then as a depolarizing trigger for secondary activation of Ca_L^{2+} channels. Interestingly, Figs. 3 and 4 show that PE-induced constriction may be fully abolished, even though some residual Ca^{2+} rise in SMC could be detected after BEL treatment. Stronger inhibition of contractile responses may reflect the involvement of iPLA$_2$ in agonist-induced Ca^{2+} sensitization of contractile proteins (13), which may amplify the effect of the reduction on agonist-induced Ca^{2+} influx.

The use of functional inhibition of iPLA$_2\beta$ in our study (in addition to a widely used SOC inhibitor) introduces a new effective way to selectively impair the SOCE pathway in microvascular SMC and provides a more reliable method for assessing the role of SOC in physiology and pathology of microcirculation. Indeed, direct SOC inhibitors (e.g., 2-APB) may not exclude the possibility of involvement of additional

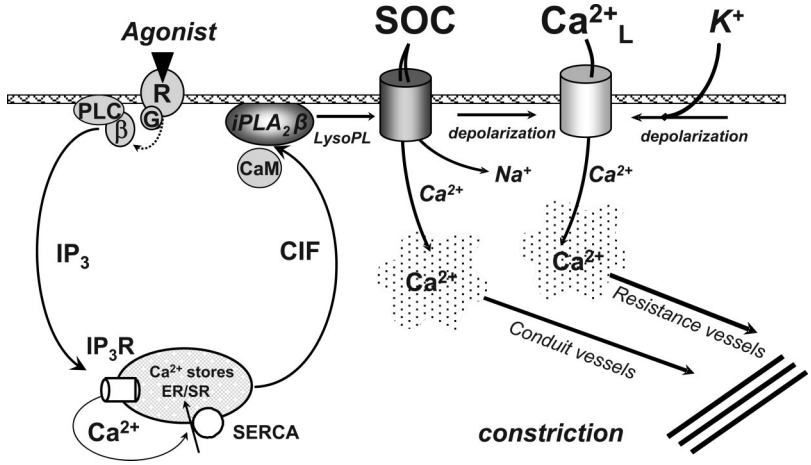

Fig. 7. A model for agonist-induced Ca^{2+} entry and constriction of conduit and microvessels. Agonist stimulation triggers inositol trisphosphate (IP_3) production and depletion of Ca^{2+} stores, leading to production of Ca^{2+} influx factor (CIF). CIF displaces inhibitory calmodulin (CaM) from iPLA$_2$, causing its activation and production of lysophospholipids (LysoPL) and, in turn, activates SOC. Nonselective cation SOC in SMC allow Ca^{2+} and Na^+ entry. In conduit vessels, SOC-mediated Ca^{2+} entry may cause vessel constriction; in microvessels, this pool of Ca^{2+} may be spatially separated from the contractile apparatus. Instead, in microvessels, SOC-induced depolarization may trigger activation of L-type Ca^{2+} (Ca_L^{2+}) channels, which allow Ca^{2+} entry and, in turn, lead to vessel constriction. Thus SOC may play an important, but slightly different, role in constriction of different vessels: in conduit vessels, SOC allow Ca^{2+} influx, which is sufficient for constriction; in resistance vessels, SOC serve as a trigger for secondary activation of Ca_L^{2+} channels, which mediate Ca^{2+} influx and, in turn, cause vessel constriction. IP_3R, IP_3 receptor; PLC, phospholipase C; ER, endoplasmic reticulum; SR, sarcoplasmic reticulum; SERCA, sarco(endo)plasmic reticulum Ca^{2+}-ATPase. R, G:G-coupled receptor.

non-SOC, in as much as 2-APB is known to inhibit agonist-induced Ca^{2+} release (17), as well as other non-SOC, which could also participate in agonist-induced responses. Recently, we demonstrated (31) that a TRPC1-encoded inositol trisphosphate (IP_3) receptor-operated channel (which can be clearly distinguished from SOC) may be activated by agonist-induced IP_3 rise and, potentially, may be involved in SMC and vessel responses to agonists. Importantly, because 2-APB is able to block both channels (SOC and IP_3 receptor-operated channels), it is impossible to distinguish their role in agonist-induced responses solely on the basis of 2-APB-induced inhibition. In our present study, in addition to 2-APB, we used BEL-induced inhibition of iPLA$_2$ as a selective way to impair SOC activation, in as much as only SOC require its functional activity (4, 9, 16, 22–25, 28). BEL (and its chiral enantiomers) provides new specific tools for assessing the role of iPLA$_2\beta$ and SOC activation in intact vessels, in which molecular knockdown of proteins poses significant difficulties.

In summary, we have demonstrated that iPLA$_2$-dependent activation of SOC, as well as Ca^{2+}_L channels, is crucial for agonist-induced Ca^{2+} entry and constriction in conduit and microvessels (Fig. 7).

ACKNOWLEDGMENTS

We thank Dr. Gokina for help in establishing the method for simultaneous measurement of Ca^{2+} and vessel diameter.

Present address of N. Serban: Department of Physiology, University of Medicine and Pharmacy, Universitatii 16, Iasi 700115, Romania.

GRANTS

This work was supported by National Heart, Lung, and Blood Institute Grants HL-054150 and HL-071793. K. M. Park was supported by National Heart, Lung, and Blood Institute Fellowship HL-007969.

REFERENCES

1. **Albert AP, Large WA.** Store-operated Ca^{2+}-permeable non-selective cation channels in smooth muscle cells. *Cell Calcium* 33: 345–356, 2003.
2. **Balsinde J, Dennis EA.** Function and inhibition of intracellular calcium-independent phospholipase A_2. *J Biol Chem* 272: 16069–16072, 1997.
3. **Beech DJ.** SOCs—store-operated channels in vascular smooth muscle? *J Physiol* 544: 1, 2002.
4. **Boittin FX, Petermann O, Hirn C, Mittaud P, Dorchies OM, Roulet E, Ruegg UT.** Ca^{2+}-independent phospholipase A_2 enhances store-operated Ca^{2+} entry in dystrophic skeletal muscle fibers. *J Cell Sci* 119: 3733–3742, 2006.
5. **Bolotina VM, Csutora P.** CIF and other mysteries of the store-operated Ca^{2+}-entry pathway. *Trends Biochem Sci* 30: 378–387, 2005.
6. **Bolotina VM, Najibi S, Palacino JJ, Pagano PJ, Cohen RA.** Nitric oxide directly activates calcium-dependent potassium channels in vascular smooth muscle. *Nature* 368: 850–853, 1994.
7. **Bolotina VM.** Store-operated channels: diversity and activation mechanisms. *SciSTKE* 2004: pe34, 2004.
8. **Cohen RA, Weisbrod RM, Gericke M, Yaghoubi M, Bierl C, Bolotina VM.** Mechanism of nitric oxide-induced vasodilation. Refilling of intracellular stores by sarcoplasmic reticulum Ca^{2+} ATPase and inhibition of store-operated Ca^{2+} influx. *Circ Res* 84: 210–219, 1999.
9. **Csutora P, Zarayskiy V, Peter K, Monje F, Smani T, Zakharov S, Litvinov D, Bolotina VM.** Activation mechanism for CRAC current and store-operated Ca^{2+} entry: calcium influx factor and Ca^{2+}-independent phospholipase $A_2\beta$ mediated pathway. *J Biol Chem* 281: 34926–34935, 2006.
10. **Facemire CS, Arendshorst WJ.** Calmodulin mediates norepinephrine-induced receptor-operated calcium entry in preglomerular resistance arteries. *Am J Physiol Renal Physiol* 289: F127–F136, 2005.
11. **Flemming R, Cheong A, Dedman AM, Beech DJ.** Discrete store-operated calcium influx into an intracellular compartment in rabbit arteriolar smooth muscle. *J Physiol* 543: 455–464, 2002.
12. **Flemming R, Xu SZ, Beech DJ.** Pharmacological profile of store-operated channels in cerebral arteriolar smooth muscle cells. *Br J Pharmacol* 139: 955–965, 2003.
13. **Guo Z, Su W, Ma Z, Smith GM, Gong MC.** Ca^{2+}-independent phospholipase A_2 is required for agonist-induced Ca^{2+} sensitization of contraction in vascular smooth muscle. *J Biol Chem* 278: 1856–1863, 2003.
14. **Hill MA, Zou H, Potocnik SJ, Meininger GA, Davis MJ.** Arteriolar smooth muscle mechanotransduction: Ca^{2+} signaling pathways underlying myogenic reactivity. *J Appl Physiol* 91: 973–983, 2001.
15. **Jenkins CM, Han X, Mancuso DJ, Gross RW.** Identification of calcium-independent phospholipase A_2 (iPLA$_2$)-β, and not iPLA$_2\gamma$, as the mediator of arginine vasopressin-induced arachidonic acid release in A-10 smooth muscle cells. Enantioselective mechanism-based discrimination of mammalian iPLA$_2$s. *J Biol Chem* 277: 32807–32814, 2002.
16. **Martinez J, Moreno JJ.** Role of Ca^{2+}-independent phospholipase A_2 and cytochrome *P*-450 in store-operated calcium entry in 3T6 fibroblasts. *Biochem Pharmacol* 70: 733–739, 2005.
17. **Maruyama T, Kanaji T, Nakade S, Kanno T, Mikoshiba K.** 2APB, 2-aminoethoxydiphenyl borate, a membrane-penetrable modulator of Ins(1,4,5)P_3-induced Ca^{2+} release. *J Biochem (Tokyo)* 122: 498–505, 1997.
18. **Morales S, Camello PJ, Alcon S, Salido GM, Mawe G, Pozo MJ.** Coactivation of capacitative calcium entry and L-type calcium channels in guinea pig gallbladder. *Am J Physiol Gastrointest Liver Physiol* 286: G1090–G1100, 2004.
19. **Nelson MT, Standen NB, Brayden JE, Worley JF.** Noradrenaline contracts arteries by activating voltage-dependent calcium channels. *Nature* 336: 382–385, 1988.
20. **Nelson MT, Worley JF.** Dihydropyridine inhibition of single calcium channels and contraction in rabbit mesenteric artery depends on voltage. *J Physiol* 412: 65–91, 1989.
21. **Poteser M, Wakabayashi I, Rosker C, Teubl M, Schindl R, Soldatov NM, Romanin C, Groschner K.** Crosstalk between voltage-independent Ca^{2+} channels and L-type Ca^{2+} channels in A7r5 vascular smooth muscle cells at elevated intracellular pH: evidence for functional coupling between L-type Ca^{2+} channels and a 2-APB-sensitive cation channel. *Circ Res* 92: 888–896, 2003.
22. **Ross K, Whitaker M, Reynolds NJ.** Agonist-induced calcium entry correlates with STIM1 translocation. *J Cell Physiol* 211: 569–576, 2007.
23. **Singaravelu K, Lohr C, Deitmer JW.** Regulation of store-operated calcium entry by calcium-independent phospholipase A_2 in rat cerebellar astrocytes. *J Neurosci* 26: 9579–9592, 2006.
24. **Smani T, Zakharov S, Csutora P, Leno E, Trepakova ES, Bolotina VM.** A novel mechanism for the store-operated calcium influx pathway. *Nat Cell Biol* 6: 113–120, 2004.
25. **Smani T, Zakharov SI, Leno E, Csutora P, Trepakova ES, Bolotina VM.** Ca^{2+}-independent phospholipase A_2 is a novel determinant of store-operated Ca^{2+} entry. *J Biol Chem* 278: 11909–11915, 2003.
26. **Stevens T.** Is there a role for store-operated calcium entry in vasoconstriction? *Am J Physiol Lung Cell Mol Physiol* 280: L866–L869, 2001.
27. **Trepakova ES, Gericke M, Hirakawa Y, Weisbrod RM, Cohen RA, Bolotina VM.** Properties of a native cation channel activated by Ca^{2+} store depletion in vascular smooth muscle cells. *J Biol Chem* 276: 7782–7790, 2001.
28. **Vanden Abeele F, Lemonnier L, Thebault S, Lepage G, Parys J, Shuba Y, Skryma R, Prevarskaya N.** Two types of store-operated Ca^{2+} channels with different activation modes and molecular origin in LNCaP human prostate cancer epithelial cells. *J Biol Chem* 279: 30326–30337, 2004.
29. **Vig M, Peinelt C, Beck A, Koomoa DL, Rabah D, Koblan-Huberson M, Kraft S, Turner H, Fleig A, Penner R, Kinet JP.** CRACM1 is a plasma membrane protein essential for store-operated Ca^{2+} entry. *Science* 312: 1220–1223, 2006.
30. **Winstead MV, Balsinde J, Dennis EA.** Calcium-independent phospholipase A_2: structure and function. *Biochim Biophys Acta* 1488: 28–39, 2000.
31. **Zarayskiy V, Monje F, Peter K, Csutora P, Khodorov BI, Bolotina VM.** Store-operated Orai1 and IP$_3$R-operated TRPC1 channel: separation of the Siamese twins. *Channels* 1: 246–252, 2007.