Store-operated calcium entry and intracellular calcium release channels in airway smooth muscle

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IT HAS LONG BEEN KNOWN that release of intracellular stored Ca2+ [presumably in the sarcoplasmic reticulum (SR)] plays a major role in initiating contraction in airway smooth muscle (ASM) from a variety of species (6) including human (17). Therefore, the issue of how extracellular calcium ions enter the cell to refill the SR is of particular importance to better understand Ca2+ homeostasis in ASM, from both physiological and pathophysiological points of view. Indeed, modulation of Ca2+ homeostasis may play a role in altered ASM responsiveness in asthma (2). Because both agonist-induced sustained contraction and Ca2+ influx in ASM are relatively insensitive to inhibitors of voltage-operated Ca2+ channels (VOCC) despite their established presence (12, 14, 16), attention is being paid to alternative Ca2+ influx pathways that include receptor-operated Ca2+ channels (ROCC) (19, 20) and store-operated Ca2+ channels (SOCC). A current article in focus by Ay et al. (Ref. 3, see p. L909 in this issue) examines the role of intracellular Ca2+-permeable channels in triggering SOCC in ASM.

SOCC are Ca2+-permeable channels in the plasma membrane that are open following depletion of intracellular Ca2+ stores underlying the so-called “store-operated” or “capacitative” Ca2+ entry. The model of such capacitative Ca2+ entry was initially proposed by Putney (22) and, since then, consistently developed and improved (8, 18, 23). However, comprehensive characterization of SOCC in smooth muscle is far from complete, since membrane currents underlying store-operated Ca2+ entry have been difficult to record in smooth muscle cells (1, 18). Moreover, highly selective blockers of SOCC are still lacking. Cations including Ni2+, La3+, or gadolinium inhibit store-operated Ca2+ entry in a variety of smooth muscle but also block ROCC in some others (18). Similarly, SKF-96365, the most commonly used SOCC inhibitor, does not inhibit store-operated Ca2+ entry in some smooth muscle (10), whereas it blocks ROCC or even VOCC and exerts nonspecific effects. Consequently, an important tool for examining capacitative Ca2+ entry has been, and remains, represented by inhibitors of the SR Ca2+-ATPase pump, such as thapsigargin (TG) or cyclopiazonic acid (CPA), that inhibit active uptake of Ca2+ in the store leading to passive depletion (7, 9, 26). Additionally, there is now evidence that members of the transient receptor potential (TRP) superfamily, the mammalian homolog of the Drosophila phototransduction pathway, form the channels supporting store-operated Ca2+ entry (23). The TRP superfamily is composed of three subfamilies: TRPC (classic cation channel), TRPV (vanilloid-receptor like), and TRPM (melastatin-like), with TRPC (including at least seven members, TRPC1–7) being the most studied (4). Accordingly, identification of TRP is also of interest for studying SOCC. With respect to the overlapping properties of ROCC and SOCC listed above, it is noteworthy that recent evidence indicates that the two channels may be formed from proteins of the TRPC family (18).

In airway smooth muscle, Ito et al. (11) have shown that TG triggers capacitative Ca2+ entry in guinea pig ASM. Likewise, Sweeney et al. (25) have observed both CPA-induced Ca2+ entry and bronchial contraction in rat ASM. In addition, these authors have been able to record store-operated Ca2+ current (I_{so}) in both rat and human ASM cells at the whole cell level under different experimental conditions. Finally, they have related changes in I_{so} with changes in mRNA expression of TRPC1 (25) according to different experimental conditions. Expression of additional isoforms of TRPC, in particular TRPC6, has also very recently been reported in human ASM (5).

Ay et al. (3) further establish, in freshly isolated single ASM cells, the above-mentioned characteristics of SOCC in terms of 1) activation by CPA or agonists, 2) pharmacological profile, and 3) presence of several TRPC isoforms. Moreover, these authors demonstrate the implication of intracellular Ca2+ release channels, i.e., both inositol 1,4,5-trisphosphate (InsP3) and ryanodine receptors ( RyR) in triggering SOCC. The presence and the role of these receptors in Ca2+ homeostasis and Ca2+ oscillations in ASM have been recently extensively studied (for review see Ref. 24). In the same species as that examined in the Ay et al. report (3), Prakash et al. (21) and Kannan and colleagues (13, 27) have shown that RyR are involved in agonist-induced intracellular Ca2+ oscillations and tone via the involvement of a novel second messenger, cyclic ADP ribose. Therefore, the present data provide strong evidence for the contribution of SOCC to agonist-induced Ca2+ oscillations and tone in ASM under physiological conditions.

Further studies are required to determine the coupling mechanisms linking depletion of intracellular Ca2+ stores to SOCC activation in ASM. There are currently no data to favor any of the proposed mechanisms, i.e., the release of a diffusible factor e.g. Ca2+ influx factor or the fusion of vesicles containing SOCC with the plasma membrane (exocytosis model) or, finally, the conformational coupling, i.e., conformational alteration in the InsP3 receptor leading to an interaction with SOCC following depletion of intracellular Ca2+ stores (23). The data from Ay et al. confirm that, if the latter hypothesis is applicable to ASM, the conformational coupling of the InsP3 receptor occurs in an InsP3-independent manner, since SOCC is activated by Ca2+ release via RyR (23). Also, the implication of TRPC and SOCC under pathophysiological conditions of increased airway responsiveness needs to be examined to provide additional support to the emerging concept that TRPC could be potential drug targets in respiratory disease (5, 15).
REFERENCES


