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 Ca\textsuperscript{2+} [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 Ca\textsuperscript{2+} homeostasis in ASM, from both physiological and pathophysiological points of view. Indeed, modulation of Ca\textsuperscript{2+} homeostasis may play a role in altered ASM responsiveness in asthma (2). Because both agonist-induced sustained contraction and Ca\textsuperscript{2+} influx in ASM are relatively insensitive to inhibitors of voltage-operated Ca\textsuperscript{2+} channels (VOCC) despite their established presence (12, 14, 16), attention is being paid to alternative Ca\textsuperscript{2+} influx pathways that include receptor-operated Ca\textsuperscript{2+} channels (ROCC) (19, 20) and store-operated Ca\textsuperscript{2+} channels (SOCC). A current article in focus by Ay et al. (Ref. 3, see p. L909 in this issue) examines the role of intracellular Ca\textsuperscript{2+} release channels in triggering SOCC in ASM.

SOCC are Ca\textsuperscript{2+}-permeable channels in the plasma membrane that are open following depletion of intracellular Ca\textsuperscript{2+} stores underlying the so-called “store-operated” or “capacitative” Ca\textsuperscript{2+} entry. The model of such capacitative Ca\textsuperscript{2+} 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 Ca\textsuperscript{2+} entry have been difficult to record in smooth muscle cells (1, 18). Moreover, highly selective blockers of SOCC are still lacking. Cations including Ni\textsuperscript{2+}, La\textsuperscript{3+}, or gadolinium inhibit store-operated Ca\textsuperscript{2+} 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 Ca\textsuperscript{2+} entry in some smooth muscle (10), whereas it blocks ROCC or even VOCC and exerts nonspecific effects. Consequently, an important tool for examining capacitative Ca\textsuperscript{2+} entry has been, and remains, represented by inhibitors of the SR Ca\textsuperscript{2+}-ATPase pump, such as thapsigargin (TG) or cyclopiazonic acid (CPA), that inhibit active uptake of Ca\textsuperscript{2+} 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 Ca\textsuperscript{2+} entry (23). The TRP superfamily is composed of three subfamilies: TRPC (classic cation channel), TRPV (vanilloid-receptor like), and TRPM (melastatine-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 Ca\textsuperscript{2+} entry in guinea pig ASM. Likewise, Sweeney et al. (25) have observed both CPA-induced Ca\textsuperscript{2+} entry and bronchial contraction in rat ASM. In addition, these authors have been able to record store-operated Ca\textsuperscript{2+} current (*I*\textsubscript{SOCC}) in both rat and human ASM cells at the whole cell level under different experimental conditions. Finally, they have related changes in *I*\textsubscript{SOCC} 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 Ca\textsuperscript{2+} release channels, i.e., both inositol 1,4,5-trisphosphate (InsP\textsubscript{3}) and ryanodine receptors (RyR) in triggering SOCC. The presence and the role of these receptors in Ca\textsuperscript{2+} homeostasis and Ca\textsuperscript{2+} 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 Ca\textsuperscript{2+} 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 Ca\textsuperscript{2+} oscillations and tone in ASM under physiological conditions.

Further studies are required to determine the coupling mechanisms linking depletion of intracellular Ca\textsuperscript{2+} 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., Ca\textsuperscript{2+} 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 InsP\textsubscript{3} receptor leading to an interaction with SOCC following depletion of intracellular Ca\textsuperscript{2+} stores (23). The data from Ay et al. confirm that, if the latter hypothesis is applicable to ASM, the conformational coupling of the InsP\textsubscript{3} receptor occurs in an InsP\textsubscript{3}-independent manner, since SOCC is activated by Ca\textsuperscript{2+} 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).