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Regulation of epithelial ion transport in exocrine glands by store-operated Ca^{2+} entry

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Abstract

Store-operated Ca^{2+} entry (SOCE) is a conserved mechanism of Ca^{2+} influx that regulates Ca^{2+} signaling in many cell types. SOCE is activated by depletion of endoplasmic reticulum (ER) Ca^{2+} stores in response to physiological agonist stimulation. After it was first postulated by J.W. Putney Jr. in 1986, SOCE has been described in a large number of non-excitable cell types including secretory cells of different exocrine glands. Here we discuss the mechanisms by which SOCE controls salt and fluid secretion in exocrine glands, with a special focus on eccrine sweat glands. In sweat glands, SOCE plays an important, non-redundant role in regulating the function of Ca^{2+} -activated Cl^{-} channels (CaCC), Cl^{-} secretion and sweat production. In the absence of key regulators of SOCE such as the CRAC channel pore subunit ORAI1 and its activator STIM1, the Ca^{2+} -activated chloride channel TMEM16A is inactive and fails to secrete Cl^{-} , resulting in anhidrosis in mice and human patients.

Graphical Abstract

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Keywords

CaCC; fluid secretion; ORAI1; STIM1; sweat glands; TMEM16A

1. Introduction

Store-operated Ca^{2+} entry (SOCE) is a conserved mechanism for Ca^{2+} influx in a large variety of cells [1]. Initially termed capacitative Ca^{2+} entry, SOCE was postulated 30 years ago in a seminal review published by J.W. Putney Jr. based on observations in non-excitabile salivary gland cells and hepatocytes [2]. At the time, Ca^{2+} influx was known to be critical for secretion by different exocrine glands after stimulation with secretagogues or neurotransmitters such as acetylcholine (ACh) or norepinephrine [3–8]. The concept of SOCE as a specialized mode of Ca^{2+} influx and means to refill intracellular Ca^{2+} stores was confirmed by many labs [5, 9–11], but the molecular players including the Ca^{2+} channel mediating SOCE and the mechanisms of SOCE activation remained elusive. The prototypical SOCE channel is the Ca^{2+} release-activated Ca^{2+} (CRAC) channel, which opens after depletion of Ca^{2+} from intracellular stores, mainly the ER. Active store depletion is induced by receptor agonists or passively by drugs that cause leakage of Ca^{2+} from the ER or prevent Ca^{2+} reuptake by sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) pumps. Agonists that trigger SOCE include ligands of G protein-coupled receptors (GPCRs) and antigens that bind to immunoreceptors in the plasma membrane (PM). Receptor binding results in activation of phospholipase C, production of inositol 1,4,5-trisphosphate (IP_3), and opening of IP_3 receptors (IP_3Rs), which are non-selective Ca^{2+} channels in the ER membrane that mediate the release of Ca^{2+} from that organelle [12]. How depletion of Ca^{2+} from the ER activates SOCE remained elusive until the discovery of stromal interaction molecule 1 (STIM1) and STIM2 [13–15]. Both homologues are single pass transmembrane proteins located in the ER. Their ER luminal N-termini contain EF hand motifs that are bound by Ca^{2+} in non-stimulated cells. After cell stimulation and Ca^{2+} store depletion, Ca^{2+} dissociates from the EF hands, resulting in extensive conformational changes in STIM1 and STIM2 and their translocation to ER-PM junctions. There they bind to and open the CRAC channel, which mediates sustained Ca^{2+} influx from the extracellular space [1, 16]. CRAC currents were first recorded in immune cells and subsequently in many other cell types including secretory cells, but their molecular composition remained enigmatic until the discovery of ORAI1 as their pore-forming subunit [17–20]. ORAI1 and its homologues ORAI2 and ORAI3 are tetraspanning PM proteins that are unrelated to other ion channels. They form hexameric channel complexes that have very low unitary conductance but are highly Ca^{2+} selective [21–23]. Genetic deletion of ORAI1, STIM1 and/or STIM2 in mice and other model organisms and mutations in human *ORAI1* and *STIM1* genes that result in CRAC channelopathy have shed important light on the physiological role of SOCE [1, 24–27]. In this review, we discuss the role of SOCE in exocrine gland function and our recent findings in eccrine sweat glands, in which SOCE regulates Cl^- secretion and sweat production.

2. Basic mechanisms of salt and fluid secretion

Exocrine glands produce and secrete a large variety of fluids that are important for digestion, lubrication, lactation and thermoregulation [28–32]. Examples of exocrine glands include sweat, salivary, lacrimal, and mammary glands. These glands are composed of layers of secretory epithelial cells that absorb water, ions and hydrophilic macromolecules from the blood, and secrete them onto epithelial surfaces through a duct. The mechanism of salt and fluid secretion by exocrine glands is based on the active transcellular and paracellular transport of these substances from the basolateral to the apical membrane of epithelial secretory cells. Active transcellular transport requires the function of ion channels and transporters that allow the permeation of charged ions and hydrophilic molecules across the PM of polarized epithelial cells (Figure 1). Cl^- secretion across the luminal membrane of acinar cells generates an electrical gradient that drives transepithelial Na^+ transport, and this salt enrichment in the lumen of secretory gland acini establishes an osmotic driving force for water flow via paracellular and/or transcellular routes [33–35]. The ion composition of the isotonic primary secretion is further modified by the ductal epithelium, which can reabsorb Na^+ and Cl^- ions and secrete HCO_3^- dependent on the type of gland [35–38]. Salivary gland ducts both secrete (HCO_3^- and K^+) and reabsorb (Na^+ and Cl^-) ions with net reabsorption to give a hypotonic final saliva as the water permeability of the duct is very low. In contrast in the pancreas, the vast majority of the secreted fluid is a result of ductal function due to $\text{Cl}^-/\text{HCO}_3^-$ exchange resulting in Na^+ and HCO_3^- rich secretion [34, 38].

Fluid and salt secretion in epithelial cells is triggered by many pathways including cyclic adenosine monophosphate (cAMP) and phosphatidylinositol- Ca^{2+} signaling (Figure 1). The binding of extracellular ligands to GPCRs such as the β -adrenoreceptor and some hormone receptors triggers adenylyl cyclase activation and the generation of cAMP from ATP. Increasing levels of cAMP activate protein kinase A (PKA), which in turn phosphorylates and gates the cystic fibrosis transmembrane conductance regulator (CFTR) anion channel [39, 40]. CFTR activation leads to Cl^- secretion by secretory epithelial cells in salivary glands, the pancreas and the lung as well as Cl^- reabsorption and secretion by ductal cells [41–47]. The phosphatidylinositol- Ca^{2+} pathway is activated by extracellular ligands that bind GPCRs (e.g. cholinergic and α -adrenergic receptors) located at the basolateral PM of epithelial cells. GPCR engagement activates phospholipase C and results in the subsequent formation of diacylglycerol (DAG) and IP_3 . The diffusion of IP_3 in the cytosol activates IP_3R channels triggering the release of Ca^{2+} from ER stores. Ca^{2+} store depletion by IP_3Rs determines the site of initiation and the pattern of Ca^{2+} signals in the cell, and it has been implicated in fluid secretion in the liver, pancreas, salivary and sweat glands [33, 48–52]. Ca^{2+} signals resulting from store release can potentially stimulate Ca^{2+} -activated Cl^- channels (CaCCs) in the PM that mediate the secretion of Cl^- from the cell. However, the finite amount of Ca^{2+} in the ER is likely not sufficient to maintain sustained CaCC activation required for the secretion of large amounts of fluid by secretory epithelial cells. As discussed in more detail further below, we recently demonstrated that Ca^{2+} influx via SOCE is necessary for sustained CaCC activation, Cl^- secretion and sweat production in eccrine sweat glands, whereas Ca^{2+} release from ER stores alone was not sufficient to mediate this

process [53]. These findings are consistent with reports showing that Ca^{2+} influx from the extracellular space is required for fluid secretion by different exocrine glands [5, 7, 54].

3. Mechanism of salt and fluid secretion in eccrine sweat glands

Eccrine sweat glands are one of the simplest exocrine gland systems [46]. Each eccrine sweat gland unit consists of two portions, the secretory coil and the duct, which differ in morphology and function (Figure 2A) [55, 56]. The secretory coil contains acinar epithelial cells (that can be divided further into clear and dark cells) surrounded by myoepithelial cells, whereas the duct is composed by two layers of cuboidal epithelium [55]. The main physiological function of eccrine sweat glands in humans is thermoregulation. Millions of eccrine sweat glands are spread over almost the entire skin surface to secrete sweat, which evaporates and generates the cooling effect. Sweat secretion follows the basic mechanism of salt and fluid secretion described in section 2. Sympathetic nerve terminals surrounding the secretory coil of sweat glands release the neurotransmitter ACh, which binds to muscarinic ACh receptors expressed in secretory epithelial cells [57, 58]. ACh triggers the production of IP_3 , Ca^{2+} store release and SOCE, which is required for CaCC activation and Cl^- secretion (see below) [53]. To generate the vectorial transport of Cl^- across the polarized secretory sweat gland epithelial cells, Cl^- influx is mediated by the $\text{Na}^+/\text{K}^+-2\text{Cl}^-$ co-transporter NKCC1 located in the basolateral membrane [59–62]. Other channels and pumps in the basolateral membrane are required to support Cl^- transport by NKCC1. These include the Na^+/K^+ ATPase pump [62, 63] and Ca^{2+} -activated K^+ channels [29, 55, 64, 65] that establish the membrane potential and maintain the driving force for Cl^- secretion. The main channels mediating Cl^- secretion at the luminal membrane of sweat gland acinar cells are CaCCs [53, 66, 67]. Recent studies have shed light on the molecular nature of the CaCCs in murine and human sweat glands [53, 61, 66, 68, 69]. Bestrophin 2 (BEST2) is a CaCC that is necessary for sweat secretion as *Best2*^{-/-} mice showed a complete defect in spontaneous sweat production [61]. BEST2 expression was shown to be restricted to dark cells in murine eccrine sweat glands [61], whose functional role, unlike that of clear cells, in sweat secretion is not well characterized [29, 55, 70–72]. Whether BEST2 plays a role in mediating sweat secretion in response to cholinergic stimulation in mice or in humans remains to be investigated. In the human eccrine sweat gland cell line NCL-SG3, another CaCC, TMEM16A (also known as anoctamin 1, ANO1) was shown to be expressed at the transcriptional level [66]. Overexpression of the canonical TMEM16A isoform or one of its splice variants in NCL-SG3 cells mediated Cl^- secretion, suggesting that TMEM16A may also contribute to Cl^- secretion in primary human sweat glands [66]. We confirmed expression of TMEM16A mRNA and protein in human NCL-SG3 cells and primary sweat gland cells in skin biopsies [53]. In addition, TMEM16A was also expressed in primary murine sweat glands [53]. Importantly, we demonstrate that TMEM16A is essential for Cl^- secretion in human eccrine sweat gland cells. Stable deletion of TMEM16A expression in NCL-SG3 cells by shRNAs abolished Cl^- secretion and Cl^- currents activated following direct intracellular administration of Ca^{2+} via the patch pipette or induction of SOCE by stimulation of cells with ionomycin or the PAR2 agonist trypsin. By contrast, untransduced or shBEST2 transduced NCL-SG3 cells showed robust CaCC currents, which had properties consistent with those described for TMEM16A [53, 73, 74]. While TMEM16A clearly

mediates Cl^- currents and Cl^- secretion in human sweat gland cells, its role in primary eccrine glands of mice and humans remains to be further studied. To date, no mutations in *TMEM16A* (or *BEST2*) have been reported in patients with anhidrosis.

4. Ca^{2+} release from ER stores and SOCE in eccrine sweat gland function

While Cl^- secretion in NCL-SG3 cells is well known to be dependent on increases in cytoplasmic $[\text{Ca}^{2+}]$ [66, 67, 75], the source of Ca^{2+} required for CaCC activation is unclear. Early studies have shown that Ca^{2+} influx from the extracellular space is essential for sweating in response to cholinergic and α -adrenergic stimulation [7]. The Ca^{2+} channels mediating this influx in secretory sweat gland cells, however, remained unknown [76]. Alternatively, Ca^{2+} release from intracellular stores may activate CaCCs and Cl^- secretion. However, the Ca^{2+} content of ER stores is finite and, as discussed above, may not be sufficient for the sustained activation of CaCCs and Cl^- secretion. Arguing in favor of an important role of ER stores as the source of Ca^{2+} for CaCC activation is the hypohidrotic phenotype of patients with a missense mutation in the *ITPR2* gene, which encodes IP_3R_2 , and *Itpr2*^{-/-} mice [51]. Sweat gland cells isolated from *Itpr2*^{-/-} mice had reduced ACh-induced Ca^{2+} signals and sweating of *Itpr2*^{-/-} mice after cholinergic stimulation was significantly impaired [51]. IP_3Rs were shown to colocalize with CaCCs in several cell types [77–80] and it therefore seemed plausible that Ca^{2+} release from the ER through IP_3R_2 mediates CaCC activation, Cl^- secretion and sweat production. Importantly, however, Ca^{2+} release via IP_3R_2 not only increases intracellular $[\text{Ca}^{2+}]$ but also decreases $[\text{Ca}^{2+}]$ in the ER, which activates store-operated CRAC channels. Genetic deletion or mutation of IP_3R_2 in mice or patients, respectively, will therefore also impair SOCE. We showed that human patients with loss-of-function mutations in *ORAI1* or *STIM1* that abolish CRAC channel function and SOCE are anhidrotic despite the presence of eccrine sweat gland cells in their dermis [53]. Likewise, mice with conditional deletion of *Orai1* or both *Stim1* and *Stim2* in ectoderm-derived tissues fail to sweat upon cholinergic stimulation, although sweat glands are present and express TMEM16A and BEST2 channels [53]. Furthermore, primary sweat gland cells of *Orai1*-deficient mice and human NCL-SG3 sweat gland cells lacking ORAI1 failed to secrete Cl^- due to abolished SOCE. ORAI1-deficient NCL-SG3 cells also lacked CaCC currents activated by ionomycin stimulation and the PAR2 agonist trypsin [53]. These data demonstrate that SOCE mediated by CRAC channels is required for activation of CaCCs, Cl^- secretion and ultimately sweat production by eccrine sweat glands. They also argue against Ca^{2+} release from the ER as a sufficient Ca^{2+} signal for CaCC activation and Cl^- secretion. This conclusion is supported by the normal Ca^{2+} content of ER stores in primary sweat gland cells from mice lacking *Orai1* or both *Stim1* and *Stim2*, and cells from patients with mutations in *ORAI1* or *STIM1* genes [53]. Depletion of ER Ca^{2+} stores in ORAI1-deficient cells by ionomycin or trypsin stimulation resulted in a transient increase in intracellular $[\text{Ca}^{2+}]$, which was not sufficient for sustained Cl^- secretion and activation of CaCC currents. How can the anhidrosis in IP_3R_2 -deficient patients and mice on one hand, and ORAI1 and STIM1-deficient patients and mice on the other be reconciled? While SOCE is clearly essential for activation of CaCCs and Cl^- secretion in human and mouse sweat glands, it is not fully understood whether Ca^{2+} entering via ORAI1 directly activates CaCCs, facilitated by colocalization of ORAI1 channels with CaCCs in the plasma membrane, or

whether SOCE is primarily needed to refill ER Ca^{2+} stores (Figure 2B). In the latter model, Ca^{2+} release from the ER through IP_3Rs would provide the Ca^{2+} signal required for CaCC activation and Cl^- secretion. IP_3Rs have been shown to colocalize with CaCCs in other cell types such as *Xenopus* oocytes and nociceptive sensory neurons and may therefore create microdomains with enhanced cytoplasmic $[\text{Ca}^{2+}]$ that mediate CaCC activation [77, 79–81]. Such a model is supported by studies in *Xenopus* oocytes that suggest that Ca^{2+} entering the cytosol through CRAC channels is taken up by the ER via SERCA pumps and released by IP_3Rs at different sites to activate CaCCs [77]. Whether a similar mechanism plays a role in eccrine sweat gland cells remains to be investigated. Taken together, SOCE mediated by STIM1/ORAI1 either directly provides the Ca^{2+} signal that is required for CaCC activation, Cl^- secretion and sweat production or allows cells to refill their Ca^{2+} stores, the depletion of which via $\text{IP}_3\text{R2}$ results in Ca^{2+} dependent activation of CaCCs (Figure 2B) [53, 77].

5. Effects of mutations in human genes that impair Ca^{2+} release and SOCE on sweat gland function

Human patients with CRAC channelopathy due to autosomal recessive loss-of-function and null mutations in *ORAI1* and *STIM1* genes present with a complex clinical syndrome that is characterized by anhidrotic ectodermal dysplasia (EDA) with severe immunodeficiency (ID), autoimmunity and skeletal myopathy [24]. The immunodeficiency is defined by recurrent, life-threatening bacterial and viral infections. To date, patients with 15 different mutations in *ORAI1* and *STIM1* have been observed that either abolish protein expression or impair ORAI1 or STIM1 function. In both cases, SOCE is severely impaired resulting in similar clinical phenotypes [53]. Ectodermal dysplasia in ORAI1 and STIM1-deficient patients is defined by defects in tooth development, specifically the calcification of dental enamel (amelogenesis imperfecta) and anhidrosis [24, 25, 53]. All patients with CRAC channelopathy reported to date uniformly have impaired sweat production when tested by pilocarpine iontophoresis [53, 82–85]. In many of these patients, anhidrosis or reduced sweat production (hypohidrosis) is apparent clinically and results in elevated body temperatures (hyperthermia), especially at high ambient temperature in hot summer months, and even in the absence of infections caused by the patients' immunodeficiency. It is noteworthy, that CRAC channel deficiency does not result in apparent development defects of ectodermal structures besides dental enamel that occurs in other forms of EDA [86, 87]. Sweat glands were present in the dermis of ORAI1 and STIM1-deficient patients and had a normal morphology except reduced diameters of the sweat gland lumen that is presumably due to abolished sweat production [53]. CRAC channelopathy thus represents a new form of EDA associated with immunodeficiency (EDA-ID) that has a distinctive pathophysiology compared to another form of EDA-ID caused by mutations in *IKBKG* and *NFKB1A* genes, encoding $\text{IKK}\gamma$ and $\text{I}\kappa\text{-B}\alpha$, respectively. Both proteins are essential components of the canonical NF- κB signaling pathway and their mutation results in impaired sweat gland development as the cause of anhidrosis in those patients [88–91].

Isolated hypohidrosis without other clinical features of EDA was observed in patients homozygous for a novel missense mutation in *ITPR2*, c.7492G>A, which results in a glycine-to-serine (p.G2498S) substitution [51]. All five affected family members failed to

sweat when exposed to heat (45°C) and suffered from severe heat intolerance. Skin biopsies showed normal morphology and number of eccrine glands. The *ITPR2* mutation was not associated with other symptoms characteristic of EDA such as skin, hair or tooth defects or immunodeficiency as in patients with CRAC channelopathy. The milder clinical phenotype in *ITPR2*-deficient patients (*i.e.* isolated hypohidrosis) compared to *ORAI1* or *STIM1*-deficient patients (anhidrosis and additional symptoms of EDA-ID) may be due to, for instance, the more moderate reduction in Ca^{2+} signals or compensatory effects by $\text{IP}_3\text{R1}$ and/or $\text{IP}_3\text{R3}$.

6. SOCE functions in other exocrine glands

Besides eccrine sweat glands, CRAC currents and SOCE have been reported in many exocrine gland systems including pancreas, lacrimal, salivary and mammary glands where they regulate cell function [28, 33, 92–96]. For instance, deletion of *Orai1* in mice abolishes SOCE in lacrimal glands and results in diminished lacrimal fluid secretion in response to muscarinic-cholinergic stimulation [28, 94]. In mammary glands, impaired SOCE in *Orai1*^{−/−} mice abolishes lactation due to impaired milk ejection from mammary gland secretory alveoli, which was caused by decreased myoepithelial cell contraction [93]. In salivary glands, SOCE mediated by ORAI1 has been proposed to facilitate the recruitment of the non-selective transient receptor potential channel TRPC1 to the PM, where it amplifies the Ca^{2+} signal initiated by SOCE [92]. Knockdown of ORAI1 or STIM1 in human salivary gland adenocarcinoma HSG cells abolishes SOCE, whereas knockdown of TRPC1 impaired Ca^{2+} influx by only ~ 50% [97–99]. Isolated salivary gland acinar cells from *Trpc1*^{−/−} mice, however, have significantly reduced Ca^{2+} influx upon agonist stimulation, likely accounting for the reduction in neurotransmitter-induced salivary fluid secretion in *Trpc1*^{−/−} mice [100]. In salivary gland cells from patients with Sjögren's syndrome, the loss of salivary fluid secretion was associated with reduced expression of $\text{IP}_3\text{R2}$ and $\text{IP}_3\text{R3}$, which mediate Ca^{2+} release from ER stores and thus indirectly affect SOCE [52]. A direct role for ORAI and STIM proteins in salivary gland function of mice and humans is likely but requires further study. In pancreatic acinar cells, ORAI1 was found to be expressed at the apical membrane where it colocalized with IP_3Rs [95, 101], and – in one study – at the basolateral membrane where it colocalized with STIM1 [95]. A recently developed inhibitor of ORAI1 abolished SOCE in pancreatic acinar cells in response to stimulation with thapsigargin [102, 103], cholecystokinin 8 (CCK8) [103] and the bile acid tauro lithocholic acid 3-sulfate (TLCS). The inhibitor also reduced TLCS-induced cell death, indicating that ORAI1 mediates SOCE in pancreatic acinar cells [102, 103]. Importantly, SOCE inhibition attenuated the severity of acute pancreatitis in three different mouse models, strongly suggesting that ORAI1 is responsible for the pathological Ca^{2+} influx that leads to Ca^{2+} overload of pancreatic acinar cells and tissue injury [103].

Although SOCE have been reported in many exocrine gland systems as discussed above, the only symptom related to exocrine gland dysfunction in CRAC channel-deficient patients is anhidrosis, whereas the function of the exocrine pancreas, salivary and lacrimal glands appears to be normal [24, 25]. This discrepancy may be due to species differences (as many physiological studies of SOCE in exocrine glands were conducted in mice), redundancies among ORAI and STIM isoforms, and/or compensation for impaired SOCE by other Ca^{2+}

channels. It is also possible that Ca^{2+} independent Cl^- channels and transport mechanisms compensate for the impaired activation of CaCCs and mediate Cl^- secretion in CRAC channel-deficient secretory gland cells [104].

Conclusions

SOCE is a unique and specialized mechanism for Ca^{2+} influx in many cell types including secretory cells. In exocrine glands, secretory epithelial cells use intracellular Ca^{2+} signals to control salt and fluid secretion across the luminal membrane. SOCE mediated by ORAI and STIM proteins provides secretory cells with a sustained increase in intracellular $[\text{Ca}^{2+}]$ required to activate CaCCs and to induce Cl^- and fluid secretion. In eccrine sweat glands, SOCE is indispensable for CaCC function, Cl^- secretion and sweat production as demonstrated by genetic deletion or mutation of components of the SOCE pathway (*i.e.* $\text{IP}_3\text{R2}$, ORAI1, STIM1, and STIM2) in humans and mice that result in sweat gland dysfunction and anhidrosis. Other exocrine glands also use SOCE for Ca^{2+} influx and genetic deletion or inhibition of ORAI1 in mice significantly impairs lacrimal gland function and prevents toxic Ca^{2+} influx and overload in pancreatic acinar cells. Inhibition of SOCE for the treatment of acute pancreatitis or other disorders caused by dysfunction of exocrine glands is attractive but requires further studies regarding the pathophysiological role of SOCE in these tissues.

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Highlights

Store-operated Ca^{2+} entry (SOCE) is required for sweat gland function in humans and mice

Defects in ORAI1 and STIM1 abolish

SOCE and cause anhidrosis SOCE controls activation of Ca^{2+} -activated Cl^- channels (CaCC)

CaCC function in human sweat gland cells is mediated by TMEM16A

Figure 1. Basic mechanism of salt and fluid secretion in exocrine glands

(A) Acinar cells of exocrine glands secrete Cl^- to the acinar lumen, which generates an electrical gradient that drives paracellular Na^+ transport. The hypertonic NaCl solution drives the osmotic transport of water via trans- and paracellular mechanisms. The isotonic primary fluid is subsequently modified, for instance by Na^+ and Cl^- reabsorption and bicarbonate secretion, as it flows through the ducts before is secreted as a hypotonic solution. (B) Main signaling pathways that govern salt and fluid secretion in epithelial cells. The activation of G protein coupled receptors (GPCRs) at the basolateral membrane triggers Ca^{2+} signaling and activation of Ca^{2+} -activated Cl^- channels (CaCCs) and Cl^- secretion as well as production of cAMP, protein kinase A (PKA) function and activation of cystic fibrosis transmembrane conductance regulator (CFTR), resulting in Cl^- secretion. For details see text.

Figure 2. Mechanisms of Ca²⁺-dependent Cl⁻ and fluid secretion in eccrine sweat glands
(A) Morphology of an eccrine sweat gland in the skin. Modified from [56]. The enlargement on the right shows a crosssection through the secretory coil portion of an eccrine sweat gland. *CC*, clear cells; *DC*, dark cells; *MC*, myoepithelial cells. **(B)** Schematic representation of Ca²⁺ signaling in eccrine sweat glands after cholinergic stimulation. ACh binding to the ACh receptor (AChR) induces IP₃-mediated release of Ca²⁺ from ER stores through IP₃Rs. Ca²⁺ released from the ER may directly activate the Ca²⁺-activated Cl⁻ channel TMEM16A and Cl⁻ secretion (indicated by ❶). Ca²⁺ release results in a decrease of the [Ca²⁺]_{ER} and activation of stromal interaction molecule 1 (STIM1) and STIM2, which bind to and open ORAI1 channels in the plasma membrane. The resulting store-operated Ca²⁺ entry (SOCE) is required for sustained activation of TMEM16A and Cl⁻ secretion (indicated by ❷). The dotted line indicates that SOCE mediates refilling of ER Ca²⁺ stores via Ca²⁺ uptake through sarco/endoplasmic reticulum Ca²⁺-ATPase (SERCA) pumps. Aquaporin 5 (AQP5) mediates water secretion. NKCC1, Na⁺-K⁺-2Cl⁻ co-transporter. For details see text.