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TOPICAL REVIEW

Calcium-activated chloride channels in pericytes and their role in regulating organ blood flow

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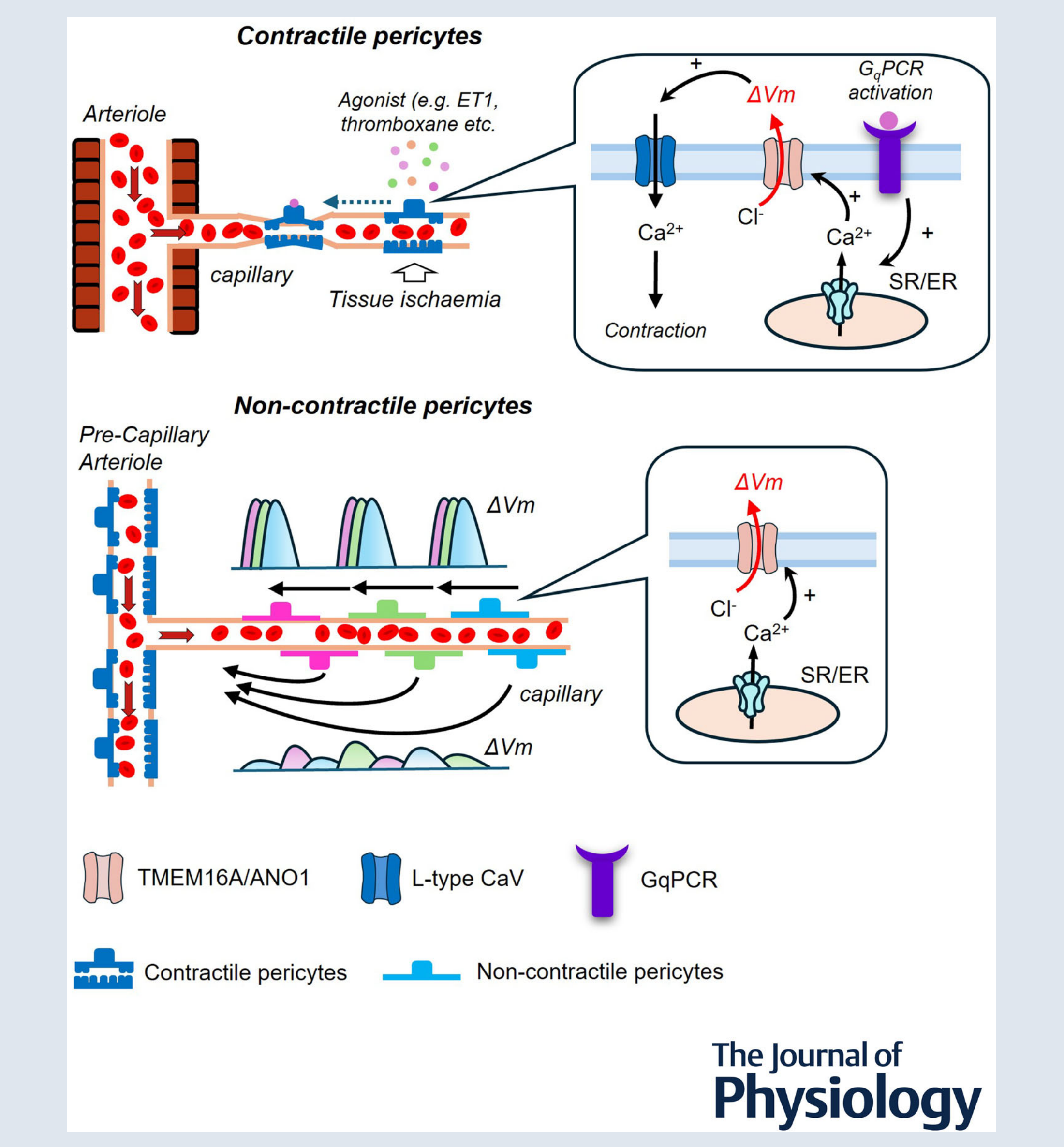

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Abstract figure legend Pericytes are microvascular mural cells with diverse roles. Contractile pericytes directly regulate local perfusion, while non-contractile pericytes coordinate upstream vascular contractility via propagating electrical signals. These functions critically depend on intracellular Ca^{2+} ($[Ca^{2+}]_i$) dynamics, which in turn are controlled by plasmalemmal ion channels and transporters, and intracellular Ca^{2+} stores. Ca^{2+}-activated Cl^- channels encoded by TMEM16A (ANO1) are emerging as key mediators linking $[Ca^{2+}]_i$ to membrane depolarisation (ΔV_m). In contractile pericytes (top panel), TMEM16A promotes ΔV_m following stimuli such neurohumoral G_qPCR activation (ligand represented by circular structures binding to the receptor shown on pericyte body) or ischaemia, to induce Ca^{2+} influx via CaV channels leading to pericyte contraction (dotted arrow signifies this change occurring within a given pericyte). In pathologies such as ischaemic stroke, TMEM16A activation promotes long-lasting pericyte constriction, leading to 'no reflow'. Non-contractile pericytes drive spontaneous transient depolarisation (STDs) that can be periodically and sequentially generated and transmitted upstream to contractile pericytes in pre-capillary arterioles to develop vasomotion (upper). Alternatively, STDs can be asynchronously generated, and their spatiotemporal summation in pre-capillary arterioles contributes to basal vascular tone developed by contractile pericytes (lower). Three non-contractile pericytes shown in light red, light green and light blue generate STDs in the corresponding colour. This review highlights the role of TMEM16A in pericyte physiology and microvascular regulation.

Abstract Pericytes are mural cells of the microvasculature, characterised by a distinctive 'bump-on-a-log' morphology and elongated processes extending along the abluminal surface of capillary and pre- and post-capillary segments. They are widely distributed across organs and exhibit functional heterogeneity. Contractile pericytes directly regulate local blood flow, whereas non-contractile pericytes contribute to electrical signalling by generating depolarising or hyperpolarising events that propagate to upstream vessels and coordinate tissue perfusion. These functions are closely linked to intracellular ion homeostasis. Recent evidence highlights a role for Ca^{2+}-activated Cl^- channels (CaCCs), particularly TMEM16A (ANO1), in coupling intracellular Ca^{2+} signals to membrane depolarisation and pericyte activity. In contractile pericytes, TMEM16A-mediated currents promote depolarisation to activate L-type voltage-gated Ca^{2+} channels, facilitating Ca^{2+} entry to support contraction. In non-contractile capillary pericytes, periodically generated TMEM16A-dependent depolarisations contribute to the initiation and propagation of spontaneous electrical activity, supporting intercellular synchrony within microvascular networks. Alternatively, asynchronous TMEM16A-dependent depolarisations could sum with each other to maintain resting membrane potentials and basal vascular tone. In this review, we summarise current understanding of CaCC channel function in pericytes across organs, and discuss emerging directions for future research and therapeutic targeting.

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Introduction

Pericytes were first characterised by Eberth (1871) and Rouget (2007) in the 1870s, as discrete, spatially isolated cells disposed along the capillary. Pericytes have a soma with a characteristic 'bump-on-a-log' morphology that is located on the abluminal surface of capillaries, both along straight segments and at capillary branch points or on the distal part of precapillary arterioles (PCAs). Pericytes are also identifiable by a range of molecular markers, including the growth factor receptor PDGFRβ and the proteoglycan NG2, which functions as a co-receptor for platelet-derived growth factor (PDGF) (Dalkara et al., 2024; Longden et al., 2023).

Pericytes are morphologically and functionally heterogeneous. In central nervous system (CNS), where pericyte function has been extensively investigated, at least three distinct pericyte subtypes have been identified based on (i) their location within the capillary network, (ii) their relative levels of α-smooth muscle actin (α-SMA) expression, and (iii) the morphology of their cellular processes. The identified subtypes include ensheathing (or contractile), mesh and thin-strand pericytes (see Alarcon-Martinez et al., 2021; Dalkara et al., 2024; Frangogiannis, 2024; Longden & Isaacs, 2025; Longden & Lederer, 2024 and references therein). In visceral organs such as the heart, lungs and kidneys, or hollow organ such as the bladder and the intestine, pericytes similarly exhibit substantial morphological diversity yet the functional significance of these subtypes in controlling organ microvascular perfusion remains only partly resolved (Chou et al., 2024; Dalkara et al., 2024; Garrison et al., 2023; Kaul et al., 2023; Longden et al., 2023; Shaw et al., 2018; Zhao & Lederer, 2025).

Pericytes play a wide range of roles, extending from their well-established ability to regulate local blood flow to the modulation of neovascularisation, maintenance of vascular integrity, and the expression of immune-like properties (Dabravolski et al., 2023; van Splunder et al., 2024). In this review for the special issue of *The Journal of Physiology* on Ca^{2+}-activated Cl^- channels (CaCCs), we examine how pericytes regulate local haemodynamics, focusing on the contribution of CaCCs and other Cl^- channels.

Chloride channels in pericytes: an emerging and underexplored field

While ion channels in vascular smooth muscle and endothelial cells (ECs) are well characterised, much less is known about the ion channel complement of pericytes, particularly Cl^- channels. Several Cl^- channel types have been described in smooth muscle cells (SMCs) and ECs including CaCCs encoded by *TMEM16A* gene (HUGO gene nomenclature: *ANO1*), bestrophins (e.g. Best3), CLC family channels, volume-regulated anion channels (VRAC; encoded by the *LRRC8A* gene) and cystic fibrosis transmembrane conductance regulator (CFTR) channels. A search of some available transcriptomic datasets (He et al., 2018; Muhl et al., 2020, 2022; Vanlandewijck et al., 2018) identifies several anion channels expressed in pericytes (Table 1). However, a targeted search of PubMed and Europe PMC identified original studies in pericytes only for CaCCs, highlighting a major knowledge gap.

Cl^- is the principal anion in both extracellular and intracellular compartments in mammals and other vertebrates. Unlike other inorganic ions such as Na^+ and K^+, which are typically maintained across mammalian cell membranes with relatively similar transmembrane concentration gradients, intracellular Cl^- concentration ($[Cl^-]_i$) can vary substantially depending on cell type. For example, in skeletal muscle fibres, $[Cl^-]_i$ closely matches the value predicted by passive distribution governed by the Donnan equilibrium (Bulley & Jaggar, 2013; Chipperfield & Harper, 2000). In contrast, cardiac muscle cells and SMCs exhibit $[Cl^-]_i$ markedly higher than those expected from passive equilibrium conditions (Chipperfield & Harper, 2000; Mulvaney et al., 2000). In some CNS neurons, $[Cl^-]_i$ may vary depending on the developmental stage (Raimondo et al., 2017; Watanabe & Fukuda, 2015). In ECs, the suggested levels of $[Cl^-]_i$ vary depending on the vascular beds between less than 30 to ~50 mM (Al-Hosni et al., 2024; Mata-Daboin et al., 2025).

Elevated $[Cl^-]_i$ is generated and maintained by active transport mechanisms, including Cl^-/HCO_3^- anion exchanger AE2 (gene name: *SLC4A2*) and Na^+, K^+, Cl^- cotransporter NKCC1 (gene name: *SLC12A2*) (Aickin & Brading, 1982b; Akar et al., 1999; Alper et al., 1999; Owen, 1984). Elevated $[Cl^-]_i$ impacts the equilibrium potential for Cl^- (E_{Cl}); for example, in vascular and non-vascular SMCs, E_{Cl} lies between −30 and −20 mV, which is significantly depolarized relative to the resting membrane potential (RMP) in these cells, which ranges from −60 to −40 mV (Goto & Kitazono, 2022; Kitamura & Yamazaki, 2001; Matchkov et al., 2013; Petrova et al., 2024; Wray et al., 2021). Since the early recording of Cl^- channels in SMCs (e.g. Dai & Zhang, 2001; Janssen & Sims, 1995; Pacaud et al., 1989; Piper & Large, 2003) it was proposed that activation of Cl^- channels would promote Cl^- efflux, leading to membrane depolarisation and subsequent activation of L-type voltage-gated Ca^{2+} (CaV) channels, ultimately resulting in an increase in intracellular Ca^{2+} concentration and SMC contraction (Large & Wang, 1996). In addition, many Cl^- channels are permeable to HCO_3^-, and their activity has also been implicated in the regulation of intracellular pH and cell volume in SMCs (Chipperfield & Harper, 2000). In comparison, the role of Cl^- channels in pericytes has been explored to a much lesser extent. Nevertheless, a growing number of functional studies demonstrate that, like SMCs,

Table 1. Expression of ion channels and transporters in pericytes across various mouse organs, based on published transcriptomic databases (He et al., 2018; Muhl et al., 2020, 2022; Vanlandewijck et al., 2018)

Organ	TMEM16A/ANO1	VRAC (LRRC8A)	Best 2	Best 3	CLC3	CFTR	AE2	NKCC1
Bladder	++	++	n/a	−	+	n/a	+	++
Brain	++	++	+	+	−	−	+	++
Colon	++	++	n/a	n/a	+	n/a	+	++
Heart	++	++	n/a	−	+	n/a	+	++
Lungs	++	++	−	+	−	−	+	++
Skeletal muscle	++	++	n/a	n/a	+	n/a	+	++

++ denotes high expression relative to other cell types within the same organ, + denotes lower expression, − denotes no or very low expression and n/a indicates that the gene was not reported in the databases.

Cl^- currents can be activated in pericytes in response to contractile agonists, and that their activation leads to membrane depolarization (Heinze et al., 2014; Korte et al., 2022). These functional findings are supported by transcriptomic analyses (He et al., 2018; Muhl et al., 2020, 2022; Vanlandewijck et al., 2018) showing high expression levels of $Cl^-/HCO_3{}^-$ exchangers and NKCC1 cotransporters in pericytes (Table 1).

Despite these studies strongly supporting a depolarising role for Cl^- channels in pericytes, intracellular Cl^- concentration has not yet been directly quantified. This remains an important avenue for future research (see below, ‘Concluding remarks’).

Involvement of TMEM16A/ANO1 in the response of contractile pericytes to G_qPCR activation

The tone of contractile pericytes is regulated by intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) (Dalkara et al., 2024; Kamouchi et al., 2004; Longden et al., 2023). CaCCs encoded by *TMEM16A/ANO1* are expressed in SMCs and pericytes (Al-Hosni et al., 2022, 2024; Hawn et al., 2021; Jimenez et al., 2022) and can be activated by increases in $[Ca^{2+}]_i$ due to inositol 1,4,5-trisphosphate (IP_3)-induced Ca^{2+} release from sarco/endoplasmic reticulum (SR/ER) during activation of G_q protein coupled (G_qPCR) receptors (Agostinelli & Tammaro, 2022; Hawn et al., 2021). Opening of CaCCs causes membrane depolarisation, which is expected to activate L-type Ca_v channels, thereby amplifying Ca^{2+} entry and contractile responses (Heinze et al., 2014; Korte et al., 2022).

From a structural perspective, the channel is a homodimer, with each pore containing two binding sites and forming an independent pore (Dang et al., 2017; Lam et al., 2021; Paulino et al., 2017a; Paulino et al., 2017b). TMEM16A includes several alternatively spliced exons, termed a, b, c, d and exon 0. Exon a (under the control of an alternative promoter) and exon b are located in the N-terminus, whereas exons c (encoding four amino acids, EAVK) and d are located within the first intracellular loop; exon 0 lies upstream of exon a (Agostinelli & Tammaro, 2022). Alternative inclusion or exclusion of these segments generates multiple TMEM16A isoforms with distinct functional properties (Ko et al., 2020). At present, it remains unclear whether pericytes from different organs or from distinct segments of the microcirculation express different complements of these splice variants, and what the physiological implications of such diversity may be.

Of note, TMEM16A/ANO1 is also regulated by the phosphoinositide phosphatidylinositol 4,5-bisphosphate (PIP_2) (Ko et al., 2020; Le et al., 2019; Ta et al., 2017; Tembo et al., 2019), whose membrane levels are dynamically altered during G_qPCR-mediated activation of phospholipase C. PIP_2 is a recognised activator of cloned TMEM16A/ANO1 channels, and it has been proposed that PIP_2 depletion during PLC activation may act as a negative feedback mechanism limiting IP_3-dependent Ca^{2+} signalling downstream of G_qPCR activation (Ta et al., 2017). Whether such PIP_2-dependent modulation is functionally important for the regulation of contractile pericyte tone, and thus for the fine control of local blood flow, remains a relevant open question. TMEM16A/ANO1 is regulated by a range of stimuli, including intracellular and extracellular H^+, lipids (including dietary fatty acids), calmodulin (reviewed in Agostinelli & Tammaro, 2022; Hawn et al., 2021), and interactions with other ion channels (Takayama & Tominaga, 2024) or the cytoskeleton (Hemmi et al., 2025; Roa-Espitia et al., 2025). Whether these regulatory mechanisms operate in pericytes and how they might link local metabolic or signalling changes to blood flow via TMEM16A/ANO1 modulation remain important areas for future investigation.

CaCCs have been identified in pericytes from several tissues and organs, including the retina (Kawamura et al., 2004; Sakagami et al., 2001), kidney (Lin et al., 2010; Pallone & Huang, 2002), brain (Korte et al., 2022) and skeletal muscle (Heinze et al., 2014).

TMEM16A/ANO1 has been demonstrated to code for CaCCs in rodent and human cortical cerebral pericytes (Korte et al., 2022) and in rodent skeletal muscle pericytes (Heinze et al., 2014). In cerebral pericytes, TMEM16A currents were inhibited by the selective TMEM16A/ANO1 blocker Ani9 and accounted for a large fraction of global whole-cell Ca^{2+}-activated current (Korte et al., 2022; Fig. 1). Pharmacological inhibition of TMEM16A or reduction of intracellular Cl^- via NKCC1 inhibition suppressed pericyte contraction and prevented capillary narrowing in response to G_qPCR activation (Korte et al., 2022). Similarly, in skeletal muscle pericytes, the thromboxane analogue U46619 induced a >20 mV depolarization that was abolished by genetic deletion of *TMEM16A* (Heinze et al., 2014) as in cerebral cortical pericytes (Korte et al., 2022).

In a rodent stroke model, inhibition of TMEM16A/ANO1 reduced ischaemia-induced increases in intracellular Ca^{2+}, decreased capillary constriction, and limited pericyte death and neutrophil stalling, thereby improving cerebrovascular reperfusion *in vivo*. Mendelian randomization analyses further linked altered TMEM16A/ANO1 expression to impaired recovery following ischaemic stroke in human subjects (Korte et al., 2022). Together, these findings identify TMEM16A/ANO1 in pericytes as a key regulator of cerebral capillary function and a potential therapeutic target in stroke and disorders of impaired microvascular flow, including Alzheimer's disease and vascular dementia. Consistent with this, the TMEM16A/ANO1 activator PAM_16A enhanced cortical capillary constriction (Al-Hosni et al., 2025), whereas Ani9, 10bm or niclosamide – an FDA-approved anthelmintic that inhibits TMEM16A/ANO1 – prevented agonist-induced contraction of cerebral pericytes (Al-Hosni et al., 2025; Kaye et al., 2025; Korte et al., 2024).

Before TMEM16A/ANO1 was identified as the molecular basis of CaCCs, Cl^- currents with similar electrophysiological properties were observed in contractile pericytes of the murine vasa recta (Lin et al., 2010; Pallone & Huang, 2002). In this setting, CaCCs have the potential to control pericyte tone and possibly medullary blood flow, which is essential for establishing the renal medullary concentration gradient and thus impact the extent of pressure natriuresis/diuresis and long-term control of blood pressure.

Spontaneous Ca^{2+} transients-induced TMEM16A/ANO1 activation

As noted above, TMEM16A/ANO1 channels are activated by GqPCR-mediated Ca^{2+} entry and IP_3-mediated SR/ER Ca^{2+} release in contractile cerebral cortical pericytes. However, evidence suggests that spontaneous Ca^{2+} release may also be important for TMEM16A activation in pericytes of other organs.

Involvement of TMEM16A in the generation of spontaneous transient inward currents and associated spontaneous transient depolarisations. In isolated microvessels of the retina (Sakagami et al., 2001; Wu et al., 2003) or the descending vasa recta (Zhang et al., 2008), pericytes generated spontaneous transient inward currents (STICs) that gave rise to corresponding spontaneous transient depolarisations (STDs). STICs were potentiated by G_qPCR agonists such as angiotensin II (AT-II) or serum-derived factors (Kawamura et al., 2004; Sakagami et al., 1999; Zhang et al., 2008) and enhanced STICs were greatly attenuated by broad-spectrum Cl^- channel inhibitors (e.g. niflumic acid or 9-anthracene carboxylic acid, A9C), indicating that STICs arise from the opening of CaCCs. Consistently, the enhanced STICs with ATII in pericytes of the vasa recta occurred in synchrony with Ca^{2+} transients. The ATII-induced STICs were largely attenuated by the inhibition of SR/ER Ca^{2+} release with ryanodine or caffeine, indicating the primary role of SR/ER Ca^{2+} release in the generation of CaCC-dependent STICs/STDs (Zhang et al., 2008). STICs/STDs were also suppressed by the removal of extracellular Ca^{2+} or SKF96365, an inhibitor of store-operated calcium entry (SOCE), but not by nifedipine, an L-type CaV channel inhibitor (Zhang et al., 2008); thus, Ca^{2+} influx via CaV-independent pathway(s), for example, mediated by the transient receptor potential C3 (TRPC3) channel or Orai-mediated SOCE, might be involved in the generation of CaCC-dependent STICs/STDs in pericytes. Consistent with this proposition, spontaneous Ca^{2+} transients in mouse brain mid-capillary pericytes were attenuated by SKF96365 and GSK-7975A, both potent Orai inhibitors, but not by nifedipine or Z944, L-type or T-type CaV inhibitors (Phillips et al., 2023).

Asynchronous spontaneous Ca^{2+} transients. Spontaneous Ca^{2+} transients have been demonstrated in mid-capillary pericytes of the mouse brain (Glück et al., 2021; Hill et al., 2015; Phillips et al., 2023). These events do not exhibit synchrony either between neighbouring pericytes or within individual cells, and therefore occur as asynchronous spontaneous Ca^{2+} transients. As noted above (see 'Role of TMEM16A/ANO1 in contractile pericytes'), high TMEM16A/ANO1 expression and large CaCC currents have been observed in ensheathing brain capillary pericytes (Korte et al., 2022), namely contractile pericytes located near the arteriolar end of the capillary bed. Assuming that TMEM16A/ANO1 expression is also maintained in mid-capillary pericytes, it is conceivable that asynchronous spontaneous Ca^{2+} transients, as described above (Glück et al., 2021; Phillips et al., 2023),

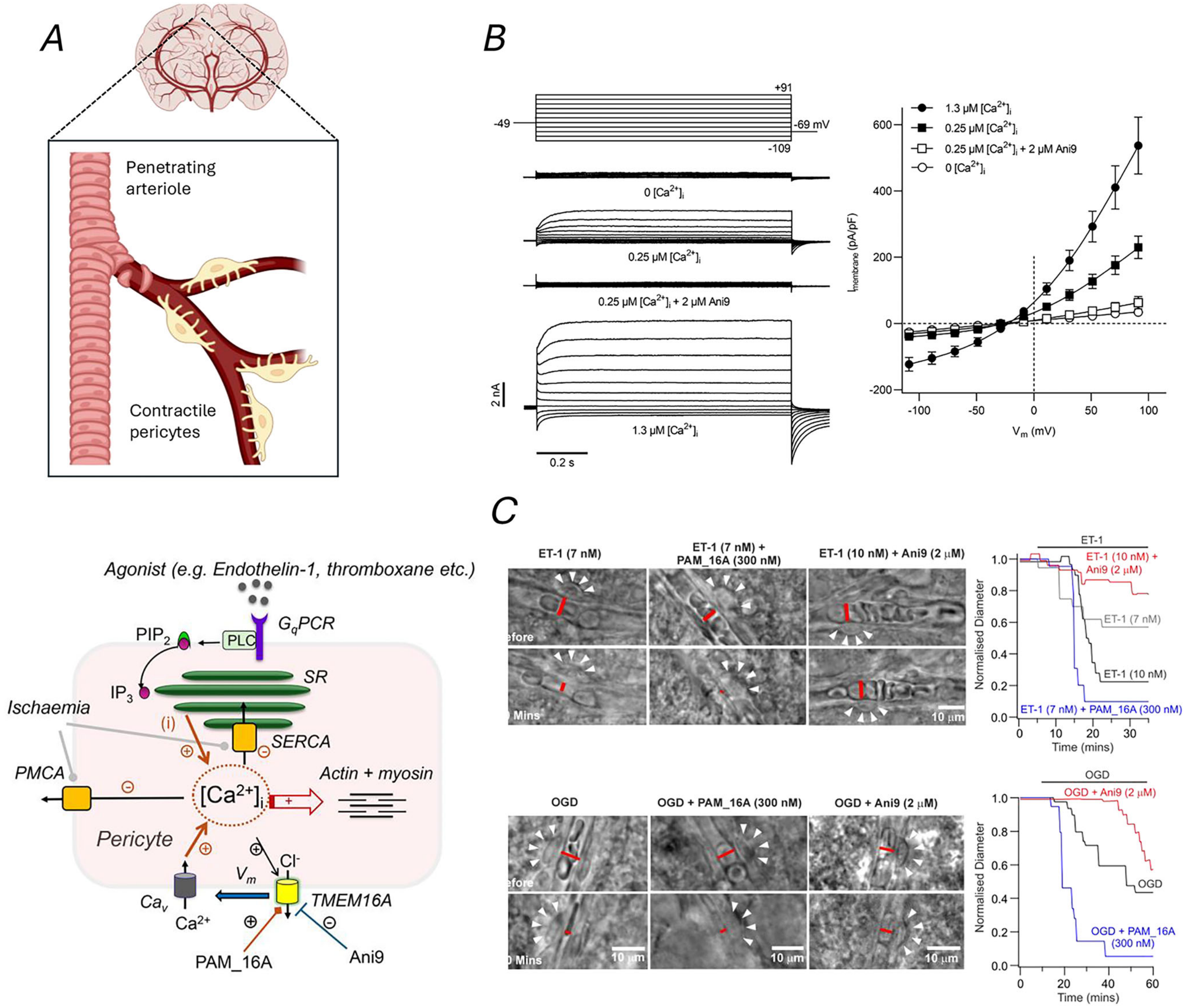

Figure 1. Role of TMEM16A/ANO1 in contractile cerebral pericytes

A, top panel: diagrammatic representation of cortical capillaries showing contractile pericytes near the arteriolar end of the capillaries. Lower panel: schematic illustration of signalling pathways in the contractile pericytes. Increases in intracellular Ca^{2+} ($[Ca^{2+}]_i$) may arise via several mechanisms: (i) agonist binding to plasmalemmal receptors activates Gq proteins, leading to Ca^{2+} release from the sarcoplasmic reticulum (SR) via the inositol trisphosphate (IP_3) pathway. Elevated $[Ca^{2+}]_i$ activates TMEM16A/ANO1 channels, causing Cl^- efflux, membrane depolarisation (V_m, blue arrow) and opening of CaV channels, ultimately leading to actomyosin activation and contraction. (ii) During ischaemia, reduced intracellular ATP ($[ATP]_i$) slows Ca^{2+} sequestration and extrusion via inhibition of the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and the plasma membrane Ca^{2+}-ATPase (PMCA), respectively. The resulting rise in $[Ca^{2+}]_i$ can activate TMEM16A/ANO1 channels. Modulation of TMEM16A/ANO1 activity (e.g. inhibition by Ani9 or activation by PAM-16A) may therefore influence pericyte relaxation or contraction. *B*, representative families of whole-cell TMEM16A currents recorded from individual rat cortical pericytes using Cl^--selective pipette solutions and defined intracellular Ca^{2+} concentrations, in the absence or presence of the TMEM16A inhibitor Ani9. Right, mean current density–voltage relationships for TMEM16A/ANO1 currents at different intracellular Ca^{2+} concentrations ± Ani9. Image adapted from Korte et al. (2022). *C*, effect of endothelin 1 (ET-1) and oxygen glucose deprivation (OGD) on rat cortical capillary diameter in the absence or presence of PAM_16A or Ani9. Image adapted from Al-Hosni et al. (2025). The top part of panel *A* was prepared with BioRender.

may promote TMEM16A/ANO1 channel opening and thereby generate STICs and STDs in these pericytes. It can be speculated that asynchronous spontaneous Ca^{2+} transients would cause STICs/STDs in individual capillary pericytes to maintain their RMP at the relatively depolarised values of around −40 mV (Ferris et al., 2025; Klug et al., 2023). In venules of the bladder suburothelium, where pericytes express, albeit at lower level, TMEM16A/ANO1 (Sugiura et al., 2025), niflumic acid hyperpolarised the membrane by about 10 mV (Hashitani et al., 2018), suggesting the contribution of TMEM16A/ANO1 to their RMP.

In the retinal microvascular tree, particularly within capillary segments, changes in membrane potential spread efficiently through the underlying endothelial syncytium (Zhang et al., 2011). Consequently, CaCC-dependent depolarisation of individual pericytes is likely to be transmitted to neighbouring pericytes, even though STICs/STDs are generated independently in each cell. The summed CaCC-dependent depolarisation within capillaries therefore contributes to a relatively depolarised RMP, which lies close to the activation threshold of L-type CaV channels. This depolarised RMP can propagate to upstream microvascular segments containing contractile mural cells in which Ca^{2+} influx via L-type CaV channels is triggered, thereby contributing to basal microvascular tone.

Consistent with the electrical syncytial properties of the pericyte network and the microvasculature, both agonist-evoked (Borysova et al., 2013) and spontaneous Ca^{2+} transients (Hashitani et al., 2018) can propagate within the microvascular networks of visceral organs. Given the high input resistance of pericytes (Korte et al., 2022), even modest hyperpolarising signals are likely to produce large shifts in RMP, moving it away from the activation threshold of L-type CaV channels. This can promote relaxation of contractile mural cells and dilation of contractile microvascular segments. In the brain, non-contractile thin-strand pericytes within capillaries sense the metabolic demands of neighbouring neurons and generate propagating ATP-sensitive K^+ (K_{ATP})-dependent hyperpolarisations, thereby increasing blood supply to active neurons (Hariharan et al., 2022; Isaacs et al., 2024).

In the heart, increased metabolic demand in ventricular cardiomyocytes lowers intracellular ATP concentration ($[ATP]_i$) resulting in the opening of K_{ATP} channels to cause hyperpolarisation that could transmit to neighbouring capillaries via gap junction-mediated electrical coupling between cardiomyocytes and capillary ECs (Zhao et al., 2020). The resultant endothelial hyperpolarisation would also be transmitted to pericytes and arteriolar SMCs to reduce their $[Ca^{2+}]_i$, leading to their relaxation to increase local coronary blood flow to the active cardiomyocytes (Zhao et al., 2020). It remains to be established whether K_{ATP}-mediated modulation of Ca^{2+} handling can influence TMEM16A/ANO1 activity in cardiac pericytes, and what the physiological implications of such coupling might be for pericyte function (Zhao et al., 2020). As an avenue for future research, it will be relevant to determine whether this type of functional coupling may occur in pericytes in organs other than the heart. This may be particularly relevant in tissues such as the pancreas (Almaça et al., 2018), where K_{ATP} channels have a well-established role in regulating hormone secretion from β, α and δ cells (Ashcroft & Rorsman, 2013). Pericytes are involved in the control of pancreatic blood flow in health and disease (Almaça et al., 2018; Andrade Barboza et al., 2024); whether the activity of the endocrine cells may be coupled with local control of blood and the involvement of CaCCs in pericytes remains to be elucidated.

Involvement of TMEM16A/ANO1 in synchronous spontaneous Ca^{2+} transients in pericytes of visceral organs

In the microvascular network of the bladder suburothelium, thin-strand pericytes are distributed along capillaries, whereas PCAs are covered by ensheathing pericytes that are distinct from the circumferentially arranged arteriolar SMCs. Post-capillary venules (PCVs) and collecting venules are wrapped by mesh-like pericytes (Hashitani et al., 2018) (Fig. 2). Thin-strand pericytes in the bladder suburothelium do not express α-SMA, and are therefore considered non-contractile, while α-SMA-expressing pericytes (α-SMA$^+$) located in other microvascular segments, together with arteriolar SMCs, are contractile (Fig. 2). Thus, the heterogeneity of morphological and contractile properties of pericytes across different microvascular segments parallels that found in the CNS (Attwell et al., 2016; Hartmann et al., 2021, 2022; Hill et al., 2015). Interestingly, pericytes located along capillaries of the bladder suburothelium, as well as those in PCAs, PCVs and venules generate spontaneous Ca^{2+} transients that display temporal synchrony across their network (Hashitani et al., 2012, 2018; Sugiura et al., 2025; Tanaka et al., 2021). Spontaneous Ca^{2+} transients drive spontaneous phasic constrictions (SPCs) in pre- and post-capillary microvascular segments containing α-SMA$^+$ contractile pericytes. Arteriolar SPCs enhance capillary–tissue exchange by regulating microvascular resistance and blood flow distribution, whereas venular SPCs facilitate venular drainage (Dongaonkar et al., 2012; Gould et al., 2017; Meyer et al., 2002; Sakurai & Terui, 2006).

In the bladder microcirculation, pericytes exhibit a hierarchical pattern of TMEM16A/ANO1 expression, with the highest levels in capillary pericytes, intermediate levels in PCAs and PCVs, and the lowest levels in venular in venular pericytes (Fig. 2). Consequently, TMEM16A/ANO1-dependent depolarisations triggered by spontaneous Ca^{2+} transients in individual pericytes may propagate along microvascular segments – particularly capillaries – thereby promoting intercellular synchrony of Ca^{2+} transients. Consistent with their high TMEM16A/ANO1 expression, non-contractile capillary pericytes appear to function as pacemaker cells, driving spontaneous Ca^{2+} transients in PCAs.

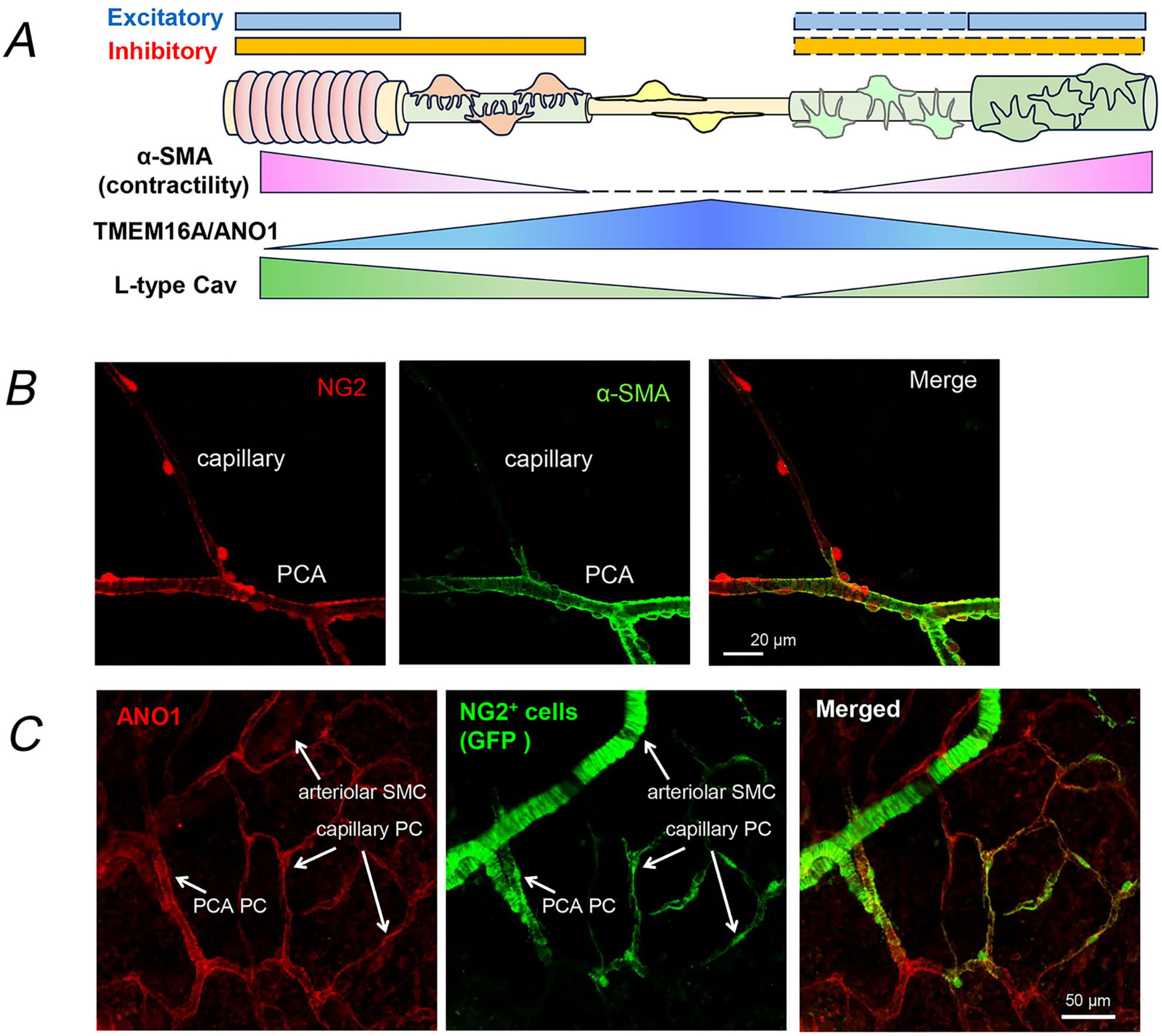

Figure 2. Pericyte phenotypes in different microvascular segments of the bladder
A, schematic illustration of the microvasculature in the urinary bladder. The arteriolar segment is wrapped by circumferentially arranged arteriolar SMCs expressing α-SMA (α-SMA^+), low TMEM16A/ANO1 (TMEM16A/$ANO1^+$) and L-type CaV channels. Pre-capillary arterioles (PCA) are covered by ensheathing pericytes that are α-SMA^+, exhibit higher TMEM16A/ANO1 expression, and express L-type CaV channels. Capillary pericytes express high levels of TMEM16A/ANO1 but lack α-SMA, and L-type CaV channels play a limited role in their Ca^{2+} dynamics. Post-capillary venules are covered by relatively sparse, mesh-like pericytes expressing α-SMA, TMEM16A/ANO1, and L-type CaV channels, whereas venular pericytes are more densely distributed and exhibit lower TMEM16A/ANO1 expression. Arterioles and venules receive excitatory sympathetic innervation, while PCAs receive inhibitory NO- and CGRP-containing innervation. Capillary pericytes show no clear morphological or functional innervation. *B* and *C*, representative immunohistochemistry illustrating gradient α-SMA (*B*) and TMEM16A/ANO1 (*C*) in NG2 positive cells of the bladder microvasculature. Adapted from Hashitani et al. (2018) and Sugiura et al. (2025).

Gap-junction blockade with carbenoxolone prevents the generation of Ca^{2+} transients in PCA pericytes, while simultaneously disrupting the intercellular synchrony of Ca^{2+} transients among capillary pericytes (Hashitani et al., 2018). The broad-spectrum Cl^- channel inhibitor 4,4′-diisothiocyanatostilbene-2,2′-disulfonic acid (DIDS) exerted similar inhibitory actions on PCA and capillary Ca^{2+} transients, respectively. Moreover, Ani9 – a specific TMEM16A/ANO1 inhibitor (Al-Hosni et al., 2025) – disrupted the synchrony of spontaneous Ca^{2+} transients in capillaries (Sugiura et al., 2025) (Fig. 3), indicating that synchronous spontaneous Ca^{2+} transients in capillaries are mediated by propagating TMEM16A/ANO1-dependent STDs. TMEM16A/ANO1 expressing pericytes in rectal subepithelial capillaries also appear to function as pacemaker cells that drive network-wide synchronisation of spontaneous Ca^{2+} transients (Hashitani et al., 2015, 2018; Mitsui et al., 2023).

Spontaneous Ca^{2+} transients in pericytes of capillaries (Hashitani et al., 2015, 2018; Mitsui et al., 2023), PCAs (Hashitani et al., 2018; Mitsui & Hashitani, 2017) and PCVs (Hashitani et al., 2012, 2018) of visceral microvascular beds are abolished by SERCA blockade with cyclopiazonic acid (CPA), indicating that these events predominantly arise from Ca^{2+} release from intracellular SR/ER stores.

In the bladder and gastrointestinal tract, spontaneous Ca^{2+} transients in pericytes are abolished by inhibiting either IP_3 receptor-mediated or ryanodine receptor-mediated Ca^{2+} release, depending on the microvascular segment (Hashitani et al., 2012, 2015, 2018; Mitsui & Hashitani, 2017; Mitsui et al., 2023). Consequently, TMEM16A/ANO1 CaCCs act as a key link between intracellular Ca^{2+} signalling to membrane depolarisation, thereby initiating and coordinating spontaneous electrical activity in pericytes (Fig. 3).

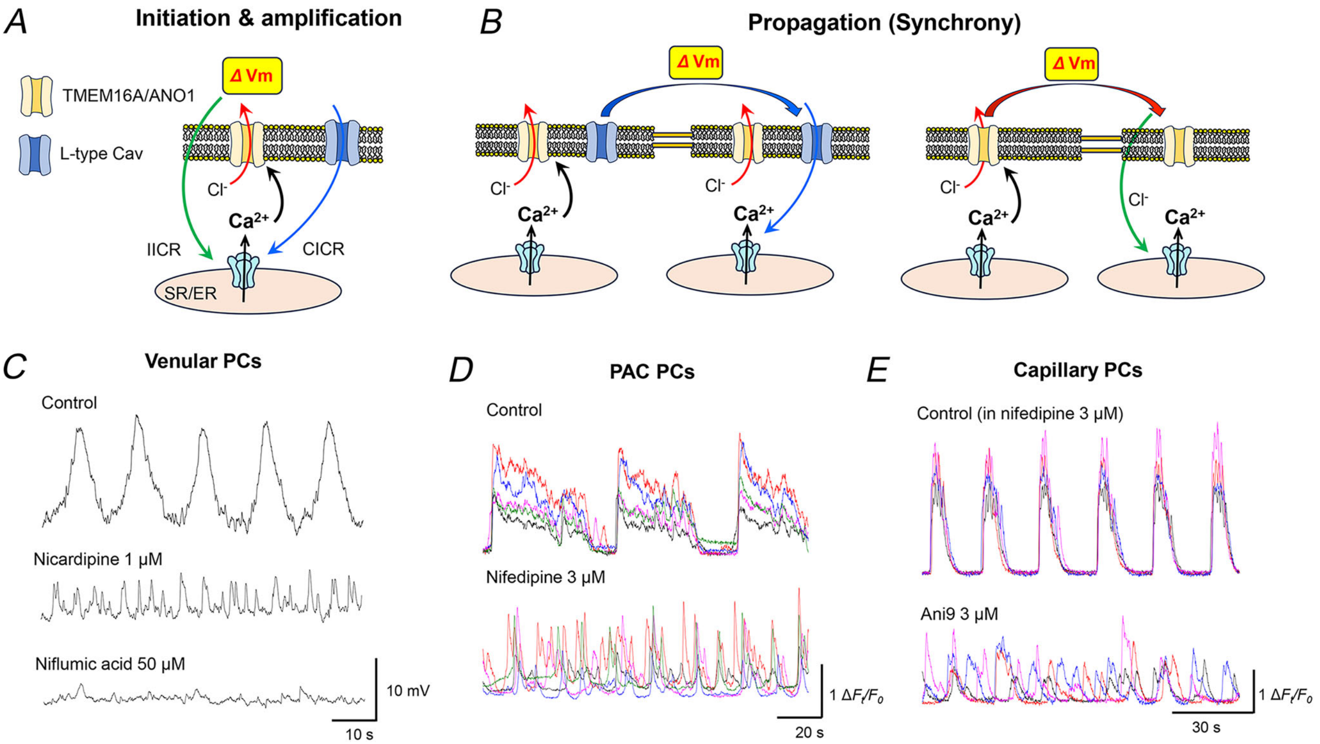

Figure 3. Roles of TMEM16A/ANO1 CaCCs in the generation of spontaneous pericyte activity in the bladder

A, diagrammatic representation of spontaneous SR/ER Ca^{2+} release in pericytes activating plasmalemmal TMEM16A/ANO1 channels, thereby converting intracellular Ca^{2+} signal into depolarisation (ΔV_m). The resulting ΔV_m can activate L-type CaV, leading to Ca^{2+} influx and subsequent Ca^{2+}-induced Ca^{2+} release. Alternatively, the ΔV_m may stimulate IP_3 production, amplifying Ca^{2+} release via IP_3-induced Ca^{2+}release (IICR). *B*, left, intercellular synchrony of spontaneous Ca^{2+} transients can arise through gap junction-mediated intercellular propagation of L-type CaV-dependent, regenerative depolarizations. Right, TMEM16A/ANO1-dependent ΔV_m may also become regenerative via IICR, enabling intercellular propagation. *C*, in venular pericytes of the bladder suburothelium, niflumic acid-sensitive, CaCC-dependent STDs trigger slow waves via activation of CaV. *D*, in PCA pericytes, the synchrony of spontaneous Ca^{2+} transients is disrupted by the CaV blockade with nifedipine. *E*, in capillary pericytes, synchrony of spontaneous Ca^{2+} transients is unaffected by nifedipine but disrupted by the TMEM16A/ANO1 inhibitor Ani9. Adapted from Hashitani et al. (2018) and Sugiura et al. (2025).

TMEM16A/ANO1-mediated spreading depolarisations

The contribution of CaV channels to synchronous Ca^{2+} transients varies across pericytes in different microvascular segments. In bladder pericytes located in PCAs (Hashitani et al., 2018) and PCVs (Hashitani et al., 2011, 2012), inhibition of L-type CaV channels disrupted synchronised Ca^{2+} transients, leaving only asynchronous Ca^{2+} events that arise independently in individual pericytes (Fig. 3).

In venules of the bladder suburothelium, nicardipine abolished periodic slow waves, leaving smaller, niflumic acid-sensitive STDs (Fig. 3). This suggests that CaCC-dependent STDs are insufficient to propagate effectively to neighbouring cells, likely due in part to low TMEM16A/ANO1 expression (Sugiura et al., 2025). Accordingly, intercellular synchrony within these microvascular segments appears to rely on the spread of regenerative L-type CaV channel-mediated depolarisations, which trigger Ca^{2+}-induced Ca^{2+} release (Fig. 3). In contrast, pericyte Ca^{2+} transient synchrony in rectal PCAs (Mitsui & Hashitani, 2017) and gastric myenteric PCAs (Hashitani et al., 2015) was not affected by the inhibition of L-type CaV channels alone, but was interrupted by combined inhibition of L-type and T-type CaV channels.

Pericyte Ca^{2+} transient synchrony in capillaries was not disrupted by inhibition of L-type or T-type CaV channels (Hashitani et al., 2018; Mitsui et al., 2023), but was abolished by classical CaCC inhibitors (Hashitani et al., 2018; Mitsui et al., 2023) or Ani9 (Mitsui et al., 2023; Sugiura et al., 2025) (Fig. 3). This indicated that TMEM16A/ANO1-dependent STDs were sufficient to propagate effectively across the capillary pericyte network.

Because electrotonic depolarisations decay with distance, TMEM16A/ANO1-dependent STDs likely required regenerative mechanisms to support long-distance propagation. Spontaneous Ca^{2+} transients in capillary pericytes may have been amplified by depolarisation-induced Ca^{2+} release from SR/ER stores as has been demonstrated in isolated central neurons where depolarisation itself triggers Ca^{2+} release by activating PLC-dependent IP_3 production (Ryglewski et al., 2007). Intercellular synchrony of slow waves, which underlies spontaneous smooth muscle activity, has been well modelled by depolarisation-induced, IP_3-mediated store Ca^{2+} release, enabling distant cells to oscillate synchronously through the spread of depolarising currents via gap junctions (Imtiaz et al., 2006). Thus, depolarisation-induced, IP_3-mediated SR/ER Ca^{2+} release may have conferred regenerative capacity on TMEM16A/ANO1-dependent STDs, allowing their propagation within pericyte networks (Fig. 3).

Plasmalemmal TMEM16A/ANO1 is known to tether SR/ER Ca^{2+} stores to membrane raft compartments, allowing co-localisation of TMEM16A/ANO1 with IP_3 receptors (IP_3Rs) (Cabrita et al., 2017; Lin et al., 2025) in cells such as dorsal root ganglion neurons (Jin et al., 2013, 2016; Liu et al., 2010) and skeletal muscle (Dayal et al., 2019). Thus, in capillary pericytes that express high levels of TMEM16A/ANO1, compartmentalised SR/ER Ca^{2+} release may be tightly coupled to TMEM16A/ANO1 activation, enabling robust and efficient channel activation. Capillary pericytes in the CNS also exhibit high TMEM16A/ANO1 expression and large TMEM16A/ANO1-mediated currents (Heinze et al., 2014; Korte et al., 2022); however, whether these cells are capable of generating synchronous spontaneous Ca^{2+} transients remains unclear. A greater SR/ER Ca^{2+} release capacity or higher intracellular IP_3 levels in capillary pericytes of visceral organs, compared with those in the brain, may account for their enhanced ability to develop synchronous spontaneous Ca^{2+} transients.

Pericyte–endothelium interaction (conducting pathway)

CaCC-dependent STICs/STDs generated in pericytes can be transmitted to neighbouring pericytes either through direct pericyte–pericyte electrical coupling or indirectly through the endothelial syncytium. In vasa recta, where pericytes are densely packed along the microvasculature, intercellular electrical coupling is highly coordinated even in the absence of an intact endothelium (Zhang et al., 2016), indicating effective pericyte-to-pericyte coupling. In contrast, in capillaries of the isolated retinal microvasculature, intercellular voltage transmission is predominantly mediated by the endothelium (Zhang et al., 2011).

Consistently, in mid capillaries of the brain, where pericytes possess thin, elongated processes and are sparsely distributed, the tips of adjacent pericyte processes often come into close proximity without direct contact or overlap (Berthiaume et al., 2018). Although inter-pericyte tunnelling nanotubes – proposed conduits of intracellular Ca^{2+} waves – have been demonstrated in the retina (Berthiaume et al., 2018), their functional significance in other vascular remains unclear. Therefore, the endothelium appears to play a central role in transmitting both CaCC- or CaV channel-dependent depolarising signals in pericytes of visceral organs and K_{ATP}-dependent hyperpolarising signals in CNS pericytes (Hariharan et al., 2022; Isaacs et al., 2024).

Besides the role of the endothelium as a low-resistance electrical conduction pathway, endothelium-derived electrical and humoral signals appear to play a critical role in the maintenance of synchronous spontaneous Ca^{2+} waves and, in turn, CaCC-dependent slow waves. In PCA pericytes of the rectal submucosa, elevated extracellular

K^+ concentration of ~30 mM, Ba^{2+}, a known blocker of inwardly rectifying K^+ (Kir) channels, or XE991, a Kv7 channel inhibitor, all converted synchronous Ca^{2+} transients into high-frequency asynchronous Ca^{2+} transients, suggesting that membrane depolarisation disrupts both the periodicity and synchrony of spontaneous Ca^{2+} transients (Mitsui & Hashitani, 2019). Synchrony of Ca^{2+} transients can be restored by levcromakalim, a K_{ATP} channel opener that promotes membrane repolarisation. Levcromakalim alone, which hyperpolarises the membrane, prevents the generation of Ca^{2+} transients or reduces their frequency. These results indicate that an appropriate RMP is required for the development of synchronous Ca^{2+} transients and the associated CaCC-dependent slow waves (Mitsui & Hashitani, 2019, 2020). Kir2.1 channels are predominantly expressed in ECs but not in pericytes of the rectal submucosa (Mitsui & Hashitani, 2019), although Kir2.1 expression has been demonstrated in brain pericytes (Sancho et al., 2024); thus, endothelial Kir2.1-dependent hyperpolarising signals are likely transmitted to pericytes to stabilise their RMP. In capillary pericytes of the rectum, endothelial cyclooxygenase-2 (COX-2)-dependent production of prostacyclin (PGI_2) appears to contribute to the maintenance of synchrony of spontaneous Ca^{2+} transients by stabilising pericyte RMP through K_{ATP} channel activation (Mitsui et al., 2023).

Modulation of spontaneous activity by neighbouring cells

In visceral organs, the microvascular network receives segment-specific neural innervation (Fig. 2). Arteriolar SMCs receive dual autonomic innervation, comprising excitatory sympathetic nerves and inhibitory nitric oxide (NO)-releasing parasympathetic nerves, as well as calcitonin gene-related peptide (CGRP)-releasing sensory nerves (Hashitani et al., 2018, 2024; Tanaka et al., 2021). Low TMEM16A/ANO1 expression in arteriolar SMCs (Sugiura et al., 2025), together with a highly hyperpolarised resting membrane potential (~−70 mV) (Hashitani et al., 2018), may account for the lack of sensitivity of sympathetic arteriolar constrictions to Ani9.

Contractile ensheathing pericytes in PCAs receive NO-releasing and CGRP-releasing neural inputs, which can reduce intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), while sympathetic Ca^{2+} elevations are absent. Since PCA pericytes express TMEM16A/ANO1, reductions in $[Ca^{2+}]_i$ would hyperpolarise the membrane through closure of TMEM16A/ANO1 CaCCs, resulting in deactivation of L-type CaV channels and dilation of PCAs. Venules receive α-adrenergic excitatory and β-adrenergic NO-mediated inhibitory sympathetic innervation (Shimizu et al., 2014). Despite low TMEM16A/ANO1 expression in venular pericytes, Ani9 prevents spontaneous venular contractions that are associated with venular dilation (Sugiura et al., 2025). Because of the relatively depolarised RMP of venular pericytes (~−45 mV), even small TMEM16A/ANO1-dependent STDs appear sufficient to activate L-type CaV channels (Hashitani et al., 2018). β-Adrenergic, NO-mediated venular dilation may therefore result from NO-induced reductions in $[Ca^{2+}]_i$, which are associated with membrane hyperpolarisation through closure of TMEM16A/ANO1 CaCCs.

Non-contractile capillary pericytes appear to lack direct morphological or functional innervation (Hashitani et al., 2018); thus, their functions is expected to be modulated by the local tissue environment. As noted above, non-contractile capillary pericytes serve as metabolic sentinels that respond to local energy deficits due to increased activity of neighbouring cells, such as neurons in the CNS or cardiac myocytes in the heart, by generating K_{ATP}-dependent hyperpolarising signals that dilate upstream contractile microvascular segments. In skeletal muscle, capillary pericytes can sense muscle contractions by detecting diffusible factors, such as NO, adenosine or K^+, to generate hyperpolarising signals to dilate the upstream arterioles (Murrant & Fletcher, 2022). In the external urethral sphincter (EUS), striated muscle fibres expressing neuronal NO synthase (nNOS) on their sarcolemma release NO during EUS contractions, thereby reducing $[Ca^{2+}]_i$ in adjacent capillary pericytes (Mitsui et al., 2025). Since capillary pericytes express TMEM16A/ANO1, this reduction in $[Ca^{2+}]_i$ could induce membrane hyperpolarisation by closing TMEM16A/ANO1 CaCCs. These hyperpolarising signals can propagate upstream, dilating contractile microvascular segments and thereby increasing blood supply to active EUS muscle fibres. In skeletal muscle, muscle contraction induces remote arteriolar dilation originating at the capillary level; this response was attenuated by either inhibition of NO synthesis or blockade of K_{ATP} channels (Cohen & Sarelius, 2002). In contrast, remote arteriolar dilatation induced by local application of the NO donor sodium nitroprusside to capillaries was not affected by the K_{ATP} channel blockade (Cohen & Sarelius, 2002). Considering the expression of TMEM16A/ANO1 in skeletal muscle capillaries (Heintz et al., 2014), muscle-derived NO may reduce $[Ca^{2+}]_i$ in pericytes, leading to membrane hyperpolarisation through closure of TMEM16A/ANO1 channels.

Clinical relevance

TMEM16A/ANO1 channels are highly expressed in pericytes across multiple organs and tissues, where they play a key role in functions such as regulation of pericyte excitability and local microvascular blood flow. TMEM16A/ANO1 has also been implicated in human vascular disease. Mendelian randomisation studies have associated altered TMEM16A expression with poor clinical recovery following ischaemic stroke (Korte et al., 2022). Single-nucleotide mutations have been linked to moyamoya disease (Pinard et al., 2023), although the mechanistic relationships between altered channel activity, vascular stenosis and collateral vessel formation remain poorly defined. TMEM16A/ANO1 has been proposed as a potential therapeutic target in disorders with a microvascular component, including ischaemic stroke, vascular dementia and Alzheimer's disease (Al-Hosni et al., 2022, 2024; Jimenez et al., 2022). The prominent contribution of TMEM16A/ANO1 to pericyte physiology highlights its potential relevance in a wider range of disorders, such as overactive bladder or renal or cardiac ischaemia.

The overall structural architecture of TMEM16A/ANO1 is unrelated from that of other ion channels and transporters, offering opportunities for the development of selective compounds that specifically target TMEM16A/ANO1 (Al-Hosni et al., 2022; Le et al., 2021; Shi et al., 2020). However, the pharmacology of TMEM16A/ANO1 is still evolving, and no TMEM16A/ANO1 inhibitor has yet progressed to clinical use (Al-Hosni et al., 2022; Genovese & Galietta, 2024; Zhang et al., 2025). Progress in this area will require the generation of selective, drug-like TMEM16A/ANO1 modulators with appropriate bioavailability, pharmacokinetics, physicochemical properties, safety and toxicology profiles. Evaluation of potential off-target effects, given the widespread expression of TMEM16A/ANO1 in tissues such as the airway epithelium and interstitial cells of Cajal will also be critical.

Concluding remarks

The field of Cl^- channel biology holds considerable promise. However, intracellular Cl^- concentration has not yet been directly quantified in pericytes using approaches commonly applied to SMCs, such as radioisotope flux analysis (Aickin & Brading, 1982a, 1983), Cl^--sensitive fluorescent indicators (Koncz & Daugirdas, 1994) or ion-selective microelectrodes (Aickin & Vermuë, 1983), which have established $[Cl^-]_i$ values of approximately 30–50 mᴍ in SMCs. In the future, direct measurement of $[Cl^-]_i$ in pericytes using advanced techniques such as fluorescence lifetime imaging microscopy (FLIM) of the Cl^--sensitive dye *N*-(ethoxycarbonylmethyl)-6-methoxyquinolinium bromide (MQAE; MQAE-FLIM), combined with optogenetic manipulation of Cl^-, will be essential to define the precise role of Cl^- in pericyte physiology and to determine how alterations in $[Cl^-]_i$ may contribute to disease pathogenesis or represent novel therapeutic targets.

Transcriptomic studies continue to uncover a broad repertoire of Cl^- channels expressed within the microvasculature of various organs and tissues. It can be envisaged that future studies employing CITE-seq (cellular indexing of transcriptomes and epitopes by sequencing), REAP-seq (RNA expression and protein sequencing), or spatial transcriptomics combined with immunohistochemistry or immunofluorescence (Campos et al., 2025; Han et al., 2023; Liu et al., 2023; Wang et al., 2024) will further elucidate patterns of Cl^- channel expression within the microvasculature of diverse organs and tissues, and help to clarify how Cl^- currents regulate the function of both contractile and non-contractile pericytes across distinct vascular beds.

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Additional information

Competing interests

The authors declare they have no competing interests.

Author contributions

P.T. and H.H. contributed equally to this work. Both authors researched the literature, wrote and edited the manuscript. Both authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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