Review Article

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Transient receptor potential channel-dependent myogenic responsiveness in small-sized resistance arteries

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It is well documented that the inherent ability of small arteries and arterioles to regulate intraluminal diameter in response to alterations in intravascular pressure determines peripheral vascular resistance and blood flow (termed myogenic response or pressure-induced vasoconstriction/dilation). This autoregulatory property of resistance arteries is primarily originated from mechanosensitive vascular smooth muscle cells (VSMCs). There are diverse biological apparatuses in the plasma membrane of VSMCs that sense mechanical stimuli and generate intracellular signals for the contractility of VSMCs. Although the roles of transient receptor potential (TRP) channels in pressure-induced vasoconstriction are not fully understood to date, TRP channels that are directly activated by mechanical stimuli (e.g., stretch of VSMCs) or indirectly evoked by intracellular molecules (e.g., inositol trisphosphate) provide the major sources of Ca^{2+} (e.g., Ca^{2+} influx or release from the sarcoplasmic reticulum) and in turn, evoke vascular reactivity. This review sought to summarize mounting evidence over several decades that the activation of TRP canonical, TRP melastatin, TRP vanilloid, and TRP polycystin channels contributes to myogenic vasoconstriction.

Keywords: Ion channel, Mechanotransduction, Microcirculation, Pressure-induced vasoconstriction, Vascular smooth muscle cells

INTRODUCTION

The microcirculation that consists of feed arteries, arterioles, and capillaries contributes to supplying blood to every organ in the body and is involved in the exchange of oxygen, carbon dioxide, nutrients, hormones, and immune cells (Jackson, 2020). Among those vascular beds in the microcirculation, small-sized resistance arteries serve to evoke homeostasis in the cardiovascular system by regulating blood flow and pressure based on their metabolic and physiological demands (Davis and Hill, 1999). The vascular smooth muscle cells (VSMCs) of resistance arteries are empowered with intrinsic properties that maintain blood flow in response to fluctuations in systemic arterial pressure (Hong et al., 2016). Specifically, arterial vasoconstriction and vasodilation occur during increases and decreases in intravascular blood pressure, respectively, which is referred to as the myogenic response or pressure-induced vasoconstriction/dilation (Davis and Hill, 1999). This inherent capacity prevents delicate resistance arteries from exposure to damaging excessive intravascular pressure (Griffin, 2017).

The myogenic reactivity is known to be mechanosensitive-dependent. Mechanical stresses (e.g., stretch of VSMCs oriented circumferentially around resistance artery during elevation in intravascular pressure) sensed by biological machinery in VSMCs stimulate intracellular signaling pathways that lead to pressure-induced vasoconstriction (Hill et al., 2010). Numerous studies over several decades have established biological mechanosensitive apparatus in VSMCs including extracellular matrix, integrins, cytoskeleton, and G protein-coupled receptors (Hill et al., 2016; Hong et al., 2020). Furthermore, mechanical stimuli-mediated activation of ion channels in VSMCs contributes to myogenic vasoconstriction. In particular, transient receptor potential (TRP) ion channels are reported to be directly and indirectly involved in myogenic vasoconstriction as mechanosensors or downstream sig-

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nal amplifiers (Nemeth et al., 2020; Tykocki et al., 2017). Thus, this study will focus on one of the key determinants, TRP channels, for pressure-induced vasoconstriction in the microcirculation.

TRANSIENT RECEPTOR POTENTIAL CHANNELS

Mounting evidence indicates that TRP channels play a critical role in regulation of membrane potential and Ca^{2+} signaling of VSMCs and endothelial cells (ECs). TRP channels exist in families typically classified as canonical (TRP canonical, TRPC), TRP vanilloid (TRPV), TRP melastatin (TRPM), TRP ankyrin, mucolipin, and TRP polycystin (TRPP) channels (Montell, 2001). This classification is based on homology of amino acid sequence. Importantly, TRP channels appear to participate in various physiological or pathological situations within the cardiovascular system. For example, TRP channels modulate pacemaker function and contractility of the heart, and their dysfunction causes cardiac hypertrophy, fibrotic disease, and arrhythmias (Earley and Brayden, 2015). In addition, Ca^{2+}-permeable TRP channels in ECs have been implied to be involved in Ca^{2+} entry-mediated endothelium-derived hyperpolarization and subsequent vasodilation as well as regulation of vascular permeability, angiogenesis, and vascular remodeling (Zhang and Gutterman, 2011). The TRPC1 channel has been identified to show mechanosensitivity in Xenopus oocytes (Maroto et al., 2005). Further, the TRPC3 channel has been demonstrated to participate in membrane depolarization induced by agonist-dependent activation of pyrimidine receptors in pressurized cerebral arteries (Reading et al., 2005). However, subsequent studies have failed to show that TRPC1 or 3 channels are mechanosensitive in VSMCs or that they contribute to myogenic constriction of cerebral arteries (Dietrich et al., 2007; Reading et al., 2005). Therefore, of direct relevance to the current discussion, TRPC6, TRPM4, TRPV4, and TRPP1/2 channels have been chosen, selectively, for further discussion in the following section since they have been implicated in the regulation of myogenic responsiveness.

TRANSIENT RECEPTOR POTENTIAL CANONICAL 6

TRPC6 channel is a non-selective cation channel (permeable to Na^+, K^+, and Ca^{2+}) which is found in both arteriolar and venous myocytes of diverse vascular beds (Inoue et al., 2006). In studies of human embryonic kidney-293 (HEK-293) cells expressing the channel, TRPC6 channel was thought to exhibit inherent mechanosensitivity when the cells were mechanically stretched by stimulation with either hypoosmotic buffer or negative pressure (Spassova et al., 2006). The fact that antisense oligodeoxynucleotides-dependent inhibition of TRPC6 channel markedly attenuates membrane depolarization and myogenic constriction in cerebral arteriolar myocytes and arteries indirectly implied mechanosensitivity of TRPC6 channel (Welsh et al., 2002). However, these data have been debated and the direct activation of TRPC6 channel has been questioned in subsequent studies (Geffeney et al., 2011; Inoue et al., 2009; Mederos y Schnitzler et al., 2008). More recently, while TRPC6 channel is linked to myogenic vasoconstriction, this channel is identified to be primarily expressed in the cytoplasm of dissociated cerebral VSMCs, but not the plasma membrane surface (Nemeth et al., 2020). These findings imply that TRPC6 channel may not be considered a compelling mechanosensor in cerebral VSMCs. In addition, it has been suggested that the TRPC6 channel cooperates with G protein-coupled receptors (GPCR) to regulate contractility of VSMCs. Consistent with this, earlier studies showed that the activation of α1-adrenergic receptors results in increased TRPC6 channel-mediated currents in VSMCs of portal vein, which is markedly inhibited by antisense oligonucleodtides targeting TRPC6 channel (Inoue et al., 2001). Activation of GPCR leads to phospholipase C-mediated production of diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3), which have been demonstrated to independently or synergistically activate TRPC6 channel (Albert and Large, 2003; Helliwell and Large, 1997; Hofmann et al., 1999; Itsuki et al., 2014). As the angiotensin II type 1 receptor (AT_1R), a member of the superfamily of GPCR, has been suggested to be a primary mechanosensor (Blodow et al., 2014; Mederos y Schnitzler et al., 2008; Mederos y Schnitzler et al., 2011; Schleifenbaum et al., 2014; Storch et al., 2012), it is hypothesized that the membrane deformation of arteriolar myocytes evoked by increased intraluminal pressure or stretch elicits the AT_1R-mediated production of DAG and/or IP_3, which in turn results in TRPC6 channel activation (Fig. 1). This is supported by prior studies showing that the interplay of TRPC6 channel with mechanosensitive AT_1R activation gives rise to membrane depolarization and subsequently contributes to pressure-induced vasoconstriction (Mederos y Schnitzler et al., 2008). However, myogenic responsiveness of mice mesenteric arteries with a genetic deficiency of TRPC6 channels is almost identical to that of control arteries (Schleifenbaum et al., 2014), suggesting that cooperation between the

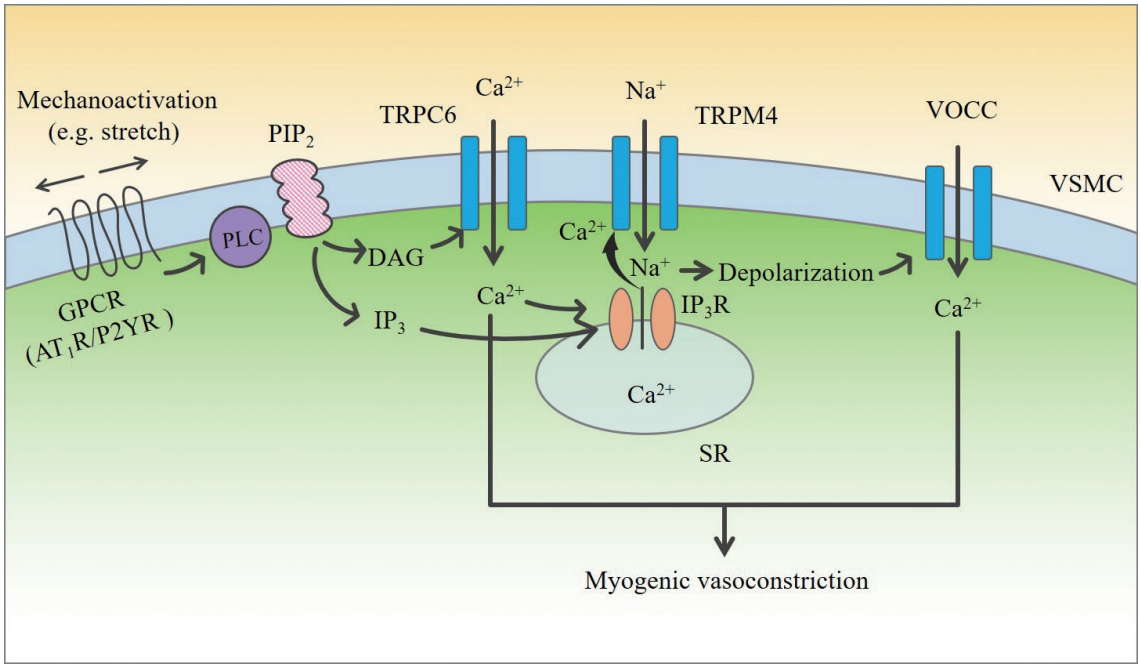

Fig. 1. An interplay between mechanosensitive GPCRs and TRP channels for myogenic vasoconstriction in cerebral arteries. The GPCRs that are activated by the longitudinal stretch of VSMCs during increases in intravascular pressure stimulate their downstream pathways (i.e., the production of DAG and IP_3). These second messengers evoke TRPC6 channel-mediated Ca^{2+} and then pressure-induced vasoconstriction. Furthermore, IP_3 generation from mechanoactivation of the GPCRs or Ca^{2+} influx via TRPC6 channel results in IP_3R-induced Ca^{2+} release, which contributes to TRPM4 channel-mediated depolarization and Ca^{2+} entry through VOCC. Along with Ca^{2+} influx via TRPC6 channel, this Ca^{2+} mobilization is also responsible for myogenic vasoconstriction. GPCRs, G protein-coupled receptors; TRP, transient receptor potential; AT_1R, angiotensin II type 1 receptor; DAG, diacylglycerol; IP_3, inositol trisphosphate; IP_3R, inositol trisphosphate receptor; P2YR, purinergic receptor; PIP_2, phosphatidylinositol bisphosphate; PLC, phospholipase C; SR, sarcoplasmic reticulum; TRPC6, transient receptor potential canonical 6; TRPM4, transient receptor potential melastatin 4; VOCC, voltage-operated Ca^{2+} channel; VSMC, vascular smooth muscle cells.

AT_1R and the TRPC6 channel may not be critical for myogenic constriction in some vascular beds or species. Further, the knockout of TRPC6 channel surprisingly causes increased myogenic constriction that is accompanied by overexpression of TRPC3 channel possibly evoked by compensatory mechanisms against the deficiency in TRPC6 channel (Dietrich et al., 2005).

TRANSIENT RECEPTOR POTENTIAL MELASTATIN 4

Channels formed by TRPM4 protein are selectively permeable to monovalent cations (e.g., Na^+, K^+), but not to divalent cations (e.g., Ca^{2+}) (Launay et al., 2002; Nilius et al., 2003). In contrast to TRPC6 channel that functions in a Ca^{2+}-independent manner, while being activated by second messengers (i.e., DAG, IP_3), the TRPM4 channel is regulated by the intracellular level of Ca^{2+}. Evidence collected from whole-cell patch clamp measurements has shown that high levels of intracellular Ca^{2+} are essential to activate TRPM4 channel on HEK-293 cells (EC_{50} = 15 μM; Nilius et al., 2003) and intact VSMCs (EC_{50} = 10 μM; Earley et al., 2007). Interestingly, it has been observed under inside-out patch clamp conditions that the sensitivity of TRPM4 channel to intracellular Ca^{2+} is profoundly diminished (EC_{50} = 370 μM), indicating that intracellular components are required to regulate the Ca^{2+} sensitivity of TRPM4 channel (Earley, 2013; Nilius et al., 2005). These investigations and their interpretation are supported by previous studies showing that protein kinase C (PKC) activation and point mutation at PKC phosphorylation sites affect the sensitivity of TRPM4 channel (Nilius et al., 2005). As described above, since higher levels of intracellular Ca^{2+} are necessary, local Ca^{2+} signaling events such as Ca^{2+} sparks (a robust focal Ca^{2+} increase in the range of 1–100 μM) released from the sarcoplasmic reticulum (SR) are required for activation of TRPM4 channel, rather than global changes in cytoplasmic Ca^{2+} which are typically in the order of 100–500 nM (Rubart et al., 1996; Zhuge et al., 2004). Consistent with this, TRPM4 channel-mediated cation currents are significantly suppressed by inhibitors of SR calcium transport ATPase (Gonzales and Earley, 2012; Gonzales et al., 2010). In addi-

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tion, the activity of TRPM4 channel is governed by PKC-dependent trafficking of the channels. Interestingly, PKCδ, but not PKCα and β, has been identified to cause translocation of TRPM4 channel toward cell membrane (Crnich et al., 2010; Garcia et al., 2011).

It has been reported that the TRPM4 channel is functionally significant in the regulation of myogenic constriction in cerebral resistance arterioles. Thus, knockdown of TRPM4 channel expression using antisense oligodeoxynucleotides has been demonstrated to inhibit increased intraluminal pressure-mediated membrane depolarization and myogenic constriction of cerebral arteries (Earley et al., 2004). Further, specific pharmacological inhibition of TRMP4 channel with 9-phenanthrol similarly inhibits myogenic responsiveness (Gonzales et al., 2010). As there is no apparent evidence supporting inherent mechanosensitivity of TRPM4 channel, a link between mechanosensitive GPCR and TRPM4 channel has been assumed (Fig. 1). Regarding this, when the purinergic P2Y4 and P2Y6 receptors are mechanically stimulated, their downstream signaling pathways (i.e., IP_3, PKC) influence TRPM4 channel activation, membrane depolarization, and pressure-induced vasoconstriction in cerebral resistance arteries (Brayden et al., 2013; Li et al., 2014). TRPM4 has also been demonstrated to be activated by the mechanoactivation of $AT_{1b}R$ (a member of GPCR family) and then induce pressure-induced vasoconstriction (Pires et al., 2017).

TRANSIENT RECEPTOR POTENTIAL VANILLOID 4

TRPV4 channel shows selectivity for Ca^{2+} influx in both VSMCs and ECs (Earley et al., 2005; Marrelli et al., 2007). Although extracellular Ca^{2+} influx is a key determinant for vasoconstriction, TRPV4 channel-mediated Ca^{2+} entry in arteriolar myocytes has been postulated, surprisingly, to induce vasorelaxation (Earley et al., 2005; Earley et al., 2009). A specific activator of TRPV4 channel, endothelium-derived arachidonic acid metabolite 11,12 epoxyeicosatrienoic acid (11,12-EET), results in Ca^{2+} influx in cerebral arteriolar myocytes that subsequently leads to the generation of Ca^{2+} sparks through Ca^{2+}-induced Ca^{2+} release (CICR). The local and robust Ca^{2+} release activates large conductance Ca^{2+}-activated K^+ channels (BK_{Ca}) and evokes hyperpolarization-mediated vasodilation (Earley et al., 2005; Earley et al., 2009). In addition, genetic ablation of TRPV4 channel markedly increases angiotensin II-mediated vasoconstriction of pressurized cerebral arteries (Mercado et al., 2014), suggesting that TRPV4 channel-dependent vasodilation functions as a negative feedback mechanism to presumably prevent exaggerated vasoconstriction. PKC-mediated phosphorylation of the TRPV4 channel allows for Ca^{2+} entry (termed Ca^{2+} sparklets) which presumably induces a CICR-dependent vasodilation (Mercado et al., 2014; Navedo et al., 2006). Thus, consistent with previous studies, it is likely that inhibition of TRPV4 channel may potentiate mechanosensitive GPCR (e.g., AT_1R, P2Y4R, P2Y6R)-dependent myogenic constriction.

TRANSIENT RECEPTOR POTENTIAL POLYCYSTIN 1/2

TRPP channels are considered as non-selective cation channels for Na^+ and Ca^{2+} (Clapham et al., 2005). TRPP channels are comprised of TRPP1 and TRPP2 channels that have been detected by immunohistochemical staining in human cerebral arteriolar myocytes (Griffin et al., 1997; Torres et al., 2001). Alternative approaches including real-time quantitative polymerase chain reaction and Western blotting have also observed TRPP1 and TRPP2 channels in cultured VSMCs isolated from mouse aorta (Beech et al., 2004; Qian et al., 2003) and rat cerebral resistance arteries (Narayanan et al., 2013). Interestingly, it has been suggested that TRPP1 and TRPP2 channels make different contributions to myogenic constriction of mouse mesenteric arteries (Sharif-Naeini et al., 2009). While knockout of TRPP1 channel impairs pressure-induced vasoconstriction, TRPP2 channel-directed siRNA enhances myogenic responsiveness in mouse mesenteric arteries (Sharif-Naeini et al., 2009). However, in rat cerebral arteries showing 4-fold higher expression of TRPP2 channel than TRPP1 channel, knockdown of TRPP2 channel reduces myogenic reactivity of rat cerebral arteries (Narayanan et al., 2013). Further, hypotonic buffer-mediated membrane stretch of rat cerebral arteriolar myocytes permits TRPP2 channel-mediated influx of cation currents. As the effects of knockdown of TRPP2 channel on pressure-induced vasoconstriction are reportedly disparate in mouse mesenteric and rat cerebral arteries (enhanced vs. reduced myogenic reactivity, respectively), it has been thus suggested that the role of TRPP2 channel in myogenic responsiveness appears different according to the type of vasculature bed and/or species.

CONCLUSIONS

A variety of TRP channels expressed in VSMCs of small-sized resistance arteries play a crucial role in regulating membrane potential and Ca^{2+} dynamics that are required for VSMC contractile

activity and myogenic reactivity. As pressure-induced vasoconstriction and vasodilation contributes to appropriately controlling blood flow in response to moment-to-moment changes in intravascular pressure, it is likely that the dysfunction of TRP channels in VSMCs may result in cardiovascular disorders such as hypertension, vasospasm, or ischemic stroke. However, while there is convincing evidence that TRP channels are significant types of machinery in VSMCs for myogenic responsiveness, it is still debatable that TRP channels act as an independent mechanosensor or downstream signal amplifier for pressure-induced vasoconstriction or vasodilation. Thus, further investigation is needed to decipher the unanswered questions.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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