T-type Ca\textsuperscript{2+} channels and autoregulation of local blood flow

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ABSTRACT

L-type voltage gated Ca\textsuperscript{2+} channels are considered to be the primary source of calcium influx during the myogenic response. However, many vascular beds also express T-type voltage gated Ca\textsuperscript{2+} channels. Recent studies suggest that these channels may also play a role in autoregulation. At low pressures (40–80 mmHg) T-type channels affect myogenic responses in cerebral and mesenteric vascular beds. T-type channels also seem to be involved in skeletal muscle autoregulation. This review discusses the expression and role of T-type voltage gated Ca\textsuperscript{2+} channels in the autoregulation of several different vascular beds. Lack of specific pharmacological inhibitors has been a huge challenge in the field. Now the research has been strengthened by genetically modified models such as mice lacking expression of T-type voltage gated Ca\textsuperscript{2+} channels (CaV3.1 and CaV3.2). Hopefully, these new tools will help further elucidate the role of voltage gated T-type Ca\textsuperscript{2+} channels in autoregulation and vascular function.

ARTICLE HISTORY

Received 30 September 2016
Revised 1 December 2016
Accepted 7 December 2016

KEYWORDS

autoregulation; blood flow; calcium; T-type channel

Introduction

In many organs such as kidneys, brain, heart and skeletal muscles changes in perfusion pressure only elicits a minimal change in steady-state blood flow. This phenomenon, autoregulation, depends on the active response of resistance vessels independently of neurohumoral and endothelial stimuli. Increases in perfusion pressure lead to vasoconstriction whereas decreases in perfusion pressure leads to vasodilation. Autoregulation operates only within specific pressure ranges. In the kidney this range extends between 80 mmHg and 180 mmHg\textsuperscript{1} and in the brain between 60 and 130 mmHg.\textsuperscript{2} Changes in perfusion pressure beyond these limits will induce changes in blood flow. During pathophysiological conditions such as hypertension these limits will adapt to the new blood pressure.\textsuperscript{3}

The aim of overall autoregulation is to maintain constant organ perfusion and stabilization of capillary pressure when acute every-day changes in blood pressure occur. The main mechanism in autoregulation is the myogenic response (Bayliss response) intrinsic to vascular smooth muscle cells (VSMC).\textsuperscript{4} In the kidney a second local mechanism, the tubuloglomerular feedback mechanism (TGF), also participates in renal autoregulation.\textsuperscript{5}

Autoregulation maintains a near-constant blood flow but changes in metabolism still affect organ blood flow.\textsuperscript{6} Increased oxygen consumption increases flow, but flow is still autoregulated if acute changes in perfusion pressure occur. This metabolic hyperemia is also a local event eliciting vasodilation of small arterioles. To be effective the vasodilatory response needs to spread through the vascular tree. A vascular conducted response is believed to travel through gap junctions coupling either via the endothelial cell or vascular smooth muscle cell layers.\textsuperscript{7,8} In addition, a local vasodilation may cause increased flow and endothelial shear stress in upstream feed arteries thus contributing to the increased organ blood flow.\textsuperscript{9,10} Thus, myogenic tone provides the set point from which local metabolic signals, conducted vasomotor signals and shear stress-mediated signaling can regulate vessel diameter.

Role of membrane potential and ion channels in regulation of vascular tone

The tone of resistance vessels, and thus vascular resistance, is dependent on the intracellular Ca\textsuperscript{2+}
concentration ([Ca^{2+}])i in VSMC. Ca^{2+} is recruited from intracellular stores and/or via entry from the extracellular space.\textsuperscript{11-13} The increase in [Ca^{2+}]i varies temporally and spatially between different vascular beds and different stimuli. Thus, it can be transient or sustained, cover the whole cell or only restricted compartments.\textsuperscript{14} In VSMC global increases in [Ca^{2+}]i is supposed to play a prominent role in the myogenic response.\textsuperscript{15} The Ca^{2+} entry occurs largely via voltage-gated Ca^{2+}-channels (VGCC).\textsuperscript{11,13} However, nonselective non voltage dependent cation channels such as transient receptor potential potential (TRP) may also play a role in several vascular beds, also in the initiation of the myogenic response.\textsuperscript{16,17} As the VGCC are the dominant Ca^{2+}-entry pathway in most vascular beds, VSMC membrane potential greatly affects the control of vascular tone. The major VGCC in most resistance vessels is the dihydropyridine-sensitive L-type channel (CaV 1.2).\textsuperscript{18,19} In addition, T-type channels have been found in several vascular beds including renal pre- and postglomerular\textsuperscript{20} but their role in regulating intracellular Ca^{2+} is controversial and remains to be clarified.

The cell membrane potential (V_m) in VSMC is determined by the chemical gradients and the relative ion conductances over the VSMC membrane. Endothelial cells may affect V_m of VSMC via gap junctions but it is mainly ion gradients and permeabilities over the VSMC membrane that governs V_m.\textsuperscript{15} In practice, it is the intra- and extracellular concentrations of K\textsuperscript{+}, Na\textsuperscript{+} and Cl\textsuperscript{−} ions and their membrane conductances that control V_m (see eq. 1;\textsuperscript{21}).

\[
V_m = \frac{E_{KgK} + E_{Na}g_{Na} + E_{Cl}g_{Cl}}{g_K + g_{Na} + g_{Cl}} \quad (\text{eq} \ 1)
\]

E_x is the equilibrium potential and g_x the conductance for the particular ion x

K\textsuperscript{+} channels are the dominant cation channels in VSMC.\textsuperscript{22,23} Therefore V_m is primarily determined by E\textsubscript{K} as the conductance for K\textsuperscript{+} normally exceeds that of the other ions. E\textsubscript{K} is \(\sim -90 \text{ mV} \) but due to the conductance for other ions, V_m in VSMC is more positive in the range of \(-55 \text{ to } -40 \text{ mV}\).\textsuperscript{15,24} These values are close to the activation potential of L-type channels but more positive than the activation potential for T-type channels. However, they are in the range for T-type window currents and thus a role for these channels in the maintenance of V_m is possible (for review, see\textsuperscript{25}). There are 4 major classes of vascular K\textsuperscript{+} channels: ATP sensitive (K\textsubscript{ATP}), calcium activated (K\textsubscript{Ca}), voltage activated (K\textsubscript{V}) and inward rectifier (K\textsubscript{IR}). Vasoconstriction elicited by the myogenic response may theoretically be exerted by inactivation of K\textsuperscript{+} channels with concomitant depolarization and activation of VOCC.\textsuperscript{23,26} It is suggested that the general closure of K\textsuperscript{+} channels may be orchestrated by activation of protein kinase C (PKC).\textsuperscript{27} Conversely, vasodilation could be initiated by activation of VSMC K\textsuperscript{+} channels.\textsuperscript{27} Some VSMC, e.g. from renal cortical efferent arterioles, lack L-type VOCC but activation of K\textsuperscript{+} channels will still cause hyperpolarization.

The permeability of Cl\textsuperscript{−} channels also participates in the regulation of VSMC V_m. In accord with this, Cl\textsuperscript{−} channels have been suggested to participate in the myogenic response.\textsuperscript{28,29} Influx of Na\textsuperscript{+} into the VSMC also leads to depolarization. This influx may occur via members of the TRP channel family.\textsuperscript{16,17} These channels also carry an influx of Ca\textsuperscript{2+} which directly increase [Ca\textsuperscript{2+}]i. Different members of the TRP channel family are activated by stimulation of cell surface receptors, emptying of intracellular Ca\textsuperscript{2+} stores and/or mechanical stretch.\textsuperscript{17} It has been suggested that activation of TRPM4 and/or TRPC6 channels contribute to the depolarization leading to the myogenic response\textsuperscript{30-33}

\textbf{Voltage gated calcium channels}

In mammalian cells, VGCCs are expressed by at least 10 different genes that encode Ca\textsuperscript{2+} selective channels with somewhat different biophysical and regulatory properties, expression patterns, and thus physiologic roles. The CaV1 and CaV2 families of channels belong to the so-called high-voltage activated (HVA) type as they require relatively large depolarization to be activated. Conversely, the CaV3 channel family belongs to the low-voltage activated (LVA) channels as they are activated by small depolarization at relatively hyperpolarized resting membrane potentials.\textsuperscript{34,35} The CaV1 family (CaV1.1-1.4 channels) carries the Ca\textsuperscript{2+} currents known as L-type (Large, Long-Lasting). This current is characterized by the relatively large unitary currents and long opening times due to slow inactivation kinetics (reviewed by\textsuperscript{36}). The CaV1 channels are primarily expressed in muscle (smooth, skeletal, cardiac), neurons and endocrine cells where they serve important roles in excitation-contraction (EC) -coupling and
regulation of gene transcription, hormone- and neurotransmitter release (see 34). In resistance-sized arteries, CaV1.2 channels are primarily responsible for EC-coupling and control of blood pressure.15,37,38 The L-type channels are all blocked by dihydropyridines, phenylalkylamines and benzothiazepines with similar potencies; however, some peptide toxins (calcisepine, FS-2) may specifically inhibit CaV1.2 channels.20,39,40 The CaV1.2 α1-subunit isoforms cloned from human intestinal smooth muscle and the heart were both shown to be inherently mechano-sensitive when expressed in HEK-293 cells.41

The CaV2 family (HVA) encoding the P/Q-type (CaV2.1a/b; splice variants of the Cacna1a gene), N-type (CaV2.2) and R-type (CaV2.3) currents are primarily expressed and functional in neurons where they participate in neurotransmitter release, action potentials, and local Ca2+ transients. Several peptide toxins such as ω-agatoxins (P/Q-type), some ω-conotoxins (N-type) and SNX-482 (R-type) inhibit the CaV2 channels specifically and are therefore valuable pharmacological tools (see 34). The P/Q-type channels seem to be expressed in renal preglomerular arterioles,42 but none of the P/Q-, N- or R-type channels are expressed and functional in mesenteric-terminal arterioles.40

The CaV3 family (LVA) T-type (Tiny, Transient) channels consisting of small and fast-inactivating CaV3.1–3 currents are primarily expressed in the peripheral and central nervous system where they are important for repetitive firing of action potentials (for review, see Perez-Reyes, 200335). However, CaV3.1 and CaV3.2 channels are also expressed in the heart where they are involved in pacemaking in the sinoatrial node (CaV3.1; 43) as well as in ventricular hypertrophy where CaV3.1 and CaV3.2 channels seem to play opposite roles.44,45 Moreover, in resistance vessels CaV3.1 and CaV3.2 T-type channel protein expression has been demonstrated by immunolocalization to VSMCs46–51 as well as ECs.48,49,51,52 Interestingly, in human cerebral arteries the T-type isoforms expressed are the CaV3.2 and CaV3.3 channels, with no expression of CaV3.1 channels.53 Application of 15 mmHg extracellular pressure to SW620 human cancer cells causes mechanical activation of Ca2+ influx through CaV3.3 T-type channels (but not through CaV3.1 or CaV3.2 channels), which activates PKC-β and stimulates proliferation of cancer cells.54 There are no reports of direct mechano-sensitivity of CaV3.1 channels. Although not directly mechano-sensitive, the CaV3.2 T-type channels are important for normal excitability of skin D-hair receptors in mice. The high sensitivity of D-hair receptors to light touch is facilitated by CaV3.2 channel expression due to a lowering of the threshold for mechanical activation of action potentials.55–57 No specific T-type channel blockers are available, so knockout mice are currently the golden standard for deciphering the function of these channels in the resistance vasculature. Mibebradil and its derivative NNC 55-0396 are used to investigate the physiologic role of T-type channels, but they are shown to block HVA channels in a use-dependent manner.46,58,59 and to lower blood pressure through inhibition of L-type channels.60 Thus, the exact function of CaV3.1 and CaV3.2 channels in the resistance vasculature is currently under investigation using knockout mice.46,50,61–64

Myogenic response

The myogenic response is considered a local response where changes in transmural pressure affect the circumferential stress in the vascular smooth muscle cell.65 How the change in stress is translated into changes in vascular diameter is still not fully understood. Several suggestions including changes in extracellular matrix connections, cytoskeleton structure, mechano-sensitive TRP channels and micro-domains in the membrane are currently under investigation (reviewed in 46).

The resting membrane potential (RMP) of VSMC in most vascular beds during physiologic pressures ranges between −60 mV to −35 mV.67–70 This range of RMP is a prerequisite for setting the basal tone upon which vasodilators can act. Increases in perfusion pressure further depolarize VSMC.71 As mentioned above this RMP is within the activation window for voltage-gated (L-type) Ca2+ channels but also affects KV channels and BKCa channels to modify myogenic constriction.71,72 Activation of BKCa depends on subunit composition, membrane potential and Ca2+ levels.73 and therefore one could speculate that tissue specific activation exists.

Inhibition of L-type Ca2+ channels significantly reduces the myogenic response in most vascular beds indicating a need for Ca2+ entry.74–77 Recently T-type channels have also been implicated in the myogenic
response of several vascular beds although some studies show that the influence of T-type channels on the myogenic response is more pronounced in the lower pressure range where the VSMC are less depolarized.61,78,79

In the renal vascular bed inhibition of T-type channels reduce autoregulation,80,81 but whether this effect is caused by an attenuation of the myogenic response alone or also affects the TGF is unknown. Both mechanisms affect resistance in the afferent arteriole. The myogenic response is induced by increased pressure but TGF is a conducted vasoconstriction elicited most likely by ATP or adenosine. Thus, the pathway inducing vasoconstriction is not similar and may affect T-type channels differently. However, in cremaster, cerebral, mesenteric, and retinal arterioles T-type channels have been suggested to play a role in the myogenic response. The following paragraphs will review the literature on T-type channels and autoregulation in several vascular beds.

**Renal autoregulation**

In the renal microcirculation expression of T-type channels (CaV3.1 and CaV3.2) has been shown in both pre- and postglomerular vessels.20 Using patch-clamp studies in VSMC isolated from rat afferent arterioles Smirnov et al. failed to demonstrate T-type currents while they were able to detect these currents in VSMC from the rat tail artery.84 Nevertheless, T-type currents have been found in larger preglomerular vessels such as interlobar and arcuate arteries.85 In contrast, L-type channels are only expressed in preglomerular vessels.86,87 Preglomerular vessels are the main effectors of the renal autoregulation as both the myogenic response and the TGF exert their action in these vessels.88,89 Inhibition of L-type channels abolishes renal autoregulation.90,91 Some studies have also shown that inhibition of renal T-type channels significantly affects autoregulation.80,81 However, due to the lack of specific inhibitors of T-type channels results have been difficult to interpret.

In vivo experiments using inhibitors of T-type channels have revealed no effect on baseline renal blood flow indicating that the channels are not significantly activated at normal physiologic perfusion pressures.61,80,92,93 However, recent findings from T-type knockout mice showed that lack of CaV3.1 led to increased renal blood flow (RBF) whereas lack of CaV3.2 led to increased glomerular filtration rate (GFR).94 This suggests that CaV3.1 maintains afferent tone whereas CaV3.2 supports efferent dilatation.

The expression pattern of voltage gated Ca2+ channels in the renal vasculature suggests a dual role in the renal autoregulation. Renal autoregulation affects both RBF and GFR. The renal circulation is a portal system where the glomerular capillaries are positioned between the afferent and efferent arterioles. Increased afferent resistance reduces both RBF and GFR whereas increases in efferent resistance decreases RBF and increases GFR within certain limits. Inhibition of L-type channels abolishes autoregulation of both RBF and GFR whereas the role of T-type channels are less elucidated. Inhibitors of L-type channels are often used in treatment of hypertension and it has been suggested that this leads to increased glomerular capillary pressure due to loss of renal autoregulation leading to increased proteinuria and glomerulosclerosis.95,96 Therefore focus has increased on the role of T-type channels in renal protection97,98 as they are hypothesized to reduce glomerular pressure.

Examinations of the role of T-type channels in renal autoregulation are limited. In isolated perfused rat kidneys pimozide significantly attenuated the afferent vasoconstriction in response to increases in renal perfusion pressure.81 In rats treated with mibefradil in the drinking water for 2–4 d renal autoregulation was also significantly attenuated. However, the effects of these T-type inhibitors are very concentration-dependent and the above-mentioned results are likely to reflect an L-type channel effect as well.99 In isolated kidneys from mice lacking the expression of CaV3.1 we showed that T-type channels play no apparent role in the afferent arteriolar autoregulation at renal perfusion pressures between 75 and 155 mmHg.61 Also, in normo- and hypertensive rats the changes in RBF after acute increases in renal perfusion pressure was identical in saline-treated and mibefradil-treated rats.61 The concentration of mibefradil used in this study is suggested to be specific for T-type channels but nevertheless these results have to be interpreted with caution.100 Taken together it appears as there is no major role for T-type channels in the renal autoregulation at pressures within the physiologic range. Whether they play a role at lower pressures as in the mesenteric circulation46 is unknown.
Coronary circulation

Perfusion of cardiac tissue is tightly coupled to metabolic demands and thus hyperemic mechanisms are the prime determinants of flow. As hyperemia induces vasodilation, it only works in the presence of basal tone in part determined by the myogenic response. Isolated coronary vessels have significant tone and demonstrate myogenic vasoconstriction in the physiologic pressure range. The myogenic response relies on calcium influx via L-type channels as demonstrated by its sensitivity to L-type channel blockers.

Few studies have addressed the role of T-type channels in the coronary circulation, but knockout of Cav3.2 blunts the vasodilation to ACh and NO in coronary arteries. A possible mechanism may be that localized calcium influx through Cav3.2 activates BKCa channels, leading to hyperpolarization and a reduction of global calcium influx. Since direct vasodilation by NO was also affected, it is unlikely that Cav3.2 acts by modifying NO production in the endothelial cells. The study by Chen et al only implicates Cav3.2 in vasodilation and the authors found no effect on vessel diameter (at 40 mmHg) or on agonist induced constriction. Although this argues against a role for Cav3.2 in coronary vasoconstriction, the study did not specifically address the myogenic mechanism and the application of 40 mmHg is probably too low to expect a detectable myogenic response.

Knockout of Cav3.1 affected the myogenic response of mesenteric arteries, but only in the low pressure range. The relevance of this phenomenon has not been investigated in coronary vessels, but no overt coronary phenotype has been reported for the Cav3.1 KO mice.

Skeletal muscle circulation

Both Cav3.1 and Cav3.2 are present in arterioles from rat cremaster muscle and pharmacological evidence suggests that T-type currents contribute significantly to myogenic tone in this vascular bed at physiologic pressures (75 mmHg). Furthermore, T-type channels contributed to basal tone in cremaster muscle vessels in vivo and their contribution was increased at reduced NO levels, most likely via an increase in reactive oxygen species. Such regulation may explain differences between studies and should be considered when comparing experiments from different species, vascular beds and experimental settings. However, a role for T-type channels in the autoregulation of blood flow in skeletal muscles seems possible at pressures within the physiologic range.

Cerebral autoregulation

In normotensive humans, autoregulation of cerebral blood flow is kept constant at approx. 50 mL/min/100 g brain tissue at mean arterial pressures between 60–130 mmHg and is believed to be entirely dependent on a myogenic response of cerebral arteries and arterioles. Increases in transmural pressure from 10 to 100 mmHg caused a graded depolarization of rat small cerebral artery VSMCs from about −63 mV to about −36 mV. Addition of the VGCC blockers diltiazem (30 μM) or nisoldipine (10 nM) inhibited intracellular Ca2+ increases and a myogenic response in this pressure range. This and later studies have unequivocally demonstrated a pivotal role of L-type channel mediated Ca2+ entry in the myogenic response and thus cerebral autoregulation. Activation of whole-cell L-type currents in VSMCs occurs at a Vm between −55 mV and 10 mV, with window currents through overlapping activation and inactivation curves in the range from approx. −30 mV to 0 mV. Therefore, it may be speculated that T-type channels play a role in myogenic tone at lower pressures at which VSMC membrane potential is outside the activation range of L-type channels. This hypothesis was independently confirmed by 2 studies showing that several T-type channel blockers inhibited myogenic tone at lower pressures in rat middle cerebral artery and that genetic deletion of Cav3.1 T-type channels abolished myogenic tone in the pressure range from 40–80 mmHg in mouse small mesenteric arteries.

However, also at higher pressure (100 mmHg) did low concentration of mibebradil (60 nM) significantly reduce cerebral myogenic responses. Conversely, myogenic tone in rat middle cerebral arteries was increased by the Cav3.2 T-type channel blocker Ni2+ (50 μM) which is in line with the results found in the renal vasculature in Cav3.2 T-type KO mice where efferent arteriolar resistance increased. This increase in myogenic tone following addition of Ni2+ was not seen in mesenteric arteries from Cav3.2−/− mice. The increased tone was mimicked by addition of the specific BKCa channel blocker paxilline (1 μM) in rat cerebral arteries and this effect of paxilline was not seen in small
mesenteric arteries from young CaV3.2-deficient mice.50 These results are generally in agreement with the hypothesis that pressure-dependent activation of CaV3.2 channels in the VSMC plasma membrane causes activation of Ca\(^{2+}\) sparks via Ryanodine receptors (RyRs) closely apposed to Sarcoplasmatic Reticulum (SR). This leads to activation of spontaneous transient outward currents (STOC) via BK\(_{Ca}\) channels, and negative feedback on the cerebral myogenic tone,\(^{63,105}\) as previously suggested for the involvement of CaV3.2 channels in relaxation of coronary arteries.\(^{103}\) These effects of CaV3.2 channel deletion on myogenic tone were only observed in young mice (2–4 months) but not in mature adult mice (7–12 months) leading to the conclusion that CaV3.2 channel expression may protect against excessive tone and high blood pressure in young individuals.\(^{50}\) Human cerebral arteries express the CaV3.2 and CaV3.3 isoforms, and interestingly Ni\(^{2+}\) (50 \(\mu\)M) also increased myogenic tone in human arteries.\(^{53}\) Moreover, the T-type blocker NNC 55-0396 (1 \(\mu\)M) inhibited the myogenic tone at lower pressures in human cerebral arteries in the presence of the L-type blocker nifedipine (200 nM), an effect that is reminiscent of the CaV3.1-mediated effects on myogenic tone in rodent arteries\(^{46,78}\) but might be mediated via CaV3.3 channels in human cerebral arteries\(^{53}\)

**Mesenteric circulation**

The superior mesenteric artery supplying the small intestine carries >10% of cardiac output at rest. Sympathetic nerves densely innervate mesenteric arteries and arterioles, and \(\alpha_1\)-adrenoceptor mediated sympathetic vasoconstriction is of paramount importance during maximal physical activity, fight-or-flight syndrome, and hypotensive crises. Adjustment of O\(_2\) delivery occurs partly at the level of O\(_2\) uptake, which is maintained constant over a wide range of perfusion pressures. Autoregulation does occur but seems to be mainly coupled to release of local metabolic factors, such as adenosine, interstitial K\(^+\) or altered osmolality. Rat mesenteric arteries (2nd–3rd order) do not possess much myogenic tone in vitro unless it is triggered by low agonist-induced tone.\(^{106,107}\) However, 5th order rat mesenteric arteries, as well as 2nd–3rd order mouse mesenteric arteries do exhibit spontaneous myogenic tone in vitro, and the diameter-pressure curve usually has a negative slope in the pressure range from 60–120 mmHg\(^{108-110}\) suggesting that the mesenteric arteries have the inherent capacity to autoregulate blood flow via a myogenic mechanism. As a large body of mechanistic evidence has been gathered in studies using isolated mesenteric arteries we will present data on VGCCs and the myogenic response from this vascular bed.

While the essential role of L-type channels in myogenic tone in rat and mouse mesenteric arteries is well established,\(^{111,112}\) the role of other HVA channels remains unexplored. However, specific peptide toxins targeting P/Q-type, N-type and R-type VGCCs did not inhibit high-KCl induced Ca\(^{2+}\) entry in rat mesenteric arterioles,\(^{40}\) so most likely these HVA channels do not play a role in myogenic tone.

Previous studies have shown abundant expression of CaV3.1 and CaV3.2 T-type LVA channels at the mRNA and protein level in rat and mouse mesenteric arteries and arterioles.\(^{40,46,48,50,113}\) In small mesenteric arteries from wild-type mice nifedipine (1 \(\mu\)M) abolished myogenic tone at higher pressures, whereas there was no effect on tone at 40 mmHg. In age-matched mice deficient in the CaV3.1 T-type channels, myogenic tone was abolished at lower pressures (40–80 mmHg), but at pressures above 80 mmHg the spontaneous myogenic tone was abolished by 1 \(\mu\)M nifedipine.\(^{46}\) These data are consistent with the hypothesis that at lower pressures, at which the VSMC membrane potentials are relatively hyperpolarized, the L-type channels are inactive whereas the CaV3.1 channels are active and sustain myogenic tone possibly via a window-type current. At higher pressures, where the myogenic depolarization activates the L-type channels, the CaV3.1 channels will inactivate accounting for the complete inhibition of myogenic tone by nifedipine at pressures above 80 mmHg.\(^{46}\)

Conversely, the expression of CaV3.2 T-type channels in mesenteric artery VSMCs seems to participate in a negative feedback mechanism on the myogenic tone. In young mice, deletion of CaV3.2 channels causes a significant enhancement of myogenic tone at pressures above 40–60 mmHg.\(^{50,63}\) This was shown to be dependent on generation of Ca\(^{2+}\) sparks via superficial SR ryanodine receptors causing activation of spontaneous transient outward currents via BK\(_{Ca}\) channels and hyperpolarization to give negative feedback modulation on myogenic tone.\(^{63}\) A potential role of CaV3.2 channels in protection of the myocardium against excessive arterial tone and age-dependent
hypertension was indicated by the finding that the role of CaV3.2 channels in opposing myogenic tone found in young mice was completely absent in mature adult mice. This protection could also be relevant in the kidney to protect glomerular capillaries as CaV3.2 deletion in mice resulted in an increased GFR. This effect of aging was not caused by a reduced mRNA expression of CaV3.2 channels or BKCa α1 and β1 sub-units, but it might be coupled to a dramatic reduction of CaV3.1 channel expression in VSMCs, which was seen at the mRNA and protein level in mature adult mice. How this putative coupling between CaV3.1 and CaV3.2 channels can exert an effect on myogenic tone remains to be established.

Both CaV1.2 and CaV3.3 channels were previously shown to be directly activated by pressure or stretch. However, a direct pressure-dependent activation of Ca2+ influx via VGCCs cannot play a major role in the myogenic response, since myogenic depolarization is dependent on opening of non-selective cation channels and is not affected by application of the L-type antagonist nifedipine. The role of CaV3.1 channels (and perhaps Cav3.3 channels in human MCAs) in myogenic tone at lower pressures can be explained by a corresponding low myogenic depolarization in the range from approximately −65 to −50 mV, which activates a non-inactivation window-type Ca2+ current through these channels.

**Figure 1.** T-type calcium channels in spontaneous myogenic tone development in the rat middle cerebral artery and mouse small mesenteric artery, as explained in the text. The well-established role of L-type calcium channels is omitted here. At VSMC membrane potentials more hyperpolarized than the activation threshold for L-type channels, increases in pressure in the low range from 40–80 mmHg leads to low voltage-activation of CaV3.1 and/or CaV3.2 T-type calcium channels. The activation of CaV3.1 in this pressure range leads to myogenic tone development either via low sustained window-type Ca2+ currents, or as proposed here, via subsequent activation of Ca2+–dependent signaling molecules in membrane micro-domains (caveolae). The activation of CaV3.2 channels leads to Ca2+–dependent activation of RyRs in closely apposed SR causing increased Ca2+ spark activity. This in turn will activate nearby BKCa channels to increase STOC activity leading to hyperpolarization of VSMCs, which causes a negative feedback on the pressure-dependent depolarization and on spontaneous myogenic tone development. Thus activation of T-type channels at lower pressures may cause both an activation as well as an inhibition of myogenic tone, and the balance between the 2 opposing roles presumably relies on the vascular bed and vessel diameter. Text shown in gray are proposed signaling mechanisms that are so far unexplored. Stimulation and inhibition of an activity is shown as + or −, respectively. SR (sarcoplasmic reticulum); BKCa (large-conductance calcium-activated potassium channel); STOC (spontaneous transient outward current); ClCa (calcium-activated chloride channel, such as TMEM16A); PLA2 (Ca2+-dependent cytosolic phospholipase A2); PLC (calcium-dependent phospholipase C-δ); PKC (protein kinase C-α/β); RhoA/ROCK (small G-protein RhoA/Rho-kinase pathway).
CaV3.1/CaV3.3 might be situated in plasma membrane micro-domains in close apposition with Ca\(^{2+}\)-dependent signaling molecules (such as Cl\(^{-}\) channels, PLA\(_2\), PLC, PKC, RhoA/Rho-kinase, etc.), and this could potentially amplify the development of myogenic tone due to opening of T-type channels via further depolarization and/or Ca\(^{2+}\) sensitization. This micro-domain model of CaV3.1/CaV3.3 may exist in parallel with the already demonstrated role of the Cav3.2 T-type channels, which upon activation to an increase in pressure causes stimulation of SR Ca\(^{2+}\) spark activity, spontaneous outward currents, VSMC hyperpolarization and negative feedback on the myogenic tone development. Fig. 1 shows a model in which the suggested signaling pathways upon pressure-dependent activation of T-type channels in VSMCs are shown.

**Concluding remarks**

The role of voltage gated T-type Ca\(^{2+}\) channels in autoregulation is still unsettled. Depending on the vascular bed investigated the results vary. In the renal and coronary vascular beds there seems to be no role for T-type channels whereas a role has been shown in the skeletal, cerebral and mesenteric autoregulation. Furthermore, the actual pressures experienced by the vasculature in the organs have been shown to greatly affect the results. At low pressures (40–80 mmHg) T-type channels have been shown to affect myogenic responses in cerebral and mesenteric vascular beds. However, also at higher pressures do T-type channels seem to play a role in the cerebral autoregulation. The lack of specific pharmacological inhibitors has been a huge challenge in the field but now the research has been strengthened by genetically modified models such as mice lacking expression of CaV3.1 and CaV3.2 channels. Hopefully, these new tools will help further elucidate the role of voltage gated T-type Ca\(^{2+}\) channels in autoregulation.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

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