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K_V channel trafficking and control of vascular tone

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Abstract

Membrane potential is a principal regulator of arterial contractility. Arterial smooth muscle cells express several different types of ion channel that control membrane potential, including voltage-gated K^+ (K_V) channels. K_V channel activation leads to membrane hyperpolarization, resulting in inhibition of voltage-dependent calcium (Ca^{2+}) channels, a reduction in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) and vasodilation. In contrast, K_V channel inhibition leads to membrane depolarization and vasoconstriction. The ability of K_V channels to regulate arterial contractility is dependent upon the number of plasma membrane-resident channels and their open probability. Here, we will discuss mechanisms that alter the surface abundance of K_V channel proteins in arterial smooth muscle cells and the functional consequences of such regulation. Cellular processes that will be described include those that modulate K_V channel transcription, retrograde and anterograde trafficking and protein degradation.

Keywords

smooth muscle; ion channel; vasoconstriction; trafficking; voltage-dependent K^+

Introduction

Membrane potential is a key regulator of arterial contractility. [1,2] Arterial smooth muscle cells express several different types of ion channel that control membrane potential, including voltage-gated K^+ (K_V) channels. [3–5] K_V channel activation leads to membrane hyperpolarization, which reduces the activity of voltage-dependent calcium (Ca^{2+}) channels, leading to a reduction in $[Ca^{2+}]_i$ and vasodilation. [5–11] In contrast, K_V channel inhibition leads to membrane depolarization and vasoconstriction. Physiological stimuli, including intravascular pressure and receptor ligands regulate K_V currents in arterial smooth muscle cells to modify vascular contractility. Mechanisms by which these stimuli alter K_V currents may involve modification of channel expression, retrograde and anterograde trafficking, post-translational modification, degradation and activity. [7–9,12–17]

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Conflict of Interest

The authors declare that they have no competing interests.

The current (I) generated by a plasma membrane population of ion channels is determined by the number of channels (N), single channel open probability (P_o) and single channel current (i), such that $I=N.P_o.i$. Previous studies primarily investigated mechanisms that regulate the gating (P_o) of plasma membrane ion channels. In contrast, processes that control the surface abundance (N) of ion channels and functional significance are poorly understood. The focus of this review is to summarize studies that have described mechanisms that can regulate the surface abundance (N) of K_V channels in arterial smooth muscle cells.

Expression and distribution of K_V channels in arterial smooth muscle cells

K_V channels are tetramers of four pore-forming α subunits that can associate with accessory β-subunits. [18,19] Each K_V α subunit is a six transmembrane domain (S1–S6) protein in which S5 and S6 form the central pore and S4 acts as the voltage sensor. [18,19] K_V channels are a family of ~40 proteins classified into 12 subtypes (K_V1-12) that can assemble as homo- or hetero-tetramers. This diversity generates a vast array of K_V current phenotypes that can differ in their kinetics, amplitude and responses to different modulators. [20–23] Tissue- and species-specific expression of K_V channel isoforms has also been described, which further contributes to K_V current heterogeneity. [24,25]

Arterial smooth muscle cells express multiple different K_V channel isoforms. [9,10,24–29] Using PCR, Western blotting and immunofluorescence, K_V1.2, K_V1.3, K_V1.5 and K_V2.1 channels were identified in rat mesenteric artery smooth muscle cells, whereas K_V3.2 was absent. [24] Message for K_V1.1, K_V1.2, K_V1.4, K_V1.5, K_V1.6, K_V2.1 and K_V9.3 was detected in cultured rat pulmonary arterial smooth muscle cells. [25] Nishijima et al. reported the expression of K_V1.3, 1.4, 1.5 and 1.6 channels in whole human adipose arteries, with K_V1.5 a principal isoform in smooth muscle cells isolated from these vessels. [17] K_V7.1, K_V7.4 and K_V9.3 channel message was detected when using RT-PCR in rat cerebral arteries. [30,31] Thus, arterial smooth muscle cells express multiple different K_V channel isoforms, with diversity that may depend upon the anatomical location of the vascular bed.

A recent study by Kidd and co-authors (2015) demonstrated that when several different K_V channel isoforms were quantified in fresh-isolated rat mesenteric artery smooth muscle cells, Kv1.5 accounted for ~60% of mRNA transcripts, with K_V2.1 and K_V2.2 each ~15%. [9] Using arterial biotinylation, the abundance and cellular distribution of K_V1.5 and K_V2.1 proteins were measured in rat resistance-size mesenteric arteries. ~50% of total K_V1.5 and ~80% of total K_V2.1 proteins were located in the plasma membrane. [9] Evidence obtained using pharmacological blockers indicates that these surface K_V channel proteins are functional and generate K^+ currents in arterial smooth muscle cells. [7,9,14,16,17]. The detection of intracellular pools of K_V1.5 and K_V2.1 raised the possibility that the surface abundance of these channels may be dynamically altered by physiological and/or pathological stimuli that modulate K_V currents. [9,14] This possibility was particularly high for K_V1.5, for which a large proportion of total protein was intracellular. [9,14] As mechanisms that regulate the surface abundance of K_V1 and K_V2 channels in arterial smooth muscle cells are best described in the literature, this review article will primarily discuss these proteins.

Regulation of K_V1 channel trafficking and surface protein in arterial smooth muscle cells

To control smooth muscle cell membrane potential, K_V channels must traffic from the ER-golgi complex to the plasma membrane. A recent study reported the regulation of $K_V1.5$ trafficking by physiological intravascular pressure and membrane potential in smooth muscle cells of rat mesenteric arteries. [9] Using a combination of Western blotting, biotinylation and immunofluorescence, the authors showed that arterial depressurization reduced surface $K_V1.5$ protein by ~60%. Internalized $K_V1.5$ did not accumulate in an intracellular compartment, suggesting that the protein was degraded. [9] In line with this finding, $K_V1.5$ loss was prevented by both lysosomal and proteasomal degradation inhibitors. Physiological intravascular pressure and membrane depolarization, through the activation of $Ca_V1.2$ channels, prevented the loss of both surface and total $K_V1.5$ protein in arteries. Concanavalin A, an internalization inhibitor, increased the plasma membrane abundance of $K_V1.5$ protein, consistent with the concept that $K_V1.5$ channels continuously recycle between an intracellular compartment and the plasma membrane and that membrane potential controls this process in smooth muscle cells. [9] The loss of surface $K_V1.5$ protein reduced $K_V1.5$ currents in isolated arterial smooth muscle cells through a process that was prevented by bafilomycin, a lysosomal degradation inhibitor. [9] To examine the functional impact of intravascular pressure on $K_V1.5$ trafficking, mesenteric artery segments were pressurized to pre-experimental pressures of either 10 or 80 mmHg prior to measurement of contractile responses at 80 mmHg. Arteries maintained at a pre-experimental pressure of 80 mmHg constricted more to Psora-4, an inhibitor of $K_V1.5$ channels, than those that had been maintained at 10 mmHg. These data indicate that intravascular pressure stimulates $Ca_V1.2$ channels, leading to an increase in $[Ca^{2+}]_i$ that inhibits proteasomal and lysosomal degradation of $K_V1.5$ channels in arterial smooth muscle cells. As $K_V1.5$ channels continuously recycle between the plasma membrane and an intracellular compartment, Ca^{2+}-dependent inhibition of degradation allows these proteins to return to the surface increasing their abundance and $K_V1.5$ current density (Fig. 1). [9] Thus, membrane depolarization increases $K_V1.5$ currents (I) in arterial smooth muscle cells through two distinct mechanisms: 1) through elevating the number (N) of channel proteins at the plasma membrane and 2) by directly increasing the open probability (P) of surface-localized channels. These mechanisms combine to oppose pressure-induced vasoconstriction.

The regulation of $K_V1.5$ trafficking by angiotensin II (Ang II), a potent vasoconstrictor, has also been investigated in arterial smooth muscle cells. [14] Ang II reduced both total and surface $K_V1.5$ protein without altering the relative cellular distribution of channels. Data suggested that Ang II binding to a $G_{q/11}$-coupled receptor activated protein kinase C (PKC), which reduced both surface and total $K_V1.5$. [14,32] Ang II did not promote $K_V1.5$ internalization, but stimulated lysosomal degradation of constitutively internalized $K_V1.5$ protein, thereby reducing the number of channels that could recycle back to the plasma membrane, decreasing surface abundance. [14] Patch-clamp electrophysiology experiments indicated that Ang II-induced PKC activation decreased $K_V1.5$ current density by reducing the number of functional proteins at the plasma membrane. [14] Similarly, experiments in pressurized mesenteric arteries showed that the Ang II-induced reduction in surface $K_V1.5$

protein in arterial smooth muscle cells reduced the ability of these channels to regulate contractility (Fig. 1). [14] Thus, Ang II stimulates the degradation of $K_V1.5$ channels, leading to a reduction in $K_V1.5$ current density in arterial smooth muscle cells. As $K_V1.5$ channel activation leads to vasodilation, a reduction in surface channel number promotes vasoconstriction.

These studies described how different physiological stimuli can act through distinct mechanisms to regulate $K_V1.5$ trafficking and surface expression. Membrane depolarization stimulates $Ca_V1.2$ channels, leading to an increase in nanomolar $[Ca^{2+}]_i$ in arterial smooth muscle cells. [9] Thus, $K_V1.5$ channel degradation may be inhibited by proteins that are activated by $[Ca^{2+}]_i$ within the nanomolar range, such as calmodulin. [9] Ang II has been shown to selectively stimulate protein kinase Cε (PKCε), a DAG-dependent PKC. [33] Ang II-mediated PKCε activation reduced whole-cell K_V currents in smooth muscle cells and PKCε inhibition reduced Ang II-induced vasoconstriction in mesenteric artery rings. [34] Thus, Ang II may stimulate Ca^{2+}-independent PKCε, leading to $K_V1.5$ degradation. Collectively, these studies not only show that different physiological stimuli regulate the abundance of surface $K_V1.5$ channels, but support the concept that $K_V1.5$ degradation is regulated by both Ca^{2+}-dependent and Ca^{2+}-independent processes. Future studies will be required to understand the mechanisms by which an increase in $[Ca^{2+}]_i$ inhibits $K_V1.5$ degradation and protein kinase C activation stimulates $K_V1.5$ degradation to differentially control arterial contractility.

Serotonin (5-hydroxytryptamine, 5-HT) internalized $K_V1.5$ channels in rat pulmonary artery smooth muscle cells, as measured using immunofluorescence. [12] Consistent with this finding, 5-HT reduced K_V currents in isolated smooth muscle cells and contracted pulmonary arteries. [12] Data pointed to 5-HT signaling through a $G_{q/11}$-coupled $5\text{-}HT_{2A}$ receptor to stimulate a signaling cascade involving PLC, which activates PKC or tyrosine kinases to modify vascular tone. [12] $K_V1.5$ protein coimmunoprecipitated with $5\text{-}HT_{2A}$ receptors and caveolin-1, a caveolar protein, in pulmonary artery homogenate. The authors suggested that an interaction between $K_V1.5$, $5\text{-}HT_{2A}$ and caveolin-1 may underlie 5-HT-induced $K_V1.5$ internalization, leading to a decrease in surface $K_V1.5$ protein and pulmonary vasoconstriction. [12]

$K_V1.2$ channels coimmunoprecipitated with Postsynaptic density-95 (PSD95), a scaffolding protein, in cerebral arteries. [13] $K_V1.2$ also co-localized with PSD95 in immunofluorescence experiments performed on cerebral artery smooth muscle cells. Antisense knockdown of PSD95 reduced $K_V1.2$ channel protein and K_V current density in cerebral artery smooth muscle cells. A peptide sequence identical to the $K_V1.2$ PSD95 binding sequence decreased smooth muscle cell K_V currents and stimulated depolarization and vasoconstriction in cerebral arteries, suggesting that an interaction with PSD95 is essential for function. [15] This study suggested that PSD95 acts as a molecular scaffold that increases the surface abundance of $K_V1.2$ channels to control cerebral artery contractility.

$K_V1.5$ channel activation underlies H_2O_2-induced vasodilation in adipose arterioles from healthy human subjects. [17,18,35,36] In contrast, in adipose arterioles from patients with coronary artery disease (CAD), H_2O_2-induced vasodilation is preferentially mediated

through the activation of large-conductance Ca^{2+}-activated K^+ channels (BK_{Ca}). [35–40] PCR, Western blotting and immunofluorescence data identified the expression of $K_V1.3$, $K_V1.4$, Kv1.5 and $K_V1.6$ proteins, with $K_V1.5$ abundance being the highest in human adipose arteries. [17] Immunofluorescence suggested a lower abundance of surface $K_V1.5$ protein in smooth muscle cells of CAD arteries compared to those of non-CAD subjects. K_V currents sensitive to DPO-1, a $K_V1.5$ channel specific blocker, were also smaller in smooth muscle cells of CAD patients. Accordingly, H_2O_2-elicited vasodilation was attenuated in CAD arteries due to the loss of $K_V1.5$ channels. [17] A chronic elevation in reactive oxygen species (ROS), reported to reduce $K_V1.5$ expression in hypoxia, hyperglycemia and hypertension, was proposed to underlie reduced $K_V1.5$ surface expression and $K_V1.5$ function in arteries from CAD subjects. [17,41–44] This study demonstrated that a reduction in $K_V1.5$ surface expression in arterial smooth muscle cells leads to a loss of $K_V1.5$-mediated vasodilation to H_2O_2 in CAD patients.

Pial arteriole smooth muscle cells from (Tg)$Notch3^{R169C}$ mice, a genetic model of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), had larger whole-cell K_V current density than control cells. [45] Isolated pial artery segments from (Tg)$Notch3^{R169C}$ mice also produced greater vasoconstriction in response to K_V channel inhibitors than control arteries. Stimulation of surface K_V1 endocytosis with HB-EGF, an epidermal growth factor receptor agonist, decreased K_V current density and restored myogenic responses in pial arteries from (Tg) $Notch3^{R169C}$ mice. [45] Thus, an increase in surface K_V1 channels that blunts pressure-induced depolarization and vasoconstriction in cerebral arteries contributes to the cerebrovascular manifestations of CADASIL. [45]

Following subarachnoid hemorrhage, an increase in extracellular oxyhemoglobin stimulates cerebral artery vasospasm. [46] Immunofluorescence data showed that oxyhemoglobin stimulated $K_V1.5$ endocytosis. [47] Consistent with this finding, oxyhemoglobin decreased 4-AP-sensitive K_V currents in rabbit cerebral artery smooth muscle cells. [47] Inhibition of tyrosine kinases abolished both oxyhemoglobin-induced suppression of K_V currents in isolated smooth muscle cells and oxyhemoglobin-induced constriction of isolated cerebral arteries. [47] Data suggested a model in which oxyhemoglobin reduces $K_V1.5$ channels via a mechanism involving an increase in tyrosine kinase activity and channel endocytosis, leading to depolarization and vasoconstriction. [48–50]

Mechanisms that regulate K_V2 channel surface abundance

K_V2 channels are important contributors to K_V currents in smooth muscle cells of cerebral and mesenteric arteries. [7] $K_V2.1$ and $K_V2.2$ transcripts each represented the second highest level of message when several different K_V1 and K_V2 isoforms were quantified in fresh dissociated rat mesenteric artery smooth muscle cells. [9] Arterial biotinylation experiments revealed that $K_V2.1$ is primarily plasma membrane-localized, with ~80% of total protein located at the surface. [9] In contrast to $K_V1.5$, the surface abundance of $K_V2.1$ protein was not regulated by intraluminal pressure, membrane potential or Ang II, at least during acute exposures in rat mesenteric arteries. [9,14] Thus, distinct processes control the surface abundance of $K_V1.5$ and $K_V2.1$ channels in arterial smooth muscle cells. Additional studies

will be required to dissect out the differential mechanisms involved, but possibilities include that $K_V1.5$ channels continuously recycle, whereas $K_V2.1$ channels do not and that the regulatory mechanisms controlling surface abundance occur intracellularly, such as degradation. If this is the case, only once channels are internalized can their abundance be reduced to decrease surface levels of these proteins.

$K_V2.1$ transcription was investigated in cerebral artery smooth muscle cells of Ang II-infused hypertensive rats. [7] Chronic Ang II exposure stimulated arterial depolarization and Ca^{2+} influx, leading to an increase in $[Ca^{2+}]_i$ and the activation of calcineurin (CaN), a Ca^{2+}/calmodulin-dependent protein phosphatase. Activated CaN stimulated the transcription factor NFATc3 to promote its nuclear translocation, leading to transcriptional downregulation of $K_V2.1$. Studies suggested that while short-term Ang II exposure does not alter $K_V2.1$ trafficking, chronic Ang II treatment reduces $K_V2.1$ transcription and the amount of protein available for surface trafficking, leading to a decrease in current density and vasoconstriction (Fig. 2). [7,14]

Western blotting and immunofluorescence experiments demonstrated that $K_V2.1$ protein was reduced in cerebral and mesenteric artery smooth muscle cell from mice fed a high-fat diet, a model of type-2 diabetes. [16] Whole-cell currents sensitive to stromatoxin, a K_V2 channel blocker, were smaller in smooth muscle cells and K_V2 function was lost in pressurized arteries of diabetic mice, leading to an increase in arterial tone. [16] This reduction in $K_V2.1$ channels was attributed to hyperglycemia-induced suppression of $K_V2.1$ transcription. Downregulation of $K_V2.1$ transcription was mediated via AKAP150, which anchored CaN to dephosphorylate and activate the transcription factor NFATc3. Nuclear translocation of activated NFATc3 reduced $K_V2.1$ transcription and surface expression in smooth muscle cells. These studies provided a functional link between AKAP150-CaN/NFATc3-mediated nuclear signaling, reducing the pool of $K_V2.1$ protein available for trafficking in arterial smooth muscle cells and enhanced arterial tone during diabetes (Fig. 2). [7,16]

Conclusions

Plasma membrane ion channels regulate smooth muscle cell membrane potential and $[Ca^{2+}]_i$ to alter arterial contractility. Understanding mechanisms that control the surface abundance of ion channels in arterial smooth muscle cells is therefore, important to determine. Although ion channel trafficking in smooth muscle cells is poorly understood, some recent studies have identified mechanisms that control K_V channel surface abundance and their functional significance. Future studies should identify mechanisms that regulate the trafficking of these and other K_V channel isoforms, their functional significance, pathological modification and potential for therapeutic intervention in arterial smooth muscle cells.

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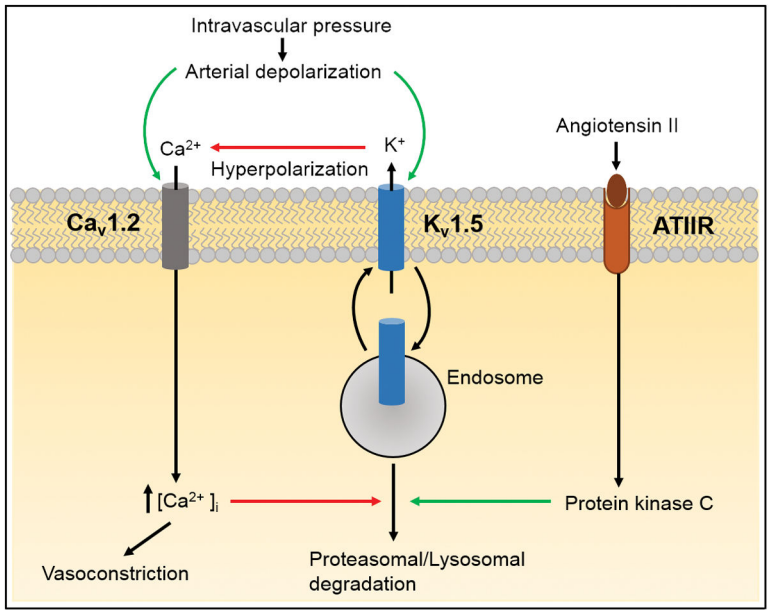

Figure 1. Mechanisms that regulate K_V1.5 channel trafficking in arterial smooth muscle cells

K_V1.5 continuously recycles between the cytosol and plasma membrane. Intravascular pressure stimulates arterial smooth muscle cell membrane depolarization, leading to Ca_V1.2 channel activation. The increase in $[Ca^{2+}]_i$ inhibits K_V1.5 channel degradation, allowing K_V1.5 to recycle to the plasma membrane. A reduction in intravascular pressure leads to membrane hyperpolarization which promotes the degradation of K_V1.5 protein through a process that involves both proteasomes and lysosomes. Angiotensin II binding to a surface receptor (ATIIR) activates protein kinase C, which stimulates the degradation of internalized K_V1.5 channels, leading to a reduction in the amount of protein that is returned to the surface. Through this mechanism angiotensin II reduces surface K_V1.5 protein, which decreases K_V1.5 current density, leading to vasoconstriction. Green and red arrows indicate activation and inhibition, respectively.

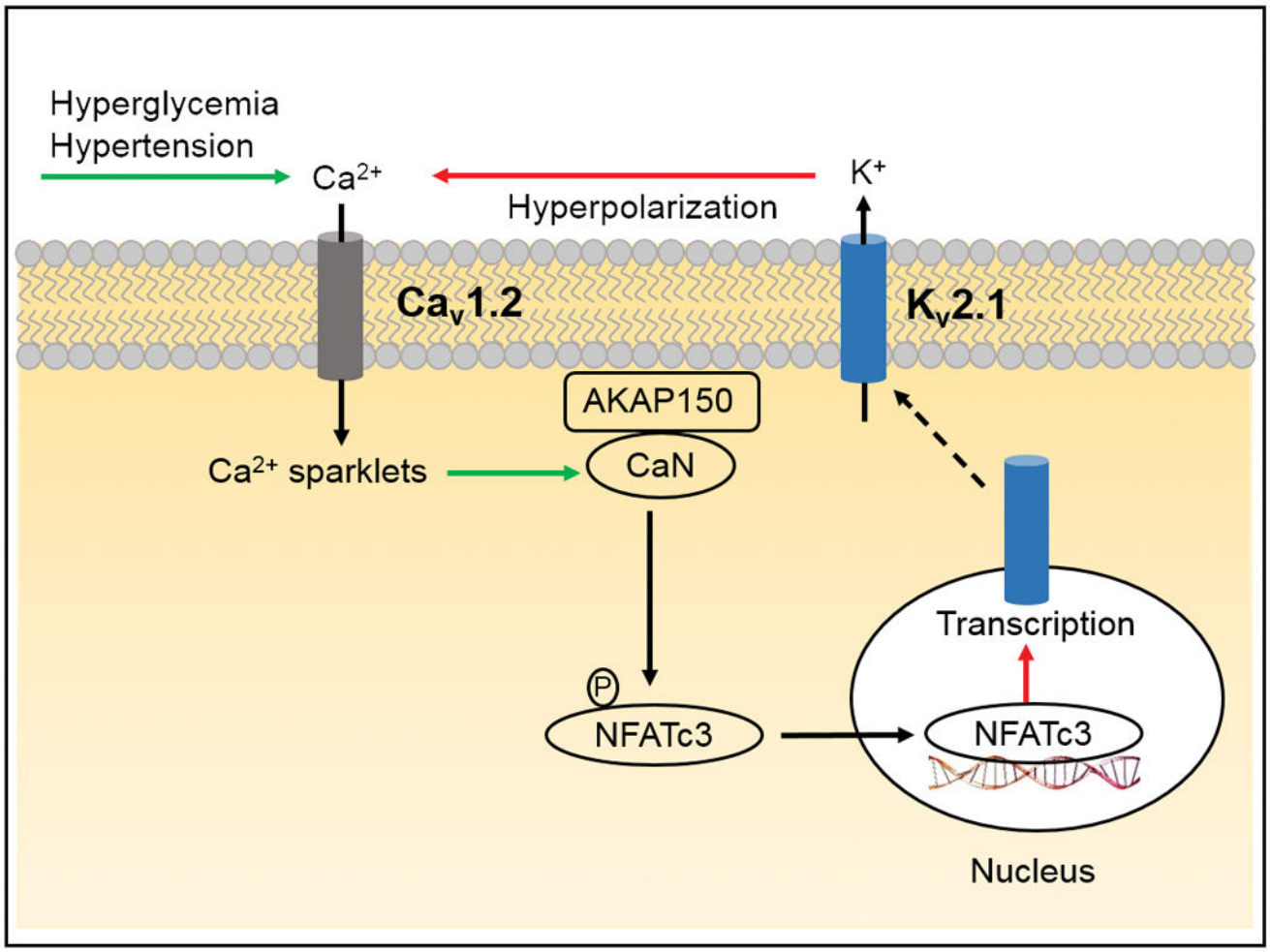

Figure 2. K_V2.1 expression in diabetes and hypertension

Chronic hyperglycemia and in-vivo Ang II treatment, a model of hypertension, activate Ca_V1.2 channel-mediated Ca^{2+} sparklets and calcineurin (CaN). AKAP150 anchors activated CaN to dephosphorylate and activate NFATc3. Subsequently, nuclear translocation of activated NFATc3 leads to reduced transcription of K_V2.1, which decreases K_V current density. Green and red arrows indicate activation and inhibition, respectively.