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Regulation of voltage-gated potassium channels in vascular smooth muscle during hypertension and metabolic disorders

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Abstract

Voltage-gated potassium (K_V) channels are key regulators of vascular smooth muscle contractility and vascular tone, and thus have major influence on the microcirculation. K_V channels are important determinants of vascular smooth muscle membrane potential (E_m). A number of K_V subunits are expressed in the plasma membrane of smooth muscle cells. Each subunit confers distinct kinetics and regulatory properties that allow for fine control of E_m to orchestrate vascular tone. Modifications in K_V subunit expression and/or channel activity can contribute to changes in vascular smooth muscle contractility in response to different stimuli and in diverse pathological conditions. Consistent with this, a number of studies suggest alterations in K_V subunit expression and/or function as underlying contributing mechanisms for small resistance artery dysfunction in pathologies such as hypertension and metabolic disorders, including diabetes. Here, we review our current knowledge on the effects of these pathologies on K_V channel expression and function in vascular smooth muscle cells, and the repercussions on (micro)vascular function.

Introduction

The microcirculation is greatly influenced by vascular smooth muscle cells lining the arterial wall of small resistance arteries and arterioles. The contractile state of vascular smooth muscle determines the diameter of these vessels and helps establish the level of vascular tone. This contributes to proper regulation of blood pressure and blood flow to meet metabolic demands of surrounding tissue. The association of microvascular dysfunction in humans with a number of pathological conditions, including hypertension and diabetes, underscores the significance of this mechanism (40, 47, 67).

Vascular tone is largely determined by a dynamic interplay between different ionic conductances in vascular smooth muscle that help control its membrane potential (E_m) and the level of intracellular calcium (Ca^{2+}) (75). Accordingly, the activity of potassium (K^+) channels, including a number of voltage-gated K^+ (K_V) channels, is a major regulator of vascular smooth muscle $E_{m\ (38)}$. K_V channels, through their regulation of E_m, have a major

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influence on intracellular Ca^{2+} by modulating the open probability of L-type Ca^{2+} channels (and perhaps T-type channels (25)). This is important as Ca^{2+} influx through L-type Ca^{2+} channel $Ca_V1.2$ (e.g. Ca^{2+} sparklets) is essential for vascular smooth muscle contraction (3, 37, 52). Physiological activation of K_V channels hyperpolarizes and relaxes vascular smooth muscle by decreasing the activity of voltage-gated Ca^{2+} channels and therefore Ca^{2+} influx, whereas their inhibition promotes contraction (56). Thus, K_V channels are important regulators vascular tone.

K_V channels represent a diverse group of membrane proteins, with 12 distinct families identified to date (K_V1-K_V12) (24). Each K_V channel comprises a K_V α subunit that forms the ion conducting pore and an ancillary K_V β subunit that modulates activity of K_V α subunits. The K_V α subunit consists of six transmembrane helices (S1-S6) with the S4 transmembrane domain containing the voltage sensor. A tetramer of K_V α subunits forms the ion-conducting pore, through interactions of the S6 domain and the P-loop between the S5 and S6 domains. Vascular smooth muscle cells express a variety of K_V channels in different vascular beds, including K_V1 ($K_V1.1$, $K_V1.2$, $K_V1.3$, $K_V1.5$, $K_V1.6$), K_V2 ($K_V2.1$) as well as members of the K_V7 (K_V 7.1-5) and silent K_V subunits ($K_V9.3$) (Table 1) (2, 5, 15, 75, 81). K_V channels can exist as homo- or heterotetramers with distinct biophysical and pharmacological properties. In vascular smooth muscle, for example, $K_V1.2$ and $K_V1.5$, as well as $K_V7.4$ and $K_V7.5$ can form heteromeric channels with profound implications for cell excitability (36, 75). Likewise, co-assembly with auxiliary K_V β subunits and silent K_V subunits confers further functional diversity (36).

K_V channels represent key substrates underlying vascular smooth muscle excitability in response to not only pressure-induced depolarization (e.g. vascular tone), but also vasoactive substances. For example, K_V channels have been shown to participate in the response to vasodilators such as adenosine and β-adrenergic agonists. These vasodilators promote cAMP production, activation of protein kinase A (PKA) and phosphorylation of K_V channels to positively modulate K_V function to promote vasodilation (1). K_V inhibitors also blunt nitric oxide (NO)-induced arterial dilation, suggesting that K_V channels, at least partially mediate NO-dependent vasorelaxant effects in some vascular beds (21, 68, 70). Conversely, molecules that activate protein kinase C (PKC) are generally associated with K_V channel inhibition and membrane potential depolarization. For example, the potent vasoactive peptide angiotensin II and elevations in extracellular glucose have been shown to induce vasoconstriction, at least in part by inhibiting K_V channels through a PKC-mediated pathway (16, 65, 71). Therefore, changes in the expression of one or more K_V subunits or signaling pathways regulating K_V function may impact vascular smooth muscle excitability and (micro)vascular function during physiological and pathological conditions. K_V channel remodeling could represent an underlying mechanism for microvascular dysfunction affecting vascular tone and blood flow leading to organ damage. In support of this, studies using animal models have shown that modifications in K_V channel expression and/or function can contribute to changes in vascular smooth muscle contractility during different pathological conditions such as hypertension and metabolic disorders, including diabetes. Here, we review our current knowledge related to the changes in K_V expression and function in vascular smooth muscle cells associated with hypertension and metabolic disorders, and its repercussions on (micro)vascular function. The role of K_V channels in pulmonary artery

hypertension and in the renal vasculature will not be addressed here, but extensive, recent reviews on the subject can be found elsewhere (26, 46, 50, 66).

Vascular voltage-gated K_V channels in hypertension

In hypertension, the function of the microcirculation is altered. Enhanced vascular tone and reduced vasodilator response have been suggested to contribute, at least in part, to impaired tissue perfusion and end-organ damage during this pathological condition (40). Changes in K_V channel expression and/or function may contribute to this outcome. A reduction in K_V channel activity during hypertension has been reported in vascular smooth muscle from rat mesenteric arteries (9, 19, 32, 79), rat thoracic aorta (17, 32) mouse aortic arteries (48), rat renal arteries (12, 45), rat pial arteries (4, 74), mouse mesenteric arteries (32, 48) and mouse pial arteries (4). These changes are independent of the animal model employed. An early study however, reported augmentation of K_V channel activity in hypertensive vascular smooth muscle (18). The difference between this study and the rest has been attributed to methodological differences associated with intracellular Ca^{2+} levels that mediate K_V channel inhibition. This was not apparent in subsequent work examining the influence of intracellular Ca^{2+} on K_V channel function in hypertensive vascular smooth muscle from the same arterial bed (9). Thus, additional research is still required to further elucidate this conundrum.

The mechanisms for changes in K_V channel activity in hypertensive vascular smooth muscle have been associated, at least in part, with altered expression in the mRNA and/or protein levels of one or more of the K_V subunits underlying the K_V current in these cells. A reduction in the expression of mRNA and/or protein levels for $K_V1.2$, $K_V1.5$ or both subunits has been found in different vascular beds from genetic animal models of hypertension (8, 74, 79). A number of other studies have reported downregulation of $K_V2.1$ subunit mRNA/protein expression with no apparent change in $K_V1.X$ levels in cerebral and mesenteric arteries from an angiotensin II-induced hypertension model and a genetic mouse model of hypertension, respectively (4, 5, 48). More recently, downregulation in the expression of $K_V7.4$ was suggested to contribute to increased vascular smooth muscle contractility in spontaneous hypertensive rats (12, 32, 35). These results suggest a key role for several K_V subunits in the regulation of K_V currents, vascular smooth muscle contraction, and vascular reactivity during hypertension. Furthermore, they underscore the importance of the methodological conditions, species, animal models of hypertension and vascular beds in the development of experimental design and interpretation of results.

Detailed mechanistic information for changes in $K_V2.1$ expression in vascular smooth muscle from pial and mesenteric arteries during angiotensin II-induced hypertension involving the activation of the Ca^{2+}-dependent calcineurin - **n**uclear **f**actor of **a**ctivated **T** cells isoform **c3** (NFATc3) signaling pathway (Figure 1) (4, 5). Accordingly, chronic activation of angiotensin II signaling mediated by targeted PKC stimulates L-type Ca^{2+} channel activity leading to enhanced Ca^{2+} influx and calcineurin activity (51, 53). Calcineurin-mediated dephosphorylation of the transcription factor NFATc3 promotes its nuclear translocation (57). Once in the nucleus, NFATc3 suppresses the expression of $K_V2.1$ mRNA and protein levels, which results in decreased voltage-dependent K^+ currents.

Decreased $K_V2.1$ function leads to membrane depolarization, further activation of L-type Ca^{2+} channels and Ca^{2+} influx (4, 57). This may create a positive feedback loop that could potentially perpetuate the pathological signal. This loop may be interrupted by inhibition of L-type Ca^{2+} channels, calcineurin or NFATc3 (4). Conversely, the molecular mechanisms underlying alterations in $K_V1.X$ and $K_V7.X$ subunit expression in vascular smooth muscle during hypertension are unclear, and will certainly need further scrutiny. Moreover, given that most studies use rodent male tissues/cells, it will be important to extend studies to samples using female tissue, and when possible, the human vasculature.

Vascular voltage-gated K_V channels in metabolic disorders

As with hypertension, changes in the function of the microcirculation are also apparent in metabolic disorders. Diet-mediated changes in plasma membrane lipid composition may impact cellular function by influencing the activity of ion channels, including K_V channels (39, 69). Initial studies suggested a reduction in K^+ channel function in rabbit portal vein smooth muscle during dietary hypercholesterolemia (20) and in the mouse aorta from a genetic mouse model of atherosclerosis (34). Subsequently, a reduction in vascular K_V channel function was confirmed in arteries and arterioles from animal models of diet-induced hypercholesterolemia, obesity and metabolic syndrome (7, 22, 28, 29, 33, 60, 77). This reduction in vascular K_V channel function resulted in impaired coronary vasodilation and blood flow during diet-induced metabolic syndrome (7, 60), aberrant adenosine-mediated dilation of porcine coronary arteries and arterioles in animal models of hypercholesterolemia (22, 29) that is not corrected with exercise (28, 77), and reduced sildenafil and sodium nitroprusside-induced penile artery relaxation in a genetic model of metabolic syndrome (33). Interestingly, K_V channel function in coronary smooth muscle varies under basal conditions, in response to diet and vasoactive molecules, and during exercise in a sex-dependent manner (27, 77).

For the most part, the mechanisms underlying aberrant K_V channel function in smooth muscle cells during diet-induced hypercholesterolemia, obesity and metabolic syndrome are unclear. No change in the mRNA expression of K_V subunits in coronary arterioles has been observed in a Yucatan swine model of hypercholesterolemia (28). Rather, it was suggested that changes in the signaling pathway by which adenylyl cyclase regulates K_V channel activity seemed to contribute to impaired adenosine-mediated vasodilation of coronary arterioles in this animal model (28). In contrast, a reduction in protein levels of $K_V1.5$ in coronary arteries was associated with decreased K_V channel function, leading to impaired coronary blood flow in an Ossabaw swine model of metabolic syndrome (7). The differences between these two studies may be accounted for by differences in the extent of metabolic abnormalities in response to diet between animal models (55). More recently, altered function of K_V7 channels, but not changes in mRNA or protein expression levels, was suggested to contribute to impaired dilation in different arterial beds in several animal models of metabolic syndrome (33, 60). These studies raise important questions about the specific mechanisms underlying altered K_V channel activity in smooth muscle that contribute to impair vasodilation during metabolic disorders, which may be the basis for future experiments. Therefore, a concerted effort should be undertaken to rigorously assess the effects of changes in vascular smooth muscle membrane lipid composition as well as

cholesterol content, as a potential mechanism impacting its fluidity and ion channel function, including that of K_V channels.

Vascular voltage-gated K_V channels in hyperglycemia

High blood glucose (e.g. hyperglycemia) is a major metabolic abnormality that contributes to vascular complications in diabetes. Changes in extracellular glucose content may have a major impact on K_V channel function and vascular reactivity. Accordingly, studies have demonstrated distinctive regulation of K_V channel function in vascular smooth muscle cells from several vascular beds in response to acute and chronic elevations in extracellular glucose concentration (31, 41-43, 58, 65, 71, 72). During acute increases in extracellular glucose, K_V channel activity is inhibited in vascular smooth muscle cells from small diameter mesenteric arteries and cerebral parenchymal arterioles (31, 65, 71). This glucose-mediated inhibition of K_V channels is concentration dependent and resulted in vascular smooth muscle E_m depolarization (31, 65), leading to enhanced vasoconstriction (31, 71) (also see Figure 2) and impaired neurovascular coupling (71). The mechanism underlying the reduction in K_V channel activity in response to acute increases in extracellular glucose did not appear to depend on changes in K_V subunit expression, but was attributed to a PKC-dependent pathway (31, 65, 71). More recently, a study revealed that differential engagement of PKCβ and PKCα isoforms may contribute to inhibition of K_V channels in a glucose concentration-dependent manner (31). However, whether glucose-mediated inhibition of K_V channel function is due to direct K_V subunit phosphorylation or activation of a different PKC-dependent pathway is unclear. Furthermore, and in contrast to the proposed PKC-mediated inhibition of K_V channels in response to elevated glucose, we recently found that PKA activity was necessary for glucose-induced vasoconstriction of cerebral parenchymal arterioles (Figure 2). These results are consistent with recent work in pial arteries (62), and suggest an unexpected role for PKA in vasoconstriction of these small resistance arteries that requires further investigation.

A reduction in the function of K_V channels in response to chronic elevations in extracellular glucose has also been reported for vascular smooth muscle from small coronary and cerebral arteries (41-43, 58, 72). Interestingly, multiple pathways have been described to account for reduced K_V channel activity in response to chronic hyperglycemia. Earlier studies correlated a reduction in K_V currents in vascular smooth muscle of small coronary arteries incubated in elevated glucose for 24 hours to glucose-mediated production of superoxide and peroxynitrite. This was associated with specific nitration of the $K_V1.2$ subunit (with no change in $K_V1.2$ or $K_V1.5$ protein expression), impairment of K_V channel function and loss of cAMP-mediated dilation of small coronary arteries (41-43). A recent study using primary coronary vascular smooth muscle cells incubated in elevated glucose for 48 hours, linked the reduction in K_V channel function to a decrease in $K_V1.2$ and $K_V1.5$ mRNA and protein levels (72). This process was mediated by advanced glycation end products (AGE) and required AGE interaction with its surface receptor RAGE (72). A reduction in $K_V2.1$ mRNA expression was observed in mouse cerebral arteries incubated in elevated glucose for 48 hours through a mechanism that requires targeting of the phosphatase calcineurin by the scaffold protein A kinase anchoring protein 150 (AKAP150) (Figure 3) (58). On the other hand, the effects of acute and chronic elevations in extracellular glucose on K_V7 function are

poorly understood and require additional studies. Nevertheless, the differences in mechanisms between the aforementioned studies (even in cells/arteries from the same vascular bed) may be due to experimental conditions and use of distinct animal models. Furthermore, these observations also raise the possibility that different mechanisms may synergize to impair K_V channel function and vascular reactivity during chronic elevations in extracellular glucose with major implications for vascular complications in diabetes.

Vascular voltage-gated K_V channels in diabetes

The function of vascular smooth muscle cells in the microcirculation during diabetes is impaired (47), and changes in K_V channel expression and/or function may contribute to this outcome. Indeed, the bulk of the published data suggest a reduction in K_V channel function in smooth muscle from different vascular beds and in several models of diabetes (10, 11, 13, 58, 72). Not surprisingly and similar to chronic hyperglycemia, multiple mechanisms have been described to account for altered K_V channel activity in vascular smooth muscle during diabetes. In a rat model of type 1 diabetes (e.g. streptozotocin-induced diabetes), a reduction in K_V channel function in vascular smooth muscle from small coronary arteries was associated with downregulation of $K_V1.2$ subunit expression and increased $K_V1.2$ nitration (but not $K_V1.5$) due to enhanced superoxide production (10, 11). This was shown to contribute to impaired cAMP-mediated dilation (10, 11, 13). Interestingly, treatment with the anti-oxidant compound Ebselen decreased $K_V1.2$ nitration, and improved $K_V1.2$ expression, K_V channel activity as well as cAMP-mediated coronary dilation, in type 1 diabetic rats (11). These results suggest a potential beneficial effect of Ebselen in treating vascular complications during diabetes.

In a high fat diet (HFD) rat model of type 2 diabetes however, aberrant K_V channel activity in coronary vascular smooth muscle and impaired small coronary artery dilation were correlated with reduced mRNA and protein levels of $K_V1.2$ and $K_V1.5$ subunits (72). In this study, altered K_V subunit expression, K_V channel function and forskolin-mediated coronary artery dilation during diabetes were ameliorated in diabetic rats treated with the AGE inhibitor aminoguanidine (72). Interestingly, aminoguanidine treatment did not improve blood pressure in diabetic rats when compared to non-diabetic rats, perhaps suggesting a distinct role for AGEs in regulation of K_V channels or any other target in different vascular beds. No changes in K_V subunit expression, K_V channel function and forskolin-mediated coronary artery dilation were observed in arteries/cells from non-diabetic rats treated with aminoguanidine. These results suggest that excessive production of AGEs may be an upstream pathological signal leading to impaired K_V channel function and coronary artery reactivity during diabetes.

Alterations in K_V channel function and impaired vascular reactivity were also described for cerebral and mesenteric arteries in a HFD mouse model of type 2 diabetes (58). In this study, selective transcriptional suppression and reduced protein levels of the $K_V2.1$ subunit (but not $K_V1.2$ and $K_V1.5$) were associated with impaired K_V currents and enhanced vascular tone during diabetes. This result is important as changes in $K_V2.1$ expression and function may have prominent effects on intracellular Ca^{2+} and E_m regulation, as revealed by mathematical simulation experiments (49, 61). The mechanisms underlying this selective suppression of

$K_V2.1$ expression and function are dependent on L-type Ca^{2+} channel activity and targeting of PKA and calcineurin by AKAP150 (Figure 3) (54, 58, 62). Accordingly, a PKA-mediated increase in Ca^{2+} influx through L-type Ca^{2+} channels activates a subpopulation of AKAP150-targeted calcineurin (54, 62). Calcineurin then dephosphorylates NFATc3 and promotes its nuclear translocation (61). Once in the nucleus, NFATc3 can downregulates $K_V2.1$ mRNA expression, leading to a reduction in $K_V2.1$ protein levels and impaired K_V channel function (58). As is the case in hypertension, blocking L-type Ca^{2+} channels, preventing the interaction between calcineurin and AKAP150 or inhibiting NFATc3 could disrupt this pervasive pathway. Taken together, all of these studies on K_V function leading to vascular complications during diabetes reveal fundamental differences and divergent mechanisms that vary between vessels and animal models. Thus, the relative contributions of all of the aforementioned pathways to altered K_V channel expression and function during diabetes should be carefully evaluated and integrated.

Conclusions

K_V channels represent major substrates underlying vascular smooth muscle excitability in small resistance arteries and arterioles. Under physiological conditions, the ability of K_V channels to respond to pressure-induced depolarization, as well as to vasoactive molecules, such as vasodilators and/or vasoconstrictors, helps maintain a delicate balance between constriction and relaxation of small resistance arteries and arterioles that is necessary for appropriate myogenic response and tissue perfusion. Not surprisingly, alterations in K_V channel function have been associated with impaired vascular reactivity in a variety of diseases affecting the vasculature. K_V channel function is impaired in hypertension and in several metabolic disorders, including diabetes. The mechanisms underlying impaired K_V channel function in different pathological conditions (i.e. hypertension vs. diabetes) are variable. This most likely reflects the activation of unique signaling pathways that distinctively impact K_V expression and/or function in vascular smooth muscle cells for a specific disease. Interestingly, different mechanisms have also been reported to account for changes in K_V expression and/or function within the same pathological condition. The differences, in this case, may be related to different experimental conditions, use of cells from different vascular beds, and /or the disease state at which the experiments were performed. Regardless of the cause, these observations indicate that a single mechanism does not account for all the remodeling in K_V function during a pathological condition and suggest that multiple pathways could synergize to alter K_V channel activity with major implications for vascular smooth muscle membrane potential and vascular reactivity, particularly in the microcirculation. Therefore, further research is required to completely appreciate mechanisms underlying alteration in K_V channel activity in disease states.

Given the diverse population of homo- and heteromeric K_V channels in vascular smooth muscle from small resistance arteries, additional approaches are necessary to tease out and integrate the specific contribution of each subunit to the regulation of membrane potential and vascular tone in health and disease. Computational approaches, as well as variations of the membrane-clamp sequential dissection technique, which have been extensively employed in the cardiac field (6, 23, 49), can be implemented to quantify the relative contribution of each K_V subunit that may interact non-linearly to regulate vascular smooth

muscle excitability and vascular reactivity. In addition, the development of optical sensors that can selectively report the activity of different K_V subunits in response to changes in membrane potential in live cells may aid in this task (73). Future studies should also address in more detail differences in K_V function between sexes and vascular beds. Improved understanding on how inflammation and oxidative stress, which are processes common to many disease states, impact K_V channel activity in native cells is also needed. The modulation of K_V channels in vascular smooth muscle by differences in lipid membrane composition and its regulatory mechanisms, which may ensue in certain pathological conditions, has to be further explored. A recent study in HEK cells revealed a complex, yet functionally relevant interaction between phosphatidylinositol 4,5-bisphosphate (PIP_2) and the G protein βγ subunit in control of $K_V7.4$ channel activity (64). Whether this interaction between PIP_2, Gβγ and K_V7 or any other K_V channel also occurs in native vascular smooth muscle to play a role during pathological conditions is not clear and should be addressed in future research. Finally, the expression, function, and regulation of K_V channels in human vascular smooth muscle from small resistance arteries and arterioles should be comprehensively examined. This may reveal novel mechanisms regulating K_V channel function in health and disease. A recent study using vascular smooth muscle from coronary arterioles of patients with coronary artery disease suggested a key role for $K_V1.5$ in vascular reactivity and revealed that altered K_V channel function in these cells was not due to changes in $K_V1.5$ expression, but to reduced surface localization of this subunit (59). Thus, a better understanding of the mechanisms underlying alterations in K_V function in human small resistance arteries and arterioles may lead to the identification of potential novel therapeutic targets to “correct” K_V dysfunction and treat (micro)vascular complications during pathological conditions.

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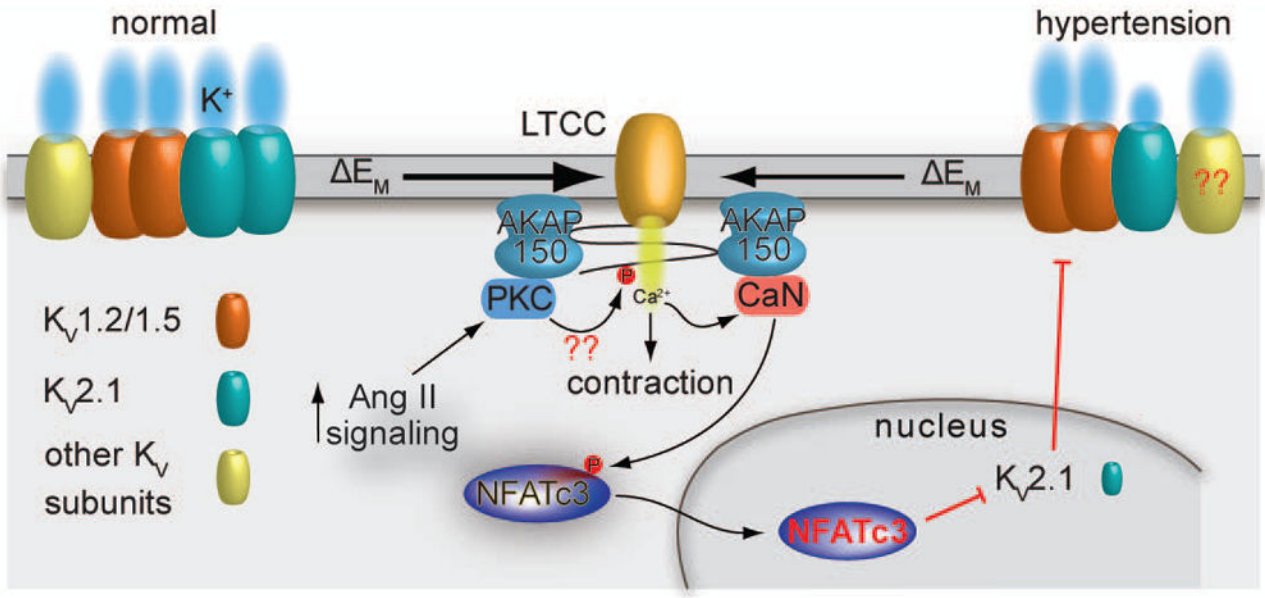

Figure 1. Proposed mechanism for suppression of K_V channel expression and function during angiotensin II-induced hypertension

Under physiological conditions, expression and function of several K_V subunits, including K_V1.X, K_V2.1 and K_V7.X, oppose pressure-induced depolarization to limit LTCC activity and vascular smooth muscle contraction. During chronic angiotensin II signaling activation, as in hypertension, activation of PKC stimulates LTCC activity, thus increasing global Ca^{2+} influx and promoting contraction. This increase in Ca^{2+} influx can also stimulate the activation of the Ca^{2+}/calmodulin-dependent, AKAP150-targeted phosphatase calcineurin. This phosphatase dephosphorylates the transcription factor NFATc3, allowing its translocation to the nucleus. Once in the nucleus, NFATc3 can regulate gene expression, including suppression of the expression of K_V2.1 (but not K_V1.2 and K_V1.5) subunits. This reduces feedback membrane potential hyperpolarization leading to increased activity of LTCC and Ca^{2+} influx, vascular smooth muscle contraction and enhanced vascular tone during angiotensin II-induced hypertension. This feedback loop may be interrupted by LTCC blockers, inhibition of calcineurin or NFATc3, or disruption of the interaction between AKAP150 and calcineurin. Whether direct phosphorylation of LTCCs by PKC, as well as alterations in K_V7.X expression in response to angiotensin II-induced hypertension occurs is unclear (indicated by ??). Illustration of the interaction between AKAP150 and LTCC does not necessarily reflect the native interaction between these proteins. The cartoon was drawn as such for simplicity.

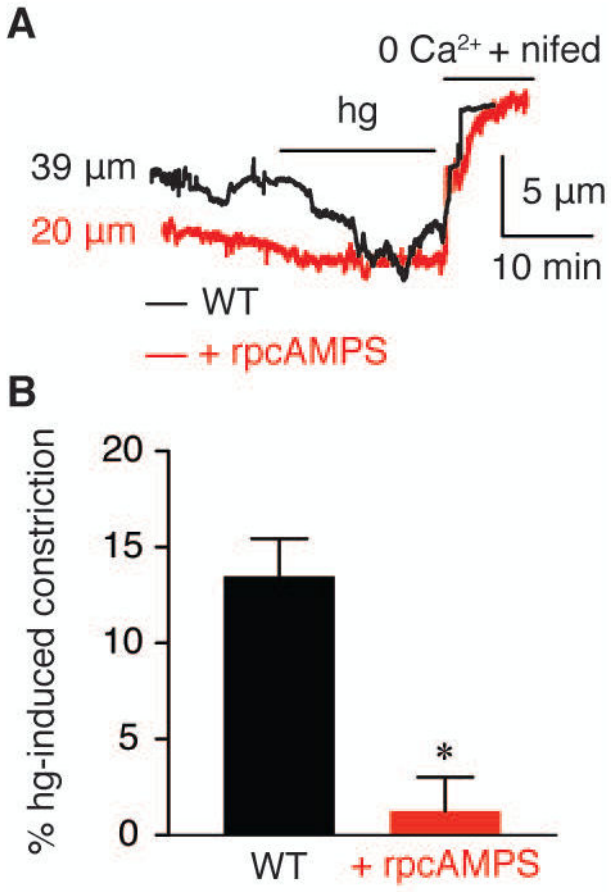

Figure 2. PKA is required for vasoconstriction of cerebral parenchymal arteries in response to elevated glucose

A) Representative diameter recordings and **B)** summary hg-induced constriction in the absence or presence of the PKA inhibitor rpcAMPs (10 µM). A solution containing 0 mM extracellular Ca^{2+} and the LTCC blocker nifedipine (1 µM) was used to obtain the passive diameter. $*P < 0.05$.

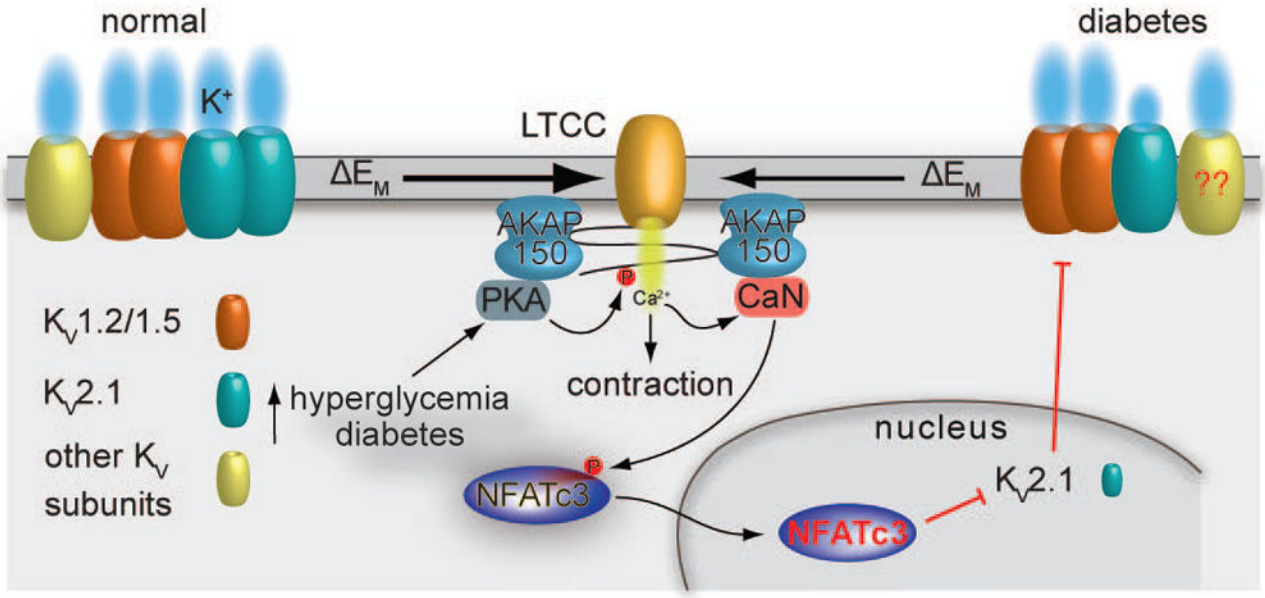

Figure 3. Model for suppression of K_V channel expression and function in diabetes

PKA-mediated phosphorylation of activation of serine 1928 induces potentiation of LTCCs in response to hyperglycemia and during diabetes (62). This leads to increased global Ca^{2+} influx and contraction. The increase in Ca^{2+} influx promotes activation of the AKAP150-targeted calcineurin, which dephosphorylates NFATc3 and allows its nuclear translocation where the transcription factor can suppress the expression of $K_V2.1$ (but not $K_V1.2$ and $K_V1.5$) subunits. This reduction in $K_V2.1$ expression and function decreases voltage-gated K^+ currents and the negative feedback membrane potential hyperpolarization, thus leading to membrane potential depolarization, further Ca^{2+} influx through LTCCs, vascular smooth muscle contraction and enhanced vascular tone. Whether changes in $K_V7.X$ subunits during diabetes proceed through the calcineurin/NFATc3 signaling pathway and similar changes occur in the human vasculature require further investigation. Illustration of the interaction between AKAP150 and LTCC does not necessarily reflect the native interaction between these proteins. The cartoon was drawn as such for simplicity.

Table 1

Expression of K_V subunits in blood vessels from different species

vascular bed	species	K_V subunits	references
cerebral arteries	mouse	1.2, 1.5, 1.6, 2.1	(15, 58)
	rabbit	1.5, 1.6	(14)
	rat	1.2, 1.5, 2.1, 7.4, 7.5, 9.3	(2, 4, 5, 80, 81)
mesenteric arteries	mouse	1.2, 1.5, 2.1, 6.3, 7.4	(48, 58, 78)
	rat	1.2, 1.5, 2.1	(18, 44, 76)
coronary arteries	mouse	1.2, 1.5, 2.1, 7.4, 7.5	(63, 78)
	rat	1.2, 1.5, 7.1, 7.4, 7.5	(30, 35)
	human	1.5	(59)