

Potassium Channels in the Uterine Vasculature: Role in Healthy and Complicated Pregnancies

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INTRODUCTION

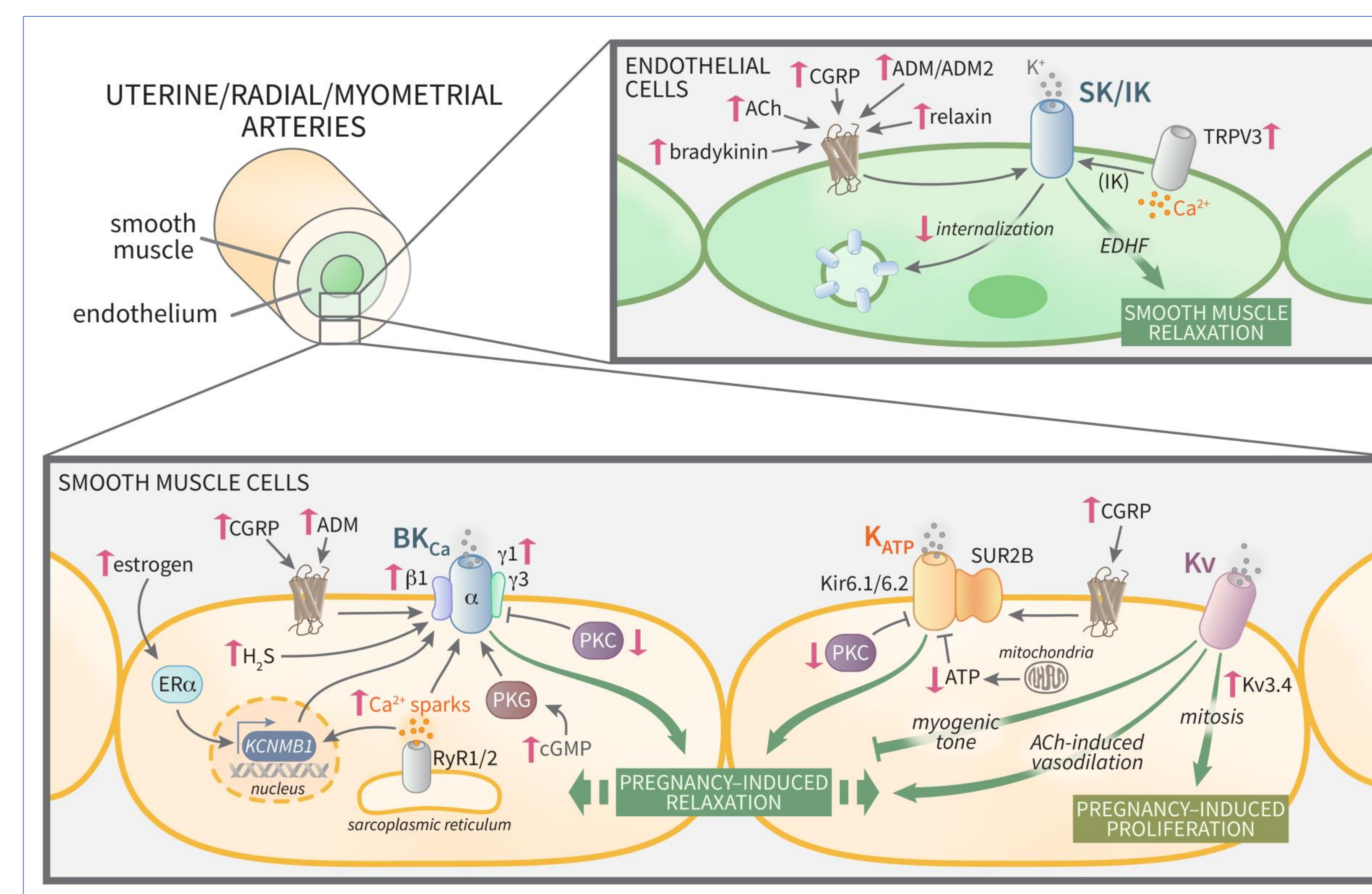
During pregnancy, the uterine vasculature must undergo a process including vasodilation and remodeling in order to progressively increase uterine artery blood flow. This is required to sustain the growth and development of a fetus. Factors affecting endothelial and vascular smooth muscle function are imperative to this process. Abnormalities in this vasodilatory and remodeling process are known to be associated with pregnancy complications including intrauterine growth restriction (IUGR) and pre-eclampsia.

Current literature suggests that potassium (K⁺) channels are important modulators in this process of uterine vascular adaptation to pregnancy in healthy pregnancies, and that impaired function of these channels is associated with pregnancy complications. K⁺ channels are ion channels that, when activated, allow passage of K⁺ down their electrochemical gradient across cell membranes, inducing hyperpolarization of the membrane. In smooth muscle cells of resistance arteries, this leads to closing of calcium (Ca²⁺) channels, thereby reducing Ca²⁺ entry into the cell and preventing cell contraction. In endothelial cells, K⁺ channels are involved in endothelium-derived hyperpolarizing factor (EDHF) responses which are independent of other known vasodilatory factors such as nitric oxide (NO) and prostaglandin (PG). Greater activation of these K⁺ channels in smooth muscle and endothelial cells appears to be a critical mechanism of the increased vasodilation necessary in the uterine vasculature during pregnancy. Multiple types of K⁺ channels have been described to participate in this vasodilatory process, including Ca²⁺-activated K⁺ channels, ATP-sensitive K⁺ channels, and voltage-dependent K⁺ channels.

OBJECTIVE

In this review article, the current literature supporting the important role of these K⁺ channels in the uterine vascular adaptation to pregnancy is discussed in the context of both healthy and complicated pregnancies. This information may be relevant for researchers aiming to elucidate complex factors underlying pregnancy-dependent changes in uterine vasculature, and also for those aiming to identify potential therapeutic targets for prevention or alleviation of pregnancy complications associated with impaired uteroplacental perfusion.

LITERATURE REVIEW



Ca²⁺-activated K⁺ channels

BKCa (large conductance) channels:

- When BKCa channels were blocked in pregnant sheep, UtA myogenic tone increased.
- In UtAs of pregnant mice, blockage of BKCa channels augmented vasoconstrictor responses.
- Chronic hypoxia is a condition in which increased UtA vascular tone has been observed with a concomitant reduction in BKCa channel activity.

SK (small conductance) and IK (intermediate conductance) channels:

- Blocking SK and IK channels in human myometrial arteries reduced the vasodilation response to bradykinin.
- Activation of IK channels resulted in increased vasodilation in pregnant rats.
- When endothelial cells were treated with serum from pre-eclamptic women, localization of these channels in the cell membrane was reduced.
- Expression of SK channels was reduced in pregnant sheep exposed to chronic hypoxia.
- IK-dependent vasodilatory responses and ion currents were reduced in endothelial cell radial arteries in diabetic pregnant rats.

ATP-sensitive K⁺ channels

- In sheep, a KATP channel activator induced UtA vasorelaxation by decreasing intracellular Ca²⁺.
- Blocking KATP channels evoked an increase in systemic and uterine vascular resistance to a greater degree in pregnant animals.
- Pregnant sheep exposed to chronic hypoxic conditions showed decreased KATP-dependent vasodilation compared to pregnant sheep under normoxic conditions.
- mRNA and protein expression of a KATP channel subunit were lower in the umbilical arteries from cases of severe pre-eclampsia compared to healthy pregnancies

Voltage-gated K⁺ channels

- Kv channel activity was reduced in smooth muscle cells of small resistance uteroplacental arteries, contributing to vasoconstriction in late pregnancy

CONCLUSIONS

Pregnancy induces major changes in maternal uterine vasculature that enable a rise in UtA blood flow to the uteroplacental circulation required to meet the demand for nutrients and oxygen for normal fetal development. K⁺ channels have been widely described as effectors for multiple vasodilators, many of which are upregulated during pregnancy. Conversely, in cases of pregnancy complications or under harmful conditions (such as hypoxic conditions), K⁺ channels in uterine vessels are downregulated and their activity is impaired. The specific localization of different K⁺ channels, their selective gestational upregulation, and their modulatory role in the vascular adaptation to pregnancy make them potential therapeutic targets. However, since complications of pregnancy are likely the result of multiple factors (maternal, fetal, placental, genetic, environmental, etc.), additional research is needed for addressing the complex factors involved to prevent or treat pregnancy complications associated with dysfunctional uterine vascular adaptation to pregnancy. We expect that this comprehensive literature review will help researchers to identify the complex nature of the vascular adaptations to pregnancy and use this review as a tool for the development of new approaches.

REFERENCES



ACKNOWLEDGEMENTS

We thank Lorna G. Moore and Heather Aldrich for critically reading and editing the manuscript.

DISCLOSURE AND FUNDING

We declare no conflicts of interest.

This work was funded by the National Institutes of Health (R03 HD101659 and R21 HD102628 to R.A.L.) and the American Heart Association (201PA35320027 to R.A.L.) grants.