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COMMENTARY

Dysfunction of large-conductance Ca^{2+}-activated K^+ channels in vascular: risks developed in fetal origins

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Over the last two decades, progress in the study of the fetal origins of hypertension or other cardiovascular diseases has demonstrated that environmental and maternal conditions during pregnancy may impact blood pressure in later life.[1–4] Recent studies have shown that altered vascular tone and function are important for the fetal origins of hypertension.[3–5] These findings indicate that vascular smooth muscle cells (VSMCs) could be the cause of the increased cardiovascular risk that develops in the prenatal period. Therefore, the roles of ion channels on these smooth muscle cells have begun to attract attention.

Large-conductance, Ca^{2+}-activated K^+ (BK) channels are abundantly expressed in VSMCs. They are activated by increased intracellular Ca^{2+} ($[Ca^{2+}]_i$) and membrane depolarization. BK channel activation leads to hyperpolarization of the cell membrane, which in turn contributes to maintaining the membrane potential and counteracting vasoconstriction.[6–8] Thus, Ca^{2+}-dependent BK channel activation has a key role in regulating vessel tone and blood pressure by providing a negative feedback for extracellular Ca^{2+} influx through voltage-gated Ca^{2+} channels. However, whether these channels are involved in altered vascular function due to altered development from prenatal insults remains unclear.

During pregnancy, environmental and maternal factors, such as malnutrition, have been shown to adversely affect vascular function in the fetus and offspring.[9,10] Therefore, investigating the influence of malnutrition, including high sugar intake, high salt consumption and low-protein diets, on the development of vascular systems and vascular function is important. In this issue, Li *et al.*[11] used a prenatal high sugar model to determine the link between ion channel function and vascular tone in the offspring, providing interesting new information on altered BK channel function due to prenatal influences.

Li *et al.*[11] made an important contribution to further clarifying the role of ion channels in smooth muscle cells in the development of hypertension following exposure to prenatal insults. Maternal high sucrose (HS) intake during pregnancy was shown to increase angiotensin (Ang) II-mediated vascular tone due to BK channel dysfunction. BK channel activity was attenuated, which could influence the role of BK channels in the negative regulation of vascular tone. Although many previous studies have described the down-regulation of BK channels in diabetes,[12–14] there are no data regarding whether HS intake during pregnancy may affect BK channels and cause an upregulation of vascular tone in the offspring. The study by Li *et al.*[11] demonstrated that the expression and function of BK channels could be depressed in the VSMCs of rats prenatally exposed to high sugar concentrations.

The work by Li *et al.*[11] demonstrated that the resting membrane potential in HS offspring depolarized more compared with the control offspring, and Ang II could further depolarize the cellular membrane by inhibiting BK channels. BK channel activity has been shown to significantly contribute to membrane potential and vascular tone.[6–8] As a result, $[Ca^{2+}]_i$- and Ang-induced vascular tone increased markedly in the HS offspring.[11] In VSMCs, calcium influx through the voltage-gated Ca^{2+} channels has a crucial role in increasing the overall $[Ca^{2+}]_i$, which can be enhanced by the depolarization linked to decreased BK current.[15] Li *et al.*[11] showed that protein expression of the BK channel α subunit in mesenteric arteries decreased in the HS offspring, contributing to impaired BK channel activity.[11] In addition, increased AT1 receptor and decreased AT2 receptor expression was responsible for the Ang II-mediated inhibition of BK current. These findings provide new information on the relationship between BK channel dysfunction and enhanced vascular tone by Ang II in the HS offspring.

In most cases of essential hypertension, increased peripheral vascular resistance is well known to account for the increase in blood pressure.[16] The increased peripheral vascular resistance in hypertension is primarily attributable to structural remodeling in small arteries and arterioles and increased vasoconstriction.[17,18] In control of vascular tone and contractile activity for VSMCs in small arteries, Ca^{2+}, as a trigger for contraction, has a key role in determining peripheral resistance and thus the regulation of blood pressure.[19] Ca^{2+} influx through voltage-gated Ca^{2+} channels in the plasma membrane and Ca^{2+} release from intracellular stores are the primary mechanisms that activate Ca^{2+}. The membrane potential is mainly affected by BK channel activity, which regulates $[Ca^{2+}]_i$ and the sensitivity of the contractile machinery to Ca^{2+}.[6–8,20] Therefore, BK channels have an important

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role in regulating vascular tone and blood pressure in both physiological and pathological conditions.

The study by Li *et al.*[11] suggested that an imprinting mechanism is involved in altering renin–Ang system and BK channels in vascular dysfunction in the adult offspring due to prenatal insults. Ang II in renin–Ang system, as one of the most important vasoconstrictors, is critical for vascular regulation via increasing $[Ca^{2+}]_i$.[21,22] Similar to other vasoconstrictors, Ang II induces vasoconstriction via AT1 receptors. A rapid increase in $[Ca^{2+}]_i$ is a major determinant of vascular contraction.[21,23] The binding of Ang II to its receptors leads to GTP-binding protein activation of phospholipases, which hydrolyze phosphatidylinositol 4,5-bisphosphate to generate diacylglycerol and inositol 1,4,5-triphosphate. 4,5-Bisphosphate to generate diacylglycerol can activate protein kinase C by phosphorylation, resulting in BK channel inhibition in VSMCs, which contributes to membrane depolarization.[24–26] Inositol 1,4,5-triphosphate, in turn, induces Ca^{2+} release from the sarcoplasmic reticulum through triphosphate receptors, which further promotes depolarization.[27] When intracellular Ca^{2+} levels are elevated by an extracellular Ca^{2+} influx through voltage-gated calcium channels due to membrane depolarization, cytoplasmic Ca^{2+} can induce further release of Ca^{2+} from the sarcoplasmic reticulum via ryanodine receptors.[19] Then, Ang II causes vasoconstriction. Considering that the fetus is sensitive to antenatal insults, such as malnutrition, cardiovascular function could be impaired in the fetal stage. Li *et al.*[11] demonstrated that Ang II significantly increased vascular tone in the HS offspring, which might be linked to altered BK channel and AT1/AT2 receptor activity and expression.

Intrauterine stress is associated with an increased risk of cardiovascular disease later in life. In this issue, Li *et al.*[11] showed that antenatal exposure to high sugar decreased whole-cell BK currents in VSMCs. This resulted in elevated intracellular Ca^{2+} and increased vascular vessel tone in adult offspring rats and led to Ang II-induced vasoconstriction and susceptibility to hypertension later in life. Their results contribute to the understanding of how blood vessels and smooth muscle cells change vascular tone in response to prenatal insults. More importantly, the link between BK channel dysfunction and the development of cardiovascular disease offers new opportunities to further investigate possible molecular targets for vascular diseases with fetal origins.

The work by Li *et al.*[11] is a pioneering study of ion channels in smooth muscle cells examining the *in utero* influence on the structural and functional development of vascular systems. The data and information that they provided are interesting and important for further understanding the mechanism underlying the increased risk of developing hypertension. Nevertheless, this investigation represents a preliminary step in determining the fundamental mechanisms of fetal-programmed adult vascular diseases, and there are still many questions that need to be addressed in future studies. For example, how are BK channel activity and protein expression affected by prenatal malnutrition, such as high sugar intake? Answering such questions may aid in the discovery of novel approaches for the early prevention of hypertension.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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