Hypertension Research (2014) 37, 796–798

www.nature.com/hr

COMMENTARY

Fetal programming by high-sucrose diet during pregnancy affects the vascular angiotensin II receptor–PKC–L-type Ca^{2+} channels ($Ca_v1.2$) axis to enhance pressor responses

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Hypertension Research (2014) **37,** 796–798; doi:10.1038/hr.2014.105; published online 19 June 2014

Hypertension is highly prevalent worldwide and is one of the major risk factors for cardiovascular and renal diseases. Pathogenesis of hypertension reportedly involves alterations in a variety of tissues and cells, and vascular smooth muscle cells (VSMCs) have important roles in the physiological control of vessel tone and pathophysiological modulation of vascular tone during the development of hypertension. In addition, the 'fetal origin of adult disease hypothesis, that is, fetal programming' identified the relationship between impaired *in utero* growth and adult cardiovascular disease risk and death.[1] Recent studies have shown that altered vascular tone and function are also important for the fetal origins of hypertension, as one possible mechanism of fetal programming in the pathogenesis of cardiovascular disease.[2–4] Since the recent genetic discoveries implicating ion channels in human cardiovascular diseases,[5] the ion channels on VSMCs could be considered to play a role in the pathophysiology of the increased cardiovascular risk that develops in the prenatal period.

Among various K^+ channels such as voltage-gated K^+ channel and inwardly rectifying K^+ channel, large-conductance Ca^{2+}-activated K^+ channels (BK) are abundantly expressed in VSMCs and involved in repolarization and negative feedback in the regulation of vessel tone. Either opening or closing of BK channels affects resting membrane potential and vascular tone remarkably.[6] They are activated by increased intracellular Ca^{2+} concentration 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] Thus, Ca^{2+}-dependent BK channel activation has a key role in regulating vascular tone and blood pressure by providing a negative feedback for extracellular Ca^{2+} influx through voltage-gated Ca^{2+} channels. Angiotensin II (Ang II) in renin–angiotensin system, as one of the most important vasoconstrictors, has critical roles in vascular regulation via increasing intracellular Ca^{2+} concentration. One of the mechanisms by which Ang II controls vasoconstriction is linked to a direct inhibition of BK channels, contributing to depolarization and contraction.[7]

Recently Li *et al.*[8] provided an important finding to reveal a pathophysiological role of the BK channel in VSMCs in the development of hypertension following exposure to prenatal insults. They showed that maternal high-sucrose intake during pregnancy increased Ang II-mediated vascular tone in small mesenteric arteries due to the reduction in BK channel activity by BK channel dysfunction, which blunted the negative regulation of vascular tone, thereby indicating that intake of high sugar during pregnancy affects vascular tone and intracellular Ca^{2+} concentration in the offspring.[8] They also showed that the altered expression of BK channels and AT1/AT2 receptors and their activities in the mesenteric arteries of the high sucrose-fed rats affected membrane potential of VSMCs, which partly contributed to the elevation of intracellular Ca^{2+} concentration and increased vascular tone induced by Ang II in the offspring of high sucrose-fed rats.

In the current issue of *Hypertension Research*, in order to further elucidate the plausible molecular mechanism of the pathogenesis of hypertension under influences exerted by maternal environment during pregnancy, Wu *et al.*[9] extended their previous study showing the involvement of dysfunctional BK channels in the increased vascular tone induced by Ang II in the offspring of high sucrose-fed rats and analyzed the effects of intake of high-sucrose diet during pregnancy on angiotensin II-mediated pressor response and micro-vessel tone via the protein kinase C (PKC)/$Ca_v1.2$ pathway. In VSMCs, increases in intravascular pressure cause a graded depolarization of the sarcolemma of VSMCs that activates $Ca_v1.2$ sparklets.[10] $Ca_v1.2$ sparklets are local elevations in intracellular Ca^{2+} concentration, resulting from the opening of a single or small cluster of voltage-gated, dihydropyridine-sensitive $Ca_v1.2$ channels. Activation of $Ca_v1.2$ sparklets is an early event in the signaling cascade that couples membrane

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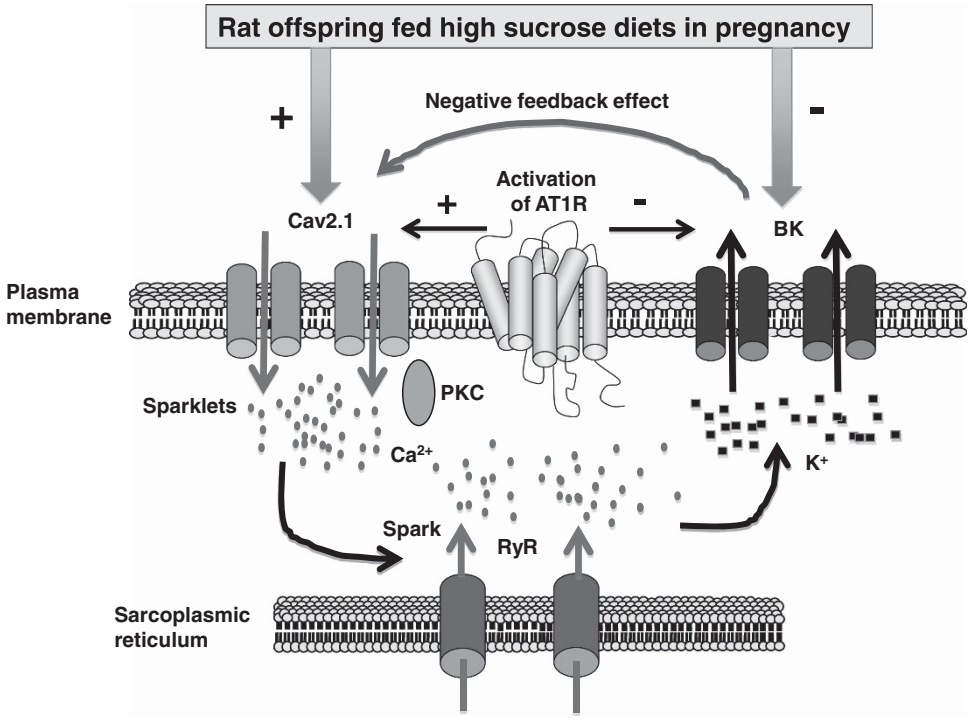

Figure 1 Proposed schema of 'fetal programming' for the increased angiotensin II (Ang II)-mediated vascular tone by the maternal high-sucrose intake during pregnancy. The activation of L-type Ca^{2+} ($Ca_v1.2$) channel activity as well as the reduction in BK channel activity would contribute to the enhancement of the Ang II-mediated pressor responses and micro-vessel tone, at least partly via protein kinase C/$Ca_v1.2$ pathway, in rat offspring fed high-sucrose diets in pregnancy. RyR, ryanodine receptor. A full color version of this figure is available at *Hypertension Research* online.

depolarization to contraction (that is, excitation–contraction coupling) in cardiac and arterial smooth muscle, and the $Ca_v1.2$ channels play a critical role in cardiac and smooth muscle excitation–contraction coupling.[11] Wu *et al.*[9] showed that high-sucrose diets in pregnancy altered Ang II-mediated pressor responses and micro-vessel tone related to PKC/$Ca_v1.2$ pathway in the offspring, which could be partially attributed to altered AT1R, PKCα and $Ca_v1.2$. On the other hand, Wu *et al.*[9] also showed that nifedipine partially reduced the Ang II-enhanced vasoconstriction in mesenteric arteries, thereby suggesting that the PKC/$Ca_v1.2$ signaling pathway may not be the only route for Ang II-increased vasoconstriction and pressor responses in the offspring of high sucrose-fed rats.[9]

The actions of the stretch-activated channels and $Ca_v1.2$ channels on VSMC membrane potential and intracellular Ca^{2+} concentration are reported to be opposed by three types of K^+ channels, including BK channels. BK currents are activated by Ca^{2+} sparks caused by the opening of a small cluster of ryanodine receptors located in the sarcoplasmic reticulum. Activation of BK channel, voltage-gated K^+ channel and inwardly rectifying K^+ channel hyperpolarizes VSMCs, which decreases $Ca_v1.2$ channel activity, Ca^{2+} influx and intracellular Ca^{2+} concentration, and thus causes relaxation. Previous studies showed that changes in the molecular composition of $Ca_v1.2$ and BK channels alter local Ca^{2+} signaling in VSMCs during the development of hypertension.[12,13] Wu *et al.*[9] showed that the activation of $Ca_v1.2$ channel activity demonstrated in this issue as well as the reduction in BK channel activity shown in the preceding study of the same laboratory contributed to the enhancement of the Ang II-mediated pressor responses and micro-vessel tone via PKC/$Ca_v1.2$ pathway in rat offspring fed high-sucrose diets in pregnancy.[8,9] Therefore, it would be important to reconcile these findings for the better understanding of the mechanisms of the Ang II-mediated pressor responses in the rat offspring fed high-sucrose diets in pregnancy. For example, what are relevant molecular mechanisms for possible relationship between changes in $Ca_v1.2$ channel activity and those in BK channel activity in their model (Figure 1)?

The K^+ channels in VSMCs is likely to be one of candidates to have a key role in the control of membrane potential and in this way, BK channels can affect the opening and closing of $Ca_v1.2$.[8] In this issue, Wu *et al.*[9] showed that the enhanced activity of $Ca_v1.2$ may be partly related to the depolarized membrane potential in the VSMCs derived from small mesenteric arteries of the rat offspring fed high-sucrose diets in pregnancy, which may be caused by decreased activity of BK channels. Serving as a key determinant in negative feedback against depolarization, the decreased activity of BK channels could contribute to the enhanced activity of $Ca_v1.2$ and increased intracellular Ca^{2+} concentration. In addition, PKC is reported to be able to activate $Ca_v1.2$ by direct phosphorylation or altering membrane potential in the way of inhibiting BK channels. Thus the decreased activity of BK channels could make $Ca_v1.2$ easier to be activated by PKC. A recent study suggests a model for the local control of Ca^{2+} influx via $Ca_v1.2$ channels, in which a signaling complex formed by the anchoring protein A-kinase anchoring protein 150 (AKAP150), PKC, PKA and calcineurin regulates the activity of individual $Ca_v1.2$ channels and also facilitates the coordinated activation of small clusters of these channels.[11] Therefore, further investigation is necessary to elucidate the changes in the molecular composition of $Ca_v1.2$ and BK channels and the relevant molecular mechanism for the alteration in vascular pressor responses and micro-vessel tone in

response to Ang II stimulation in the rat offspring fed high-sucrose diets during pregnancy.

Finally, Li *et al.*[8] and Wu *et al.*[9] of the same laboratory showed that the increased expression of vascular AT1R may be involved in the activation of $Ca_v1.2$ channel activity as well as the reduction in BK channel activity, which provoked the enhancement of the Ang II-mediated pressor responses and micro-vessel tone via PKC/$Ca_v1.2$ pathway in rat offspring fed high-sucrose diets in pregnancy (Figure 1).[8,9] Therefore, the pathological activation of vascular AT1R signaling, which could be also related to modulation of vascular activity of AT2R, angiotensin-$^{1–7}$/ACE2 and AT1R-associated inhibitory protein (ATRAP), is another candidate mechanism in the altered Ang II-mediated pressor responses and micro-vessel tone related to PKC/$Ca_v1.2$ pathway in the offspring.[14–16]

CONFLICT OF INTEREST

K Tamura received honoraria, consulting fees or funds from Novartis, Takeda, Daiichi-Sankyo, Dainippon-Sumitomo, Kyowa-hakko Kirin, Chu-gai, Shionogi, Boehringer Ingelheim, Astellas, Mochida, Pfizer, Mitsubishi Tanabe and Sanofi. The remaining authors declare no conflict of interest.

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