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Mechanism of Salt-Sensitive Hypertension in Low-Birth Weight Babies

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Summary

The Developmental Origin of Health and Disease (DOHaD) theory is the concept that post-adult lifestyle-related diseases such as hypertension, diabetes, and ischemic heart disease are affected by fetal conditions. Especially, hypertension is one of the most prominent non-communicable diseases, which relate to the DOHaD theory. There are many robust epidemiological evidences, however, underlying mechanisms are unclear.

In order to clarify the pathogenic mechanism of the DOHaD theory of cardiovascular disease, we created a low birth weight model using calorie restriction or preterm delivery. We conducted an analysis focusing on the neonatal period to see what kind of changes occur when born as low birth weight.

Microarray analysis revealed that HMG-CoA synthase 2 (Hmgcs2), which is a rate-limiting enzyme for ketone body synthesis, is decreased in the low-weight mouse model. We found that the blood ketone body concentration was always high in the neonatal period. Subsequently, in order to clarify the significance of ketogenic body synthesis in the neonatal period, Hmgcs2 knockout mice (Keto-less mice) were created using the CRIPR/Cas9 system, and the phenotype was examined. Although Keto-less mice did not show a remarkable phenotype at birth, it was revealed that fatty liver progressed more rapidly than after the start of lactation. We also found that mitochondrial dysfunction was complicated. Since a decrease in the continuous enzyme reaction in the citric acid cycle was observed, we performed the acetylation-specific proteomics analysis. Ontology analysis revealed that mitochondrial proteins were strongly acetylated.

A series of results revealed that neonatal ketone body synthesis has the effect of alleviating the accumulation of acetyl-CoA in mitochondria and avoiding excessive acetylation of mitochondrial proteins. In the future, we will verify the significance of ketone body metabolism in the process of salt-sensitive hypertension formation by making full use of this genetically modified mouse. In addition, it is known that ketone bodies are strongly expressed in the kidney, mainly in the proximal tubule, and in the future, we will create a kidney-specific ketone body synthesis deficiency mouse model and work on phenotypic analysis.