Defective Branched-chain Amino Acid Catabolism Impairs Glucose Metabolism and Sensitizes the Heart to Ischemia/Reperfusion Injury

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The branched-chain amino acids (BCAA) are essential amino acids required for protein homeostasis, energy balance, and nutrient signaling. It has been shown recently that elevations in the circulating BCAAs and related metabolites are associated with insulin resistance and ischemic heart disease, suggesting an important link between BCAA metabolism and cardiac pathology. BCAA catabolism in mitochondria is regulated by the branched-chain keto acid dehydrogenase complex (BCKDC). A mitochondria localized phosphatase 2C (PP2Cm) has been identified to activate BCKDC, serving as a key regulator of BCAA catabolism. Deletion of PP2Cm (KO) increased blood BCAA levels but did not alter cardiac function in unstressed mice. Using ^{13}C- and ^{31}P-NMR spectroscopy, we found a significant reduction in the contribution of glucose to oxidative metabolism in KO hearts (16±3 vs. 26±2% for KO and wild-type (WT), respectively, $P<0.05$), which was accompanied by an ~25% reduction in glucose uptake rate ($P<0.05$). Cardiac glycogen content was also reduced (4.4±0.5 vs. 10.9±1.8 µmol glucose/g, $P<0.05$). In isolated mitochondria from KO or WT hearts treated with BCAAs, significant reductions in pyruvate supported respiration were observed. In enzyme kinetics experiment, acute exposure to BCAAs inhibited pyruvate dehydrogenase complex (PDH) activity in a dose-dependent manner. In isolated perfused hearts subjected to ischemia/reperfusion (I/R), KO hearts showed a greater increase of diastolic pressure during ischemia ($P<0.05$), which persisted throughout the reperfusion ($P<0.05$). The contractile function in KO barely recovered while it recovered to ~40% of baseline in WT at the end of reperfusion. Increasing glucose supply via overexpression of GLUT1, an insulin-independent glucose transporter, fully restored the impaired recovery to I/R in KO mice. These results show that BCAA catabolism deficiency, as a result of PP2Cm deletion, disrupts normal glucose metabolism and renders the heart highly sensitive to acute ischemia/reperfusion (I/R) injury. These findings reveal an important role of BCAA catabolism in regulating glucose metabolism and cardiac stress response.

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