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Molecular mechanisms underlying insulin resistance in skeletal muscle during catch-up growth

Juan Zheng[1, 2], Lulu Chen[1], Xiang Hu[1, 2] and Chaodong Wu[2]
[1]Huazhong University of Science and Technology, China
[2]Texas A&M University, USA

Nutritional recovery after malnutrition produces a phase of rapid growth following a temporary period of growth retardation, which is termed as catch-up growth (CUG). The CUG phenomenon has been implicated as a predisposing factor for the development of insulin resistance (IR) and related diseases, especially in Asian populations. Our group inducted CUG in rats by 60% caloric restriction (CR) for a time period of 4 weeks and followed by normal chow re-feeding for an additional 8 weeks. Catch-up growth-induced IR was evidenced by significant reductions in both average glucose infusion rate under euglycemia clamp and skeletal muscle glucose uptake. During CR, activity of complexes I, III, and IV was decreased and activity of complex II was increased in skeletal muscle. After re-feeding, activities of complexes I to IV in the CUG group and mitochondrial citrate synthase were significantly lower than their respective activities in the NC group. In contrast, reactive oxygen species levels were significantly higher and activities of antioxidant enzymes were significantly lower in intermyofibrillar and SS mitochondria of skeletal muscle than those, respectively, in the NC group. Additionally, the activity of silent information regulator 1 (SIRT1), along with the expression of genes related to mitochondrial biogenesis (PGC-1α, NRF-1, and mtTFA), was reduced after CR, and remained low upon re-feeding. In contrast, the gene for lipid transportation, FAT/CD36, was up-regulated after re-feeding. In a parallel study, resveratrol (an activator of Sirt1) supplementation or SIRT1 overexpression was shown to increase SIRT1 activity and prevent decreases in activities of complexes I, III, and IV during CR, which were accompanied by improved mitochondrial biogenesis and insulin sensitivity in CUG rat after re-feeding. Together, these results suggest that the impaired insulin sensitivity in CUG rats was associated with decreases in subsarcolemmal and intermyofibrillar mitochondria, increases in mitochondrial redox level, and impaired activity of antioxidant enzymes and complexes I to IV in mitochondria.

Biography

Juan Zheng received her MD and PhD from Tongji Medical College, Huazhong University of Science and Technology. In December 2012, she started her postdoctoral training at University of Toronto. Currently, she is continuing her postdoctoral training at Texas A&M University. Her research is focused on nutrition and insulin resistance related metabolic diseases. She is the principal investigator on grants funded by the national natural science foundation of China (NSFC) and China international medical foundation (CIMF).

zhengjuan25@163.com