Xiao Fei, Transl Med 2014, 4:3
http://dx.doi.org/10.4172/2161-1025.S1.012

OMICS Group Conferences
Accelerating Scientific Discovery

3rd International Conference on
Translational Medicine
November 03-05, 2014 Las Vegas, USA

Mechanism for improved insulin sensitivity by branched-chain amino acids

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We have previously shown that serum insulin levels decrease three-fold whereas blood glucose levels remain normal in mice fed leucine-deficient diet, suggesting increased insulin sensitivity. The goal of the present study is to investigate this possibility and elucidate underlying mechanisms. Here we showed that leucine deprivation improves hepatic insulin sensitivity by activating General Control Non-derepressible (GCN)2 and decreasing mammalian Target of Rapamycin (mTOR)/ ribosomal protein S6 kinase 1 (S6K1) signaling. Activation of AMP-activated protein kinase (AMPK) also contributes to this phenomenon. In addition, we showed that leucine deprivation improves insulin sensitivity under insulin-resistant conditions. This study describes mechanisms underlying increased hepatic insulin sensitivity under leucine deprivation and demonstrates a novel function for GCN2 in the regulation of insulin sensitivity. Besides, we found that valine or isoleucine deprivation for 7 days produces similar effects as leucine on insulin sensitivity regulated in a similar manner. Different from leucine, valine or isoleucine deprivation for 7 days significantly decreases fed blood glucose levels, possibly by decreasing expression of a key gluconeogenesis gene glucose-6-phosphatase. We also found that insulin sensitivity is rapidly improved in mice following maintenance on a diet deficient for any individual BCAAs for 1 day. Our results showed that the effect of leucine deprivation represents a general effect of BCAAs on regulation of insulin sensitivity, but not glucose levels, suggesting that each individual BCAA has unique feature in metabolic regulation. These observations also provide a rationale for short-term dietary deprivation or restriction of BCAAs for the treatment of insulin resistance and associated metabolic diseases.

Biography

Xiao Fei has completed her PhD and Postdoctoral studies from Institute for Nutritional Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences. Her research interest is to understand the cellular and molecular mechanisms underlying genetic and nutritional regulation of metabolic diseases including obesity, diabetes, and fatty liver. She has published several papers in *Diabetes, Diabetologia and Metabolism* as first author.

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