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Insulin action in the brain regulates branched-chain amino acid (BCAA) metabolism

Andrew C Shin
Icahn School of Medicine at Mount Sinai, USA

Circulating Branched-Chain Amino Acid (BCAA) levels are elevated in obese and diabetic individuals, and are the earliest and most predictive marker for risk of diabetes. Furthermore, supplementation of amino acids or BCAAs has been shown to induce insulin resistance in rodents and humans, implicating BCAAs in the pathogenesis of diabetes. Thus, identifying the regulatory mechanisms of BCAAs is critical for understanding their rise seen in obese and/or diabetes. We have shown that insulin dose-dependently lowers plasma BCAAs while glucose per dose does not seem to have an important regulator of BCAA metabolism. Insulin induced the hepatic expression and activity of Branched-Chain α Keto-Acid Dehydrogenase (BCKDH), the rate-limiting enzyme in BCAA degradation pathway. The selective induction of hypothalamic insulin signaling in rats as well as inducible and lifelong genetic modulation of brain insulin receptors in mice demonstrated that brain insulin signaling is a major regulator of BCAA metabolism by inducing hepatic BCKDH. Further, short-term overfeeding impaired the ability of brain insulin to lower circulating BCAA levels in rats. Chronic high-fat feeding in non-human primates and obesity and/or diabetes in humans was associated with reduced hepatic BCKDH protein expression. Lastly, *C. elegans* that lack insulin receptor homologue (Daf-2) in neurons showed increased BCAAs. These findings demonstrate that neuroendocrine pathways control BCAA homeostasis and these are evolutionarily conserved from worms to mammals. The findings also suggest that hypothalamic insulin resistance may account for impaired BCAA metabolism in obesity and diabetes, and that plasma BCAAs may be a marker for hypothalamic insulin action.

Biography

Andrew C Shin received PhD in Neuroscience at Michigan State University. Thereafter, he worked as a Post-doctoral fellow at Pennington Biomedical Research Center and at Icahn School of Medicine at Mount Sinai. He was promoted to a junior faculty at Mount Sinai. His main interest is in studying how brain controls acute nutrient metabolism as well as long-term energy homeostasis using genetic, molecular, surgical, and integrative physiological approaches. He has published more than 25 papers in peer-reviewed journals like *Cell Metabolism, Endocrinology, Neuroscience, and International Journal of Obesity.*

andrew.shin@mssm.edu

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