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Editorial

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Are BCAAs Mere Biomarkers of Diabetes?

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Branched-chain amino acids (BCAAs; ie. leucine, isoleucine, and valine) are essential amino acids we need to ingest through our diet.While circulating BCAA levels were first found to be elevated in obese individuals back in 1969 by Felig and colleagues,[1] the potential role of BCAAs in obesity and diabetes development has been re-highlighted in the last decade. Using advanced metabolomic platforms, many independent investigators were able to reproduce the earlier finding and further demonstrate that not only plasma BCAAs, but also their partially oxidized intermediates such as α-keto acids and short-chain (C3-C5) acylcarnitines are increased in obese or insulin resistant/diabetic individuals, including Caucasians and Asians.[2-9] Moreover, plasma BCAAs are found to be the earliest and the most predictive marker for future risk of diabetes,[10] and elevated plasma leucine levels precede the development of fatty liver,[11] suggesting that circulating leucine is a predictive marker of hepatic steatosis. Interestingly, plasma BCAAs and their derived short-chain acylcarnitines are effectively lowered by bariatric surgery in obese and/or diabetic individuals.[5,8,12,13] Whether this normalized BCAA metabolism after RYGB surgery in morbidly obese patients contributes to improved insulin sensitivity and glycemic control or is just a secondary effect of the surgery needs to be examined further. Nonetheless, collectively these studies implicate a role of plasma BCAAs and their metabolites in the pathogenesis of insulin resistance and diabetes.

The unresolved question in the field today is whether or not they are mere biomarkers or they are one of the potential culprits for derangement of glucose metabolism and development of obesity and insulin resistance/diabetes. While a number of studies demonstrate that either amino acid mixture or BCAA supplementation have beneficial effects on protein turnover and muscle wasting in patients with cirrhosis, kidney failure, cancer, or sepsis,[14-25] mounting evidence suggests that amino acids/BCAAs or their metabolized keto acids lead to hyperactivation of mTOR signaling,[7,26-28] induction of oxidative stress,[29-32] mitochondrial dysfunction,[33,34] apoptosis,[35,36] and more importantly, insulin resistance and/or impaired glucose metabolism.[7,26-28,37-44] Consistent with these findings, recent studies demonstrate that a BCAA metabolite elevated in diabetic individuals can drive vascular fatty acid transport in muscle and induce insulin resistance in mice[44] and a defective muscle BCAA metabolism induces impaired lipid metabolism and insulin resistance.[45] On the other hand, deprivation of a single or all three BCAAs improves insulin sensitivity and glycemic control in either chow- or High-Fat Diet (HFD)-fed, or genetically diabetic rodents.[46-48] These findings strongly indicate not only a correlative, but also a causative role of circulating BCAAs and their oxidized intermediates in the development of insulin resistance and diabetes. As such, it is important to advance our understanding of BCAA regulatory mechanisms that would allow us to explain the reasons for high circulating levels of BCAAs found in obese and diabetic individuals.

The rise of plasma BCAAs in the obese and/or diabetic individuals may be simply because they take in more BCAAs due to their increased food consumption in general. But BCAAs levels are still higher in these individuals even after overnight fasting, or even when they match the amount of protein intake with lean individuals.[9,10] Alternatively, the higher plasma BCAAs may be attributed to an increased release of endogenous BCAAs through protein breakdown or decreased BCAAs utilization in tissues due to decreased protein synthesis in these individuals, but both whole-body proteolysis and protein synthesis are not different between diabetic and normal individuals, as they have been extensively reviewed by Tessari and colleagues.[49] Rather, the increased circulating BCAAs and their intermediates may be because

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of decreased or impaired BCAAs degradation in tissues like liver, muscle, and adipose tissue. This concept of impaired BCAAs metabolism in obesity and diabetes is supported by findings demonstrating decreased gene expressions of BCAA- degrading enzymes in subcutaneous and omental fat tissues in obese twins compared to their lean monozygotic co-twins,[50] decreased protein or activity of branched-chain α-keto acid dehydrogenase (BCKDH), the rate-limiting enzyme in BCAA degradation pathway, in livers of obese *ob/ob* mice and diabetic *fa/fa* rats,[8] in HFD fed rats and diet-induced obese men and monkeys,[51] as well as in obese Pima Indians.[52] The reasons for dysregulated BCAA metabolism in obese and diabetics are unclear. Systemic insulin lowers circulating BCAAs in normal healthy subjects but less so in obese and diabetic individuals, indicating insulin resistance as a major cause for the elevated BCAA in obesity and diabetes.[53-56] We have recently revealed for the first time the role of insulin in the regulation of BCAA metabolism by demonstrating that insulin dose-dependently lowers plasma BCAAs independent of glycemia *via* induction of hepatic BCAA catabolism.[51] We further showed that this control of BCAA metabolism is mediated primarily through insulin action in the brain, and that impaired BCAA metabolism and the resultant higher plasma BCAA levels ensue in a state of central insulin resistance.[51]

Future studies examining the underlying mechanisms of BCAA-induced impairment of glucose or lipid partitioning, and the role of this novel neuroendocrine control of BCAA metabolism in either glucose or lipid homeostasis would give us new mechanistic insights into development of insulin resistance and diabetes and offer interventional or preventive therapeutic strategies to fight them.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

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