CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Taking a BAT to the Chains of Diabetes

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Diabetes is widely understood to be a disease associated with sugars and fats. But extensive epidemiologic data going back 50 years have also shown that plasma levels of the branched-chain amino acids (BCAAs; leucine, valine, and isoleucine) are consistently elevated in patients with insulin resistance and diabetes.[1] Numerous additional studies based on human genetics, metabolomics, and animal models have strongly supported the notion that these elevations actively contribute to the development of insulin resistance. In animal models of diabetes, for example, pharmacologic lowering of BCAA levels is sufficient to improve insulin sensitivity.[2] These observations have led to a new theory that BCAAs synergize with excess fat and carbohydrates to trigger insulin resistance. What causes elevations in BCAA levels? And does BCAA metabolism present therapeutic opportunities? A recent study of BCAA catabolism in brown adipose tissue (BAT) reported by Yoneshiro et al.[3] provides some answers.

BAT is specialized fat tissue dedicated to thermogenesis, in contrast to white adipose tissue, which serves largely to store calories.[4] Until recently, BAT in humans was thought to be present only in newborns, but studies that used positron-emission tomography have shown the variable presence of BAT in adults. In response to exposure to cold, BAT activates "futile" cycles of energy consumption, wasting calories and releasing heat. This capacity to waste calories has made BAT an attractive therapeutic target for treatment of obesity. To better understand the metabolic consequences of BAT activation, Yoneshiro et al. quantified the effects of exposure to cold on the plasma metabolites of persons who had either high or low BAT activity. The investigators found that cold exposure significantly lowered levels of BCAAs in plasma, but only in persons who had high levels of BAT activity, which suggests that cold exposure activates catabolism of BCAA in BAT and that BAT can be a primary site of BCAA breakdown. The authors then showed that mice engineered to lack (specifically in BAT) a key enzyme required for BCAA catabolism could not clear the bolus of plasma BCAAs that followed a large ingestion of BCAAs. Moreover, BAT in the mutant mice failed to efficiently activate thermogenesis in response to cold. These data thus unveiled a striking and previously unknown dependence of BAT thermogenesis on BCAA catabolism, as well as a reciprocal dependence of BCAA homeostasis on BAT.

Most important, the authors then showed that mild obesity, glucose intolerance, and insulin resistance developed in mice that lacked the capacity for BCAA catabolism in BAT. BCAA combustion in BAT thus not only drives thermogenesis but is also an effector in systemic glycemic homeostasis. This study does not address whether the glycemic benefits of BCAA combustion in BAT stem from reduction in blood BCAA levels or from the thermogenesis itself, but the data nevertheless point to enzymes of BCAA combustion in BAT as new potential targets for the treatment of insulin resistance. In addition, the authors determined that the mitrochondrial carrier protein SLC25A44 is the transporter that shuttles BCAAs from the cytoplasm into the mitochondrial matrix, where all enzymatic steps of BCAA breakdown occur, and they showed that genetic depletion of SLC25A44 in BAT in mice leads to loss of control of BCAA homeostasis and of thermogenesis in response to cold exposure.

The study by Yoneshiro and colleagues does not address the mechanism by which BCAAs cause insulin resistance. But the study points squarely to BAT as an important site of control of BCAA catabolism and therefore of insulin resistance, at

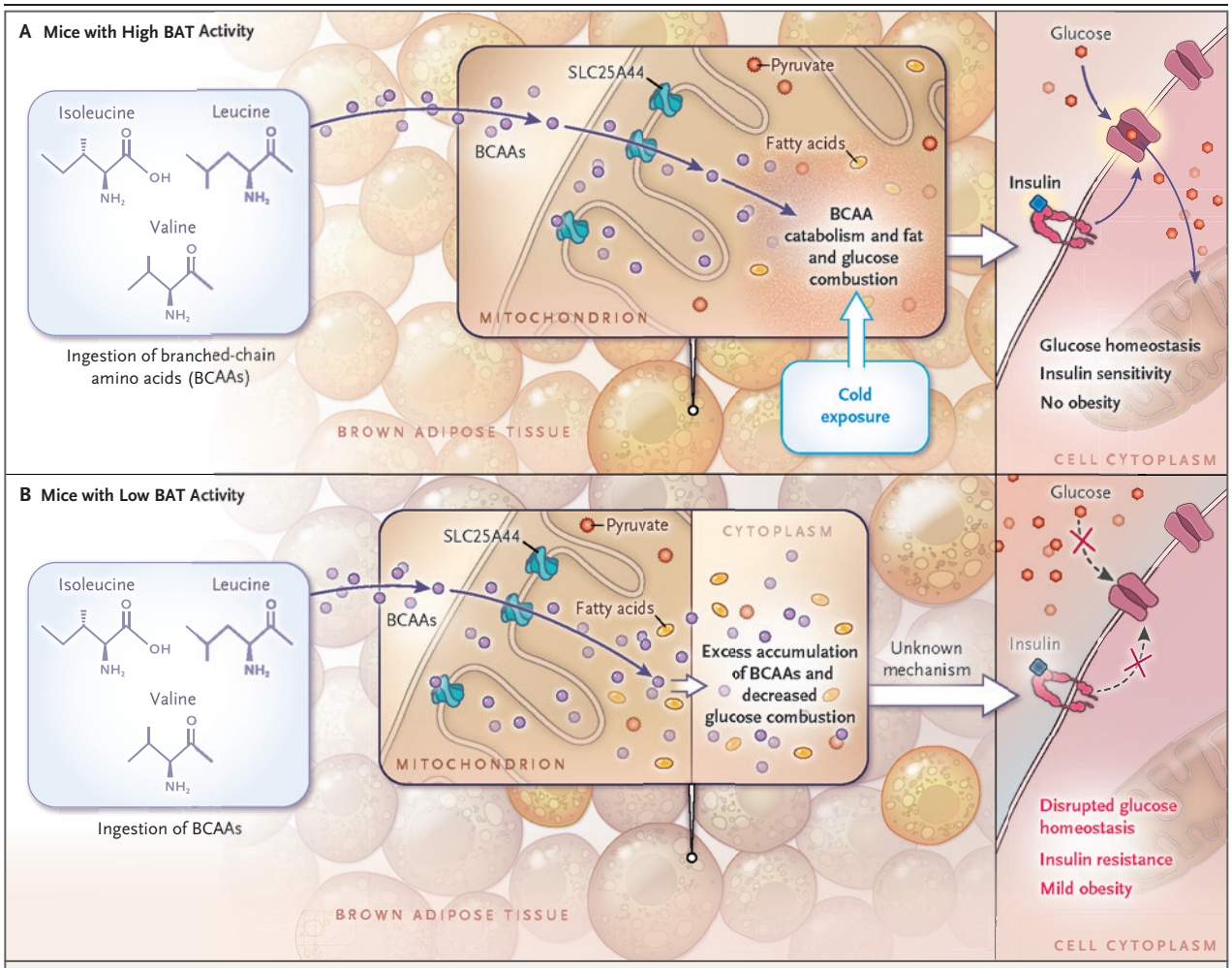

Figure 1. BAT and BCAAs.

The effects of ingestion of branched-chain amino acids (BCAAs) are balanced by BCAA catabolism in numerous organs. Yoneshiro et al. recently reported that brown adipose tissue (BAT) contributes to this catabolism, and they identified SLC25A44 as the key transporter of BCAAs into mitochondria, the site of catabolism. Mice with high BAT activity (Panel A) have a greater capacity to catabolize BCAAs than do mice with low BAT activity, potentially leading to higher levels of plasma BCAA levels in the latter population (Panel B). Elevations in BCAAs are thought to contribute to insulin resistance in diabetes through mechanisms that are as yet unknown. Activation of BCAA catabolism in BAT may therefore provide a new approach to treating insulin resistance in humans.

least in animal models (Fig. 1). The findings also suggest that lower levels of functional BAT in persons with metabolic syndrome may in part explain the observed elevations in plasma BCAAs in those patients. Indeed, some epidemiologic studies have correlated BAT activity with improved insulin sensitivity independent of body weight[4,5]; BAT-mediated clearance of plasma BCAAs may in part explain these observations.

Tantalizingly, the study by Yoneshiro et al. suggests that activation of BAT thermogenesis, with the use of pharmaceutical agents or otherwise, could represent a new approach to treating insulin resistance by activating BCAA catabolism and therefore lowering systemic BCAA levels. BAT has already received much attention as a potential target for the treatment of obesity, although some have questioned whether humans have enough BAT to achieve the levels of calorie wasting necessary to affect whole-body weight.[5] The study by Yoneshiro et al. suggests that activating BAT could provide an alternative benefit (independent of calorie wasting): the lowering of circulating BCAAs. In the best-case scenario, activating BCAA combus-

tion in BAT could provide two benefits — treating both obesity and insulin resistance — for the price of one.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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