The Effect of Amino Acid Metabolites on Insulin Stimulated Glucose Transport in Muscle Cells

is Modulated by Inflammatory Factors

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Branched-chain amino acids (BCAAs) have displayed metabolic benefits, playing a role in muscle protein synthesis. However, elevated levels of BCAAs and their metabolites have been linked to the pathogenesis of insulin resistance. It has been demonstrated in our lab that α-ketoisocaproic acid (KIC), a metabolite of leucine, inhibits insulin-stimulated glucose uptake at 200 μM by 45%, but only if branched-chain aminotransferase 2, the enzyme that catalyzes the reversible conversion of leucine to KIC, was present. Inflammation is a big component of insulin resistance, so the effect of KIC on insulin resistance may be modified by an inflammatory environment. Thus, we aim to analyze whether or not KIC’s role in insulin stimulated glucose transport in L6 myotubes will change if co-incubated with homocysteine, a pro-inflammatory factor. KIC suppressed insulin stimulated glucose uptake by 25%. With co-incubation with homocysteine, there was a further 7% and 34% suppression of insulin stimulated glucose transport at [50] and [500] μM of homocysteine respectively. KIC suppressed S6K1 and S6 phosphorylation by 43% and 64% respectively, this was worsened by co-incubation with homocysteine, especially at 15 μM. Because the effect of homocysteine was rather modest, we attempted to produce a more robust inflammatory response by co-incubating the myotubes with additional pro-inflammatory factors. KIC with 10ng/ml of tumor necrosis factor-α, 50 μM of homocysteine, and 10ng/ml of interleukin-6, resulted in a further decrease of 43% in insulin stimulated glucose uptake compared to just KIC. These data suggest that the effect of amino acids and their metabolites on insulin action in skeletal muscle are modulated by an
inflammatory environment seen in obesity and insulin resistant states. Ultimately, interventions that can affect BCAA metabolism can have implications on the management of insulin resistance seen in type 2 diabetes and cardiovascular diseases.