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Branched-chain Amino Acid and Tryptophan Metabolism and the Pathogenesis of Youth-Onset Type 2 Diabetes Mellitus (T2D)

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Objectives: We have previously demonstrated that insulin resistance (IR) in youth is associated with elevated levels of branched-chain amino acids (BCAAs). BCAAs compete with aromatic amino acids (AAA) including tryptophan, the precursor of serotonin, for uptake into β-cells and other tissues via the large neutral amino acid transporter. Serotonin has been reported to increase β-cell mass and glucose-dependent insulin secretion. In this study we have explored how BCAA, tryptophan (one of the AAA), and a subset of their metabolites are modulated in youth-onset T2D. Based on our prior studies in neuronal BCAA metabolism, we hypothesized that elevated BCAA could induce diversion of tryptophan metabolism towards production of kynurenine rather than serotonin in youth with T2D. To test this, we analyzed 24-hour urine samples and compared levels of byproducts of BCAAs and tryptophan metabolism in obese youth with T2D with those in non-diabetic obese and lean youth of comparable age, pubertal status and ethnicity.

Methods: 56 non-diabetic adolescents with overweight/obesity ("obese"), 42 adolescents with T2D ("T2D"), and 43 normal weight controls ("lean"), ages 12-21 years-old were studied. Weight, height, BMI, BMI% were extracted from medical charts. Body fat percent (BF%) was measured by TANITA. We also measured metabolites derived from BCAA catabolism, including the branched-chain ketoacids (BCKAs), and tryptophan metabolism, including intermediates of the serotonergic and kynurenine pathways, in spot and 24-hour urine samples by liquid chromatography/tandem-mass spectrometry (LC/MS-MS). Levels were normalized to urine creatinine. Group differences were assessed by Kruskal Wallis or ANOVA.

Results: Groups were comparable for age (obese 14.8 +/- 1.9; T2D 15.7 +/- 2.1 and lean 14.9 +/- 1.9-yr), pubertal status, and ethnicity. Youth with T2D were predominantly female (T2D, 28 F, 14 M; obese 33 F, 23 M and lean, 17 F, 26 M), and had highest BF% (obese 37.3 +/- 9.5; T2D 42.9 +/- 9.9; lean 20.1 +/- 6.3%; p=2.58e-22). In 24-hour urine samples, BCKAs, tryptophan, and kynurenine levels were higher in T2D (p=0.0002, p= 0.0045 and p= 0.00009 respectively) than in either lean controls or non-diabetic youth with obesity; in contrast, there were no differences between lean controls and non-diabetic youth with obesity. The levels of 5-HIAA, the principal metabolite of serotonin, were comparable across groups; however, the ratio of kynurenine/tryptophan was higher (p= 0.0112) in youth with T2D and the ratios of 5-HIAA/ tryptophan (p=0.027) and 5-HIAA/Kynurenine (p=0.0067) were lower compared to the other two groups. Those ratios were comparable between lean controls and non-diabetic youth with obesity.

Conclusions: Increased BCKAs are accompanied by diversion of tryptophan metabolism from the serotonin pathway to the kynurenine pathway, suggesting perturbations in both BCAA and AAA metabolism in youth-onset T2D. These alterations could contribute to development of beta-cell dysfunction and progression to T2D in youth.

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