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2-Aminoadipic acid is a novel biomarker of diabetes risk and modulates glucose homeostasis

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Improvements in metabolite profiling techniques provide increased breadth of coverage of the human metabolome and may highlight novel biomarkers and pathways in common diseases such as diabetes.

We developed an LC-MS method capable of profiling 70 small molecules preferentially ionized in negative ESI mode. We conducted a nested case-control study of 188 individuals who developed diabetes and 188 propensity-matched controls from 2,422 normoglycemic participants followed for 12 years in the Framingham Heart Study (FHS). Replication analyses were performed in the Malmö Diet and Cancer Study (MDC). Analyses were conducted using multivariable conditional logistic regression relating baseline metabolite values with future diabetes risk.

The metabolite most strongly associated with the risk of developing diabetes was 2-aminoadipic acid (2-AAA) (p=0.0009). Individuals with 2-AAA concentrations in the top quartile had > four-fold risk of developing diabetes. These findings were replicated in the MDC Study (p=0.004). Levels of 2-AAA were not well correlated with other metabolite biomarkers of diabetes, suggesting they report on a distinct pathophysiological pathway. In animal studies, administration of 2-AAA lowered fasting plasma glucose levels in mice fed both standard chow and high fat diets. Further, 2-AAA treatment enhanced insulin secretion in both pancreatic beta cell line as well as murine and human islets.

These data highlight a metabolite not previously associated with diabetes risk that is increased up to 12 years before the onset of overt disease. Our findings suggest that 2-AAA is a novel marker of diabetes risk and a potential modulator of glucose homeostasis in humans.

Biography

Nikolaos -Psychogios has a BA in Physics, an MS in Medical Physics and a Ph.D. in Clinical Chemistry. His master and doctorate studies were focused on NMR metabolomics and he carried out his postdoctoral research at the University of Alberta and the Massachusetts General Hospital, respectively. Using mainly LC/MS-based metabolomics he aimed at identifying novel biomarkers and pathways in translational studies of well-phenotyped human cohorts by testing various functional hypotheses in experimental animals. He is currently leading the metabolomic analytical platform at Shire supporting cell line and media engineering efforts as well as cell culture process development.

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