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Metabolomic analysis of rat serum in streptozotocin-induced diabetes and after treatment with oral triethylenetetramine (TETA)

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Abstract

Background: The prevalence, and associated healthcare burden, of diabetes mellitus is increasing worldwide. Mortality and morbidity are associated with diabetic complications in multiple organs and tissues, including the eye, kidney and cardiovascular system, and new therapeutics to treat these complications are required urgently. Triethylenetetramine (TETA) is one such experimental therapeutic that acts to chelate excess copper (II) in diabetic tissues and reduce oxidative stress and cellular damage.

Methods: Here we have performed two independent metabolomic studies of serum to assess the suitability of the streptozotocin (STZ)-induced rat model for studying diabetes and to define metabolite-related changes associated with TETA treatment. Ultraperformance liquid chromatography-mass spectrometry studies of serum from non-diabetic/untreated, non-diabetic/TETA-treated, STZ-induced diabetic/untreated and STZ-induced diabetic/TETA-treated rats were performed followed by univariate and multivariate analysis of data.

Results: Multiple metabolic changes related to STZ-induced diabetes, some of which have been reported previously in other animal and human studies, were observed, including changes in amino acid, fatty acid, glycerophospholipid and bile acid metabolism. Correlation analysis suggested that treatment with TETA led to a reversal of diabetes-associated changes in bile acid, fatty acid, steroid, sphingolipid and glycerophospholipid metabolism and proteolysis.

Conclusions: Metabolomic studies have shown that the STZ-induced rat model of diabetes is an appropriate model system to undertake research into diabetes and potential therapies as several metabolic changes observed in humans and other animal models were also observed in this study. Metabolomics has also identified several biological processes and metabolic pathways implicated in diabetic complications and reversed following treatment with the experimental therapeutic TETA.

Background

Diabetes mellitus (DM) is a chronic debilitating condition that is rapidly increasing in prevalence worldwide, as a consequence of increases in obesity, changing patterns of diet and physical activity, and ageing populations. The World Health Organization estimated that 154 million people in the world had DM at the beginning of the 21st century [1]. In the USA the prevalence is estimated to increase from 4.0 to 7.2% (or 29 million) between 2000 and 2050 [2].

DM is a metabolic disorder characterized by hyperglycemia. The hyperglycemia is caused as a consequence of a deficiency in insulin in type 1 diabetes (T1D), and is a feature of late type 2 diabetes (T2D) along with insulin resistance. T2D is significantly more prevalent than T1D. Molecular pathophysiological mechanisms that precede hyperglycemia, or are observed with the clinical symptoms of DM, include, among others, alterations in lipid and amino acid metabolism [3-5], changes in

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