Lipotoxicity alters the genome-wide epigenetic pattern in human pancreatic islets
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Background and aims: Circulating levels of free fatty acids are often increased in subjects with type 2 diabetes (T2D). Long-term exposure to lipids has harmful effects on islet function and insulin secretion. Epigenetic modifications such as DNA methylation may contribute to T2D. However, there is limited information on whether fatty acids alter the epigenetic pattern in human pancreatic islets. Our aim was therefore to analyse the genome-wide DNA methylation pattern in human pancreatic islets exposed to palmitate for 48 hours and relate methylation to gene expression and insulin secretion in the islets.

Materials and methods: mRNA expression and DNA methylation were analysed genome-wide in human islets using microarrays.

Results: Palmitate treatment for 48 hours decreased glucose-stimulated insulin secretion but did not affect apoptosis in the human islets. We found 1860 genes with differential expression in palmitate-treated human islets. These include candidate genes for T2D such as GLIS3, HNF1B and SLC30A8. Additionally, palmitate altered the expression of genes in glycolysis/gluconeogenesis, pyruvate metabolism, fatty acid metabolism, glutathione metabolism in human islets. The global DNA methylation level and DNA methylation levels of CpG island shelves and shores, 5'UTR, 3'UTR and gene body regions were altered in human islets exposed to palmitate. Moreover, 290 genes with differential expression had a corresponding change in DNA methylation e.g. several candidate genes for T2D. Importantly, 67 of these genes were also associated with BMI and 37 were differentially expressed in islets from T2D patients.

Conclusion: We demonstrate that lipotoxicity gives rise to epigenetic modifications as well as transcriptional changes in human pancreatic islets. These changes may contribute to impaired insulin secretion and T2D.

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