ABSTRACT

Type 2 diabetes mellitus (T2DM) is a global health challenge associated with impaired insulin signaling and its prevalence varies among the major ethnicities of Trinidad and Tobago. The biochemical underpinnings of T2DM have not been fully elucidated but mechanisms of genetic and epigenetic inheritance could partially account for this observation; this thesis sought to investigate some of these mechanisms. Cord blood DNA genotyping revealed that the frequencies of T2DM risk variants, PPARG rs1801282 (allele C, genotype CC) and FTO rs9939609 (allele A, genotype AA), were greatest, intermediate and lowest for Trinidadian neonates of African, mixed and South Asian ethnicity, respectively. However, neither risk alleles nor genotypes were significantly associated with neonatal anthropometric indices of obesity ($p > 0.05$). Feeding Sprague Dawley rats a gestational high-fat, high-sucrose (HFS) diet exposed their male offspring to significant weight gain and hyperglycaemia compared with controls ($p < 0.05$); folic acid-supplementation of HFS (HFS/F) significantly ameliorated these effects ($p < 0.05$). HFS/F offspring showed significantly greater hyperinsulinemia compared with control offspring ($p < 0.05$). Several genes were differentially expressed in HFS and HFS/F offspring as compared to controls, with implications for altered long-chain fatty acid synthesis via hepatic Acaca and Fasn downregulation and impaired insulin signaling through skeletal muscle Akt2, Raf1 and Slc2a4 downregulation. HFS/F rat dams had hypomethylated Irs1 and Lpl genes ($p < 0.05$), but offspring DNA methylation was not altered by HFS

or HFS/F. DNA methylation patterns varied between human umbilical vein endothelial cells from Trinidadian neonates of South Asian (SA-HUVEC) and African (AF-HUVEC) ethnicity following incubation with glucose concentrations akin to pre-diabetes and diabetes. For the majority of insulin signaling genes, 4, 8 and 12 mM glucose elicited the lowest, intermediate and highest DNA methylation percentages in AF-HUVEC, respectively. In contrast, 4 or 12 mM glucose induced the lowest and 8 mM glucose the highest DNA methylation percentages in SA-HUVEC. It is concluded that DNA methylation, gene and protein expression changes, modulated by maternal over-nutrition and folic-acid supplementation, can influence the insulin signaling pathway.

Keywords: type 2 diabetes, insulin signaling, foetal programming, gestational diets, Western diets