UNIVERSITI TEKNOLOGI MARA

THE EFFECTS OF TRANS FAT DIET INTAKE ON METABOLIC PARAMETERS AND DNA METHYLATION PROFILE IN MALE OFFSPRING OF IN-UTERO BPA EXPOSED RATS

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ABSTRACT

Bisphenol A (BPA) is a plasticizer used in the manufacturing of many products, and its involvement in metabolic syndrome risk and development is still not fully understood. Exposure to BPA during critical windows such as pregnancy is known to affect the programming of metabolically active tissues in offspring and increase susceptibility to adverse effects of excessive trans fat diet (TFD) intake. In this study, we aimed to investigate the effect of prenatal BPA exposure with postnatal TFD intake on metabolic and biochemical parameters, pancreatic tissue histology, peroxisome proliferator-activated receptor γ (PPARγ) protein expression, and global DNA methylation expression on adult SD rat offspring. Eighteen pregnant rats were divided into three groups: control (CTL), vehicle tween 80 (VHC), and BPA (5 mg/kg/day) from pregnancy day (PD) 2 to PD 21. Their male rats offspring were then fed either with normal diet (ND) or TFD from postnatal week (PNW) 3 to PNW 14 and were divided into six groups; ND control group (CTLND), TFD control group (CTLTFD), ND vehicle control group (VHCND), TFD vehicle control group (VHCTFD), ND BPA exposed group (BPAND) and TFD BPA exposed group (BPATFD). In offspring, the physiological parameters including body weight, waist circumference, water, and food intake were measured weekly. The rats were then sacrificed and the blood, pancreas, and liver tissue were collected. Glucose, insulin, and lipid profile were measured. At PNW 9, BPATFD (389.5 ± 9.99 g) and VHCTFD (389.7 ± 13.45 g) offspring rats began to exhibit about a 15% significant increase in body weight compared to CTLND offspring rats (339 ± 7.22 g; $p < 0.05$). Furthermore, the significance in the body weight gains persisted until adulthood (PNW 13). In addition, the study has displayed that there was no significant difference between groups in relation to biochemical parameters including glucose, insulin, and lipid profiles. All pancreatic tissues showed normal architecture with irregular islets of Langerhans in TFD intake groups compared to offspring that consumed ND. Furthermore, the pancreatic histomorphometry was also affected whereby the study findings revealed that there was a significant increase in the mean number of pancreatic islets in BPA rats exposed and fed with TFD (5.987 ± 0.3159 islets/field, $p < 0.01$) compared to those fed with CTLND (3.667 ± 0.1706 islets/field) and VHCTFD (3.117 ± 0.2442 islets/field) rat offspring groups. In addition, the results showed that prenatal BPA exposure resulted in about 200 μm significant decrease in the pancreatic islet's diameter of the BPAND group (183.3 ± 23.28 μm, $p < 0.01$) compared to all other groups (> 420 μm). The study has shown that there was no significant difference between groups with regard to PPARγ protein expression. There was a significant increase in the global DNA methylation in BPATFD (4.92 ± 0.952 %, $p < 0.05$) group rat offspring compared to compared to all other groups. To the best of our knowledge, this is the first study to investigate whether the disruptions programmed by prenatal BPA exposure could aggravate changes on the metabolic parameters in response to TFD intake. Furthermore, this knowledge will create more awareness among researchers to further understand the impact of BPA and the consumption of TFD in the development of metabolic diseases. In conclusion, prenatal BPA exposure with postnatal TFD in the offspring may affect body weight, pancreatic islets, and global DNA methylation in adulthood, and the effect may be more aggravated in late adulthood.

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CHAPTER 1
INTRODUCTION

1.1 Research background

Non-communicable diseases (NCDs) are one of the major players leading to an increase in the prevalence of mortality in the world, which includes cardiovascular diseases, cancer, chronic respiratory illnesses, and diabetes mellitus (DM) accounting for 71% of all deaths worldwide (WHO, 2021a). Furthermore, over 15 million individuals die yearly from NCDs ranging from 30 to 69 years old (WHO, 2021a). In Malaysia, NCDs contribute to approximately 71% of premature deaths (Institute for Public Health (IPH) et al., 2020). Interestingly, according to data from the National Health and Morbidity Survey (NHMS) 2019, about 8.1% of the Malaysian population with an estimated 1.7 million people are currently living with three major risk factors for NCDs which are DM, hypertension and high cholesterol (Institute for Public Health (IPH) et al., 2020). DM accounts for one of the major four types of NCDs affecting 1.5 million people yearly (WHO, 2021a). It is one of the major worldwide health problems that is worrying in the last few decades since it has been considered among the top ten causes of death in the world. The majority of DM patients worldwide have type 2 diabetes (T2DM), representing 90–95% of all cases with DM (American Diabetes Association, 2012). According to NHMS 2019, 1 in 5 Malaysian population aged 18 and above suffer from DM. Additionally, this survey reported that 50.1% of adults in Malaysia were either overweight or obese, with 30.4% and 19.7% respectively (Institute for Public Health (IPH), National Institutes of Health, and Ministry of Health Malaysia 2020). Notably, T2DM has also become a serious concern in children and youth as a result of an increasing prevalence of obesity (Bansal & Pinney, 2017).

Metabolic Syndrome (MS) is a cluster of metabolic traits that include obesity, insulin resistance, dyslipidemia, hypertension, and hyperglycaemia (Meigs, 2002). Although the pathogenesis of MS is still not fully understood, insulin resistance is considered a hallmark. T2DM is a common chronic metabolic disease characterized by peripheral insulin resistance (Farrugia et al., 2021). It is a complex disorder with