Effects of Cigarette Smoke on the High Fat Diet-Induced ApoE/- Mouse Model of Diabetic Atherosclerosis

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Introduction

Type 2 diabetes mellitus (T2DM) is characterized by both insulin resistance (IR) and a compensatory hyperinsulinemia (1). Smoking has been associated with reduced insulin sensitivity or increased IR, as well as increased plasma glucose (Cena 2013). Studies have reported that cigarette smoking is a strong independent risk factor for T2DM (Cena 2013). Moreover, both smoking and diabetes are known risk-factors for cardiovascular disease (Gazi and Malik 2013). Recently, the report of the US Surgeon General (USSG 2014) indicated that the risk of diabetes increases 30-40% in smokers compared to non-smokers. Nevertheless, the mechanisms of cigarette smoke (CS)-induced IR are poorly understood. Because atherosclerotic cardiovascular disease is known to be the leading cause of morbidity and mortality among patients with diabetes, the apolipoprotein (ApoE/-) mouse was more relevant as a model for studying diabetes than mice that do not develop atherosclerosis (Li 2011). The high fat diet (HFD)-fed ApoE/- mice have shown marked cholesterol and diabetes atherosclerosis; therefore, utilization of this mouse model could be relevant to examine the mechanisms of CS-induced IR in the context of CVD development. Here, we report the effects of CS exposure for 11 weeks in the HFD-fed ApoE/- mice. We hypothesized that CS would exacerbate the IR-related changes in the HFD-fed mice.

Body Weights

HFD-fed mice had increased body weights as compared with the chow-fed mice. CS exposure reduced the body weight of the chow-fed mice. However, CS exposure did not alter the body weights of the HFD-fed mice. Mean ± SD are shown.

Fasting Glucose Levels

At the end of the study, HFD-fed mice had increased fasting glucose levels as compared with the chow-fed mice. CS exposure was associated with reduced fasting glucose levels in both chow- and HFD-fed mice. Mean ± SD are shown.

Fasting Insulin Levels

At the end of the study, HFD-fed mice had increased fasting insulin level as compared with the chow-fed mice. CS exposure was not associated with alterations of fasting insulin levels in both chow- and HFD-fed mice. Mean ± SD are shown.

Blood Lipid Profiles

HFD-fed mice had increased levels of triglycerides, cholesterol, HDL, and LDL as compared with the chow-fed mice. Furthermore, CS exposure significantly increases the lipid levels. Mean ± SD are shown (*p < 0.05 vs. ANOVA, Tukey adjustment for multiple comparisons).

Serum Metabolic Biomarkers

HFD-fed mice had increased levels of plasminogen activator inhibitor 1 (PAI-1), which has been shown to be correlated with insulin resistance syndromes, as compared with the chow-fed mice. There was a tendency of increased levels of leptin (which has been shown to be elevated in individuals with insulin resistance type 2 diabetes) and insulin-like growth factor 1 (IGF-1), which has 50% sequence homology to insulin, in the HFD-fed mice as compared with the chow-fed mice. CS exposure was not associated with alterations of these markers in both chow- and HFD-fed mice. Cortisol levels were increased in the CS-exposed mice only in the mouse model, possibly because of the increased cortisol which could be induced by HFD. Mean ± SD are shown (*p < 0.05 ANOVA, Tukey adjustment for multiple comparisons).

Summary & Conclusion

HFD-fed mice had greater body weights as compared with the chow-fed mice. The effect of CS exposure on the body weights was dependent on the type of diet. CS-fed mice had reduced levels of fasting plasma glucose and insulin as compared with the chow-fed mice. Furthermore, CS exposure was associated with reduced levels of fasting plasma glucose in both chow- and HFD-fed mice. Moreover, CS exposure did not affect insulin levels in both chow- and HFD-fed mice.

Liver Weight

Liver liver weights were observed in the HFD-fed mice as compared to the chow-fed mice. There was no effect of CS exposure. Mean ± SD are shown (*p < 0.05 ANOVA, Tukey adjustment for multiple comparisons).

Aortic Plaque Area

Increased plaque area is linked to cardiovascular risk, density, and IR. Plaque areas were increased in the HFD-fed mice as compared with the chow-fed mice. Furthermore, exposure of CS significantly increased plaque area in HFD-fed mice. Mean ± SD are shown (*p < 0.05 ANOVA, Tukey adjustment for multiple comparisons).

Islet Area

There was a slight increase of islet size in the HFD-fed mice as compared with the chow-fed mice, although this difference was not statistically significant. CS exposure was not associated with alteration of islet area in both chow- and HFD-fed mice.

References