A Crucial Role of Nox2 in Middle-age Obese-related Hyperglycaemia and Endothelial Dysfunction in Mice

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Middle-age obese is often associated with multiple organ oxidative stress and is a major risk factor for the development of cardiovascular diseases. In this study, we investigated the role of Nox2, a superoxide-generating enzyme, in a mouse model of high fat diet-induced middle-age metabolic disorders and vascular dysfunction. Littermates of C57BL/6J wild-type and Nox2 knockout mice (7 m old, n=10 per group) were fed with high fat diet (HFD, 45% kcal fat, 20% kcal protein and 35% kcal carbohydrate) or normal chow diet (NCD, 12% kcal fat, 28% kcal protein and 60% kcal carbohydrate) for 16 weeks, and were used at 11 m of age. Compared to age-matched NCD-fed mice, wild-type (WT) mice fed with HFD showed significant increases in body weight (NCD 42 ± 2.3 vs HFD 56 ± 3.2g, $P<0.05$) and the levels of fasting glucose (NCD 7.4 ± 3.3 vs HFD 8.8 ± 2.2 mM, $P<0.05$). These metabolic changes were accompanied by significant increases (42 ± 5%) in NADPH-dependent ROS production by aortas as measured by lucigenin-chemiluminescence, and a decrease in endothelium-dependent vessel relaxation to acetylcholine (E_{max} NCD 80.45 ± 7.39% vs HFD 74.41 ± 1.74%, $P<0.05$; 2 way ANOVA) as assessed by an organ bath. The systolic BP was also significantly elevated (NCD 127 ± 8 vs HFD 142 ± 12 mmHg, $P<0.05$). Compared to WT mice, Nox2 knockout mice fed with HFD had similar scale of increase in body weight (NCD 38 ± 3.6 vs HFD 49 ± 2.6 g, $P<0.05$). However, there was no significant increase in the levels of fasting blood glucose (NCD 7.5 ± 0.8 vs HFD 6.7 ± 1.5 mM). The aortic NADPH-dependent ROS production remained unchanged and the endothelium-dependent vessel relaxation to acetylcholine was well preserved (E_{max} NCD 80.53 ± 11.3 vs 78.18 ± 5.6%, $P=0.621$; 2 way ANOVA). There was no significant increase in systolic BP (NCD 123 ± 14 vs HFD 130 ± 9 mmHg) in HFD-fed Nox2 knockout mice. In conclusion, Nox2 and Nox2-derived ROS play a key role in mediating dietary obesity-related hyperglycaemia and endothelial dysfunction after middle-age, and Nox2 may present a therapeutic target for the prevention and treatment of these diseases.