Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol12Issue3abst056P.pdf

Crucial role of NADPH oxidase and oxidative stress in high-fat diet-induced metabolic disorders in ApoE knockout mice

A Mai, JM Li. University of Surrey, Guildford, Surrey, UK

High fat diet is associated with obesity, hyperglycaemia, hyperlipidaemia and risks for the development of cardiovascular diseases. However, the mechanism of high fat diet (HFD)-induced vascular dysfunction remains unclear. In this study we investigated the role of a Nox2-containing NADPH oxidase in high fat diet (HFD: 45% kcal fat)-induced metabolic disorders using Nox2/ApoE double knockout mice in comparison to age-matched $ApoE^{-/-}$ mice on the C57BL/6 background (n=9). $ApoE^{-/-}$ mice under 10 weeks of HFD had significant increases in body weight (NCD 27.9±1.5 vs HFD 31.3±1.1g) and blood pressure (NCD 114±3.6 vs HFD 128.5±5.7mmHg) together with hyperglycaemia and hyperinsulinaemia as compared to age-matched littermates under a normal chow diet (NCD: 9.3% kcal fat). Aortas from HFD $ApoE^{-/-}$ mice had significant increases in $O_2^{\cdot-}$ production as detected by lucigenin-chemiluminescence and DHE fluorescence, and this was accompanied by increased endothelium Nox2 expression, ERK1/2 phosphorylation and decreased Akt (immunofluorescence), and impaired endothelium function as assessed by an aorta organ bath. However, all these HFD-induced abnormalities were absent in Nox2/ApoE double knockout mice under the same HFD. *Ex vivo* organ culture (24 h) further confirmed that high levels of glucose (30 mM) plus insulin (1.2 nM) caused damages to $ApoE^{-/-}$ vessels (but not to vessels from Nox2/ApoE double knockout mice) characterised by ERK1/2 activation, reduced insulin receptor expression and deterioration of endothelial function. In conclusion, Nox2-derived oxidative stress plays an important role in the pathogenesis of dietary obesity-associated metabolic syndrome and endothelial dysfunction. Targeting Nox2-derived ROS represents a valuable therapeutic strategy to these diseases.