A CRUCIAL ROLE OF NOX2-DERIVED OXIDATIVE STRESS IN AGEING-ASSOCIATED METABOLIC DISORDERS AND VASCULAR DYSFUNCTION

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Ageing has been recognised to be a major risk factor for the development of cardiovascular disease and growing evidence suggests a role for oxidative stress. NADPH oxidase 2 has been reported to be a major source of reactive oxygen species (ROS) generation in the cardiovascular system, however, the role of this enzyme in age-related metabolic disorders and vascular diseases remains unclear. In this study we used age-matched wild-type (WT) and Nox2-deficient (Nox2−/−) mice on a C57BL/6 background at young (3–4 month) and ageing (20–24 month) to investigate the role of Nox2 in age-related oxidative stress, metabolic disorders and vascular dysfunction. There was an age-related increase in blood pressure in WT mice (126 mmHg for young and 148 mmHg for ageing) (P<0.05); however the blood pressure remained at lower levels in Nox2−/− ageing mice. Compared with young WT mice, WT ageing mice had significantly high levels of fasting serum insulin and this was accompanied with delayed clearance of glucose (P<0.05) indicating insulin resistance. However, no indication of insulin resistance was found in Nox2−/− ageing mice. The endothelial function was examined using aortic rings in an organ bath. Compared to the young controls, there was a significant decrease in the endothelium-dependent relaxation to acetylcholine in WT ageing aortas (Emax 72% for young and 64% for ageing, P<0.05). However, endothelial function was well preserved in Nox2−/− ageing aortas (Emax 83% for young and 80% for ageing. The ROS production was then measured in aortic sections by DHE fluorescence and a significant increase was found in ROS production in WT ageing aortas as compared to WT young controls (P<0.05). However, there was a significantly lower level of ROS production (P<0.05) in both age-matched Nox2−/− aortas. In conclusion, Nox2-derived oxidative stress plays an important role in age-related metabolic disorders and vascular dysfunction, and targeting Nox2 represents a valuable therapeutic strategy to treat these aging-related diseases.