NADPH oxidase 1 and 4 are relevant sources of oxidative stress and therapeutic targets in hypertension and stroke

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Oxidative stress has been suggested to be a key pathomechanism of vascular disease. However, all therapeutic attempts to exploit this with antioxidants have been clinical failures. Here we present an alternative approach by identifying a relevant source of oxidative stress and its role in cardiovascular disease, NADPH oxidases (NOX). NOX are the only known enzymes with reactive oxygen species (ROS) as their sole product. In the vasculature, NOX1 may contribute to endothelial dysfunction by scavenging NO and its anti-hypertensive and anti-atherosclerotic effects. Aged spontaneously hypertensive rats (SHR) develop endothelial dysfunction and increased ROS compared to aged matched WKYs. This was inhibited by a NOX inhibitor. In contrast, eNOS or xanthine oxidase inhibition did not decrease ROS levels. NOX1 and NOX2 were upregulated in SHR aortae compared to WKY rat aortae, whereas NOX2 and 4 expression remained unchanged. Also, NOX4 knockout mice had normal basal blood pressure. NOX1 showed strong positive staining in the intima of SHR, where it co-localized with an endothelial cell marker. Aortic endothelial function was significantly impaired in SHR versus WKY rats. The NADPH oxidase inhibition improved aortic relaxation more pronounced in SHR. In conclusion, ROS formation and NOX1/2 expression are increased in aged SHR aortae. Ectopic expression of NOX1 in endothelial cells appears to affect vascular function in a NOX inhibitor-reversible manner. NOX1 may thus represent a novel target for the treatment of hypertension. Conversely, the more abundant isoform, NOX4, plays no role in blood pressure regulation and is induced in hypoxia/ischemia and essential for the subsequent reperfusion injury in stroke. Thus NOX1 and NOX4 represent novel cardiovascular targets for specific treatment of pathological oxidative stress.