Small vessel disease and hypertension – molecular mechanisms and clinical implications

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Pathophysiological mechanisms contributing to hypertension include injury to small arteries, characterised by endothelial dysfunction, vascular remodeling, fibrosis and inflammation, (so called hypertensive vascular phenotype). These changes are initially adaptive but in the long term become maladaptive leading to vascular damage and loss of function, particularly important in small resistance arteries, critically involved in the regulation of peripheral vascular resistance and consequently in blood pressure control. Common to these processes are changes in vascular cells that make up vessels (endothelial cells, vascular smooth muscle cells, adventitial fibroblasts and adipocytes) to a pro-inflammatory, vasoconstrictory, proliferative, pro-fibrotic, pro-migratory phenotype, influenced in large part by oxidative stress (increased bioavailability of reactive oxygen species). Increased reactive oxygen species production, due to activation of NADPH oxidases (Nox), and decreased cellular antioxidant defense mechanisms contribute to oxidative stress, which influences redox-sensitive signaling molecules that impact on endothelial dysfunction and vascular remodeling and inflammation. Our recent studies also elucidate a novel mechanism whereby microparticles may play a role in vascular dysfunction. Clinical studies demonstrate that improved endothelial function, regression of arterial remodeling and decreased vascular inflammation are associated with decreased cardiovascular events and reduced hypertension-related target organ damage. Accordingly strategies to promote vascular health should be a therapeutic priority. Such strategies include drugs (RAAS inhibitors, calcium channel blockers) and lifestyle modifications (exercise, healthy diet, smoking cessation), which reduce oxidative stress and dampen activation of injurious signaling pathways (pro-fibrotic, pro-inflammatory, proliferative pathways). Novel approaches, such as Nox inhibitors, agents that increase antioxidant capacity (e.g. Nrf-2 activators) and anti-inflammatory immune-modulators, may have potential in promoting vascular health and reducing blood pressure. This presentation highlights some molecular and cellular mechanisms that underlie vascular injury in hypertension, and focuses on processes of oxidative stress and redox-sensitive pro-inflammatory and pro-fibrotic signaling pathways. By elucidating such mechanisms it is hoped that new disease-specific molecular targets will be identified for development of innovative therapies that would prevent or regress vascular injury and thereby improve management of hypertension and associated target organ damage.