Changes in endothelium-derived hyperpolarising factor in ageing and hypertension: response to chronic treatment with renin-angiotensin system blockers

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Endothelial cells play an important role in the regulation of vascular tone through the release of relaxing factors such as nitric oxide, prostacyclin, and endothelium-derived hyperpolarising factor (EDHF). EDHF appears to be a dominant vasodilator in resistance arteries although its identity is still elusive. Several clinical and experimental studies have shown that endothelial function is impaired in ageing and hypertension, which may be associated with an increase in cardiovascular disease. In addition, several clinical studies have shown that blocking the renin-angiotensin system (RAS) improves endothelial function not only in hypertensive patients but also in normotensive patients with other cardiovascular diseases, such as chronic heart failure and/or myocardial infarction. The aim of the present study was to test whether or not EDHF-mediated hyperpolarisation and relaxation change in ageing and hypertension, and if so, whether or not chronic treatment with RAS blockers (an angiotensin-converting enzyme inhibitor enalapril and an angiotensin II receptor antagonist candesartan) improves such change. EDHF-mediated hyperpolarisation and relaxation were examined in mesenteric arteries obtained from 3-, 6-, 12-, and 24-month-old normotensive Wistar-Kyoto rats (WKY) and 12-month-old spontaneously hypertensive rats (SHR). Furthermore, both strains were treated for three months with either RAS blockers or a conventional therapy with hydralazine and hydrochlorothiazide from 9- to 12-month-old. The rats used were anaesthetised with ether and killed by decapitation. In arteries of WKY, EDHF-mediated hyperpolarisation and relaxation were impaired at the age of 12- and 24-months compared with 3- and 6-month-old rats, with the response tending to be further impaired in 24-month-old rats. Three months of treatment with RAS blockers but not with a conventional therapy with hydralazine and hydrochlorothiazide improved the age-related impairment of EDHF-mediated responses, despite a similar reduction in blood pressure in both treatments. In arteries of SHR, EDHF-mediated hyperpolarisation and relaxation were impaired at the age of 12-months compared with age-matched, 12-month-old WKY. In SHR, all antihypertensive treatments improved the impairment of EDHF-mediated responses; however, the improvement achieved by RAS blockers was greater than that with a conventional therapy with hydralazine and hydrochlorothiazide. These findings suggest that: (1) EDHF-mediated hyperpolarisation and relaxation decline with ageing and hypertension in rat mesenteric arteries; (2) chronic treatment with RAS blockers improves the age-related impairment of EDHF-mediated responses presumably through the blockade of RAS but not lowering the blood pressure alone; (3) antihypertensive treatment restores the impaired EDHF-mediated responses in hypertension; and (4) RAS blockers may be more efficacious in improving the endothelial dysfunction associated with hypertension.