Vascular remodeling and changes in cellular coupling during vascular disease

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Changes in blood vessel morphology and function, including vascular remodeling and endothelial dysfunction, accompany the increase in peripheral vascular resistance and blood pressure, characteristic of hypertension. Altered gap junction expression has also been described during hypertension (Severs, 1999; Rummery *et al.*, 2002). This study examined the nature of vascular remodeling in two functionally different blood vessels, and correlated this with changes in the distribution of Cxs during the development of hypertension.

The development of hypertension in the spontaneously hypertensive rat (SHR) begins at approximately 4 weeks of age, animals becoming hypertensive compared to age matched control Wistar-Kyoto rats (WKY) at 9 weeks of age (Rummery *et al.*, 2002). In all experiments, rats were anaesthetised with ketamine/rompun (44/8 mg/kg respectively, i.p.) and tissue was prepared for electron microscopy, RNA extraction or immunohistochemistry.

Electron microscopy was used to determine structural characteristics of thoracic aorta (ThA) and caudal artery (CA) obtained from 12 week SHR and WKY. In the CA, but not the ThA, luminal diameter was decreased, while the number of smooth muscle cell layers and the medial cross-sectional area was increased in SHR compared to the WKY. Remodeling of the endothelium was examined in the ThA and CA using immunohistochemistry (IHC). In the 3-week old CA, there was no difference in endothelial cell (EC) morphology between strains, while at 12 weeks, area, length and perimeter of ECs was reduced in SHR. Between 3 and 12 weeks, there was an increase in area and a decrease in length of ECs in WKY, while the area, length and perimeter of ECs in SHR decreased. EC morphology was not different in the ThA of SHR compared to WKY at 12 weeks.

Expression of mRNA and protein for Cxs 37, 40, 43 and 45 was quantified in the ThA and CA of the WKY and SHR using real-time PCR and IHC. At 12 weeks, Cx43 predominated in the ThA, punctate labeling being found in the media. Cx45 was detected in the media of the ThA and CA. Expression of both Cxs was significantly reduced in the SHR. Cx37 was abundantly expressed in the media of the CA, and sparsely in the ThA. This expression did not differ in either artery during hypertension. In the endothelium, Cxs 37, 40, and 43 were detected in both vessels. The density of Cx37 expression was significantly reduced in the endothelium of the ThA in SHR compared to WKY, while Cx40 was decreased in the CA. Between 3 and 12 weeks, the density of Cx40 was reduced in the SHR at 12 weeks compared to 3 weeks of age.

At 3 weeks, mRNA for Cxs 37 and 43 was equally expressed in the ThA of both WKY and SHR, while Cxs 40 and 45 were sparse. In the ThA, expression of protein for Cx43 was similar in both strains, while Cxs 37, 40 and 45 were not detected. In the CA, mRNA for Cx37 was abundantly expressed in both WKY and SHR however expression was significantly less in the WKY. Similarly, mRNA for Cx45 was decreased in the WKY. In the CA, there were no differences in Cx protein expression between strains. Between 3 and 12 weeks, there was no difference in mRNA expression in the ThA. In the CA, mRNA for Cxs 37 and 40 was greater at 3 week compared to 12 weeks in both strains, while Cx45 was greater in the CA of the WKY at 3 weeks. Expression for Cxs 37 and 43 in the ThA was greater in the WKY at 12 compared to 3 weeks. In the CA of both WKY and SHR, protein for Cx45 was greater at 12 compared to 3 weeks, however in the SHR, this was not significant. Expression for Cxs 37, 40 and 43 was not altered in the media of the CA during development.

Results indicate that vascular remodeling occurs in the media and endothelium of muscular but not elastic arteries during hypertension. In the endothelium this remodeling develops coincident with the increasing blood pressure. Changes in Cx expression during hypertension differed depending on the vessel studied, with significant changes occurring with the development of hypertension. The changes described here may have significant consequences for blood vessel function during the development of hypertension.

Severs, N.J. (1999) *Novartis Foundation Symposium*, 219:188-211.

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