922

EDRF AND RESISTANCE VESSELS. T.M. Griffith, D.H. Edwards, R.L. Davies, T.J. Harrison, K.T. Evans, Departments of Radiodiagnosis and Cardiology, University of Wales College of Medicine, Cardiff, UK.

The influence of endothelium on vasomotion in resistance vessels was studied in an isolated, buffer-perfused rabbit ear preparation using novel microangiographic techniques and haemoglobin as a specific inhibitor of EDRF. In constricted preparations acetylcholine and Substance P, whose action is EDRF-dependent in large vessels, induced dilatation in vessels down to 25um in diameter which was inhibited by haemoglobin. Log ($IC_{50}$) values calculated from diameter changes were the same in the central artery, G0, and its first three generations of branch vessels G1, G2 and G3 (ie down to 70um) being -7.7 and -9.8 respectively. Consistent with this, almost identical values were derived from the pressure responses of the intact network. Such spatial homogeneity has not been found when the same vessels are studied in isolation. In contrast, constrictor responses to 5HT or histamine exhibited spatial heterogeneity (in the rank order G0>G1>G2>G3) which was exaggerated by inhibition of basal EDRF activity. In terms of normalised diameter changes EDRF and its analogue GTN were equipotent in reversing these constrictor responses in G0 to G3. In terms of hydraulic resistance however, dilator responses paralleled relative changes in resistance induced by the constrictor agents. EDRF and GTN thus appear more potent in vessels exhibiting high degrees of tone.

In control preparations (i.e. in the absence of pharmacological constriction) basal EDRF activity was found to exert maximal influence in vessels in which calculated shear stress and hydraulic resistance were highest, and continuously inhibited myogenic tone in G1 and to a lesser extent G2 and G3. In the absence of haemoglobin, diameter and flow were related by the expression $\dot{Q}=aD^4+b$ in G0, G1 and G2 over an 8-fold range of flow rates. In the high-flow limit this implies constancy of pressure gradient and pressure drop in these vessels so that the energy expended in delivering a given volume of perfusate to the terminal elements of the bed would be effectively independent of flow rate, rather than directly proportional to it as in a rigid tube. Basal EDRF activity also conferred identical flow-related distensibility in G0 through G3 in control and partially constricted preparations over the same range of flow rates. This implies independence of flow distribution from flow rate. Flow dependent release of EDRF may provide a mechanism which links network topography with vessel function, thus optimising perfusion characteristics.

923

PLATELETS, ENDOTHELIUM AND VASOSPASM. Paul M. Vanhoutte, M.D., Ph.D., Professor of Physiology and Pharmacology, Mayo Clinic and Mayo Foundation, Rochester, MN 55905, USA.

The endothelium can secrete both relaxing and contracting substances. One of the most powerful stimuli to the release of the former are thrombin and aggregating platelets. This contributes to the protective role of the endothelium against inappropriate intraluminal platelet aggregation and coagulation in blood vessels with an intact intima. Thrombin-induced, endothelium-dependent relaxations have been obtained in isolated arteries of different species, including humans. Endothelium-dependent relaxations can be evoked by autologous platelets in isolated blood vessels of the dog, pig and rat; they can be obtained in canine coronary arteries with human platelets. The major platelet-products involved in these endothelium-dependent relaxations are 5-hydroxytryptamine (serotonin) and the adenine nucleotides. Although platelet-activating factor (PAF) can evoke endothelium-dependent relaxation it only does so at concentrations much higher than those occurring under physiological conditions; since the relaxations are not prevented by PAF-antagonists, they are non-specific in nature. The receptor mediating the endothelium-dependent relaxations to serotonin released from the aggregating platelets can be subtyped as a $S_1$-($5HT_1$) serotonergic receptor; those mediating the response to the adenine nucleotides as $P_{2y}$-purinergic receptors. In the absence of the endothelium aggregating platelets cause contractions of vascular smooth muscle; these are mediated by a mixture of $S_1$-like and $S_2$-serotonergic receptors in coronary arteries of the dog, and by $S_2$-serotonergic receptors in those of the pig. Thus, in the porcine coronary artery, the $S_2$-serotonergic antagonist ketanserin markedly enhances the platelet-induced endothelium-dependent relaxation. After previous (four weeks) injury, the regenerated endothelium of the porcine coronary artery loses the ability to respond to serotonin, and is unable to prevent the constrictions evoked by aggregating platelets. The endothelium-dependent relaxations of porcine coronary arteries evoked by aggregating platelets are potentiated by chronic treatment of the donor animals with cod liver oil. These studies emphasize the protective role of the endothelial cells against the vasoconstriction (vasospasm) induced by aggregating platelets. This role is depressed after previous injury, and can be facilitated by dietary adjustments.