

Investigation On The Involvement Of Reactive Oxygen Species And Mitogen-Activated Protein Kinase In Endothelium-Dependent Relaxation In Spontaneously Hypertensive Rats

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The endogenous cannabinoid system is up-regulated in the spontaneously hypertensive rat (SHR), probably as a compensatory mechanism to oppose the high blood pressure [Bátkai et al., 2004; Wheal et al., 2007]. More recently, activation of CB1 receptors is shown to cause endothelial cell death through generation of reactive oxygen species (ROS) and activation of mitogen-activated protein kinases (MAPK) [Rajesh et al., 2010]. The present study investigated whether or not ROS/MAPK is activated in the blood vessels of SHR, and if so, whether or not these mechanisms contribute to endothelial dysfunction in this animal model. Isometric tension was measured in isolated aortae and superior mesenteric arteries of SHR and the normotensive Wistar Kyoto (WKY) rats in organ chambers. Relaxations were expressed as percentage (%) of phenylephrine (1 μ M)-induced contraction. Endothelium-dependent relaxations to acetylcholine (1 nM - 100 μ M) were not different between aortae of WKY rats and SHR at 12 weeks old (n=3), but were significantly reduced in 36 weeks SHR aortae (n=3, p<0.05). Endothelium-independent relaxations to sodium nitroprusside (a nitric oxide donor, 100 μ M) in aortae of 12 and 36 weeks WKY rats and SHR were not significantly different (12 week WKY rats: 99.4 \pm 5.4%; 12 weeks SHR: 99.8 \pm 1.6%; 36 weeks WKY rats: 99.3 \pm 1.8%; 36 weeks SHR: 94.0 \pm 3.5%; n=3). The impairment of acetylcholine-induced relaxations in 36 weeks SHR aortae were inhibited by indomethacin (a cyclooxygenase inhibitor, 10 μ M; n=3, p<0.05) or U0126 (a MAPK inhibitor, 10 μ M; n=3, p<0.05), but not by the combination of Tiron and diethyldithiocarbamate acid (membrane permeable antioxidants, 10 mM and 100 μ M, respectively; n=3). In superior mesenteric arteries, endothelium-dependent hyperpolarization-mediated relaxations, but not nitric oxide-mediated relaxations, to acetylcholine (1 nM - 100 μ M) were smaller in 12 weeks SHR than in age-matched WKY (n=4-7; p<0.05). This impairment was not affected by U0126 (n=7), PD98056 (a MAPK inhibitor, 10 μ M; n=8) or catalase (antioxidant enzyme, 1200 U/ml; n=8). There was no significant difference between relaxations to SKA-31 (an activator of intermediate- and small-conductance calcium-activated potassium channels, 1 nM - 100 μ M) in 12 weeks WKY and SHR superior mesenteric arteries (n=4). Therefore, the present data suggest that the mechanisms underlying endothelial dysfunction in SHR are different in different blood vessels. Endothelial dysfunction occurs at an earlier age in mesenteric arteries of SHR and this impairment is mainly limited to signalling pathways involved in the initiation of endothelium-dependent hyperpolarization. As SHR ages, endothelium-derived nitric oxide-mediated relaxation in aortae is also impaired. This latter endothelial dysfunction is attributed to activation of MAPK and cyclooxygenase, but not to the generation of ROS. Further experiments will be needed to determine whether or not the activation of MAPK in SHR aortae is related to the up-regulation of the cannabinoid system in this hypertensive animal.

References:

Bátkai S et al, Circulation 110:1996, 2004.

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