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Hsp90 and sGC-mediated vasorelaxation

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Vascular soluble guanylate cyclase (sGC) exists in multimeric complexes with endothelial nitric oxide synthase (eNOS) and heat shock protein 90 (hsp90). Whereas disruption of hsp90-eNOS complexes clearly attenuates eNOS-depended vascular relaxation, the contribution of sGC-hsp90 complexes to eNOS- or NO donor-dependent relaxations remains controversial. Isolated rat thoracic aortic rings were pre-incubated with structurally diverse hsp90 inhibitors, radicicol (RA) or geldanamycin (GA) or vehicle for 0.5, 1 or 15 hrs and exposed to ACh, 8-Br-cGMP, forskolin or one of three NO donors: nitroglycerin (NTG), sodium nitroprusside (SNP) or spermine nonoate (SNN). Both RA and GA inhibited endothelium-dependent relaxations dose-dependently. Long-term (15 hrs.) exposure to RA inhibited all NO donor-induced relaxations; however GA inhibited SNN-induced relaxation only. 15 hrs. exposure to RA, but not to GA, decreased hsp90-bound sGC protein expression and NTG-stimulated cGMP formation in aortic rings, whereas RA more than GA reduced SNN-stimulated cGMP formation. Thus hsp90 inhibitors selectively inhibit sGC-dependent relaxations of aortic rings by reducing sGC expression, disrupting sGC-hsp90 complex formation and decreasing cGMP formation. Since hsp90 inhibitors promote proteasomal degradation of hsp90 client proteins, we then investigated whether CHIP, a chaperone-dependent ubiquitin E3 ligase, could play a role in the process of degradation of sGC. Transient overexpression of CHIP in Cos-7 or rat aortic smooth muscle cells degraded sGC and this was abrogated by the proteasome inhibitor, MG 132 in a TPR- and U-box domain-sensitive manner. Co-immunoprecipitation and immunofluorescent studies suggest that CHIP is associated with sGC, hsp90 and hsp70 and increased the association of hsp70 with sGC. Furthermore, CHIP directly ubiquitinated sGC and this was potentiated by geldanamycin and was followed by proteasomal degradation. Ad-CHIP infected rat aortic rings exhibited a decreased SNN-induced relaxation. Taken together, these studies suggest that hsp90 is a physiologic regulator of sGC vascular function.

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