VASCULAR SMOOTH MUSCLE RELAXATION IN SOLUBLE GUANYLYL CYCLASE 1 HIS 105 PHE MUTANT MICE

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The binding of nitric oxide (NO) on the heme group of soluble guanylyl cyclase (sGC) is known to induce important changes within the cardiovascular system such as smooth muscle relaxation, thereby controlling blood pressure and blood flow. The $sGC\alpha_1\beta_1$ and $sGC\alpha_2\beta_1$ heterodimer are reported to be physiologically active, in which the β_1 subunit acts as dimerizing partner for both α subunits. As the histidine (His) residue at position 105 of the β_1 subunit functions as axial ligand for the heme prosthetic group, substitution of His by phenylalanine (Phe) will abolish the heme-dependent activation of sGC. This is the case in the $sGC\beta_1^{ki/ki}$mice from which aortic and femoral artery segments were isolated and mounted on a small vessel myograph for isometric tension recording. In comparison with the preparations isolated from the wild type littermates, the response to endogenous NO (released from the endothelium in response to acetylcholine (ACh)) and exogenous NO (from the NO-donor sodium nitroprusside (SNP)) were practically completely abolished in the preparations from the $sGC\beta_1^{ki/ki}$mice. This confirms the exclusive functional importance of sGC as receptor for NO. The response to the NO-independent sGC-activator (BAY 41-2272) was also significantly reduced in the $sGC\beta_1^{ki/ki}$mice, indicating that the heme group plays a role in the BAY 41-2272-induced activation of sGC. In conclusion, the completely attenuated NO-induced response in the $sGC\beta_1^{ki/ki}$mice, demonstrates the importance of sGC as the sole target for NO in regulating vasodilatation. Furthermore, the remaining relaxing effect of BAY 41-2272 in the $sGC\beta_1^{ki/ki}$mice, suggests that the heme-binding pocket is very important but not indispensable for the interaction of BAY 41-2272 with sGC.