FUNCTIONAL IMPORTANCE OF THE SOLUBLE GUANYLYL CYCLASE 11 ISOFORM IN VASORELAXATION

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Of the two active soluble guanylyl cyclase (sGC) isoforms ($\alpha_1\beta_1$ and$\alpha_2\beta_1$), the $\alpha_1\beta_1$ isoform is predominantly present in vascular tissue and is therefore believed to play a dominant role in vasorelaxation. This was investigated on aortic and femoral artery segments isolated from $sGC\alpha_1^{-/-}$ mice and their wild type littermates and by measuring of the cGMP level and sGC enzyme activity. The functional importance of $sGC\alpha_1\beta_1$ was demonstrated by a significantly reduced response to acetylcholine, sodium nitroprusside (SNP), NO-gas, YC-1 and BAY 41-2272 in arteries of $sGC\alpha_1^{-/-}$ mice. However, those substances still had a substantial relaxing effect in these arteries, indicating that not only $sGC\alpha_1\beta_1$ is involved in vasorelaxation. The non-upregulation of the $sGC\alpha_2$ gene and the non-significant increase in cGMP-level in response to SNP, do not support the involvement of the minor $sGC\alpha_2\beta_1$ isoform and thus rather suggest (an) sGC-independent mechanism(s). The similarity in the response to the cGMP-analogue 8-pCPT-cGMP between wild type and $sGC\alpha_1^{-/-}$ mice, indicates that the $sGC\alpha_1^{-/-}$ mice are not more sensitive towards cGMP. The response to the phosphodiesterase type-5 inhibitor, T-1032 was nearly abolished in the arteries of the $sGC\alpha_1^{-/-}$ mice, indicating that in those mice there is no accumulation of basal cGMP produced by $sGC\alpha_2\beta_1$. Again those findings are against the importance of $sGC\alpha_2\beta_1$. On the other hand,the inhibition of the nitric oxide-induced relaxation and cGMP production in the $sGC\alpha_1^{-/-}$ mice by ODQ suggest that $sGC\alpha_2\beta_1$ is functionally active. This is also suggested from the significant increase in sGC activity in the $sGC\alpha_1^{-/-}$ mice after addition of BAY-41-2272. It is concluded that besides $sGC\alpha_1\beta_1$, also $sGC\alpha_2\beta_1$ and/or(an) sGC-independent mechanism(s) has a substantial role in nitric oxide-related vasorelaxation.