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Poster presentation

Activation of soluble guanylyl cyclase (sGC) by the NO/heme-independent activator HMR1766 in cells

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Most vascular diseases are characterized by an increase in the production of reactive oxygen species (ROS). The resulting oxidative stress reduces the biological activity of endothelial-derived nitric oxide (NO). In the present study we have evaluated the responsiveness of sGC in cells exposed to HMR1766, a NO-independent sGC activator that preferentially stimulates the oxidized/heme-free enzyme. Pre-treatment of rat aortic smooth muscle cells (RASMC) with 500 μM of H_2O_2 reduced the ability of both sodium nirtroprusside (SNP; a nitric oxide donor) and BAY 41–2272 (a NO-independent, heme-dependent sGC activator) to increase intracellular cGMP levels. In contrast, pre-treatment of cells with H_2O_2 significantly increased the HMR1766-stimulated cGMP accumulation. Similarly, pre-treatment of RASMC with SIN-1 (500 μM), a peroxynitrite donor, enhanced sGC activation by HMR1766. Adenovirus-mediated overepxression of catalase or superoxide dismutase in RASMC did not alter the responsiveness to HMR1766. To study if HMR1766 stimulates cGMP accumulation in cells expressing heme-deficient sGC we generated histidine 105 to phenylalanine (H105F) or cycteine (H105C) mutants of the sGC β1 subunit. In wild-type sGC-expressing cells NO-stimulated cGMP accumulation was blocked by ODQ, while HMR1766-stimulated cGMP was enhanced by ODQ. The H105F mutant was not sensitive to NO, as it is heme-deficient, but exhibited a 10-fold increase in cGMP accumulation after stimulation with HMR1766; this effect of HMR1766 was not affected by ODQ pretreatment. The α1/H105C enzyme was basally much more active than wt sGC and could be further stimulated with HMR1766, but not SNP. The above data indicate that HMR1766 is capable of activating oxidized and heme-free sGC in vivo.

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