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Oral presentation

Beyond NO and heme: biochemical and pharmacological opportunities

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Oxidative stress, defined as an alteration in the balance between the production and removal of reactive oxygen species (ROS), plays a central role in many cardiovascular diseases. ROS disturb the vasoprotective nitric oxide-soluble guanylate cyclase-cyclic GMP (NO-sGC-cGMP) signaling cascade by downregulation of the NO-sensitive form of sGC and, in addition, a direct impairment of this crucial enzyme by oxidizing its prosthetic heme moiety. Through a high-throughput screen we identified non NO-releasing sGC activators, such as BAY 58-2667, acting more potently at the oxidized or heme free recombinant sGC than at the native form. Here, we show that the activity of BAY 58-2667 is potentiated in cells, aortas from different species and *in vivo* under oxidative stress conditions (ROS generating systems, ODQ, and hypercholesteremia) indicating the presence of heme-free or oxidized sGC under pathophysiological conditions. Moreover, in various long-term trials beneficial effects on morbidity and mortality have been observed in BAY 58-2667 treated animals. Consequently, the intracellular pool of oxidation-impaired sGC can be reactivated by BAY 58-2667 to overcome the pathophysiology of the impaired NO/sGC/cGMP signaling pathway.

Moreover, by using the NO- and heme-indepent sGC activator BAY 58-2667, the heme-dependent sGC stimulator BAY 41-2272, NO, ODQ together with a novel cGMP reporter cell line, it was possible to distinguish between heme-containing and heme-free sGC in an intact cellular system. The investigation of the activation profile of different sGC mutants by transient transfection into the cGMP reporter cell led to the identification of the heme binding motif Tyr135-x-Ser137-x-Arg139 in addition to His105. Very recently, crystallization studies of a prokaryotic homologue of the sGC heme binding domain have confirmed our findings and proposed further amino acids involved in sGC signalling (Pellicena et al., 2004). Accordingly, a 3-dimensional model of sGC was constructed and we identified the β-subunit amino acids Asp44, Asp45 and Phe74 as also being crucially important for the heme-induced sGC activation.

Our studies demonstrate that sGC activators, exemplified by BAY 58-2667, offer new approaches for the understanding of sGC activation and for the treatment of oxidation-damaged vasculature by a selective targeting of oxidized sGC.