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Influence of heme metabolism and redox regulation of sGC in the control of vascular function

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The redox status of cytosolic NAD(P)H and the biosynthesis and metabolism of heme are potentially key factors regulating soluble guanylate cyclase (sGC) and the role of cGMP in vascular relaxation. The availability of both cytosolic NADH and NADPH control the generation of NAD(P)H oxidase (Nox)-derived reactive oxygen species (ROS) and their influence on sGC. Cytosolic NADPH redox appears to preserve nitric oxide-stimulation of sGC and relaxation by preventing an inhibitory effect of oxidized glutathione and by maintaining the sGC heme in its ferrous form. Studies on isolated bovine pulmonary arteries (BPA) after a 24 hour organ culture have revealed that the heme precursor aminolevulinic acid promotes the accumulation of protoporphyrin IX in amounts that stimulate sGC and cGMP-mediated relaxation, in a manner modulated by the availability of iron. Cobalt-inducers of heme oxygenase-1 (HO-1) cause a HO-1 dependent depletion of heme which can be associated with a loss of heme-dependent stimulation of sGC, and an up regulation of SOD activity which potentially alters the influence of ROS on sGC and vascular relaxation.