

## **Heme oxygenase-1 induction restores high-blood-flow-dependent remodeling and endothelial function in mesenteric arteries of old rats**

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**BACKGROUND:**

Aging is associated with reduced structural and functional adaptation to chronic changes in blood flow (shear stress) in small arteries. As heme oxygenase-1 (HO-1) is induced by hemodynamic forces in vascular smooth muscle and endothelial cells, we hypothesized that it might improve flow-dependent remodeling in aging.

**METHOD:**

First-order mesenteric arteries from 3 and 16-month-old rats were exposed to high, low, or normal flow by alternate ligation in vivo. Rats were treated with the HO-1 inducer, cobalt protoporphyrin (CoPP, 5 mg/kg) or vehicle. 14 days later, local blood flow was measured in vivo, and arteries were studied in vitro.

**RESULTS:**

Despite an equivalent change in blood flow, diameter enlargement in the high-flow arteries was blunted in old compared to young rats and was associated with decreased endothelium-dependent relaxation to acetylcholine. In old rats, HO-1 induction with CoPP restored outward remodeling, via a paradoxical reactive oxygen species-dependent mechanism, and was associated with a Mn-superoxide dismutase (SOD) overexpression, as well as a significant reduction of mitochondrial aconitase activity, used as a biomarker for oxidative stress. The heme oxygenase activity inhibitor, Sn-protoporphyrin, and the SOD-mimetic, TEMPOL, prevented the effect of CoPP on remodeling and oxidative status in old rats. Furthermore, HO-1 induction improved endothelial function, in association with increased endothelial nitric oxide synthase protein expression and phosphorylation (Ser-1177). In low-flow arteries, inward remodeling was unaffected by aging or by CoPP. Thus, in old rats, CoPP-induced up-regulation of HO-1 restored high-flow-dependent remodeling (diameter enlargement) and improved endothelial function in mesenteric arteries.

**CONCLUSION:**

This opens new perspectives in the treatment of ischemic diseases in aging.

Résumé en anglais

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