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Aspirin activates HO-1 expression in endothelial cells – role of NO/cGMP

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Aspirin is known to exert cytoprotection by presently unidentified mechanisms. This study investigates the involvement of the NO/cGMP-system and its downstream target heme oxygenase-1 in mediating aspirin-dependent cytoprotection. Hydrogen peroxide markedly reduced viability of cultured endothelial cells derived from bovine pulmonary artery. Preincubation with aspirin (3 to 30 μM, 12 hours) protected endothelial cells from hydrogen peroxide-mediated toxicity and increased viability in a concentration-dependent fashion. This effect was specific in that other nonsteroidal anti-inflammatory drugs, such as salicylate or indomethacin, did not alter hydrogen peroxide toxicity. Aspirin-induced endothelial protection was abrogated in the presence of the NO scavenger PTIO (30 μM) and the inhibitor of soluble guanylyl cyclase ODQ (1 μM). Moreover, the L-arginine antagonist L-NMMA (25 μM), but not its D-enantiomer, led to complete inhibition of aspirin-dependent cytoprotection. Correspondingly, aspirin enhanced endothelial NO synthase activity (citrulline formation) as well as intracellular cGMP accumulation. Cyclic GMP increases by both, aspirin and exogenous nitric oxide, were synergistically enhanced in the presence of YC-1, an NO-independent activator of soluble guanylyl cyclase. These observations corroborate the involvement of nitric oxide in aspirin-dependent cGMP stimulation. Aspirin-dependent NO synthase activation was associated with increased heme oxygenase-1 protein expression and enzymatic activity. Pretreatment with bilirubin, an heme oxygenase product with antioxidant properties, produced protective effects similar to those observed under the influence of aspirin or NO. Our data demonstrate that endothelial NO synthase is a site of action of aspirin and that the NO/cGMP-system assumes a crucial function in mediating the cytoprotective action of aspirin. Moreover, these findings support the concept that NO-regulated antioxidant proteins such as heme oxygenase-1 contribute to endothelial protection by aspirin.