New signaling routes for an old drug: lipoxin A₄ might mediate heme oxygenase-1 induction by aspirin. Focus on “Novel lipid mediator aspirin-triggered lipoxin A₄ induces heme oxygenase-1 in endothelial cells”

Henning Schröder
Department of Pharmacology and Toxicology, School of Pharmacy, Martin Luther University, Halle, Germany

OVER THE PAST DECADE, heme oxygenase-1 (HO-1) has emerged as an important mediator of antioxidant and anti-inflammatory actions. HO-1 antisense and knockout studies as well as clinical investigations have clearly shown that HO-1 assumes a central role in cellular antioxidant defenses, and, specifically, in vascular protection. Tissue-protective actions of HO-1 outside the vasculature have also been documented in various tissues, including the heart, kidney, and neuronal cells (14, 16, 19).

HO-1 is the inducible enzyme catalyzing the degradation of heme. This process leads to generation of bilirubin, iron, and carbon monoxide. Bilirubin exerts strong antioxidant effects at physiological plasma concentrations (17). High-normal plasma levels of bilirubin were reported to be inversely related to atherogenic risk and to provide protection against endothelial damage. Risk reduction by bilirubin was comparable to that of high-density lipoprotein cholesterol (12). Carbon monoxide has likewise been shown to produce anti-apoptotic and cytoprotective actions, and, in addition, functions as a smooth muscle-relaxing mediator via activation of the soluble guanylyl cyclase/cGMP signaling pathway (16).

The unique combination of tissue-protective and smooth muscle-relaxing properties makes HO-1 an interesting target for treatment of cardiovascular diseases, including atherosclerosis and other inflammatory disorders, among them neurodegenerative processes, such as Alzheimer’s and Parkinson’s diseases (14, 16). Support for the importance of HO-1 comes from investigations in humans demonstrating that HO-1 polymorphisms with longer (GT)n repeats are associated with lower transcriptional activity as well as diminished vascular protection from atherogenic insults (1, 7). In addition, HO-1 seems crucial for keeping the human uterus in a relaxed state during pregnancy, and a reduced level of placental HO-1 has been linked with a higher risk for preeclampsia (2). Thus therapeutic strategies aimed at moderating increasing tissue expression of HO-1 might be beneficial in several disease states. However, until recently, known inducers of HO-1, including cadmium chloride and other heavy metals, were not very promising for eventual therapeutic use in humans.

Aspirin, known as an anti-inflammatory drug for more than 100 years and used in prevention of thrombotic events since the late 1980s, has recently turned out to be one of the long-sought “benign” inducers of HO-1 (10). HO-1 induction, followed by increased formation of bilirubin, carbon monoxide, and ferritin, a secondary antioxidant protein, was characterized as a novel, prostaglandin-independent vasculoprotective action of aspirin, not shared by other nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin (10).

In the present article in focus, Nascimento-Silva et al. (Ref. 14a; see p. C557 in this issue) confirm aspirin’s role in activating HO-1 expression and offer a possible mechanistic explanation by introducing another HO-1 inducer, 15-epi-lipoxin A₄, a lipid metabolite, and anti-inflammatory mediator of aspirin in vivo. With the use of a stable aspirin-triggered lipoxin A₄ analog (ATL-1), the authors find that HO-1 induction occurs both at the mRNA and protein levels and appears to be mediated by the activation of the G protein-coupled lipoxin A₄ (LXA₄) receptor. The functional relevance of HO-1 induction by LXA₄ is highlighted in a rescue experiment where the authors reverse LXA₄-induced inhibition of VCAM and E-selectin expression by pretreating their endothelial cell culture system with SnPP, a competitive blocker of HO-1 activity.

This is the first demonstration of synergism between the lipoxin and HO-1 pathways, which until now, due to lack of direct evidence, have been considered independent and unrelated anti-inflammatory signaling routes. The observed increase in HO-1 protein in vitro elicited by aspirin in cultured endothelial cells is unlikely to be the result of ATL formation because ATL biosynthesis requires transcellular trafficking of lipid metabolites between endothelial cells and leukocytes (5), the latter not being present in the authors’ experimental setup. However, this does not tarnish the importance of their findings. To the contrary, if aspirin were able to elevate HO-1 expression in vitro via additional ATL-independent pathways, how much more potent at HO-1 induction must this drug be in vivo, where ATL formation actually does take place?

Here is where nitric oxide (NO) comes into play. Endothelial NO synthase and NO were reported earlier to mediate HO-1 induction by aspirin in vitro (9, 10). A look into last year’s literature reveals that endothelial NO synthase as well as inducible NO synthase are also targets of ATL (15). This suggests that more than one signaling route triggered by aspirin eventually leads to activation of NO formation and ensuing anti-inflammatory effects such as the inhibition of leukocyte-endothelium interactions (15). The findings of the Fierro group have, of course, implications that go beyond endothelial function or dysfunction. Thus, of all the NSAIDs used, aspirin is surprisingly well tolerated, and previous studies found that the gastric safety of aspirin, at currently used anti-inflammatory doses, is quite high compared with other cyclooxygenase (COX) inhibitors (8). Interestingly, this has been attributed in independent studies to the ability of aspirin to induce HO-1 in gastric tissue (3) and to generating ATL in the stomach (20). LXA₄ and its carbon-15 epimer ATL have potent inhibitory effects on neutrophil chemotaxis, adherence, transmigration, and superoxide anion production. There
is considerable evidence that neutrophils play a key role in the pathogenesis of NSAID-induced gastric damage and that LXA₄ formation, triggered by aspirin, exerts a gastroprotective influence (20). Because acetylation of COX-2 in epithelial cells, followed by a shift in COX-2 activity toward 15R-HETE formation, is a necessary step in aspirin-triggered LXA₄ formation, COX-2 blockers have an inhibitory effect on LXA₄ formation under these conditions (5). This is reflected by clinical observations showing that the combination of aspirin and a selective COX-2 blocker results in greater gastric injury than that observed following the administration of either drug alone (20).

Again, a similar pattern of action has been reported at the level of HO-1 expression, with aspirin but not COX-2 blockers being capable of inducing this gene in cultured gastric cells, presumably via NO-dependent pathways (4). As with vascular cells, one might expect even stronger inductions of gastric HO-1 caused by aspirin in vivo because aspirin-triggered LXA₄ is formed via transcellular biosynthetic pathways and requires the concerted action of different cell types.

Because of mixed study results, aspirin is currently not considered of therapeutic value in preeclampsia or gestational hypertension; however, the literature published to date consistently shows a protective effect of low-dose aspirin for women with risk factors for preeclampsia without an increase in bleeding complications, including placental abruption (6). Whether HO-1 induction triggered by ATL might explain some of aspirin’s beneficial effects under these conditions cannot be answered presently, but the functional profile of HO-1 characterized by anti-inflammatory as well as vasodilatory properties would certainly be in agreement with such a hypothesis (2).

Interestingly, statins have also emerged very recently as inducers of HO-1 via unknown signaling routes (11, 13), confirming once more that there is some truth to the description of aspirin as being “the poor man’s statin” (18).

From what is outlined above, it seems clear that future studies should, above all, address the in vivo relevance of LXA₄-dependent HO-1 induction. With their demonstration that aspirin-triggered LXA₄ is a potent inducer of HO-1, Nascimento-Silva and coworkers have opened up a new chapter in HO-1 research. Because of numerous clinical implications and unanswered mechanistic questions, it bears the potential of attracting even more interested researchers into this exciting and still-young field of research.

REFERENCES