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Vioxx, Celebrex, Bextra . . . Do we have a new target for anti-inflammatory and antipyretic therapy?

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Several promising targets have been recently suggested (for review, see Ref. 9), and mPGES-1, the subject of the study of Saha et al. (18), is one such target. Identified by Jakobsson et al. (13), mPGES-1 is a 16-kDa member of the so-called MAPEG (membrane-associated proteins involved in eicosanoid and glutathione metabolism) family, which catalyzes the final step of the PGE2 synthesis: a nonoxidative rearrangement of the COX product PGH2 into PGE2. Not only does this enzyme occupy the terminal position in the PGE2-synthesizing cascade, but it also preferentially couples with “bad” COX, COX-2 (3, 16). Not surprisingly, mPGES-1 is uniquely positioned to catalyze inflammation-associated PGE2 synthesis. In rats, high (120–400 μg/kg) doses of bacterial lipopolysaccharide (LPS) were shown to increase mPGES-1 mRNA and protein levels in the brain and in many peripheral organs, including the lungs and spleen (14, 16, 24). In the brain, the message was localized in the vasculature, and the protein was abundant in the perinuclear envelope of endothelial cells, where mPGES-1 was colocalized with COX-2 (24). The febrile response of rats to a low dose of LPS (50 μg/kg) was also accompanied by strong transcriptional upregulation of the mPGES-1 gene in peripheral LPS-processing organs (the liver and lungs) and in the brain (10). In the latter study, remarkable features of the mPGES-1 response were its high magnitude and long duration. Indeed, the expression of this gene was upregulated more than 1,200 fold in the liver and more than 30-fold in the lungs and hypothalamus. This upregulation persisted for several hours after a single injection of LPS. Even when COX-2 expression had returned to its baseline, mPGES-1 remained overexpressed (10). An endogenous pyrogen, IL-1β, was also found to induce mPGES-1 in brain vascular cells, presumably endotheliocytes and perivascular macrophages (4). Undisputable evidence for the crucial involvement of mPGES-1 in LPS fever was obtained by Engblom et al. (5) and Saha et al. (18) by using the recently developed mice with deletion of the Ptges gene, which encodes mPGES-1 (21, 22). These mice showed no fever and no central PGE2 synthesis after peripheral injection of LPS, but they displayed an intact pyretic capacity in response to centrally administered PGE2 (5). These mice also showed drastically reduced or completely abolished fevers in response to peripheral IL-1β or turpentine but had a normal circadian rhythm of body temperature and developed the same hyperthermia in response to a psychogenic stressor as their wild-type littermates (18).

The most downstream position of mPGES-1 in the PGE2-synthesizing cascade makes this enzyme potentially the most selective target for antipyretic and anti-inflammatory therapy. The highest magnitude of upregulation of mPGES-1 among all
PGE₂-synthesizing enzymes studied during LPS fever, the long duration of this upregulation, and the fact that mPGES-1 is strongly upregulated when expression of COX-2 declines (10) further increase the attractiveness of this target. That mPGES-1 is indispensable for the development of the febrile response to LPS (5) and other pyrogens [as demonstrated by Saha et al. in this issue (18)] warrants even more optimism. Will the next big news from the producers of Vioxx, Celebrex, Bextra, and other “coxibs” be positive? Will it be about mPGES-1?

REFERENCES


