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

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TOGETHER WITH THE ARTICLES by Ivanov et al. (11) in the previous issue and by Thompson et al. (20) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, the article of Saha et al. (18) opens the Call for Papers on Physiology and Pharmacology of Temperature Regulation. This article establishes an indispensable role for the prostaglandin (PG) E2-synthesizing enzyme, microsomal PGE synthase (mPGES)-1, in two models of experimental fever: interleukin (IL)-1β induced and turpentine induced. These findings should be viewed in the context of the major breakthroughs and setbacks that have marked the development of antipyretic and anti-inflammatory pharmacotherapy in the recent past.

Following the cloning and identification of the second isoform of cyclooxygenase (COX) by Xie et al. (23), Kujubu et al. (12), and O’Banion et al. (17), it was soon realized that this newly discovered, inducible isoform, COX-2, is involved in inflammation and fever (“bad” COX), whereas the other, constitutive isoform, COX-1, has essential housekeeping functions under normal conditions (“good” COX) and does not mediate fever (for review, see Ref. 9). Furthermore, it was realized that nonsteroidal anti-inflammatory drugs could exhibit isoform selectivity (15). This realization sparked the search for selective COX-2 inhibitors that would suppress COX-2-mediated inflammation and fever while having minimal adverse effects related to inhibition of COX-1 (such as gastrointestinal and renal toxicity). Within a few years, reports of selective COX-2 inhibitors began to appear (1, 6). Animal experiments with these agents demonstrated potent antipyretic effects with reduced gastrointestinal toxicity (7, 8). Then, a number of highly selective COX-2 inhibitors, including celecoxib, rofecoxib, and valdecoxib, were approved for clinical use in the United States and Europe. However, adverse renal effects have been observed with these agents, similar to those seen with nonselective inhibitors, which may be partially due to inhibition of constitutively expressed COX-2 in the kidney (2). When taken on a daily basis at high doses, these drugs also have adverse cardiovascular effects (see, e.g., Ref. 19). During the last few months, one drug, Vioxx (rofecoxib), has been withdrawn from the market. Two others, Celebrex (celecoxib) and Bextra (valdecoxib), appeared in the U.S. Food and Drug Administration’s Public Health Advisory suggesting that these COX-2 inhibitors can increase the risk of heart attack and stroke. These troubles with selective COX-2 inhibitors will accelerate the search for new drugs to suppress inflammation and fever.

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 perivascular enve-lope 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
REFERENCES


