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CALL FOR PAPERS | *Physiology and Pharmacology of Temperature Regulation*

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) E_2-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 (**m**embrane-**a**ssociated **p**roteins involved in **e**icosanoid and **g**lutathione metabolism) family, which catalyzes the final step of the PGE_2 synthesis: a nonoxidative rearrangement of the COX product PGH_2 into PGE_2. Not only does this enzyme occupy the terminal position in the PGE_2-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 PGE_2 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 PGE_2 synthesis after peripheral injection of LPS, but they displayed an intact pyretic capacity in response to centrally administered PGE_2 (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 PGE_2-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

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PGE_2-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

1. **Copeland RA, Williams JM, Giannaras J, Nurnberg S, Covington M, Pinto D, Pick S, and Trzaskos JM.** Mechanism of selective inhibition of the inducible isoform of prostaglandin G/H synthase. *Proc Natl Acad Sci USA* 91: 11202–11206, 1994.
2. **Crofford LJ.** Specific cyclooxygenase-2 inhibitors: what have we learned since they came into widespread clinical use? *Curr Opin Rheumatol* 14: 225–230, 2002.
3. **Dieter P, Scheibe R, Jakobsson P-J, Watanabe K, Kolada A, and Kamionka S.** Functional coupling of cyclooxygenase 1 and 2 to discrete prostanoid synthases in liver macrophages. *Biochem Biophys Res Commun* 276: 488–492, 2000.
4. **Ek M, Engblom D, Saha S, Blomqvist A, Jakobsson P-J, and Ericsson-Dahlstrand A.** Pathway across the blood-brain barrier. *Nature* 410: 430–431, 2001.
5. **Engblom D, Saha S, Engström L, Westman M, Audoly LP, Jakobsson P-J, and Blomqvist A.** Microsomal prostaglandin E synthase-1 is the central switch during immune-induced pyresis. *Nat Neurosci* 6: 1137–1138, 2003.
6. **Futaki N, Takahashi S, Yokoyama M, Arai I, Higuchi S, and Otomo S.** NS-398, a new anti-inflammatory agent, selectively inhibits prostaglandin G/H synthase/cyclooxygenase (COX-2) activity in vitro. *Prostaglandins* 47: 55–59, 1994.
7. **Futaki N, Yoshikawa K, Hamasaka Y, Arai I, Higuchi S, Iizuka H, and Otomo S.** NS-398, a novel non-steroidal anti-inflammatory drug with potent analgesic and antipyretic effects, which causes minimal stomach lesions. *Gen Pharmacol* 24: 105–110, 1993.
8. **Gans KR, Galbraith W, Roman RJ, Haber SB, Kerr JS, Schmidt WK, Smith C, Hewes WE, and Ackerman NR.** Anti-inflammatory and safety profile of DuP 697, a novel orally effective prostaglandin synthesis inhibitor. *J Pharmacol Exp Ther* 254: 180–187, 1990.
9. **Ivanov AI and Romanovsky AA.** Prostaglandin E_2 as a mediator of fever: synthesis and catabolism. *Front Biosci* 9: 1977–1993, 2004.
10. **Ivanov AI, Pero RS, Scheck AC, and Romanovsky AA.** Prostaglandin E_2-synthesizing enzymes in fever: differential transcriptional regulation. *Am J Physiol Regul Integr Comp Physiol* 283: R1104–R1117, 2002.
11. **Ivanov AI, Steiner AA, Patel S, Rudaya AY, and Romanovsky AA.** Albumin is not an irreplaceable carrier for amphipathic mediators of thermoregulatory responses to LPS: compensatory role of α_1-acid glycoprotein. *Am J Physiol Regul Integr Comp Physiol* 288: R872–R878, 2005.
12. **Kujubu DA, Fletcher BS, Varnum BC, Lim RW, and Herschman HR.** TIS10, a phorbol ester tumor promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase/cyclooxygenase homologue. *J Biol Chem* 266: 12866–12872, 1991.
13. **Jakobsson P-J, Thorén S, Morgenstern R, and Samuelsson B.** Identification of human prostaglandin E synthase: a microsomal, glutathione-dependent, inducible enzyme, constituting a potential novel drug target. *Proc Natl Acad Sci USA* 96: 7220–7225, 1999.
14. **Mancini JA, Blood K, Guay J, Gordon R, Claveau D, Chan C-C, and Riendeau D.** Cloning, expression and up-regulation of inducible rat prostaglandin E synthase during lipopolysaccharide-induced pyresis and adjuvant-induced arthritis. *J Biol Chem* 276: 4469–4475, 2001.
15. **Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, and Vane JR.** Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc Natl Acad Sci USA* 90: 11693–11697, 1993.
16. **Murakami M, Naraba H, Tanioka T, Semmyo N, Nakatani Y, Kojima F, Ikeda T, Fueki M, Ueno A, Oh-ishi S, and Kudo I.** Regulation of prostaglandin E_2 biosynthesis by inducible membrane-associated prostaglandin E_2 synthase that acts in concert with cyclooxygenase-2. *J Biol Chem* 275: 32783–32792, 2000.
17. **O'Banion MK, Sadowski HB, Winn V, and Young DA.** A serum- and glucocorticoid-regulated 4-kilobase mRNA encodes a cyclooxygenase-related protein. *J Biol Chem* 266: 23261–23267, 1991.
18. **Saha S, Engström L, Mackerlova L, Jakobsson P-J, and Blomqvist A.** Impaired febrile responses to immune challenge in mice deficient in microsomal prostaglandin E synthase-1. *Am J Physiol Regul Integr Comp Physiol* 288: R1100–R1107, 2005.
19. **Solomon DH, Schneeweiss S, Glynn RJ, Kiyota Y, Levin R, Mogun H, and Avorn J.** Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation* 109: 2068–2073, 2004.
20. **Thompson CS, Holowatz LA, and Kenney WL.** Cutaneous vasoconstrictor responses to norepinephrine are attenuated in older humans. *Am J Physiol Regul Integr Comp Physiol* 288: R1108–R1113, 2005.
21. **Trebino CE, Stock JL, Gibbons CP, Naiman BM, Wachtmann TS, Umland JP, Pandher K, Lapointe J-M, Saha S, Roach ML, Carter D, Thomas NA, Durtschi BA, McNeish JD, Hambor JE, Jakobsson P-J, Carty TJ, Perez JR, and Audoly LP.** Impaired inflammatory and pain responses in mice lacking an inducible prostaglandin E synthase. *Proc Natl Acad Sci USA* 100: 9044–9049, 2003.
22. **Uematsu S, Matsumoto M, Takeda K, and Akira S.** Lipopolysaccharide-dependent prostaglandin E_2 production is regulated by the glutathione-dependent prostaglandin E_2 synthase gene induced by the Toll-like receptor 4/MyD88/NF-IL6 pathway. *J Immunol* 168: 5811–5816, 2002.
23. **Xie WL, Chipman JG, Robertson DL, Erikson RL, and Simmons DL.** Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. *Proc Natl Acad Sci USA* 88: 2692–2696, 1991.
24. **Yamagata K, Matsumura K, Inoue W, Shiraki T, Suzuki K, Yasuda S, Sugiura H, Cao C, Watanabe Y, and Kobayashi S.** Coexpression of microsomal-type prostaglandin E synthase with cyclooxygenase-2 in brain endothelial cells of rats during endotoxin-induced fever. *J Neurosci* 21: 2669–2677, 2001.