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ANALGESICS

Time for a new COX

Those who study the cyclooxygenase (COX) enzymes, which make the local hormones known as prostaglandins and are the target for non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, have long expected other variants of the enzyme to come onto the scene to help iron out some of the anomalies in the field. For one thing, the hugely popular drug acetaminophen reduces prostaglandin levels but seems to have little affinity for either of the two known COX enzymes, **COX-1** and **COX-2**. So, the report from Dan Simmons' lab in *Proceedings of the National Academy of Sciences* of the discovery of a third COX enzyme, which seems to be sensitive to the actions of acetaminophen, will be enthusiastically read by the many working on COX-based drug development.

There have been hints of other isozymes of COX before, but on this occasion, Simmons and colleagues were able to isolate two novel messenger RNAs from canine brain, the species in which much of the original field-defining work was done 30 years ago. These transcripts were shown to encode two COX-1-derived proteins, both of which contained 90 extra residues encoded by intron 1 of the COX-1 gene, together with the signal-peptide sequence. One of these, which the authors termed partial COX-1a (PCOX-1a), lacks 219 amino acids encoded by exons 5–8 of the

COX-1 gene and has no COX activity. The other, however, is a fully functional extended version of COX-1 and has been named COX-3 on the basis of its pharmacological difference from COX-1, despite the fact that both derive from the same gene.

COX-3 (as well as PCOX-1) is also expressed in humans, with highest levels being found in the cerebral cortex and heart. When these proteins were expressed in insect cells, which have previously been shown to be highly efficient expression systems for COX enzymes, COX-3 activity seemed to be about 20% that found for COX-1, which in turn is only 20% as active as COX-2. This expression system was used to investigate their pharmacological specificity. Not only did acetaminophen show greater specificity for COX-3 than COX-1 or -2, but so did certain other common analgesic/antipyretic drugs, among them diclofenac and ibuprofen. These results suggest a greater role for COX-1 gene products

in mediating pain and fever than previously thought.

The discovery of COX-2, the inducible form of COX, in 1991 sparked a rush of drug development activity, leading to the launch of the COX-2-selective blockers Celecoxib (Celebrex) and Rofecoxib (Vioxx), just a few months apart, in 1999. The announcement of COX-3 is certainly the closest we have come to explaining the actions of acetaminophen, and has undoubtedly already created a new flurry of activity at the bench.

Adam Smith

References and links

ORIGINAL RESEARCH PAPER

Chandrasekharan, N. V. *et al.* COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proc. Natl Acad. Sci. USA* **99**, 13926–13931 (2002)

FURTHER READING Simmons, D. L. *et al.* Induction of an acetaminophen-sensitive cyclooxygenase with reduced sensitivity to nonsteroid antiinflammatory drugs. *Proc. Natl Acad. Sci. USA* **96**, 3275–3280 (1999)

WEB SITE Simmons' laboratory:
http://cpms.byu.edu/cancerresearch/html/daniel_l_simmons.html