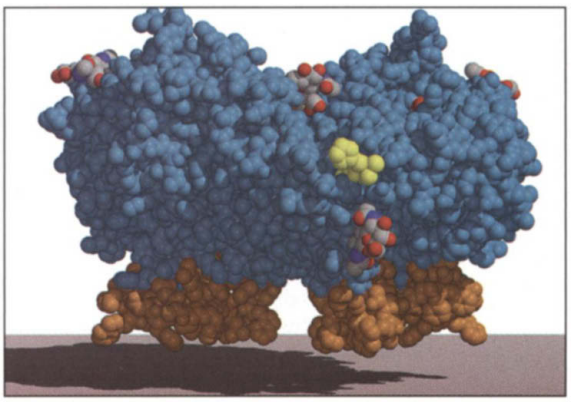
PAIN RESEARCH

Enzyme Might Relieve Research Headache

Acetaminophen is among the world's most popular pain medicines, but, agonizingly enough for researchers, how it works has been largely a mystery. Now a group led by biochemist Daniel Simmons of Brigham Young University in Provo, Utah, has discovered in dogs a new variant of the well-studied cyclooxygenase (COX) enzyme. The newfound enzyme, dubbed COX-3, fits the profile of the long-sought site of action for the drug, which is the active ingredient in Tylenol.



Pain in the neck? A newfound enzyme that is inhibited by acetaminophen resembles COX-1 (above), with an addition to the site marked in yellow.

The find "could explain the effects of acetaminophen, which we've never understood," says Timothy Warner, a pharmacologist at Barts and The London School of Medicine and Dentistry in the United Kingdom. If so, targeting COX-3 could lead to more potent painkillers, perhaps including some that lack acetaminophen's side effects, such as liver damage. The finding might also help researchers map new pathways for pain perception.

For decades, scientists thought that only one form of COX existed. But in 1991, three independent research teams—Simmons's among them—unveiled a second form, COX-2, and showed that it is the enzyme primarily responsible for inflammation. The first form, COX-1, safeguards the stomach lining, among other housekeeping jobs. Aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs inhibit both COX-1 and COX-2, accounting for both their anti-inflammatory action and side effects such as ulcers. But neither enzyme could explain the action of acetaminophen, which inhibits both molecules only very weakly.

Simmons happened upon the new COX serendipitously while trying to develop a better painkiller for dogs; traditional analgesics are toxic to them. While probing various tissues for the canine form of COX-1, he and his team were startled to find two genetic footprints, in the form of messenger RNAs (mRNAs), for COX-1 in dog brain. As the researchers report online this week in the *Proceedings of the National Academy of Sciences*, one of the mRNAs contained an additional short section of genetic code that is clipped out of COX-1.

To test whether the odd mRNA was a blueprint for a functional protein, Simmons and colleagues inserted the genetic code into insect cells. Sure enough, the cells produced novel enzymes that, like known forms of COX, churned out inflammatory molecules. The researchers exposed the COX-3–bearing insect cells to various painkillers and to their astonishment found that acetaminophen almost completely inhibited the new enzyme. Another analgesic called dipyrone, which like acetaminophen fights pain and fever but not inflammation, also inhibited COX-3. Neither drug interfered much with COX-1 or COX-2, suggesting that drugs with this constellation of activities might act at a common site.

By combing various human tissues for the COX-3 mRNA, Simmons's team found preliminary evidence that COX-3 exists in humans and is particularly plentiful in brain tissue. Warner and others caution that much more work needs to be done to determine COX-3's role in the human brain, if any. But if the finding holds up in humans, it might portend the presence of other variants of COX-1 and COX-2. This could lead to pain and fever relievers that are better tailored to individual patients or ailments. The discovery of COX-2 ignited a worldwide race to develop COX-2–specific drugs. With the discovery of COX-3, the competition is likely to increase.

–INGRID WICKELGREN

UNITED NATIONS

Bush Brings U.S. Back to UNESCO

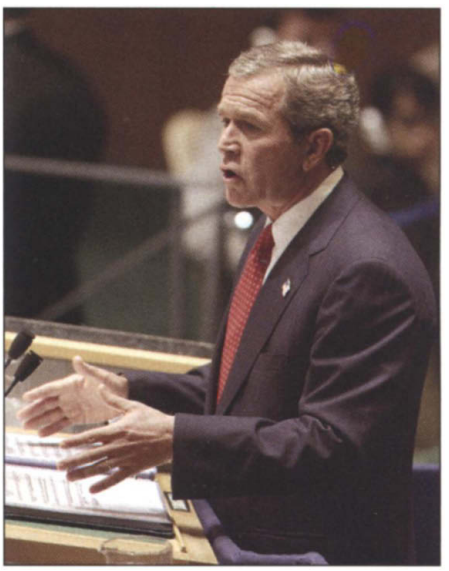
President George W. Bush tossed a surprise into his get-tough-on-Iraq speech to the United Nations General Assembly last week: The United States will rejoin the U.N. Educational, Scientific, and Cultural Organization (UNESCO) after an 18-year absence. The announcement made few headlines, but at UNESCO headquarters in Paris it's the best news in years. "This is very important and welcome," says Maciej Nalecz, director of UNESCO's Division of Basic and Engineering Sciences.

UNESCO was founded at the end of World War II by 20 nations, including the United States, "to contribute to peace and security by promoting collaboration among nations through education, science and culture." Under this wide-ranging mandate, it has initiated hundreds of conferences and projects ranging from geological research, environmental management, and renewable energy development to literacy promotion and the preservation of ancient monuments. But in the Cold War years, the organization was viewed by many as being anti-Western and under the sway of the Soviet Bloc. President Ronald Reagan ended U.S. membership in 1984, charging the UNESCO leadership with mismanagement and hostility to a free press.

Since then, many campaigns—including a 1993 petition signed by 37 Nobel laureates—have been launched to persuade the United States to rejoin. The United Kingdom, which also pulled out in 1984, rejoined in 1997. New impetus has come from the current UNESCO president, Koichiro Matsuura, who since his election in 1999 has been restructuring the organization in the hopes of enticing the United States back into the fold. These efforts apparently convinced Bush that UNESCO is "reformed," so "America will participate fully in its mission."

Membership fees for the United States, calculated according to gross domestic product, could run to $60 million per year, amounting to 22% of UNESCO's current budget. This windfall will be a boon to projects currently under consideration, such as the International Programme in Basic Sciences, which would upgrade research centers in the developing world and create fellowships for academic exchange. "This will profoundly affect our vision of where to go and what to do next," says Nalecz.

–JOHN BOHANNON



Talking tough. President Bush addressed the U.N. General Assembly last week.

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