Aspirin: How it lessens pain and swelling

"Take two aspirin and call me in the morning." Besides the Hippocratic oath, this may be the best-known phrase in modern medicine.

Yet despite more than 150 years of study, scientists have only recently begun to understand the precise chemical mechanisms that enable the legendary anti-inflammatory agent to help heal what ails us.

Now, scientists have completed a picture of the molecule's structure that shows how it connects to a key enzyme. Biochemists Patrick J. Loll and R. Michael Garavito of the University of Chicago and Daniel Picot of the Institute of Biology and Physical Chemistry in Paris have published a detailed image of a variant form of acetylsalicylic acid, otherwise known as aspirin.

"Essentially," says Garavito, "this structure shows us how aspirin works."

Scientists have known since the 1960s that aspirin and other nonsteroidal anti-inflammatory drugs relieve pain and lessen swelling by disrupting two enzymes, PGHS-1 and PGHS-2, versions of the compound prostaglandin H_2 synthase. Yet researchers had not determined until recently the details of that interaction. In its latest report, Garavito's team used X-ray crystallography to show exactly how bromo-aspirin, a slight variation of the pure form, binds to and inactivates PGHS-1.

"This work confirms what researchers have suspected about how aspirin inactivates this enzyme," says Lawrence Marnett, a biochemist at Vanderbilt University School of Medicine in Nashville. "Still, it's good to have a detailed picture of how a drug works."

"This report fills in details from their earlier work, which was ground-shaking," says Richard J. Kulmacz, a biochemist at the University of Texas Health Science Center in Houston. Garavito's team reported initial data on the structure in 1994. "Putting all of the work together, it's very important for drug design. If you don't have the structure of a target you're aiming to block, you end up flailing around."

Efforts to design a new generation of anti-inflammatory pain killers focus on blocking PGHS-2, believed to be a more effective method with fewer side effects, Kulmacz says. Yet because PGHS-1 and PGHS-2 appear so similar, Kulmacz adds, "having the structure of one enzyme may help us figure out how best to block the other." —*R. Lipkin*

Copper deficiency impairs immune cells

Nutrition is probably the last thing on the mind of someone gulping down a beer or savoring a chunk of chocolate. But both foods are rich in an essential mineral that most people don't get enough of: copper.

Most people get only about 1 milligram of copper a day, compared to the recommended 1.5 to 3.0 milligrams. A new study shows that a diet deficient in copper affects the human immune system, reducing the activity of some cells that attack invading bacteria. But no one is sure whether these effects actually compromise the body's ability to fight off infection.

Darshan S. Kelley, Judith R. Turnlund, and colleagues at the Western Human Nutrition Research Center in San Francisco conducted the study as part of a larger, U.S. Department of Agriculture project assessing the role of dietary copper in the body. Their results appear in the August American Journal of Clinical Nutrition.

The researchers put 11 men on a liquid diet—balanced in all nutrients except copper—for 90 days. At several points in the investigation, the researchers measured the number and immunological activities of various immune cells in blood samples. Some cell activities decreased markedly, while others didn't change at all. One cell population, that of antibody-producing B cells, actually increased.

Clinically, this combination of effects is difficult to sort out. "Immune function is a very, very complicated field," Turnlund says. "The other problem we still have is that we don't really know what normal ranges for some of these immune function indices are."

In a recently completed study of moderate, yet chronic, copper depletion in rats, Mark L. Failla of the University of North Carolina at Greensboro found similar changes in the immune system. Such long-term studies will give scientists a better idea of how much copper people really need, he says. "We're fine under normal conditions, but then when there's a stress to the system, be it an infection or psychological stress at the workplace . . . you may not have the appropriate amount . . . to deal with that situation."

The center plans to supplement the normal diet of outpatients with copper to see whether it enhances their immune systems. In the meantime, it won't hurt to eat more copper-rich foods, such as beans, nuts, and seafood. Beer and chocolate, though, are a different story. — *C. Wu*

Getting to the root of nodule formation

Some plants, primarily legumes, make farmers' lives a little easier. They grow nodules on their roots that enable them to fix their own nitrogen, which farmers would otherwise have to add as fertilizer. Scientists have tried for many years—with no real success—to figure out how to get nonlegumes to form these nitrogen-fixing nodules.

Researchers know, however, that this special ability of legumes depends on rhizobium bacteria, which set up shop in the plants and secrete lipo-chitooligosaccharides (LCOs), carbohydrate-like molecules that trigger the formation of nodules.

Now, a study suggests that LCOs may be able to initiate nodule growth in nonlegumes as well. What's more, LCOs may serve as general-purpose plant growth regulators, report Horst Röhrig and his colleagues at the Max Planck Institute for Plant Breeding in Cologne, Germany, in the Aug. 11 Science.

The researchers developed a fairly simple technique for making LCOs in large quantities, they report. They then applied a very small amount of synthetic LCO to the cells of a tobacco plant, which does not grow nodules. The LCOs spurred the tobacco cells to grow and divide, an activity that usually requires the hormones auxin and cytokinin.

"We think we may be mimicking the early stages of cell division that are involved in making nodules," says coauthor Richard Walden.

LCOs appear to act like auxin, which helps control many aspects of plant growth besides nodule formation, says Walden. LCOs and auxin seem to trigger the same or similar genes.

The LCO-inspired growth in nonlegumes suggests that they and legumes share a similar growth mechanism that LCOs help turn on, the authors note.

The researchers needed only about 10 molecules of LCO per cell to initiate cell division, they report. Seeing activity with such low amounts "is powerful evidence" that LCOs are plant growth regulators, says Tom LaRue of the Boyce Thompson Institute for Plant Research in Ithaca, N.Y.

Röhrig and his colleagues don't believe that their work will necessarily lead to nitrogen-fixing tobacco plants. However, synthetic LCOs may someday increase the efficiency of nodule formation in legumes, Walden speculates.

The researchers are now testing different forms of LCOs to see what key part of the molecule triggers cell division. However, "the really hot thing is finding out what is the receptor in legumes and nonlegumes for these LCOs," says Walden. — *T. Adler*