SCIENCE NEWS of the week

Enzyme Structure Points to New Drugs

Enzymes work as chemical traffic cops, keeping the body's metabolic pathways flowing. They convert inactive substances into essential ones and render dangerous substances harmless. Now, advances in understanding a bacterial enzyme suggest a new mechanism for controlling human blood pressure.

For the first time, two crystallographers have figured out the three-dimensional structure of a short-chain dehydrogenase, an enzyme belonging to a widespread class of compounds that regulate levels of sugars, prostaglandins, alcohols and other important substances. The bacterial enzyme closely resembles its human counterpart, report William L. Duax and Debashis Ghosh of the Medical Foundation of Buffalo (N.Y.), Inc. They described their findings this week at the annual meeting of the American Crystallographic Association in Toledo, Ohio.

By controlling kidney levels of natural steroids, the human enzyme figures importantly in regulating blood pressure and plays a key role in the established link between licorice and hypertension. "Maybe there is a way to manipulate this enzyme to bring blood pressure down," Duax says.

Licorice contains an ingredient that prevents the human enzyme from converting the steroid hormone cortisol into cortisone. High levels of cortisol affect the body's salt balance and can cause blood pressure to rise, sometimes to dangerously high levels. Babies born without the ability to make the enzyme develop life-threatening hypertension.

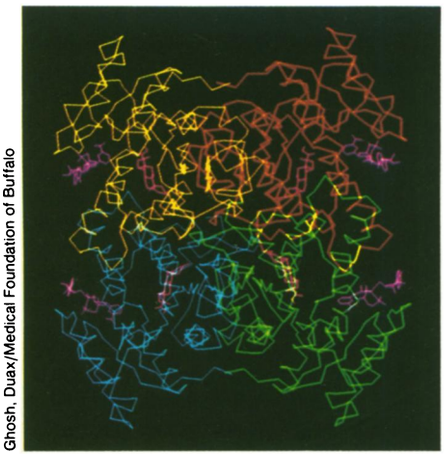
Licorice also inhibits the bacterial enzyme, the Buffalo researchers found. In addition, the amino acid sequences in the two versions look alike, even though they do not match those of longer, more intensively studied dehydrogenases containing 350 amino acids, Duax says. These similarities suggest that the bacterial enzyme can serve as a useful surrogate for the human version, which is difficult to obtain in large quantities, he says.

"We're hoping that by studying this [bacterial] enzyme we can gain some insight into how our [own] enzyme is working," says Carl Monder, an endocrinologist at the Population Council Center for Biomedical Research in New York City. That insight, he says, might suggest ways to alter the enzyme's activity to control blood pressure – and in other instances, to prolong the effects of steroidal medications.

The active form of the bacterial enzyme consists of four enzyme subunits that twist together into an asymmetric molecule. Using X-ray diffraction, Ghosh and Duax pinpointed the "handcuffs" used by this chemical cop—the twists and kinks in its molecular structure that temporarily snare steroid molecules and a "cofactor" compound necessary to metabolize them. Each of the four enzyme components contains about 250 amino acid building blocks, but most of these serve only as scaffolding to hold a few key amino acids in the proper position to create the handcuffs, Duax explains.

Its seems that a cortisol molecule nestles into one fold of the bacterial enzyme, and a cofactor molecule fits into another spot nearby. Then one of the amino acids, arginine, deactivates the cortisol by transferring a hydrogen from the steroid to the cofactor. "The enzyme is there to expedite the removal of the hydrogen," says Duax.

These findings may help pharmacologists create new drug compounds. "If you know the topology of the active site, then it should be possible to design chemical agents that fit into the active site and inhibit the enzyme," Monder says. He envisions drugs that could slow the deactivation of steroid drugs, prolonging their anti-inflammatory effects. As for hypertension, Monder says, "by knowing the [enzyme's] three-dimensional structure, we possibly gain some insight on how to enhance [its] activity." – *E. Pennisi*



Ghosh, Duax/Medical Foundation of Buffalo

Four subunits (shown in different colors) make up this bacterial dehydrogenase, which transfers hydrogen from a steroid molecule to a cofactor (both in pink).

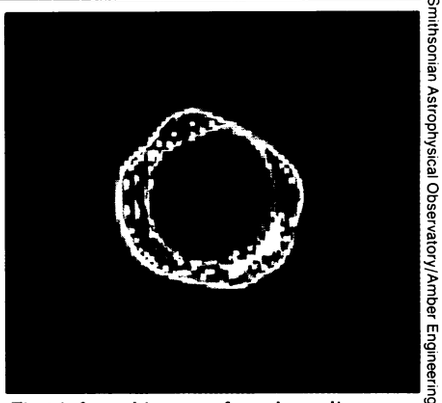
Out of the shadows: An illuminating eclipse

From the mountaintop vantage point of Mauna Kea, Hawaii, some of the world's largest and most powerful telescopes witnessed July 11's total eclipse of the sun. Using infrared, visible-light and radio-wave detectors, scientists took advantage of the event to study features of the solar atmosphere that show up clearly only when the moon blocks the brilliant light of the solar disk.

While the results remain preliminary, they have already yielded several new insights.

One set of Mauna Kea observations, made with a spectrograph attached to NASA's infrared telescope, pinpointed the location of a key spectral line of magnesium at one edge of the sun. Scientists use this infrared emission line, which splits into three components in the presence of a strong magnetic field, to gauge magnetic activity in the solar atmosphere. But uncertainties regarding the line's exact altitude have limited its usefulness, notes Donald Jennings of NASA's Goddard Space Flight Center in Greenbelt, Md. Ever since astronomers discovered the line in the early 1980s, they have debated whether it lies in the upper photosphere – a region at or just above the visible surface of the solar disk – or in a region just beyond the photosphere, called the lower chromosphere.

Two weeks ago, as the moon swept across the face of the sun like a giant shutter, Jennings and his colleagues measured the time interval between the moment when the moon first blocked the solar disk and when it later obscured the magnesium line as it moved across the sun. They then used the known velocity of the moon to calculate the altitude of the magnesium emission. The team, headed by Drake Deming of Goddard, discovered that the bulk of the emission occurs in the upper photosphere, just a few hundred kilometers above the solar surface, Jennings told SCIENCE NEWS. The



Smithsonian Astrophysical Observatory/Amber Engineering

First infrared image of a solar eclipse shows corona surrounding darkened solar disk. White denotes highest intensity; blue denotes lowest.