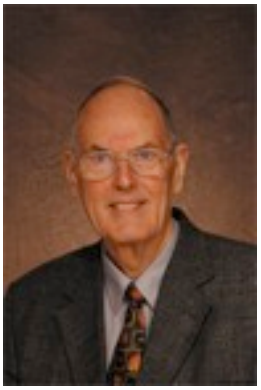
Why do some people have a high tolerance for pain, while others experience the slightest touch as painful? Why do some injured soldiers perform heroic feats and claim that they felt no pain at the time?

Truthfully, nobody yet has the answers to those questions. But new findings by Drs. Meinhart Zenk and Toni Kutchan at the Donald Danforth Plant Science Center lead to some tantalizing possibilities.



Meinhart Zenk, Ph.D
Photo courtesy of Donald Danforth Plant Science Center

Humans and other mammals excrete morphine in their urine. That has been known for a long time. The levels of morphine are also known to vary widely. The source of the morphine has been the unanswered question until now.

Zenk and colleagues in Germany showed in a recent article that mice, and presumably all mammals, have the metabolic equipment to manufacture morphine from the amino acid tyrosine, found in all proteins. Furthermore, the pathway from the starting material follows almost exactly the same chemical steps as the pathway that the opium poppy uses.

Kutchan emphasizes that the opium poppy is the only plant source of morphine. And consequently poppy seeds would be the only source in the normal human diet. (Some may remember the "Seinfeld"episode in which Elaine failed a drug test because she had eaten a poppy seed muffin.)

For the opium poppy, morphine is one of those secondary products used for communication with the environment. Secondary products are useful to the plant for various reasons such as a poison for defense, or a color that would attract a pollinator. We might use them as drugs or dyes. Familiar drugs from plants include digoxin from foxglove, quinine from the bark of the cinchona tree, and the poisons strychnine and curare.

Zenk and his research team established that rodent chow has no traces of morphine or morphine precursors; therefore the morphine in their urine does not come from their diet.

They injected the mice with a series of heavy isotope labeled molecules known to be in the poppy's morphine synthetic pathway. In each experiment they collected the urine and found the labeled precursors had been converted into other precursor molecules further along the morphine synthetic pathway—as well as into morphine itself. Since the products they detected are identical to the intermediates in the poppy's morphine synthetic pathway, the steps involved are the same. Kutchan points out that "nature has invented morphine twice"—a true case of convergent evolution.

The volume of urine that can be collected from a mouse is not great. Furthermore, morphine is at best a trace constituent of urine.

Zenk's research was made possible by a new instrument, the Orbitrap mass spectrometer, that calculates mass:charge ratios out to five decimal places. With this degree of super-precision, and super-sensitivity each molecule can be assigned a unique number and can be distinguished from other very similar molecules.

Zenk and Kutchan pointed out that although the chemical steps along the pathway are the same, the enzyme molecules that catalyze each step are somewhat different. In other words, the enzyme that gets molecule A to transform to molecule B in the opium poppy has a different amino acid sequence from the enzyme that does the same job in animals. (Enzymes are proteins, which are unique long polymer strings of amino acids.)

It would be difficult to overstate the importance of morphine in medicine. It is the drug of choice for accident victims, on the battlefield, and for easing pain and anxiety at the end of life. All morphine is extracted from the opium made by poppies—chemical synthesis would take about 30 steps and so be prohibitively costly. Opium, which is the dried latex collected by making cuts in the fruit of the poppy, also contains codeine and other non-opiate molecules.

It has a long history. It is said that the Turkish army was nearly invincible in the 17th century because along with their ultra-strong coffee they used opium to reduce fear and inhibitions. The opium wars between China and England in the 18th century opened China to trade with the west. Today, although opium poppies are grown legally in certain countries as a source of medical morphine, illegal poppy crops, from Afghanistan for example, contribute to the street drug problem throughout the world.

Opium poppy fruit with latex containing morphine oozing from shallow cuts.
Photo courtesy of Danforth Plant Science Center

What is the function of morphine made in the mammalian body? Would it be to modulate acute pain in injury? The nervous system has opiate receptors, as does the gut. Zenk and collaborator Michael Spiteller had hoped to analyze the urine collected from accident victims in Cologne, Germany, but those experiments were not successful because an injection of morphine is the first thing EMT personnel give to severely injured persons. He now plans to analyze the urine of people with extremely painful conditions, such as herpes, who are not treated with morphine.

Kutchan suggests that morphine's function may be more homeostatic. Perhaps a condition such as fibromyalgia, in which people have pain all over their bodies, is the result of underproduction of endogenous morphine. Again, such a hypothesis would be possible, albeit quite difficult to prove.

Clearly, the discovery that morphine is produced in the animal kingdom is just the beginning of new avenues of research.

Toni Kutchan was named to the prestigious German Academy of Science, The Leopoldina, in August. The Leopoldina, founded in 1652, is the oldest continuously existing acadmeny of natural sciences and medicine in the world. By her election she joins a roster that has included such scientists as Albert Einstein, Marie Curie, and Charles Darwin.

She also joins her husband, Meinhart Zenk, who was elected to The Leopolina in 1983.

Toni Kutchan, Ph.D.
Photo courtesy of Donald Danforth Plant Science Center