How lithium helps manic depression

To make an atom of lithium, take three protons, mix them with some neutrons, and add a few electrons along with a pinch each of the strong and electroweak forces. During the last 20 years, this simple atomic recipe has helped people who suffer debilitating bouts of mania, depression or both, to regain some normalcy in their lives. Retail pharmacies filled about three million prescriptions for lithium last year. Now medical researchers at the Johns Hopkins University School of Medicine in Baltimore are discovering what lithium does when it gets inside of brain cells. This understanding could enable scientists to suggest drugs that act more specifically, and therefore with fewer side effects, than lithium for treating serious mood disorders.

Earlier in the decade, several laboratories found that lithium affected a complex biochemical system — called the phosphatidylinositol cycle, or the "PtdIns cycle" — inside many types of cells. The cycle, first found in the 1950s, is known to be a widespread "second-messenger" system that relays and amplifies signals from neurotransmitters, hormones and other "trigger" molecules that are first received by a battery of specialized chemical antennae on the cell membrane.

Signals received by some of these membrane receptors trigger the PtdIns cycle into action. What follows is a cascade of biochemical events that can show up in numerous ways such as secretion of the neurotransmitter serotonin, the occurrence of glycogenolysis — the breakdown of the major food storage molecule (glycogen) in animals — or DNA synthesis. Some of these cellular processes may surface as observable behavior, such as mania and depression.

The more trigger molecules there are in the fluids surrounding PtdIns-containing cells, the more cycles the PtdIns cycle runs through, and presumably the more intense or prolonged will be the associated physiological responses. But adding lithium to the system, say by taking a pill of lithium carbonate, is like throwing thousands of molecular monkey wrenches into the turning PtdIns cycles of each cell. Based on their recent work, the Hopkins researchers suggest that wherever there is an abnormal amount of trigger molecules, lithium might moderate the RPM's of these PtdIns engines and, therefore, any abnormal cellular and behavioral responses that would otherwise follow.

Recently, Harold A. Menkes, Jay M. Baraban, Arthur N. Freed and Solomon H. Snyder published in the PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (Vol. 83, No. 15) results of a preliminary study designed to test if lithium's PtdIns connection, which was demonstrated earlier by William R. Sherman of the Washington University School of Medicine in St. Louis, has any effect on physiological responses to chemical signals carried by neurotransmitters. The scientists tied three rings of guinea pig tracheal muscle into a chain. One end was fixed and the other was attached to a tension measuring device. They showed that lithium slowed the rate at which the muscles relaxed after they had been stimulated to contract by a neurotransmitter. When muscle contraction was triggered without transmitters, relaxation rates were not affected.

The scientists conclude that lithium can indeed affect neurotransmitter responses via the PtdIns cycle. The researchers used muscle because its contractile response to neurotransmitters is far easier to detect and measure than the more subtle molecular responses to those transmitters of neural tissue.

Now the Hopkins scientists are conducting experiments to see if the mischief perpetrated by lithium on the PtdIns system has an effect on brain cells; if so, it might explain lithium's demonstrated ability to moderate extreme moods of different kinds. The scientists will present their latest findings next week in Washington, D.C. at the 16th Annual Meeting of the Society for Neuroscience.

Baraban told SCIENCE NEWS that he and several colleagues will present results of experiments with slices of rat hippocampus, which indicate that lithium *does* affect how brain cells respond to the neurotransmitter acetylcholine.

To explain the "normalizing" effects of lithium, the Hopkins researchers theorize that "lithium should be most effective at sites where the PtdIns system is overactive." So, if mania and depression are the result of such overactive systems (whether by an abnormal amount of triggering molecules or because of another more subtle reason), lithium would throttle down the system common to both. The appeal of this theory, says Martin Zatz of the National Institute of Mental Health, is that it suggests how a single material such as lithium can have such disparate therapeutic effects. Other chemicals that specifically inhibit the PtdIns cycle, the Hopkins researchers suggest, may have therapeutic effects similar to those of lithium. *— I. Amato*

Experts say force is not with SDI

The U.S. National Academy of Sciences (NAS) was founded during the presidency of Abraham Lincoln. Its purpose was to gather together the most distinguished scientists in the country to advise the government on matters related to science. It may not be entirely coincidental that the founding of the NAS took place during what historians often call the first modern technological war. Nowadays war is even more technological than it was in the 1860s. The U.S. government's latest weapons proposal, the Strategic Defense Initiative (SDI), demands technology that doesn't yet exist. Therefore the Cornell Institute for Social and Economic Research of Ithaca, N.Y., decided to poll members of the NAS for their opinions on the feasibility and desirability of SDI.

The response was overwhelmingly negative. Questionnaires went to NAS members with expertise in astronomy, physics, mathematics, chemistry, geophysics, applied physical and mathematical sciences and engineering. Of 634 "eligible" individuals, 451 returned questionnaires, 51 refused and 130 did not respond. What the pollsters call their "bottom-line question," namely: "What is your overall attitude toward the current SDI program?" elicited an eight-to-one negative response. Slightly more than 54 percent of the respondents chose to reply, "I strongly oppose it," 25 percent chose the reply "I oppose it," 10.8 percent were neutral and 9.8 percent chose either support or strong support.

One respondent commented, "SDI is an unprecedented hoax being presented to the American people." But another wrote: "It is a wonderful proposal."

According to the government itself, the SDI system must be survivable and cost-effective. On this question 55.2 percent of survey respondents rated prospects extremely poor, and another 25.5 percent called them poor. Only 3.6 percent thought them good or extremely good.

"I am afraid it won't work, and would be even more afraid if I thought it would," a respondent commented.

To be effective and survivable, a defense system has to destroy a certain proportion of the warheads sent by the enemy. Given the supposition that "the Soviet Union launched an all-out attack with its present force of approximately 9,000 strategic missile warheads," respondents were asked to estimate how many of these would have to be destroyed to provide an effective defense of the U.S. civilian population. The defense would have to take out more than 99 percent of incoming warheads according to 74.1 percent of the respondents. However, only 2.1 percent of respondents thought that an SDI system could be built in 25 years that would destroy 99 percent of incoming warheads under the assumption that Soviet strategic nuclear forces remain frozen. With the assumption that the Soviets would increase and modernize their forces and countermeasures without restraint, only 0.7 percent of respondents thought an SDI system could

be built within 25 years that would destroy 99 percent of the incoming warheads.

"I believe some research should be supported, but general population protection is a pipe dream," a respondent wrote.

A negatively phrased question, "Scientific review has not played a sufficiently important role in structuring the current SDI program," prompted 60.7 percent of the respondents to "strongly agree" and another 23.8 percent to "agree." One respondent added, "As far as I know, only those physicists where research is supported by SDI funds approve of it."

—D.E. Thomsen

Viral involvement in Kawasaki syndrome?

Researchers from several Harvard-affiliated institutions have found signs of viral involvement in Kawasaki syndrome. The cause of the illness, which can result in heart problems in young children, has remained elusive (SN: 7/6/85, p. 10).

Kawasaki syndrome includes among its symptoms fever and rash. About 15 to 20 percent of children with it develop weakened walls in their coronary arteries. The syndrome is more common in Japan, where it was discovered, than in the United States, which has several hundred cases a year.

Incidence of the disease shows a pattern consistent with an infectious agent — cases tend to occur every few years and are most common in winter and spring. Researchers have focused their attention on a retrovirus, a type of virus that can promote the type of white blood cell growth seen in the syndrome.

The Harvard group detected reverse transcriptase, an enzyme peculiar to retroviruses, in 5 of 14 children with Kawasaki syndrome. The enzyme could not be found in cells from healthy children or children with other fever-related illnesses.

The researchers were able to photograph viral particles in white blood cells through electron microscopy, and they were also able to transfer infection from one cell to another. Their work is described in the Oct. 30 NATURE.

The NATURE report confirms and extends a study in the Sept. 6 LANCET by Stanford T. Shulman and Anne H. Rowley of Children's Memorial Hospital in Chicago. They detected reverse transcriptase in 8 of 18 children with Kawasaki syndrome.

But while both studies indicate the virus is present in diseased children, neither proves it is the cause. "The exact role remains to be elucidated," says Donald Y. M. Leung of Harvard Medical School. Says Rowley, "I'd put it in the realm of an exciting possibility." *—J. Silberner*

Roach hormone: Clue to human ancestry?

The strongest hormonal evidence yet of a common ancestry for insects and mammals has been provided by a pair of newly identified neuropeptides, isolated from cockroaches. These chemicals, called leucosulfakinins (LSKs), bear a strong similarity both in structure and function to hormones present in mammals, including humans. The strong similarity between the insect and mammalian neuropeptides, says one of the researchers, Ronald Nachman, is "evidence that our [human] hormones have very ancient roots."

Biochemical similarities between primitive species, like the cockroach, and more recent branchings on the evolutionary tree, like mammals, serve as "molecular clocks" — a means for identifying and tentatively dating the evolutionary divergence of what were once closely related organisms. The high degree of similarity between the LSKs and two hormones present in humans — human gastrin II and cholecystokinin (CCK) — indicates that these neuropeptides represent one of the slowest ticking of the molecular clocks, according to Nachman, a chemist at the U.S. Department of Agriculture (USDA) Western Regional Research Center in Berkeley, Calif.

Both LSK and LSK-II — amino-acid-chain molecules released by the Madeira cockroach's brain — appear to be hormones. Fifty-five percent of LSK's amino-acid sequence is identical to human gastrin II's, half of LSK-II's matches that in the frog neuropeptide caerulin and greater than 40 percent of LSK-II's amino-acid chain matches that of CCK. These are the highest percentages of structural similarity reported between insect and vertebrate neuropeptides, according to the researchers. Even more convincing, Nachman says, is that both LSK and LSK-II contain sulfate groups — a rare occurrence in hormones of any species. This same rare sulfation is present in the vertebrate neuropeptides they resemble.

Moreover, gastrin, CCK and both LSKs stimulate muscle contraction in the digestive tract; gastrin and both LSKs stimulate blood circulation. This homology of function further establishes the neuropeptide link between insects and mammals, Nachman believes. And because the activity of the LSKs has not yet been fully characterized, it's possible they may share even more attributes in common with the mammalian hormones — such as the ability to regulate digestive tract water content, to make organisms feel sated by a meal and to secrete enzymes. Nachman, William F. Haddon and colleagues from two other research laboratories described LSK's structure and function for the first time in the Oct. 3 SCIENCE; LSK-II's have just been published in the Oct. 15 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS.

"This [work] is interesting in that it shows there's something common to us and insects that goes back 500 million years and has changed so little," says Jerold M. Lowenstein, a molecular-evolution researcher at the University of California at San Francisco. "It gives you insight into how evolution works; it conserves those things that are important and work." David Schooley, a biochemist at the Palo Alto, Calif.-based Zoecon Research Institute, agrees.

Two years ago Schooley coauthored one of the first papers identifying a homology between an insect hormone and a functionally similar mammalian hormone. But such investigations are still rare, notes G. Mark Holman, a collaborator on the LSK work at a USDA lab in College Station, Tex. "Up until about a year ago there were only four insect neuropeptides of known structure," he says. "Now there are approximately 20."

As more are found, Nachman says, one may expect to see more of these biochemical links between distant twigs on the evolutionary tree. *—J. Raloff*

New northern sky survey

When astronomers make an image of some part of the northern sky and find something new, they very often check their discovery against the image of the same area in the Palomar Sky Survey. The survey is a series of photographic plates covering the whole northern sky that serves as one of astronomers' most popular reference atlases.

Now a new Palomar Sky Survey is under way. The old one, starting in 1949, took seven years to make. In three decades many stars have changed their positions, and astronomical observing capabilities have improved substantially. The same 48-inch Schmidt camera that did the previous survey will do this one. But now the wide angle telescope-camera has been fitted with a new $380,000 lens to improve its capabilities. The survey will produce 2,682 plates to cover the entire northern sky. Completion is expected by 1991. This time there is a similar Schmidt camera in Australia doing a complementary survey of the southern sky.

The survey is expected to discover a number of new objects, quasars, galaxies, etc., on immediate inspection of the plates as they are developed. The recently reported Comet Wilson was found on one of the first plates (SN: 9/20/86, p. 181). However, nobody sees everything interesting at first look, so the survey's enduring value will be as an archive and standard of comparison for future observations. □