# 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



Science Service, Inc. is collaborating with JSTOR to digitize, preserve, and extend access to *Science News*. www.jstor.org