Opioids moonlighting in cell growth?

Discovered in normal nerve tissue more than a decade ago, substances called endorphins, with their morphine-like effects, are popular subjects of both scientific research and public attention. These compounds, along with the rest of the general class of pain relievers called opioids, have been studied for their "feel-good" role. But recent reports suggest they also may help regulate both normal and malignant cell growth.

By slowing cell division, naturally occurring opioids apparently exert an inhibitory control over brain tissue development in young mice, scientists reported at last week's meeting of the Federation of American Societies for Experimental Biology in Washington, D.C.

According to Ian S. Zagon of Pennsylvania State University's Milton S. Hershey Medical Center in Hershey, if a compound that blocks opioid receptors is injected prior to examination of the brain — thus making the body's opioids ineffective — there is a greater-than-normal proliferation of brain cells. He told SCIENCE NEWS that an abnormal increase in cell growth is seen at times when the opioid receptors are blocked, whether the blockade is continuous during the test period or intermittent.

However, when the blockade is intermittent, the overall cell growth rate is decreased to 25 percent below normal at times when the blockade is off. Zagon attributes this to overstimulation of receptor production by the cells, in an attempt to compensate for opioid deficiency caused by the blockade. The ultimate result of the blockade by opioid-like substances results in mice that appear older than their untreated counterparts, says Zagon. For example, a nine-day-old mouse may resemble another that is two weeks old, based on appearance and behavior. But when opioid-binding in brain tissue is blocked intermittently, smaller-than-normal mice result.

These growth differences disappear by 21 days after birth, an observation consistent with other studies showing that opioid receptors in certain areas of the brain disappear as the animal matures. According to Barbara H. Herman of the Brain Research Center at Children's Hospital in Washington, D.C., the level of opioids in humans drops three-fold after the first 24 hours of life.

Herman, who presented her work on opioid levels in autistic children at last fall's meeting of the Society for Neuroscience, told SCIENCE NEWS that the Pennsylvania results may help explain the link between studies suggesting abnormal opioid system development as a possible cause of autism, and her preliminary success in treating autistic children with opioid antagonists.

In other experiments, Zagon and his co-workers have expanded their earlier studies of opioid receptors on cancer cells. They had found that opioids appear to suppress the growth of neuroblastoma, a nervous system tumor. Now they have found these receptors on cells from a wide variety of human and animal tumors, says Zagon. Although it is unclear whether this opioid system is the same as that seen in the growth-regulation experiments, the Hershey scientists say they have data suggesting that opioids can inhibit growth of these cancer cells in laboratory animals. Zagon says this inhibition is blocked by opioid antagonists.

"Maybe opioids have no function at all [in cancer]. . . but they seem to be related to growth," says Zagon. He points out that the body's response to opioids is "extremely complex," making it difficult to determine exactly which mechanisms might be at work in growth regulation.

— D.D. Edwards

Space station: Cut back to go ahead

Ever since they were introduced by President Reagan in his 1984 State of the Union message, plans for a U.S. space station have had both strong advocates and equally fervent opponents, not only within NASA, but also in Congress, the Defense Department, the scientific community and almost any other group that stands to be touched by the huge project's development. A factor long cited by those on the negative side has been its cost, around which opposition has focused even more strongly since a review completed in January by NASA itself showed the projected bill to be almost twice the original estimate.

Last week, Reagan approved a revised version of the plan, cut back from the civilian space agency's previous "baseline configuration" and aimed for completion in 1996, representing a two-year slowdown. It is also cut back in cost — cut back, that is, to a level that is more than 50 percent above the originally projected price.

When Reagan first broached the idea, "directing NASA to develop a permanently manned space station, and to do it within a decade," the cited cost was about $8 billion. NASA's cost review this year yielded a sum of about $14.5 billion (in 1984 dollars, not the shrunken ones of 1987), and sources both inside and outside the agency were soon acknowledging that $15 billion to as much as $16 billion might be more likely.

The revised baseline now carries a NASA-estimated price tag of about $12.2 billion, including $10.9 billion for the station itself and about $1.3 billion for support activities at the agency's various field centers. As part of getting the project started, NASA announced on the same day that negotiations are under way to lease 110,000 square feet of property in Reston, Va., for office space and other facilities as the station's development center on earth. *— J. Eberhart*

Tumor promoters halt cell-cell 'talk'

A new test for monitoring the ability of living, touching cells to chemically "communicate" may ultimately find use as a screening test to identify chemicals involved in causing cancer. Developed by scientists at Michigan State University in East Lansing, it uses a laser-fluorescence microscope system to peer inside cells growing in culture.

At the American Chemical Society's spring national meeting in Denver this week, John Holland, a developer of the laser microscope system, described his instrument and its use in demonstrating the ability of some 100 known cancer-promoting agents — including phorbol esters (plant hormones), DDT, PCBs and saccharin — to shut down the transfer of chemical signals between adjacent cells. According to Holland, this signal shutdown may help explain why cancers are characterized by unregulated cell proliferation.

Carcinogenesis is believed to be a multistage process, initiated when exposure to some toxic agent triggers long-lived changes in a cell. The process is advanced by the cell's subsequent exposure to a promoting agent, which may not be carcinogenic by itself.

Ordinarily, healthy cells grow rapidly only until they begin touching. Then some mechanism triggers the cells suddenly to stop growing. Holland says it may be that chemical communications between touching cells serve as a stop-growth cue. If so, when these signals are blocked — as by tumor promoters — affected cells could become deaf to the "stop proliferating" message.

The new test measures cell-to-cell communications by showing the movement of a fluorescing dye. Starting as an electrically neutral molecule, the dye can pass through cell membranes. Inside cells, however, enzymes cleave the dye into charged ions that can no longer pass through intact cell membranes. The only way for this dye signal to pass to another cell is through a pore-like "gap junction" that naturally forms to bridge touching cells.

Using the microscope, the researchers focus a laser beam on a 1/25,000-inch

spot. Where it shines on dye, a fluorescing spot appears whose intensity is calibrated by the computer. After destroying the dye in one of a pair of adjacent cells, the researchers watch to see whether the dye in the other cell diffuses back into the first.

Tests headed by James Trosko showed that the dye won't move between cells that have been exposed to a cancer promoter – indicating damage to the gap junction, according to Holland. None of the dozens of non-cancer-promoting chemicals tested caused a similar breakdown.

If the association between tumor promoters and a communications shutdown proves universal and reliable, the scientists say, many carcinogen-screening studies presently using animals may be replaced by these much simpler, quicker, less costly and more easily interpreted cell-culture studies. "This test could reduce by a factor of 100 the number of animals needed" to identify new cancer promoters, says Holland.

Moreover, he says, data collected in the past few weeks by Trosko suggest that tumor promoters fall into discrete classes of potency – classes that appear to be differentiated by their mechanism in disrupting cell communications. – *J. Raloff*

Neutrino physics after the supernova

Neutrinos from supernova 1987A are beginning to change some of physicists' ideas about those elusive but important particles. The latest aspect of this is the attempt to determine whether the neutrino has mass by calculating from the time of flight between the Large Magellanic Cloud and the earth. What seems to be the first such calculation to be published – by John N. Bahcall of the Institute for Advanced Study in Princeton, N.J., and Sheldon L. Glashow of Harvard University – appears in the April 2 NATURE. When they first appeared in physics, neutrinos were not thought to have mass. More recently some theories have wanted them to have it. Now, from the supernova, it seems the original idea may have been right.

Supernova neutrinos may also help change astrophysicists' ideas of what happens in a supernova explosion. The usual theories propose that the core of the exploding star collapses – once – to become an ultradense object, either a neutron star or a black hole. At the recent Heavenly Accelerators workshop, held at Johns Hopkins University in Baltimore, Alvaro De Rújula of Boston University proposed that instead of just one collapse there might be a series of such collapses in a single supernova, each leading to a denser state than the previous one.

The first observation of neutrinos from the supernova to be reported, which came from a European collaboration working with the NUSEX detector under Mt. Blanc on the French-Swiss border, seems not to fit the standing theory – the neutrinos appear much more energetic than they ought to be. The other two observations, simultaneous determinations by the Kamiokande detector at Kamioka, Japan, and the IMB detector at Fairhaven, Ohio, seem closer to theoretical expectations. Some commentators have suggested that the Mt. Blanc observation is mistaken; these neutrinos were not from the supernova. De Rújula supposes the Mt. Blanc observation is real and combines it with the two others to see what the combination might tell about what happens in a supernova.

The Mt. Blanc detector saw five pulses of neutrinos in 7 seconds, and it saw them 4 hours 43 minutes before the simultaneous observations of Kamiokande and IMB. De Rújula makes a statistical argument to support the idea that Mt. Blanc saw something real, but then he has to explain why Kamiokande saw nothing at the time of the Mt. Blanc events. He can accomplish this by assuming that the energy of the neutrinos was somewhat less than observers have generally been postulating. Then, taking account of the characteristics of the detectors, he can make the different experiments compatible with one another. Thus he comes to the conclusion that there were two bursts of neutrinos from the supernova, 4 hours 43 minutes apart, and that leads to his suggestion of a double collapse.

Theory supposes that the collapse of the core of a star initiates a supernova explosion. During a star's life, heat produced by thermonuclear fusion processes holds it up, preventing it from collapsing under its own gravity. When a supernova begins, that support somehow fails and the core of the star collapses, producing either a neutron star or a black hole. An outward flying flux of neutrinos is a by-product of the collapse.

The core collapse also triggers a shock wave that propagates outward, blowing away the outer layers of the star. De Rújula calculates that it would take about 10 hours for the shock to cover the distance to the outermost layers of the star, and he proposes that – at least in the case of supernova 1987A – the shock didn't get all the way to the surface. A fizzling-out of the shock would have caused a second collapse of the core. The first collapse would have made a neutron star; the second would have made a denser object, a black hole. The experiments on earth would have received bursts of neutrinos from both collapses, separated by the 4 hours 43 minutes.

If this is really what happened, and a black hole is now there, De Rújula says, there should now be a steady flux of neutrinos from matter accreting around the black hole drawn by its tremendous gravity. He pleads that the detectors be kept on to look for this steady flux. Unfortunately, Kamiokande has already been shut down for maintenance and improvements.

Neutrinos from the supernova should come to us at the speed of light so long as they have no rest mass. Edward Kolb of Fermi National Accelerator Laboratory in Batavia, Ill., speaking at the Heavenly Accelerators workshop, calculated the duration of the flight at about 5 trillion seconds ($5.36 \pm 0.52 \times 10^{12}$ seconds). If the neutrinos have a small rest mass, they cannot come quite at the speed of light. The flight time of a given neutrino will be a little longer than that, and those with higher energy will come fastest. The duration of the pulses as they arrive at earth will depend on the amount of this supposed neutrino rest mass.

When the existence of neutrinos was first postulated, they were supposed to have exactly zero rest mass, and most experiments have been consistent with zero rest mass. The exceptions have been some experiments in the Soviet Union that persist in showing a neutrino rest mass of 30 or 40 electron-volts (eV). Some of the recent theories that are trying to unite all of particle physics in a single framework need to have neutrinos with a small rest mass, and these theories have spurred both the Russian and other attempts to find one. In addition, if neutrinos have a small rest mass, cosmologists can say that large gangs of them floating through the universe would constitute the majority of the matter in the universe and would provide enough unseen matter to make the universe close on itself, a condition that many cosmological theories need to have.

Unfortunately for these people, Bahcall and Glashow state that their analysis of the supernova data shows that neutrinos probably have no rest mass, or at least no more than 11 eV. This limit on the rest mass, they say, is stronger than any that has been achieved in 50 years of terrestrial experiments. The exact limit that one can set on a possible neutrino rest mass depends on certain assumptions about the relation of the duration of the neutrino pulses at earth to their duration at the source. Kolb, reviewing several yet-unpublished papers on the subject, says they set various limits from 5 eV to 25 eV.

If the supernova data are showing that neutrinos have zero rest mass, that, as De Rújula comments, "in 2 seconds would have destroyed 20 years of work by the Russians." It would also drive a nail into the coffin of some of the proposed unified theories of particle physics, and, to quote Bahcall and Glashow, "confirms the view that electron neutrinos do not constitute the major component of the matter density of the universe." – *D. E. Thomsen*