Neuronal Rescue by Refrigeration

Drug tests yield a chilling surprise

By RICK WEISS

An experimental drug that scientists had hoped might usher in the first generation of highly specific, nerve-protecting agents appears less promising with the publication of a new series of experiments, but has generated excitement about an even cooler approach.

Initial studies performed on tissue cultures and in animals had hinted that the drug, called MK-801, might dramatically reduce nerve death in the brains of people after they had suffered a heart attack or stroke (SN: 11/4/89, p.292). But recent findings in animals suggest MK-801's usefulness comes not so much from any specific neuroprotective actions as from a simple, drug-induced drop in body temperature. Since the potent drug seems to carry some risks of its own, and simpler ways exist to drop body temperature, the surprising finding has dampened some researchers' hopes for the compound.

Scientists say additional research may reveal specific conditions for which the drug has value. More immediately, however, the findings have spawned renewed interest in discovering other, less risky ways of chilling the body as a strategy for minimizing nerve death following an interruption in the brain's blood supply.

Heart attacks and strokes deprive the brain of oxygenated blood. Not only is brain tissue exquisitely sensitive to such a loss, but it suffers additional damage from the sudden *influx* of oxygen in the minutes following restoration of blood flow. Although the mechanisms behind both of these neuron-destroying events remain poorly understood, research suggests that much of the damage results from a series of biochemical reactions that start with the binding of so-called excitatory amino acids, such as glutamate, to nerve-cell docking sites called NMDA receptors. MK-801, a close chemical relative of the psychoactive street drug PCP, belongs to a class of drugs called NMDA antagonists, which can disrupt NMDA receptor function.

Developed by Merck Sharp & Dohme Research Laboratories in West Point, Pa., MK-801 was about to go into clinical trials for stroke patients last year when John W. Olney and his colleagues at the Washington University School of Medicine in St. Louis reported evidence that the drug itself might damage neurons in the cerebral cortex when given to rats in relatively low doses. Although the risk to humans remained unclear, the findings prompted an indefinite postponement of human testing.

Even before those findings, however, various experiments in gerbils and rats had provided disturbingly differing results as to whether the compound actually did or did not enhance neuronal survival when large parts of the animals' brains were deprived of oxygen for approximately five minutes — a condition mimicking a heart attack. In some of these experiments the drug appeared to provide remarkable protection; other experiments showed no benefit at all.

Alastair Buchan and William A. Pulsinelli of the Cornell University Medical College in New York City now appear to have solved the riddle behind these inconsistent results. In gerbils, they simulated a heart attack's effect on the brain by temporarily blocking the animals' carotid arteries and found that MK-801's effectiveness varied depending on body temperature.

When the researchers allowed the drug to lower the test animals' temperatures by about 4°C, as it tends to do for several hours after administration, brain-neuron damage was indeed reduced. But animals not receiving the drug did equally well if the scientists chilled them to the same lowered temperature by putting them in a refrigerated room soon after restoring blood flow. Significantly, test gerbils kept at their normal body temperatures with heating lamps showed substantial loss of neurons even if they got the drug.

By reviewing the records of previous experiments in rats and gerbils, Buchan and Pulsinelli found that other researchers had not controlled for such temperature effects. Some researchers, it appears, maintained their test animals' normal body temperatures in warm laboratories while others seem to have allowed their animals to cool. Indeed, not realizing that temperature was a relevant variable, most researchers hadn't paid any attention to temperature at all, they say.

Based on their experiments, Buchan and Pulsinelli conclude in the January JOURNAL OF NEUROSCIENCE that neural protection by MK-801 "is related largely to the prolonged hypothermia caused by this drug." In light of the ongoing disagreement over how much neural damage the drug may cause — a debate reignited in an exchange of comments in the Jan. 12 SCIENCE — the finding leaves MK-801's fate uncertain, researchers say.

"It obviously raises the specter of a very specific problem" with the studies performed so far, comments Dennis Choi, a neuroscientist at Stanford University who has tested the drug on mouse tissue cultures.

Some maintain the drug may still find a place in the physician's armamentarium. Experiments by Olney's group at Washington University, for example, indicate that in newborn rats— which respond to a lack of oxygen somewhat differently than do gerbils — MK-801 in conjunction with lowered body temperatures proves more beneficial than lowered temperatures alone. And Choi notes that the drug still shows some promise for the more localized neural asphyxiation seen in strokes, suggesting that stroke victims may someday gain some benefits from the drug even if heart attack patients don't. But in the long run, researchers say, only clinical trials will settle the issue of MK-801's true value.

Whatever the future of MK-801, Buchan and Pulsinelli's findings provide new incentive for

researchers to investigate the value of inducing lowered body temperatures in patients who have just suffered a heart attack or stroke. For years, surgeons performing operations that may temporarily limit oxygen supplies to the brain have reduced the risk of surgery-related brain damage by chilling patients in advance – generally by placing them in a cooled room and by infusing them with chilled intravenous fluids. And reports of children who have remained submerged in near-freezing water for prolonged periods without apparent brain damage indicate that low brain temperatures during oxygen deprivation can also protect brain neurons. Their new work, Buchan and Pulsinelli say, now clearly indicates that hypothermia of even a few degrees, soon after a loss of oxygen, can have an equally impressive neuroprotective effect.

Given those findings, Pulsinelli and others maintain that a degree of refrigeration might prove useful as an emergency therapy in victims of heart attacks or strokes. But for now, physicians note, hospitals are not prepared to induce hypothermia on an emergency basis.

"The question is, can you do it quickly enough?" says Buchan, now at the University Hospital in London, Ontario. He and others wonder whether any kind of drug can safely lower core temperatures with sufficient rapidity in human beings, whose body masses are substantially greater than those of any animals currently under such investigation.

Along with the challenge of dropping body temperatures quickly, researchers have yet to determine just how cold is cold enough. European researchers, who have reported successfully preventing brain damage in oxygen-deprived newborns by dunking them in chilled water for up to 15 minutes, have noted that longer exposures to temperatures below 29°C may prove detrimental. Similarly, while some early attempts to chill heart attack victims to 25°C effectively rescued brain neurons, Buchan says the treatment wreaked metabolic havoc elsewhere in the body. Among other things, the very low temperatures triggered coagulation problems and cardiac arrhythmias.

Recently, researchers have suggested cooling such patients to a more moderate 33°C. But ideally, Buchan says, physicians would like to cool the brain to these temperatures without having to chill the rest of the body – thus avoiding the various metabolic side-effects of hypothermia, including the adrenalin release that comes with intense shivering.

Buchan says one approach would be to inject cold saline directly into some of the cavities, or sinuses, in the brain. But so far, he says, no one has tested the approach in a clinical trial. □

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the future," says Iqbal Ahmad of the Army Research Office in Research Triangle Park, N.C. Adds Rogers: "I see the intelligent materials systems effort as the logical evolution of materials development in general." They and others note that a sense of community is beginning to emerge among the various scientists who have worked independently on such projects during the past 10 years.

The first major gathering of these like-minded investigators took place in the fall of September 1988 at Virginia Tech. Last March, a similar gathering occurred in Tsukuba, Japan. Researchers from the United States, Japan and Europe plan at least two more – in Hawaii and Japan – for this year. In addition, says Rogers, the organizers of as many as 20 other research conferences plan special sessions this year on smart materials and structures.

Thus a new research specialty is born. And as members of the community chalk up successes, financial support grows. In fiscal year 1989, for instance, the Army Research Office launched a three-year smart materials initiative with a budget of nearly $1 million per year. Other Defense Department research agencies have started similar programs with funding totaling more than $10 million. One researcher estimates that U.S. universities, aerospace and defense contractors, and government agencies such as NASA and the Defense Department will spend additional tens of millions of dollars this year alone on research into smart materials and structures. And when the researchers evolve a standard name for their specialty – a consensus that seems fairly imminent – funding agencies will finally have a label for the projects, which so far have been financed under the auspices of a variety of seemingly unrelated disciplines. Just having a label can mean a lot in terms of funding, Rogers says.

Although decidedly optimistic about his field's potential, Rogers cautions that terms such as "intelligent materials" tend to inspire unrealistic expectations. "We have a new and exciting concept," he says. But any talk of near-term applications to novelty items such as smart golf clubs with variable stiffness, could prematurely focus the curiosity-driven research and development necessary for the field to advance most effectively and for the benefit of the most people. "There are some snake-oil salesmen out there," he warns.

Rogers, Claus and others say U.S. researchers have an additional worry: the possibility of Japanese domination at the cutting edge of the new field. In the United States, investigations into intelligent materials and structures focus primarily on assembling smart systems using existing materials, such as shape-memory alloys and piezoelectric ceramics and polymers, as the actuators and sensors. But Japanese researchers are looking toward brand-new materials.

"We need a closet full of new sensor and actuator materials, and we don't seem to have the materials science people motivated enough [to invent them]," says Rogers. Japanese materials scientists are making significant advances, including building an artificial muscle fiber out of a novel polymer that contracts to about one-fourth its relaxed length, he says.

Claus of Virginia Tech voices the same concern: "Unless big changes happen in this country, I would expect that we'll see most of the technology developed offshore and shipped in."

No matter who capitalizes on smart materials and structures, the world is in for a change, predicts materials researcher Mukesh V. Gandhi of Michigan State University in East Lansing. As the technological innovations reach industries ranging from aerospace engineering to medicine to building construction, he says, "all aspects of our lives will be significantly touched." □