Future of neuroprotective drugs in doubt

Last month's publication of negative results from a clinical trial of a neuroprotective drug reinforces the growing belief that this class of drugs may never prove effective in the treatment of stroke despite their initial promise.

Although the NMDA (*N*-methyl-D-aspartate) receptor blocker, Aptiganel, improves outcomes in animal models of focal brain ischemia, a multicenter trial in humans showed that when administered within six hours of onset of symptoms of stroke, the drug did not improve patient outcomes and may even be harmful (*JAMA* **286**, 2673; 2001). The trial was stopped in 1997.

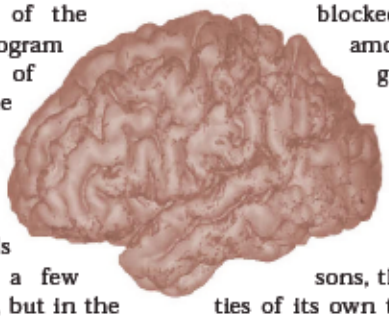
Genentech's tissue plasminogen activator (TPA), is presently the only approved treatment for stroke, and works by dissolving blood clots in the brain. TPA must be administered within three hours of symptom onset, increases the risk of brain hemorrhage, and only patients in whom cerebral hemorrhage has been excluded are eligible for treatment.

The neuroprotectives were designed to ameliorate the damage to brain cells, which follows a cerebral infarct. Aptiganel (Cerestat)—developed by the UK biotechnology company CeNeS in conjunction with the German pharmaceutical manufacturer Boehringer Ingleheim—blocks the effects of the excitatory neurotransmitter glutamate at NMDA receptors. Glutamate worsens the initial ischemic injury by causing an influx of sodium and calcium into neurons.

Aptiganel was tested in 628 patients in 156 centers in the US, Canada, Australia, South Africa, England and Scotland. However, at seven days after treatment, placebo-treated patients showed better neurological improvement than high-dose aptiganel patients and the mortality rate was higher in aptiganel-treated patients.

Aptiganel is one in a long list of neuroprotectives that have not lived up to their preclinical promise. In recent years scientists have abandoned a number of similar products at late stages of development, including Bristol-Myers Squibb's potassium channel agonist, MaxiPost, AstraZeneca's GABA modulator, Zendra and GlaxoWellcome's gavestinel, another NMDA blocker.

The continuing disappointments raise questions over where to go next in stroke treatment. Is there a future for these agents? "Absolutely yes," says James Grotta, head of the stroke protection program at the University of Texas, Houston. The main problem is treating the patient quickly enough. These drugs were effective in animals when given within a few hours of stroke onset, but in the clinic, the time lapse was a more realistic three to six hours. The researchers in the Cerestat study believe this was the most likely explanation for its failure.



And there other potential reasons for the collective failure of the neuroprotectives. One major consideration, says Grotta, is that trials have thus far only looked at the neuroprotectives as monotherapies, and not in combination with TPA. Therefore the arteries supplying the damaged area is still blocked, and "this limits the amount of drug we can get to the damaged tissue." Grotta also believes the drugs tested so far have not been potent enough.

Whatever the reasons, the brain has peculiarities of its own that need to be taken into account in the development of neuroprotectives. It is more susceptible to ischemic damage than other organs—giving a shorter therapeutic window—and, unlike the heart, it easily bleeds after injury. "Don't forget that 'protective' therapy has not been successful in other organ systems, such as the heart, either," says Grotta.

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Further concern over rules that impede research

A new rule introduced by the US Department of Health and Human Services (HHS) to assure the privacy of medical records may have created a morass of red tape that will make many types of medical research difficult or impossible. That is the concern voiced by over 180 universities and research centers in a letter to HHS secretary, Tommy Thompson.

The focus of the furor is the 'Standards for Privacy of Individually Identifiable Health Information', a rule issued by HHS at the behest of Congress. Initially proposed during the Clinton administration, the rule followed a tortuous path to reach its current form, and HHS received over 50,000 comments about the proposal from patient privacy and research advocates.

"I think there was at least the expectation that some of the [researchers'] concerns would be responded to," says Jennifer Kulynych, director of biomedical and health sciences research for the Association of American Medical Colleges, but the final rule, set to take effect in April 2003, still leaves scientists with ample cause for concern.

Currently, research involving human subjects in the US is covered by the "Common Rule," which requires an Institutional Review Board (IRB) to review each study. Under the new rule, each study will have to undergo an additional level of review, carried out either by an IRB or a newly created entity called a "Privacy Board," to determine that patients' privacy rights are protected. Unfortunately, "there isn't any agreed-upon metric for what is a privacy right," according to Kulynych, making it unclear what standards the research has to meet in order to comply with the rule. Violators could face stiff civil and criminal penalties.

The rule also covers many types of research that were previously exempt from IRB review. For example, a scientist who wants to access tissue samples that are accompanied by patient data will have to convince an IRB or Privacy Board that the data meet strict 'de-identification' requirements meant to ensure that the samples cannot be traced to a particular individual. Many researchers are concerned that the de-identification process will strip away useful demographic information, complicating public health and pathology studies.

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