Huntington's disease: Clues to the culprit

Huntington's disease starts with a genetic defect on the short arm of chromosome 4, and leads to a withering of the brain. The result: the victim's involuntary participation in a grotesque "chorea" – a jerky dance of the muscles – and dementia. Beginning and end are known, but the agent of the disease inside the body has been a mystery.

Now, researchers at Stanford University report evidence that the culprit in Huntington's disease may be one of a group of compounds called excitotoxins. According to Dennis Choi, who led the study, the work further suggests that research should focus on one of the three types of neuronal receptors for excitotoxins. He speculates that the degeneration of nerve cells in the brain seen in the disorder is triggered by the improper activation of this receptor, called the NMDA receptor. If borne out, the work may someday provide a basis for therapeutic intervention in Huntington's.

The work, reported in the Oct. 3 SCIENCE, is the latest jump in a game of research leapfrog between Choi's group and one led by Joseph Martin of Harvard Medical School. A year ago, Martin showed that the destruction of nerve cells in Huntington's does not proceed wholesale in certain areas of the brain, as had been thought, but instead shows a distinctive pattern: One group of neurons, containing the enzyme NADPH-d, is to some extent spared. The finding "showed that the natural disease process doesn't just blow away [all] the neurons," Choi says. "It leaves a fingerprint, and any hypothesis must account for it."

In the search for an offender to match the fingerprint, both groups have looked at the excitotoxins. These compounds have paradoxical actions: They can excite a neuron to fire or they can kill it, probably depending on length of exposure, according to Choi. But though they are potentially dangerous, some excitotoxins are present in "stupendous amounts" in the brain, Choi says. That has made them a suspect in many neurological disorders. With a simple failure of the mechanisms that normally compartmentalize or clean up excitotoxins, there is the potential for widespread neuronal destruction. "It's as though you were running around with a can of gasoline in one hand and a match in the other," Choi says.

Martin's group recently reported that they were able to produce the Huntington's pattern of neuronal destruction by injecting the excitotoxin quinolinic acid into rat brains. (A group at the University of Maryland in Baltimore had first suggested that quinolinic acid might be the agent.) The Harvard group speculated in the May 8 NATURE that the NADPH-d neurons survive in Huntington's because the enzyme enables them to degrade quinolinic acid.

Now, Choi's group reports that *in vitro* the NADPH-d neurons appear to be resistant to the entire class of excitotoxins that act selectively at the NMDA receptor. At the same time, these neurons are unusually vulnerable to excitotoxins that act at either of the other types of receptors. The researchers suggest that the neurons are spared in Huntington's because they have fewer NMDA receptors – and therefore are less exposed to the excitotoxins specific to that class of receptor – not because the neurons are better equipped against quinolinic acid.

That would have research and clinical implications. In the search for the culprit in Huntington's, it points toward the compounds that act specifically on the NMDA receptor. And, while a cure for Huntington's will probably wait on the ability to intervene on the genetic level, selectively blocking NMDA receptors "might delay the onset of Huntington's from 45 years of age to 55 or 65," Choi says. "That's still a huge therapeutic benefit."

Martin now plans to survey the distribution of excitotoxin receptors in the brain, to see if the NMDA receptor-Huntington's link holds up. *–L. Davis*

NASA sets shuttle launch date, schedule

Thursday, Feb. 18, 1988, two years and three weeks after the catastrophic explosion of the space shuttle Challenger, has been established by NASA as its projected date for when shuttle flights will begin again. "That's primarily for internal use. . . . My temptation was to say, 'February sometime,'" said agency administrator James C. Fletcher last week in making the announcement. But as a planning date it is real, and it is item one on a detailed "manifest" of what NASA has scheduled to fly on the shuttle extending into 1994.

As well as trying to grapple with a major backlog of planned Defense Department shuttle flights and with delays in several major space-science missions, the manifest "complies with White House policy that NASA will no longer launch commercial and foreign payloads except those that are shuttle-unique or those that have national security or foreign policy implications," according to Fletcher. Even among 44 commercial payloads for whose launchings NASA had already signed contracts before the Challenger disaster, only 19 or 20 have been rescheduled, leaving the rest of the customers with a firm message to look elsewhere, such as at expendable rockets from the United States, Europe, China or other countries.

The manifest's first year lists five launches, the first of which is to be a Tracking and Data Relay Satellite (TDRS-C), one of which was destroyed with Challenger, and whose type is projected as an essential element in NASA's space communications plans. Another TDRS is scheduled for the fourth launching (many plans for the system require a pair of satellites), tentatively listed for Sept. 22 of the same year.

Flights 2 and 3 are for the Department of Defense (DOD), which was assigned roughly a third of the shuttle manifest even before the Challenger tragedy scrambled everyone's plans. For the seven years covered by the new manifest, DOD's piece of the action will average about 41 percent, with most of the increase devoted to backlog-reducing missions through 1990. Ten shuttle launchings are scheduled in 1989, of which four are "dedicated" DOD missions while the payloads of two more each include a pair of navigation and positioning satellites for the military Global Positioning System (GPS). Four of 11 launches in 1990 are DOD-only, with GPS satellites on three more.

The final launching of 1988, the shuttle's first year back on the pads, is to deploy the 2.4-meter Hubble Space Telescope, envisioned as operating in orbit for as long as 20 years with repeated instrument changes and service calls by the shuttle. Formerly to have been launched two months ago, it is expected to be able to pick up light from stars so distant that their emissions originated during the early evolution of the universe. "We look forward to it," says Samuel W. Keller, NASA associate administrator for science and applications, "as being the greatest scientific instrument that man has ever built."

Manifested for the third mission of 1989 is Magellan, designed to map Venus by high-resolution radar. The interest of planetary scientists is focused on Magellan also because the craft will represent the first U.S. interplanetary launching in more than a decade. Also listed are the Galileo orbiter and probe of Jupiter and the European Ulysses mission to study the sun's poles (both of which were to have been launched this year) as well as the U.S. Mars Observer (which was previously expected to follow about two years behind a 1988-launched Soviet mission to Mars and its moons). None of these projects yet has a firm launch date, though the manifest lists possibilities.

Meanwhile, the shuttle manifest, though carefully wrought as a result of extensive negotiations, must still pass several major milestones, such as qualification of the craft's redesigned solid-rocket boosters. The struggle is not over.

–J. Eberhart

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