

SCIENCE NEWS of the week

Prions Linked to Nerve Regulation

Scientists probing the highly specialized junctions between nerve cells and muscles have stumbled upon a biological coincidence that may reveal the bases of several mysterious brain diseases.

The researchers, led by Gerald D. Fischbach of the Washington University School of Medicine in St. Louis, initially sought to investigate a nerve-secreted protein that regulates the interaction between nerves and muscles.

What the research led to, however, was an unplanned journey into the world of

"prions" — proteins implicated in several neurodegenerative diseases with names that Fischbach is still learning to spell, such as Creutzfeldt-Jakob disease and Gerstmann-Strassler syndrome. "I am not the world's expert in these things," Fischbach sighs, caught in a flurry of questions about his newly inherited field of study. "I'm trying to read about them now, for sure."

Researchers have found prions in normal brain tissue of humans and other mammals, but they have yet to learn the

role of these proteins. In a slightly mutated form, prions appear to either trigger or exacerbate certain neural diseases whose primary infectious agents remain unidentified. These include scrapie, a brain disease in sheep, and several diseases in humans.

For Fischbach, Douglas L. Falls, David A. Harris and their co-workers, the link between receptor regulation and prions first appeared on a computer printout. The researchers had spent years purifying a protein that triggers production of a receptor on chicken muscle fibers. Once the muscle fibers sprout these receptors, they become sensitive to subsequent chemical signals transmitted by the nerves. When the scientists entered into a computer their protein's amino acid sequence, the computer informed them it had seen some similar sequences before. Indeed, roughly one-third of their protein had stretches identical to those of prion proteins. Moreover, with the exception of only one amino acid, a 24-amino-acid length of their receptor-inducing protein was identical to a segment common in prions — a remarkable coincidence considering the proteins had been isolated from entirely different species. A high degree of sequence similarity generally indicates proteins have identical or very similar functions.

The finding strongly suggests that a prion's normal role is to regulate production of neurochemical receptors in the nervous system, Fischbach told colleagues last week at the annual meeting of the Society for Neuroscience in Phoenix, Ariz. Moreover, it provides an attractive explanation for how mutant prions might trigger neurodegenerative diseases. If receptor production becomes disrupted by faulty prions, Fischbach speculates, nerves would have trouble getting their messages transmitted. And previous work has shown that when nerves can no longer communicate with surrounding cells, they degenerate and die.

"It's exciting and startling. Everyone you tell it to can't believe it at first," says Zach W. Hall, a neuroscientist at the University of California, San Francisco. "It is one of those things that molecular biology does for us so often these days: to suddenly and dramatically bring together two completely unrelated areas of research. I don't think anyone would have dreamed of this similarity without the help of a data bank to tell you that these proteins are related."

Many questions about prions and neuroreceptors remain, Hall says. "But it means we can think about each of these problems in new ways. It'll suggest new experiments on both sides." — R. Weiss

Rat model of tardive dyskinesia gets boost

In the last decade, researchers have tried in vain to come up with a plausible animal model of tardive dyskinesia (TD), an often disabling potpourri of abnormal body movements afflicting about one in five people treated for extended periods with antipsychotic drugs (SN: 7/20/85, p.45). Rats and monkeys sometimes develop the twitches and jerks typical of TD when given antipsychotics, but there is no consensus that their reactions consistently mimic those of humans with the disorder.

Now, however, two psychologists claim they have developed a strong candidate for a rat model of TD with the aid of computerized measurements of the animals' mouth movements. "These findings are going to revolutionize rodent research on antipsychotic-induced side effects," says study director Gaylord Ellison of the University of California, Los Angeles. He and his co-worker Ronald E. See expect publication of their results in a forthcoming *PSYCHOPHARMACOLOGY*.

Other investigators are encouraged by the new findings but refuse to hail them as revolutionary. "This area of research has been dogged by the inability of different laboratories to replicate findings," says psychopharmacologist John L. Waddington of the Royal College of Surgeons in Dublin, Ireland. "Ellison's work is provocative, but it clearly needs to be examined further by other scientists."

The California researchers administered equivalent doses of the antipsychotic drug haloperidol to two groups of rats for 28 days and to another two groups for eight months. One group on each time schedule received weekly haloperidol injections; the other two groups received the drug continuously in their drinking water and, in the eighth month of long-term treatment, through a small pump implanted in each rat as well.

Mouth movements made by the rats were regularly measured during drug treatment and up to 17 days after drug

administration ended. Each rat was placed in a tube for video recording with a spot of ultraviolet-sensitive ink on its upper and lower lip. All lights were turned out save for a black light. The research team used a specially designed computer program that calculated the energy spectrum of oral movements to analyze video images of the lip spots.

The two groups of rats given antipsychotics for eight months gradually developed abnormal mouth movements with different properties, Ellison and See report. After four months of treatment, rats on the continuous schedule did not necessarily develop more frequent or more easily observable mouth movements. But computer analysis revealed a characteristic altered form to the movements, with the peak energy frequency at 1 to 3 hertz. Several recent studies reported observing this same altered frequency in humans with tardive dyskinesia, Ellison notes.

Rats given weekly drug injections developed larger, gaping mouth movements at energy frequencies between 4 and 7 hertz. Their responses are somewhat similar to temporary movement disorders distinct from TD observed in monkeys and humans administered antipsychotics, Ellison notes.

If continuous haloperidol treatment does produce TD in rats, researchers can use the animals to study the side effects of other antipsychotics and to test potential drug treatments for TD.

But it remains unclear whether Ellison and See's model applies to humans, cautions Daniel E. Casey of the Veterans Administration Medical Center in Portland, Ore. No one knows how long drug-induced abnormal mouth movements persist in rats, he says, and the movements are far less obvious and widespread than those of humans with TD.

The peak energy frequency of human TD movements is not well established, Casey adds. — B. Bower