Cholera toxin fights autoimmune disease

The many cells and chemicals that make up the body's elaborate immune system are supposed to hunt down and vanquish invaders — largely bacteria, viruses, and foreign tissues that threaten health. But for reasons no one quite understands, immune system components sometimes get confused and begin attacking familiar, benign elements of the body.

Researchers in Sweden have begun harnessing a fragment of the cholera toxin in a novel approach to thwarting autoimmune disease — the general term for immune attacks against the body's own tissue. The new therapy, described in Atlanta last week at the annual meeting of the American Association of Immunologists, held as part of Experimental Biology '95, promotes tolerance of a substance that the immune system had previously recognized as foreign by attaching it to a cholera toxin fragment.

When fed to animals, a single, small dose of this combo permanently shut down either of two experimentally induced autoimmune diseases, reported study leader Cecil Czerkinsky of the University of Göteborg in Sweden.

Of the two primary components of cholera toxin, only the A chain is actually poisonous. The B chain not only anchors the molecule to the intestine, it also stimulates the immune system. Drawing on the idea that individuals can sometimes develop a tolerance to antigens — substances that cause an immune reaction — by eating them, Czerkinsky's team fed its animals sample antigens linked to B chains.

In the intestines, the strategy "induced a very strong antibody response to the [antigen]," Czerkinsky notes. "But at the same time, these animals developed a profound state of tolerance in the periphery — the blood and lymph nodes." And that led his group to investigate the B chain for blunting undesirable immune responses in animals.

They began by "gluing" the B chain to myelin basic protein, a material that sheathes nerves and falls under immune attack in multiple sclerosis (MS). In rats experiencing MS-like autoimmunity, Czerkinsky says, a single dose of the remedy "cured them."

Other researchers have headed off MS-like diseases in animals by administering this protein. However, Czerkinsky says, that "only worked with huge amounts and *before* disease induction."

His team also prevented the joint swelling and tissue destruction normally seen in mice with autoimmune arthritis. The treatment, another B-chain-linked antigen, began weeks after the disease had been induced.

Most recently, the researchers gave B-chain-linked antigens from heart grafts to mice following tissue transplants. Immune reaction against these antigens would normally lead to rejection of the deliberately mismatched tissue in 11 or 12 days. But treated animals accepted the tissue for 22 days, which suggests that rejection might be avoided with better tissue matching and multiple follow-up doses of the B-chain-modified antigen, says Czerkinsky.

"The data look very interesting — and convincing," says Charles O. Elson, director of gastroenterology at the University of Alabama in Birmingham. Indeed, says immunologist Judith A. Kapp of Emory University in Atlanta, "I think people are pretty excited about it."

Though no one knows yet how the therapy works, Kapp suspects that the B chain somehow obstructs the precursors of a class of white blood cells known as T cells from making those T cells that produce tissue-damaging inflammatory agents.

But the big question, Elson notes, is whether humans will derive similar benefits. Hoping to find answers, he says, "we're talking about doing some studies here with them [Czerkinsky's team]" to test how well people tolerate the toxin-modified antigen. "So we should know within a year or two if this works in humans." — *J. Raloff*

Schizophrenia: Fetal roots for GABA loss

Early in some fetal development, cell connections go awry in the outer layer, or cortex, of the brain. By young adulthood, neurons at the front of the cortex that help orchestrate thinking and motivation have trouble communicating with other brain regions. Sluggish activity by cortical cells then leads to cutbacks in a key chemical messenger, further hampering brain function and mental life.

This unfortunate series of developmental disturbances may result in the cerebral malfunctioning responsible for some cases of schizophrenia, according to a report in the April ARCHIVES OF GENERAL PSYCHIATRY. Data now suggest that in many instances of this severe mental disorder, neurons in the adult brain's "prefrontal cortex" lack messenger RNA molecules to carry out genetic instructions for forming an enzyme crucial in making the neurotransmitter known as gamma-aminobutyric acid, or GABA.

"It is possible that the malfunction of the cerebral cortex in adult schizophrenics results from a defect in [fetal] brain development," assert Scharam Akbarian, a neurobiologist at the University of California, Irvine, and his colleagues. Yet because prefrontal cells do not die or dwindle in number when deprived of GABA, the brains of people with schizophrenia look healthy, the investigators contend.

Supporting data for their argument have mounted in the past decade. For instance, Akbarian's group uncovered evidence that schizophrenia involves a loss of fetal brain neurons that bear a protective enzyme (SN: 5/29/93, p.346). These cells are part of the cortical subplate, a temporary gateway to the cortex for migrating fetal neurons.

In their new project, Akbarian and his coworkers studied the brains of 20 deceased adults, 10 of whom had suffered from schizophrenia for at least 18 years and 10 who had been free of psychiatric or neurological disease.

Microscopic analyses focused on slices of tissue from a section of the prefrontal cortex in which, according to previous studies, cell activity slows in people diagnosed with schizophrenia.

Compared to brains from controls, those from people who had schizophrenia contained 30 percent to 48 percent less of the messenger RNA for an important GABA-producing enzyme. The largest of these schizophrenia-related deficits appeared in tissue layers close to the brain's surface.

Still, the total number of prefrontal neurons and the number of distinctively shaped cells known to take part in GABA synthesis were about equal in the two sets of brains, the scientists hold.

A prenatal disturbance of the cortical subplate may interfere with connections between the prefrontal cortex and other brain areas that integrate thought and sensations, such as the thalamus (SN: 10/29/94, p.284), Akbarian's team theorizes. This may eventually lower prefrontal activity enough that specific genes dispatch decreased amounts of the messenger RNA needed for GABA production, in their view.

The findings, although preliminary, may suggest a brain mechanism for the so-called negative symptoms of schizophrenia, such as apathy, emotional flattening, and disorganized thoughts, propose neuroscientists Dennis E. Lee and Allan J. Tobin, both of the University of California, Los Angeles, in an accompanying comment.

Further work is needed to clarify whether prolonged antipsychotic drug treatment of people with schizophrenia contributed to their lower GABA levels, Lee and Tobin add. Antipsychotic injections in mice increase amounts of messenger RNA employed in GABA production. This finding suggests that messenger RNA declines linked to schizophrenia did not result from years of drug treatment, Akbarian and his associates contend. — *B. Bower*