Biology

From Miami Beach, Fla., at the Society for Neuroscience annual meeting

New insight into Alzheimer's disease

When scientists take a close look at a brain devastated by Alzheimer's disease, they see plaques and tangles littering the tissue. The former are extracellular deposits of a protein fragment called beta-amyloid, while the latter are fibrous clumps of a protein, tau, inside nerve cells. Scientists have long argued whether beta-amyloid or tau causes the memory-robbing illness, but they've made few attempts to link the protein deposits.

A research group now suggests that beta-amyloid binds to a protein—the alpha 7 nicotinic acetylcholine receptor—on the surface of nerve cells and thus triggers a chemical modification of tau that might lead to tangle formation. Binding of beta-amyloid to this receptor ultimately kills nerve cells, perhaps via a previously unsuspected buildup of beta-amyloid inside the cell, the scientists suggest.

This novel view of Alzheimer's disease was offered in three presentations by investigators at the R.W. Johnson Pharmaceutical Research Institute in Spring House, Pa. In the first, Hoau-Yan Wang noted that many scientists believe that beta-amyloid directly kills certain nerve cells, so-called cholinergic neurons, but they can't yet explain how. Wang presented evidence that cholinergic neurons sport copies of the alpha 7 receptor and that beta-amyloid binds tightly to them.

"This may contribute to the dysfunction and degeneration of the neurons," he says. A compound that prevents beta-amyloid from binding to the receptor thwarts the ability of the amyloid protein to kill nerve cells, reports Wang.

Next, Daniel Lee offered data indicating that the binding of beta-amyloid to this receptor induces phosphate groups to attach to tau. Increased tau phosphorylation is a hallmark of Alzheimer's disease and may create tangles by altering tau's stability. "This is the first connection of beta-amyloid to tau phosphorylation by a known receptor," says Lee.

Finally, Michael R. D'Andrea offered the controversial idea that plaques observed in patients' brains arise from clumps of beta-amyloid in living cells. He says that the alpha 7 receptor may draw beta-amyloid into a cell until the cell dies and disintegrates, leaving an extracellular plaque. The distribution, density, and shape of plaques support this idea, he argues.

An Alzheimer's drug already in tests on patients targets the same nerve cell receptor that D'Andrea's group has highlighted, report Edwin M. Meyer of the University of Florida in Gainesville and his colleagues. The drug protects cells from amyloid toxicity, but Meyer remains skeptical that alpha 7 receptors represent a direct target of beta-amyloid.

"I love the idea because it makes the receptor more relevant to Alzheimer's disease, but it's not fitting into the data. There's an awful lot of cells affected by [beta-amyloid] that don't have alpha 7 receptors," he says. —*J.T.*

Antidepressant aids cancer therapy

Alpha-interferon, a potent chemical that the immune system produces to fight viruses, can also keep cancer cells in check. Yet when physicians use it as a drug, the compound sometimes triggers muscle problems, sleep difficulties, loss of appetite, and a debilitating depression that may include suicidal thoughts. These side effects frequently lead patients to stop taking the drug. "Clinically, it's a very important issue," says Andrew H. Miller of Emory University School of Medicine in Atlanta.

Starting cancer patients on an antidepressant before they begin receiving alpha-interferon markedly reduces the therapy's side effects, Miller and his colleagues now report. Beginning 2 weeks prior to high-dose alpha-interferon therapy, 18 people with malignant melanoma daily took either a placebo pill or paroxetine, an antidepressant better known as Paxil. The scientists then monitored patients for several months, testing them for depression and neuromuscular problems.

Of the nine people getting the placebo, seven developed depression, while only two of the nine patients taking Paxil did. The degree of depression was also significantly higher in the placebo group, Miller reports. The pretreatment reduced the amount of muscle fatigue and aches, as well.

The study shows "very nicely" that Paxil wards off the side effects of high-dose alpha-interferon, says Christina A. Meyers of the M.D. Anderson Cancer Center in Houston. She wonders, however, whether the same strategy is appropriate for people receiving the lower doses of alpha-interferon that are more typically prescribed for many cancers and viral infections. Studies suggest that these people face only about a 30 percent risk of depression.

Given those odds, physicians may hesitate to pretreat all such patients with antidepressants, which have their own side effects, Meyers warns. "The development of better predictors [of who will get depression from alpha-interferon] is key," she argues.

Miller agrees that the decision to give patients Paxil before low-dose alpha-interferon remains a difficult one. He and his colleagues plan to conduct a trial of the antidepressant therapy for hepatitis C. Millions of people in the United States alone are infected with the liver-destroying virus, he notes, and low-dose alpha-interferon is part of the only approved treatment. —*J.T.*

Stem cells track down brain cancer

Scientists are excited about the idea that transplants of immature nerve cells may provide a treatment for strokes, Parkinson's disease, and many other neurological conditions. Several studies presented in Miami Beach even hinted that these neural stem cells improve memory and learning skills when placed in the brains of aging rodents.

Karen S. Aboody of Children's Hospital in Boston and her colleagues now want to send such cells after brain tumors. Investigators have observed that neural stem cells, which are able to grow into any of the cell types in the brain, migrate to damaged areas. So, Aboody was curious whether these cells might home in on and infiltrate tumors. They do, even if injected on the opposite side of the brain from the cancer, according to her studies in rodents. The stem cells also seem to collect at the border where healthy tissue meets the tumor.

Moreover, Aboody has evidence that the stem cells follow and track down cancer cells that leave the primary tumor and invade the rest of the brain. If scientists can engineer neural stem cells to deliver a toxic compound to such wandering cancer cells, physicians might have a potent new weapon against invasive brain cancers, which are invariably fatal today, she says. —*J.T.*

Rats get hooked on testosterone

Teenagers and others looking to sculpt the perfect body often abuse anabolic steroids, compounds that mimic the body's natural hormone testosterone in their ability to promote muscle growth. About a decade ago, scientists suggested that users of the drugs may become addicted to them, much like cocaine or heroin.

Now, for the first time, researchers have shown that rats will self-administer testosterone, one of the traditional signs that a compound is addictive. In one experiment by Luke Johnson of the Yale University School of Medicine and his colleagues, rats that liked either a grape- or an orange-flavored drink gradually switched preference if the less-favored drink was laced with testosterone. In a second test, rats given the choice of two holes quickly learn to place their nose in the one that triggers an infusion of testosterone into their bloodstream via a catheter.

Like other addictive drugs, testosterone and its anabolic relatives may activate pleasure pathways in the brain, although perhaps not to as great an extent, suggest the researchers. "It's not as rewarding as cocaine, obviously," says Johnson. —*J.T.*