Neuroscience

Rick Weiss reports from Toronto at the 18th annual meeting of the Society for Neuroscience

Alzheimer's, aging and acetylcholine

Consisting of perhaps no more than 100,000 nerve cells, the basal forebrain takes up very little of the space between our ears. But with evidence that it may play a key role in Alzheimer's disease, this deeply buried clump of cells has captured many neuroscientists' attention in the past two years.

Through long neural branches, the basal forebrain supplies the more highbrow parts of the brain, such as the cortex and hippocampus, with healthy doses of the neurotransmitter acetylcholine, which scientists believe modulates the processes of learning and memory. In Alzheimer's, the basal forebrain usually degenerates, leading to depressed acetylcholine production. Many experimental Alzheimer's therapies have sought to boost acetylcholine, but with little success.

Now, researchers express excitement about the possibility of using a natural hormone, nerve growth factor (NGF), to "rescue" a withering basal forebrain and block the progression of at least some Alzheimer's symptoms. Found in low levels in most animals, NGF dramatically stimulates new outgrowths of acetylcholine-producing ("cholinergic") nerves. Until recently, scientists wanting to work with NGF had to extract it from the salivary glands of male mice — lots of male mice. But now that several laboratories have successfully cloned the NGF gene from several different species, scientists are moving quickly into what some envision as the next big wave in neuroscience research: transplantation of genetically engineered cells that make cell growth factors.

Lars Olson of the Karolinska Institute in Stockholm, Sweden, last week described the first such attempts. Olson and his colleagues inserted into a cultured line of mouse cells the gene for a form of NGF. When transplanted into the brains of rats, these gene-altered cells secreted NGF and stimulated new growth of acetylcholine-producing neurons. Moreover, when the researchers mixed the growth-factor-secreting cells with fetal nerve tissue that was about to be transplanted into adult rats' brains, they enhanced the survival and growth of the fetal tissue graft.

Beyond the possibility of rescuing basal forebrains in Alzheimer's patients, other potential applications of the technique abound. In Parkinson's disease, for example, where Olson and others have experimented with transplants of dopamine-producing fetal cells into patients' brains, gene-altered cells may behave more predictably than fetal cells. "One possibility would be to use these cells *rather* than fetal tissue, by getting them to make dopamine, for instance," Olson says.

Elsewhere on the Alzheimer's front, scientists report that monkeys, if allowed to live long enough, may be useful models for studying the disease. Alzheimer's research has long been hampered by the lack of a research animal that develops both the behavioral and neurological signs of the disease. Now, Linda C. Cork of the Johns Hopkins School of Medicine in Baltimore and her colleagues report the first identification of a protein called A68 in the brains of old monkeys. In humans, the protein — whose function remains uncertain — is uniquely found in Alzheimer's patients (SN: 11/28/87, p.348).

Moreover, Cork's co-worker Donald Price reports the first discovery of neurofibrillary tangles in the brain of a very old monkey who had died after showing symptoms of Alzheimer's. The protein tangles in brain tissue are characteristic of advanced Alzheimer's, and Price speculates that A68 may be a precursor of the tangles.

Along with ongoing, task-oriented studies of a large group of aging monkeys in his lab, he says, analyses of such changes in monkey brains may help scientists understand the connection between neural damage and the behavioral changes seen in Alzheimer's.

Marijuana's brain receptors mapped

A pharmaceutical company's futile attempt to make a medically acceptable marijuana molecule has helped researchers understand how the drug gives its "high."

Scientists at the Groton, Conn.-based Pfizer Central Research finally gave up their attempts to make a nonpsychoactive analog of marijuana's primary active ingredient — delta-9 tetrahydrocannabinol (THC) — which they believed had great potential as a painkiller. But Miles Herkenham of the National Institute of Mental Health in Bethesda, Md., and his colleagues used one of the company's especially potent versions of THC to map, for the first time, the location of THC receptors in the brain.

Normal THC is so chemically "greasy" it sticks to and contaminates laboratory glassware and doesn't lend itself to being radioactively labeled. The Pfizer analog had a classic THC-receptor binding site but was more amenable to radiolabeling experiments, allowing the researchers to see where it went in rat and marmoset brains.

"It's gratifying to see the distribution," Herkenham says, since it matches so well the drug's pharmacology. Most of the receptors are in the hippocampus — where scientists think memory consolidation may occur, and where the external world may get translated into a spatial and cognitive "map." They also found receptors throughout the cortex, the site of higher cognition. The distribution might explain marijuana's reported detrimental effects on memory — and its more popular effects on mental activity and spatial orientation.

Herkenham found very few receptors in the brainstem, where critical life-support controls are based. This might explain why it's almost impossible to die from even extremely high doses of the drug, he says. Some receptors in the spinal cord might explain pot's analgesic effects—which in this analog are more powerful than morphine, Herkenham adds.

Unfortunately, as Pfizer learned and Herkenham's animals confirmed, the psychoactive properties of pot are inseparable from the painkilling parts. His test animals "were incredibly high," he says. How could he tell? "It was obvious."

Beating the MSG clock

Monosodium glutamate (MSG), the flavor-enhancer used in Chinese restaurants and elsewhere, is a well-known neurotoxin capable of inducing convulsions when injected into a test animal's abdominal cavity, or peritoneum.

MSG's convulsive effects on rats are well studied, and the doses needed to get those effects are remarkably predictable, depending on the rat's age, weight and pedigree. Irma De la Rosa, Alfredo Feria-Velasco and their colleagues at the Unidad de Investigación Biomédica de Occidente in Guadalajara, Mexico, suspected another variable might affect MSG toxicity: time of day.

The researchers injected standardized doses of MSG into rats' abdominal cavities at 7 a.m., 3 p.m. and 11 p.m., then kept track of the number and severity of seizures. They recorded no differences in the total number of seizures in each group, but convulsions were far more severe in the 7 a.m. group. Indeed, nearly 70 percent of the MSG-for-breakfast group died of epileptic seizures, suggesting a critical interaction between MSG and one or more of the many chemicals in the body whose concentrations vary with time of day. There were no deaths in the other two groups, and control rats injected with equivalent solutions of table salt had no seizures.

While it's tempting to rule out Chinese food for breakfast, extrapolation to humans is difficult because experimental doses were more than 50 times those one might expect from a meal, and because MSG — when not injected — is largely detoxified in the digestive tract.