NEUROBIOLOGY

Unusual Cells May Help Treat Parkinson's Disease

On each side of your neck, nestled up against your carotid artery, is a helpful little organ called the carotid body. Its job is to sense how much oxygen is in your blood and signal your brain to step up your breathing if the level drops too low. New research suggests that the cells of the carotid body may one day prove useful in yet another way: as brain grafts for treating Parkinson's, the degenerative brain disease that strikes 1% to 2% of people over age 65.

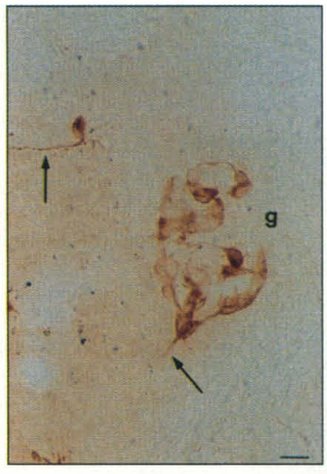
In the February issue of *Neuron*, a team headed by José López-Barneo of the University of Seville in Spain reports that in rats, carotid-body cells transplanted from the animals' necks into their brains reverse the symptoms of experimentally caused Parkinson's disease. Neuroscientist Arnon Rosenthal, who works on therapies for Parkinson's at Genentech Inc. in South San Francisco, describes the result as "quite intriguing, quite promising." Carotid-body cells will have to pass many more tests before researchers can even consider trying them in patients. But Rosenthal says they may do a better job of correcting the defect of Parkinson's disease than do the fetal-brain cells sometimes used as a treatment—and they raise fewer ethical questions.

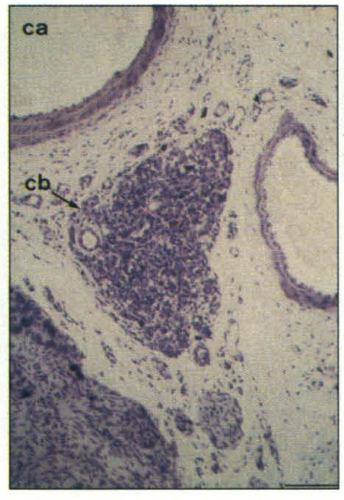
The root cause of the disease is the death of neurons in a part of the midbrain called the substantia nigra. These neurons normally send connections to an area called the striatum, where they release the neurotransmitter dopamine. The loss of this dopamine causes the movement problems characteristic of the disease. The goal of transplants is to make up for the loss by putting dopamine-releasing cells directly into the striatum. And the cells from a patient's own carotid bodies "may produce ... up to 45 times more dopamine" than fetal neurons do, says Rosenthal.

What's more, he adds, the carotid-body cells "survive much better as a transplant. They even thrive in low oxygen, which is exactly what you want." That's because brain tissue, especially when disturbed by surgery, can be quite oxygen-poor, which may explain the low survival rate of fetal and other types of grafts.

López-Barneo had been interested mainly in how carotid-body cells sense oxygen, but he recalls that colleagues kept pointing out that these cells might make great candidates for grafting into the brains of Parkinson's patients. So he and his team set out to test the idea. They turned to a standard rat model used for screening potential Parkinson's therapies, in which researchers kill substantia nigra neurons on one side of the rats' brains. This causes several symptoms, including a movement imbalance that makes the rats turn in circles. Researchers can test a therapy by seeing whether it corrects those symptoms in the rats. And López-Barneo's team found that transplants of glomus cells—the dopamine-producing cells that make up 80% of the carotid body—appear to work.

The researchers implanted chunks of carotid bodies containing about 800 glomus cells into the striatum on the damaged side of the rats' brains. The neurons fared well.





JOSÉ LÓPEZ-BARNEO *ET AL.*

Reaching out. When transplanted from the carotid body (cb, at right) into rat brains, glomus cells (above, brown stain) put out neuronlike fibers (arrows).

Three months after the surgery, 30% to 60% of the glomus cells had survived and were making dopamine, and new neural connections were visible in the striatum.

The rats' symptoms also improved over the course of 3 months, although some abnormalities, such as the turning in circles, reversed faster than others did. López-Barneo suggests that for some improvements, it's enough for the transplanted cells to secrete dopamine into the striatum. Other forms of recovery may require the new neural connections, which had not formed yet in rats examined 1 month after the surgery.

It is not yet clear, though, which cells are producing the new connections. "In several cases, you can see fibers coming out of the glomus cells," López-Barneo says. But he thinks the glomus cells can't be the source of all the new fibers. Instead, the transplant may be producing some growth factor that encourages the remaining substantia nigra neurons to sprout new extensions. If so, says Rosenthal, "that would be a major bonus." Indeed, he and others are trying to find ways to use growth factors to treat Parkinson's, in hopes that re-creating lost neural links will provide better symptom relief than grafts do. But, Rosenthal says, "a major problem with growth factor therapy is the delivery."

If the glomus cells make both dopamine and growth factors, Rosenthal adds, "you get two therapeutic approaches in one." López-Barneo's group is investigating which cells are putting out the new extensions and checking to see if glomus cells really do make growth factors.

Despite the encouraging early results, researchers caution that success in rats is only the first hurdle—and a relatively low one—for a potential Parkinson's treatment. Fetal-graft pioneer Anders Bjorklund of the University of Lund in Sweden notes that a few hundred fetal cells—about the same as the number of glomus cells used in these experiments—can also reverse Parkinsonian symptoms in rats, but it takes 200,000 to 300,000 surviving transplanted fetal neurons to treat human patients effectively. "The question," he says, "is if the human carotid body can provide that many cells."

Together, they might. Each human carotid body contains roughly 100,000 glomus cells, says López-Barneo. People can live with both carotid bodies removed, as long as they don't exercise or go to high altitudes. But the cells' high dopamine output means that one carotid body—which can be spared without any ill effects—should do the job, he argues, provided that glomus cells from elderly Parkinson's patients are as dopamine-rich and resilient as the cells tested in the experiment are. There is no reason to believe that won't be the case, he notes, but his lab is now repeating its experiment with cells from very old rats.

Even if the initial promise of the carotid-body transplants isn't borne out, researchers may find other ways to exploit the ability of these unusual cells to thrive in the brain. Rosenthal suggests, for example, that they might be engineered to enhance their growth-factor output and then placed in the brain where the factors are needed. So take a moment to appreciate your carotid bodies: You never know how they might come in handy.

–Marcia Barinaga