

GABAERGIC CELL GRAFTS CONTROL SEIZURE ACTIVITY

Transplants of Cells Engineered to Produce GABA Suppress Spontaneous Seizures

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PURPOSE: Cell transplantation into the brain is an aggressive clinical alternative. The hopes of treating diseases like intractable temporal lobe epilepsy have been subdued because the preclinical successes thus far have shown only slowing of epileptogenesis, or suppression of electrically induced seizures. Because the hallmark of epilepsy is spontaneous seizures, the clinical relevance of these studies has been questioned. The purpose of this study was to establish that cells genetically engineered to produce γ -aminobutyric acid (GABA) could suppress spontaneous seizures in an accepted model of temporal lobe epilepsy.

METHODS: Conditionally immortalized neurons were engineered to produce GABA under the control of tetracycline. These cells were transplanted into the substantia nigra of spontaneously seizing animals. After transplantation, the animals were monitored for 3 days immediately after surgery and again for 3 days beginning 7 to 8 days after surgery. Seizures and epileptiform spikes were recorded and later analyzed with detection software combined with video monitoring.

RESULTS: Animals that received genetically engineered GABA-producing cells had significantly fewer spontaneous seizures than did animals that received control cells, or animals that received GABA-producing cells plus doxycycline at the observation period starting 1 week after transplantation. A significant suppression of epileptiform spikes also was noted between the group that received GABA-producing cells and the group that received the same cells but were given doxycycline. The engineered cells show evidence of integration with the host but limited survival.

CONCLUSIONS: These data demonstrate that genetically engineered cells have the ability to suppress spontaneous seizures when transplanted into seizure-modulating nuclei. This is an important step toward

defining a clinical potential for this approach in epilepsy. The fact that the gene of interest can be regulated suggests that individualizing transplant therapy may be possible.

COMMENTARY

Transplantation of neural tissue to replace brain cells lost to disease or injury is an area of research that is already three decades old, having been pioneered by Bjorklund et al. (1). They used grafts of aminergic tissue, and growth from transplants of these cells could be readily visualized by using histochemical methods of the day, which they had developed (2). Accordingly, with fluorescence microscopy, the aminergic transplants were localized and their sprouted processes could be followed to their targets.

Certain neurodegenerative diseases (e.g., especially Parkinson's disease but also Alzheimer's disease) involve the loss of classes of neurons that use specific neurotransmitters. Interestingly, the symptoms of these diseases can be ameliorated by increasing the amount of neurotransmitter released from the surviving cells or by replacing the deficient neurotransmitter with agonists. These findings converged with those of experimental transplantation and led to speculation that neuronal transplantation also could treat these diseases. Anticipation was heightened because experimental evidence had even shown that transplanted tissue grew to the specific synaptic targets where synapses had been lost (3).

Although the experience with experimental and clinical transplantation is best known in regard to treating Parkinson's disease, the possibility of using cell transplantation to restore function after stroke or for the treatment of epilepsy currently is being explored. Certainly, the implantation of GABAergic neurons into epileptic brains could be a facile way to control hyperexcitability. The authors of the present article have taken just this approach.

However, such a design is not nearly as simple as it sounds. These investigators had to accomplish quite a bit of molecular engineering, specifically developing transplantable cortical neurons that (a) have the γ -aminobutyric acid (GABA)-synthesizing enzyme glutamate decarboxylase; (b) have their release of GABA under the control of doxycycline (i.e., GABA

off when doxycycline is present); and (c) carry complementary DNA (cDNA) for enhanced green fluorescent protein, to identify them microscopically. The authors then used the lithium-pilocarpine model to induce status epilepticus, causing significant damage within the limbic system, followed by chronic, spontaneous behavioral and electrographic seizures and epileptic spiking. With this model, they demonstrate that GABAergic neuronal grafts, when placed in the anterior substantia nigra, are functional and that GABA, thus released, significantly reduces the number of seizures (three of seven were seizure free) and epileptiform spikes seen. Moreover, GABA release was under the control of doxycycline.

Notably, of the 41 male animals, only 18 survived status epilepticus and the subsequent surgery in this protocol—a mortality rate of >50%. The authors noted that the site of transplantation would more suitably have been the lesion site within the hippocampus. Literature is cited to support the choice of the substantia nigra as the locus for implantation (i.e., its potential involvement in seizure propagation). However, transplantation in this remote site makes difficult the evaluation of the precise circuitry involved. What circuitry was involved? Are the results

due to local or remote actions of the graft? Were the effects due to a general depressant action of GABA release from the transplant, perhaps subsequent to leakage into the ventricle (i.e., a more global effect, similar to a systemic drug) versus the presumed focal release of GABA from the implanted tissue? These issues were not addressed in the article but are important if we are to entertain such an approach as a viable clinical option.

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References

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