

Current Literature

In Basic Science



The Right Cells, the Right Place, the Right Result: Transplants to Alleviate Seizures Take a Step Forward

GABA Progenitors Grafted into the Adult Epileptic Brain Control Seizures and Abnormal Behavior.

Hunt RF, Girsakis KM, Rubenstein JL, Alvarez-Buylla A, Baraban SC. *Nat Neurosci* 2013;16:692–697.

Impaired GABA-mediated neurotransmission has been implicated in many neurologic diseases, including epilepsy, intellectual disability, and psychiatric disorders. We found that inhibitory neuron transplantation into the hippocampus of adult mice with confirmed epilepsy at the time of grafting markedly reduced the occurrence of electrographic seizures and restored behavioral deficits in spatial learning, hyperactivity, and the aggressive response to handling. In the recipient brain, GABA progenitors migrated up to 1,500 μm from the injection site, expressed genes and proteins characteristic for interneurons, differentiated into functional inhibitory neurons, and received excitatory synaptic input. In contrast with hippocampus, cell grafts into basolateral amygdala rescued the hyperactivity deficit but did not alter seizure activity or other abnormal behaviors. Our results highlight a critical role for interneurons in epilepsy and suggest that interneuron cell transplantation is a powerful approach to halting seizures and rescuing accompanying deficits in severely epileptic mice.

Commentary

Synaptic inhibition critically controls neural circuit excitability in the brain; reduced functional inhibition due to loss of GABAergic neurons, dysregulation of surviving GABA cells, and altered GABA receptor responses accompanies development of spontaneous seizures in animal models of acquired temporal lobe epilepsy (TLE). In many TLE patients, altered inhibitory control is also implied by the success of anti-seizure therapy with drugs that potentiate GABA's effects in the brain. Systemic drug treatment, however, affects circuits throughout the brain—not just in seizure-producing areas—sometimes leading to unwanted side effects. Further, epilepsy symptoms are pharmacologically refractory in a significant percentage of TLE patients. Hunt and colleagues explored the attractive proposition that reinstatement of constitutive GABA function in specific neural circuitry affected by seizures might offer a novel avenue for treating seizures using medial ganglionic eminence (MGE) progenitor cells, transplanted into the hippocampus in a mouse model of acquired TLE in adults.

The pilocarpine-treated mouse model used here is a robust model of adult onset acquired epilepsy in rodents. It shares many cellular and behavioral features with TLE patients, including loss of inhibitory interneurons, axon sprouting, synaptic reorganization, memory and anxiety irregularities, and frequent spontaneous seizures that are often pharmacoresistant. The present study transplanted MGE progenitor

cells (undifferentiated, post-mitotic cells destined primarily to become GABAergic interneurons) into the hippocampi of adult mice with established epilepsy (i.e., they displayed spontaneous seizures). They found that transplanted MGE cells developed mainly into GABA neurons, as expected, and integrated into hippocampal synaptic circuitry. Concurrently, transplant recipients experienced a greater than 90% reduction in seizure frequency and restoration of several epilepsy-related behavioral deficits. Obligatory scientific caveats aside, it is tantalizing to speculate that the transplanted MGE-derived GABA neurons functionally replaced those cells lost in the initial insult (i.e., status epilepticus) used to trigger the development of TLE in these mice. The successful functional integration of GABAergic interneuron progenitors in an adult model of TLE appears to represent a significant step in developing new anti-epileptic treatments.

Successful integration of undifferentiated, embryonic stem (ES) cell progenitors transplanted into adult hippocampal circuits was demonstrated recently in the pilocarpine-treated mouse, but functional outcomes on seizures were not addressed, and many ES cell-derived neurons differentiated into non-GABAergic phenotypes (1). Adding to previous findings from immature mice by the Baraban group using a genetic epilepsy model (2), the work described by Hunt et al. significantly advances previous understanding of neural transplantation for epilepsy treatment by demonstrating that MGE progenitors differentiate into a relatively pure subset of GABAergic interneurons after transplantation in *adult* mice, including several phenotypes that are preferentially lost after SE (3), regardless of whether or not the animals' brains were lesioned by seizure activity. The most obvious “wow” factor in the report for most

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epilepsy researchers is probably the finding that after MGE progenitor transplantation, the grafted mice experienced far fewer spontaneous seizures than did the ungrafted controls. It seems likely that transplanting the appropriate cell population contributed to the success of the treatment in this regard. Grafting these cells at just the right stage of development—MGE progenitors are mainly postmitotic but undifferentiated GABA neurons—appears to have been a major contributing factor to the seizure-abating effect of the transplant.

Interestingly, similar MGE transplantation into the amygdala, another site of potential seizure initiation, did not alleviate the seizures, even though the transplanted cells appeared to disperse and become GABA neurons, potentially replacing those lost after the status epilepticus event. The amygdala develops increased synaptic excitability in similar TLE models (4), and amygdala kindling is highly effective in evoking seizures and reducing seizure threshold (5). Yet, replacing GABA neurons in the region was without anti-seizure effect, highlighting the sensitivity of seizure development and expression to altered hippocampal circuitry in this model.

In addition to GABA neuron loss in the hippocampus, a variety of cellular changes accompany epileptogenesis in models of acquired TLE, such as the one used here, including axon sprouting and synaptic reorganization in the dentate gyrus and other brain regions that likely underlie ongoing increased recurrent excitation. This represents, perhaps simplistically, an imbalance between synaptic inhibition and excitation that underlies the increased propensity for seizure generation in this and other models. After MGE transplants, mossy fiber sprouting remained robust, yet the transplanted GABA cells were effective in suppressing seizures. Pharmacoresistance to GABA receptor modulators is a characteristic of seizures in this model (6), highlighting the critical nature of precise spatial and temporal inhibitory signaling in controlling seizures. In terms of epilepsy mechanisms, it is intriguing to hypothesize that the loss of key inhibitory circuits is the most prominent feature underlying increased seizure propensity, given that some forms of cellular pathology obviously persisted after the transplant (e.g., mossy fiber reorganization). Contrarily, it is equally provocative to wonder if excitation and inhibition remain unbalanced to some degree. If so, seizure threshold might still be affected, and if seizures beget seizures by causing cell death, might transplanted cells eventually succumb to future seizure activity, if it occurs? Seizure rates, however, were suppressed for several weeks, supporting, for now, the efficacy and relative stability of the transplant.

Compared to many anti-epileptic drugs, MGE progenitor transplantation appears to come a step closer to reaching the “no seizures, no side-effects” goal of much epilepsy therapy research. The MGE progenitor grafts alleviated some cognitive co-morbidities associated with TLE development in the treated mice, underscoring the restorative nature of the transplants. Other novel approaches, including optogenetic (7) and electri-

cal (8) stimulation methods, have also yielded proof-of-principle results consistent with the hypothesis that activation of specific constituent neural circuits might represent a feasible approach to treating seizure disorders. Like these new potential therapies, MGE progenitor transplantation is not currently feasible for human treatment, as discussed by the authors. At present, MGE cells with defined GABAergic destiny are not readily available since they must be harvested directly from embryos. Conversely, neural progenitor stem cells are easier to obtain but can differentiate into a variety of cell phenotypes, including tumor cells (9). The technological advent of specific markers to identify pluripotent stem cells that are destined to become mainly GABAergic interneurons may allow harvesting of sufficient numbers of inhibitory neuron progenitors to graft for treatment of TLE. The work of Hunt and colleagues emphasizes the importance of specific hippocampal inhibitory circuitry in organizing brain functions and highlights the potential for development of novel therapies for successful alleviation of TLE symptoms.

by Bret N. Smith, PhD

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