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The Promise of an Interneuron-based Cell Therapy for Epilepsy

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Abstract

Of the nearly 3 million Americans diagnosed with epilepsy, approximately 30% are unresponsive to current medications. Recent data has shown that early postnatal transplantation of interneuronal precursor cells increases GABAergic inhibition in the host brain and dramatically suppresses seizure activity in epileptic mice. In this review, we will highlight findings from seizure-prone mice and humans that demonstrate the link between dysfunctional GABAergic inhibition and hyperexcitability. In particular, we will focus on rodent models of temporal lobe epilepsy (TLE), the most common and difficult to treat form of the disease, and interneuronopathies, an emerging classification. A wealth of literature showing a causal link between reduced GABA-mediated inhibition and seizures has directed our efforts to recover the loss of inhibition via transplantation of interneuronal precursors. Numerous related studies have explored the anticonvulsant potential of cell grafts derived from a variety of brain regions, yet the mechanism underlying the effect of such heterogeneous cell transplants is unknown. In discussing our recent findings and placing them in context with what is known about epilepsy, and how related transplant approaches have progressed, we hope to initiate a frank discussion of the best path toward the translation of this approach to patients with intractable forms of epilepsy.

Keywords

epilepsy; seizures; transplantation; GABA; interneuron progenitor

Introduction

Surges of abnormal electrical discharge in the brain lead to the spontaneously occurring and recurrent seizures that define epilepsy. These seizures vary from staring spells, or absence seizures, lasting only a few seconds to full body convulsions, or tonic clonic seizures that can last for several minutes to hours. Given the toll of human suffering due to epilepsy, the need for more effective treatments is undeniable. At present, the most common treatment for these patients is the use of anti-seizure medications many of which act by globally increasing GABA-mediated inhibition (Porter, 1997). As with all medications, antiepileptic drugs can have unpleasant side effects that can severely affect a patient's quality of life. Such side effects vary depending on the medication, but include nausea, weight loss or gain, impaired vision, drowsiness and dizziness. It is also a concern that exposure of the immature child's brain to powerful anti-seizure medications, which work by inhibiting ubiquitously expressed GABA receptors or membrane-bound ion channels, will have irreversible consequences on cognitive development (Lagae, 2006; Mandelbaum et al., 2009). Each year hundreds of patients who are unresponsive to traditional noninvasive treatments opt to undergo surgery to remove a restricted region of the brain from which seizures are thought

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to originate. One of the most common procedures – a resection of the temporal lobe or "temporal lobectomy" which contains hippocampal structures - most commonly lead to depression and deficits in both verbal and non-verbal memory. In rare cases, patients who undergo unilateral or bilateral resections of hippocampal structures suffer amnesia (Polkey, 2009). With regard to postoperative seizure outcome, a large fraction of patients reported that their condition had improved as defined by a cessation or a worthwhile reduction in seizures and improved quality of life. However, more than 10% of surgical patients experienced no improvement in their condition or a worsening of seizures (Engel Jr., 2009). Although pharmaceutical and surgical interventions provide seizure relief in the majority of epileptic patients, thousands of patients continue to experience uncontrollable seizures or only partial seizure control. Children with more severe forms of pediatric epilepsy are particularly vulnerable to the long-term consequences of these intractable seizures. Such patients experience frequent seizures, in some cases several hundred per day, that can impair brain development and cognition (Lee, 1989; Hoie et al., 2006; Carreno et al., 2008).

To develop new treatments for epilepsy, we must understand how a brain becomes hyperexcitable, how this wave of abnormal excitation spreads and, how it can be stopped. Careful studies of both healthy and epileptic animals, and when possible patients, have yielded substantial insight into the many causes of epilepsy. The mechanisms currently thought to underlie epilepsy have been thoroughly and eloquently reviewed in comprehensive texts on the disease (Schwartzkroin, 1995; Engel Jr., 1997; Delgado-Escueta, 1999) and are only briefly summarized here. Epilepsy is caused by an increase in neuronal excitability due to alterations in ion channel function, inhibitory and/or excitatory synaptic transmission, neuronal circuitry, protein levels (e.g. neurosteroids, neuropeptides) and/or the expression of genes encoding for critical proteins (e.g. receptors, trophic factors). These changes generally can occur in response to a brain insult, developmental brain malformation and genetic mutation or follow an unknown origin (i.e., idiopathic).

While acknowledging that the causes of epilepsy are numerous, in this review we will focus on how a loss of inhibition and its subsequent recovery via cell transplantation can lead to and ameliorate seizures, respectively. We will review data from acquired and genetic models of epilepsy suggesting that a reduction in inhibition due to a dysfunctional inhibitory circuit, interneuron loss or compromised interneuron function invariably results in spontaneous seizures. Based on this evidence, we propose that the addition of "new" inhibitory interneurons (with properties mimicking the endogenous interneuron population) to the epileptic brain can have therapeutic effects in a wide variety of epilepsy disorders, and will discuss this and alternative cell-based approaches to suppressing excitability in rodent models of epilepsy.

Acquired models of epilepsy

Temporal lobe epilepsy (TLE) is the most common intractable form of epilepsy. To understand what causes TLE, the development and pathology of the disease have been extensively modeled in rodents (Cavalheiro, 2006; Dudek, 2006; Galanapoulou, 2006; Curia et al., 2008). In the commonly used pilocarpine or kainate models of TLE, a prolonged period of seizure activity, or *status epilepticus*, is pharmacologically induced in a wild-type rodent. Status epilepticus is followed by a latent period of few or no seizures. Within weeks of the acute seizure episode, surviving rodents begin to exhibit spontaneous recurrent seizures (Shibley & Smith, 2002; Echauz, 2009) that gradually increase in severity over time (Williams *et al.*, 2009). The hippocampi of TLE rodents are characterized by increased adult neurogenesis in a germinal zone of the dentate gyrus (Parent *et al.*, 1997), numerous changes in gene, protein and trophic factor expression (Mudo *et al.*, 1996; Becker *et al.*, 2003; Lund *et al.*, 2008; Brooks-Kayal *et al.*, 2009), mossy fiber sprouting (Buckmaster *et al.*, 2002) and neuronal loss (Turski *et al.*, 1984).

Neuronal loss and mossy fiber sprouting have also been observed in the resected hippocampi of TLE patients. Although patients can lose both excitatory (pyramidal cells in CA1 and CA3) and inhibitory (hilar interneurons) neurons there is a consistent reduction in cells in the GABAergic interneuron-rich hilar region of the dentate gyrus (de Lanerolle *et al.*, 1989; Mathern *et al.*, 1995; Spreafico *et al.*, 1998; Wittner *et al.*, 2001). These anatomical data are further supported by electrophysiological studies which have demonstrated a reduction in GABA-mediated synaptic transmission from granule cells of TLE patients (Williamson *et al.*, 1999). TLE rodents have been used to determine how neuronal loss may affect function within the entorhinal cortex and dentate gyrus, regions which provide and receive, respectively, the majority of excitatory synaptic input to the hippocampus (Segal & Landis, 1974; Steward & Scoville, 1976; Schwartz & Coleman, 1981). In the pilocarpine TLE model, Layer II neurons within the entorhinal cortex exhibit a reduction in inhibitory synaptic transmission and recurrent inhibition, an increase in excitatory synaptic transmission, and increased action potential firing (Kobayashi *et al.*, 2003; Kumar & Buckmaster, 2006; Kumar *et al.*, 2007). Loss of GABA circuitry has also been reported in patients with cortical dysplasia (a refractory form of epilepsy common in children) and certain forms of traumatic brain injury associated with seizures (Spreafico et al., 2000; Golarai et al., 2001; Calcagnotto et al., 2005; Knopp et al., 2008). In addition to loss of synaptic GABAergic inhibition, the dentate gyrus exhibits reduced expression of postsynaptic $GABA_AR$ δ and α5 subunits that mediate tonic conductance (Houser & Esclapez, 2003; Peng *et al.*, 2004; Glykys *et al.*, 2008). Consistent with a hypothesized reduction in tonic inhibition, the dentate gyrus of epileptic brains is hyperexcitable and less sensitive to neurosteroids that act on δ subunit containing $GABA_ARs$ (Peng *et al.*, 2004).

Several recent studies suggest that the epileptic brain attempts to compensate for a lack of inhibition by increasing the inhibitory potential of surviving GABAergic interneuron populations. In a mouse model of TLE, surviving GABAergic interneurons in the dentate hilus grow larger, extend dendrites, sprout more axons and form new synapses (Zhang *et al.*, 2009). Although there are fewer GABAergic interneurons in the epileptic brain, those that remain form more inhibitory synapses than in controls (Thind *et al.*, 2009). This may be a homeostatic mechanism by which interneurons attempt to compensate for interneuron loss, increased excitation and decreased inhibition by forming abundant, albeit dysfunctional, inhibitory connections using the surviving interneurons. That the epileptic brain may have developed an endogenous program to *increase inhibition* is promising given that interneuronal precursor cell transplantation is based on the same rationale.

Taken together, these data provide valuable insight into how individual neurons contribute to abnormal excitation by receiving more excitatory and less inhibitory inputs, relaying more excitation, and forming new synapses. Studies of the developing and epileptic hippocampus suggest a cellular mechanism by which activity spreads in the hippocampus and further highlight a critical role for GABA-expressing interneurons (Morgan & Soltesz, 2008; Bonifazi *et al.*, 2009). Using a combination of imaging and electrophysiological techniques in the developing hippocampus, Cossart and colleagues have proposed the presence of GABAergic “hub” neurons that connect a large number of cells across long distances. Given the ability of GABAergic inputs to produce giant depolarizing potentials (GDPs) in early development (Ben-Ari *et al.*, 1989), electrophysiological stimulation of a single hub interneuron is able to depolarize a large number of neurons and synchronize network activity (Bonifazi *et al.*, 2009). However, stimulation of other hub neurons slows down oscillations or reduces network activity. The diverse effects of hub neuron activation on network dynamics likely reflect both the excitatory and inhibitory (Khalilov *et al.*, 1999) actions of GABA in early development. Whether GABAergic hub neurons persist in the adult brain and how they might affect network dynamics remains unknown. Computational studies using large-scale realistic models of a seizure-prone adult rat dentate gyrus have started to

examine how excitatory hub neurons may generate and propagate hyperexcitability (Morgan & Soltesz, 2008). In the presence of a small number of hub granule cells, minimal granule cell stimulation dramatically increases the number of granule cells that fire, boosts the speed at which activity spreads across the network and doubles the duration for which this activity persists. These studies, described in more detail elsewhere in this volume, will require further experiments to reveal whether hub cells exist in the adult (and epileptic) hippocampus.

Genetic models of interneuronopathy

Unlike rodent models that were designed to mimic specific behavioral and anatomical pathologies exhibited by TLE patients, genetic interneuronopathy models were generated to understand how one or two genes contribute to brain development and function. In many cases, the primary intent of generating these genetic models was not to study epilepsy, and many originate from laboratory groups studying interneuron origins and diversity (as discussed elsewhere in this volume). The relation between each of the genes, inhibition and excitability were explored only after it became evident that the genetic mutation led to a loss of interneurons, synaptic inhibition, and/or interneuron function.

For example, mice lacking the *Dlx1* gene were generated in the Rubenstein laboratory to examine interneuron development. *Dlx1* encodes a transcription factor expressed in several specific populations of GABAergic interneurons (e.g. SOM^+, CR^+ and NPY^+ interneurons) (Cobos *et al.*, 2005). Previously, *Dlx1/2* double mutants were shown to lack 80% of GABA immunoreactive cells and to die within a few hours after birth (Anderson *et al.*, 1997). In contrast, *Dlx1* mutants are indistinguishable from wild-type mice at birth and exhibited a selective loss of SOM^+, CR^+, NPY^+, and NOS^+ interneurons as they approached reproductive maturity ($P30^+$) (Cobos *et al.*, 2005). The analysis of these mice demonstrated that Dlx1 is required for interneuron survival, not development. Subsequent electrophysiological studies revealed that interneuron loss is accompanied by a reduction in synaptic inhibition and spontaneous electrographic and behavioral seizures. *Dlx1* mutant mice can now be used to examine how the loss of selective interneuron subtypes and inhibition changes in the adult brain leads to spontaneous seizures. More recently a *Dlx5/6* heterozygote mouse was found to have normal interneuronal densities, at all developmental stages, but a susceptibility to spontaneous epileptic discharge and reduced total EEG power in the 30 to 80 Hz range as young adults (Wang *et al.*, 2010),

A number of other interneuronopathy models have also been generated including, but not limited to, mice with reduced or no expression of the *ARX*, *uPAR*, *Tlx1*, *Sox2*, *cD2*, *Ppt1* genes. Additional model possibilities, including those based on selective or conditional manipulation of genes required for interneuron genesis and migration, continue to emerge. In each of these mice, a selective loss of interneuron subtypes and, when examined, abnormal electrographic activity have been demonstrated (Monaghan *et al.*, 1997; Gupta *et al.*, 2001; Powell *et al.*, 2001; Roy *et al.*, 2002; Avilion *et al.*, 2003; Powell *et al.*, 2003; Ferri *et al.*, 2004; Jalanko *et al.*, 2005; Kato & Dobyns, 2005; Glickstein *et al.*, 2007; Kielar *et al.*, 2007; Cavallaro *et al.*, 2008; Marsh *et al.*, 2009; Price *et al.*, 2009). These discoveries and the recent identification of an epileptic phenotype and reduced cortical interneuron function in children with *ARX* mutations prompt a new clinical classification for epilepsy termed ‘interneuronopathy’ (Kato & Dobyns, 2005). As an epilepsy model group, these genetically modified mice can be used to understand how specific interneuron subtypes contribute to overall brain activity and counterbalance hyperexcitability.

Aside from rodent models of interneuronopathy that result in interneuron loss, reducing expression of a voltage-gated Na^+ channel interferes with interneuron function and causes spontaneous seizures and death. Mice homozygous for the human mutation in the gene

encoding Nav1.1 (*Scna*$^{-/-}$ mice) begin exhibiting ataxia and seizures on postnatal day 9 (P9) and are dead by P15. Heterozygous mutants (*Scna*$^{+/-}$ mice) exhibit spontaneous electrographic seizures and sporadic deaths at an older age (P21-27) (Yu *et al.*, 2006) as well as seizures induced by elevated core body temperature (Oakley *et al.*, 2009). Given both the *Scna* mutation and subsequent phenotypic characteristics of these mice, heterozygous mutants are considered a model of severe myoclonic epilepsy in infancy. Hyperexcitability in mice that are homozygous and heterozygous for the *Scna* mutation is likely explained by a selective reduction of sodium current density and action potential firing recorded from mutant interneurons (Yu *et al.*, 2006). In contrast, sodium currents recorded from pyramidal cells were no different between wild-type and heterozygous or homozygous mutants. *Scna* mutants suggest that the selective interference of interneuron excitability is sufficient to induce a severe epileptic phenotype. A common theme that emerges from these studies is the possibility that seizure activity can be suppressed in *Scna* mutant mice, interneuronopathic mouse models, and acquired TLE models by recovering the loss of GABAergic inhibition through the addition of new interneurons.

Advances in cell transplantation in the treatment of epilepsy

For two decades now, the therapeutic potential of fetal and progenitor cell transplantations in suppressing seizures has been tested with mixed results. It is important to note, that early studies were not able to label grafted cells for subsequent immunohistochemical analysis of cell type as they predated the advent of fluorescently labeled mice (Fine *et al.*, 1990; Holmes *et al.*, 1991) and did not examine spontaneous seizures (Buzsaki *et al.*, 1988; Loscher *et al.*, 1998). Transplantation of fetal locus coeruleus neurons reduced the frequency of ictal spikes induced by subsequent injections of the $GABA_AR$ antagonist picrotoxin (Buzsaki *et al.*, 1988). “GABA-rich” substantia nigra tissue grafted into kindled rats transiently increased the stimulation intensity required to induce seizure-like afterdischarge activity (Loscher *et al.*, 1998). Although both of these findings suggest that transplantation increased seizure resistance, a subsequent study to transplant cells genetically engineered to express GAD65 into the piriform cortex of kindled rats did not significantly affect afterdischarge activity (Gernert *et al.*, 2002). Human neural stem cells, a promising source of pluripotent cells, transplanted into the pilocarpine-induced rat model of TLE differentiate into cells that are positive for GABAergic (26%), glutamatergic (2%) or astrocytic (21%) markers. Such grafted cells decrease the percentage of pilocarpine rats that develop behaviorally monitored spontaneous seizures and reduce both seizure frequency and severity (Chu *et al.*, 2004). Like the human stem cell grafts, striatal precursor cell grafts yield a small fraction of GABAergic cells (23%). Nonetheless, striatal precursors transplanted into rats soon after kainate-induced status epilepticus were also associated with a reduction in spontaneous, behaviorally assessed seizures (Hattiangady *et al.*, 2008).

Although these results are encouraging, they leave a number of critical questions unanswered. That is, cells are grafted and the effects on seizure behavior (or seizure-like afterdischarge activity) are monitored but little information is available with regard to what happens to the grafted cells and the host brain post-transplantation. In particular, to interpret the effects of transplants on global brain excitability it is important to know (i) how many of the grafted cells *survive* in the host brain and how far they *migrate* from the injection site, (ii) what *types of cells* (i.e. excitatory, inhibitory, glial, immature) the grafts yield, (iii) whether graft-derived cells functionally *integrate* into the host brain and (iv) how grafts affect electrographically and behaviorally monitored spontaneous *seizure activity*. In the absence of such information, the mechanisms by which grafted cells can act as an effective therapeutic option for epilepsy are left unknown. To address these questions, it would be helpful if grafted cells express fluorescent markers that would enable their identification for immunohistochemistry and electrophysiological recordings in the host brain.

As described above, a variety of fetal tissue sources have been grafted including rodent precursor cells of the hippocampus (Shetty & Hattiangady, 2007a), striatum (Loscher *et al.*, 1998), locus coeruleus (Buzsaki *et al.*, 1988; Bengzon *et al.*, 1993), spinal cord (Loscher *et al.*, 1998), medial (Alvarez-Dolado *et al.*, 2006; Baraban *et al.*, 2009) or lateral (Hattiangady *et al.*, 2008) ganglionic eminences, and human neural stem cells (Chu *et al.*, 2004). In addition to fetal tissue, neural progenitor cells derived from embryonic stem cell lines have been used (Li *et al.*, 2007; Carpentino *et al.*, 2008). When cell fate is examined, some of these grafts appear to contain a mixture of excitatory neurons, inhibitory interneurons, glial cells and immature cells (Chu *et al.*, 2004; Carpentino *et al.*, 2008). Such heterogeneity complicates interpretations of how grafts affect host brain activity. The exceptions are transplantations of the medial ganglionic eminence, and fetal CA1 and CA3 regions, which are committed to interneuronal or pyramidal cell fates, respectively (Zaman *et al.*, 2000; Alvarez-Dolado *et al.*, 2006; Baraban *et al.*, 2009).

Fetal CA1 and CA3 transplantations into rodent hippocampus have examined whether host brain variables such as age and health, both clinically relevant factors, affect graft survival. For both “middle-aged” (12–14 month old) and “aged” (22–24 month old) healthy rats, an equal fraction of cells transplanted into the hippocampus survived (18–23% of injected cells) (Zaman & Shetty, 2002). Interestingly, the epileptic hippocampus appears to be a more receptive environment for grafts e.g., a larger percentage of transplanted cells survived in the epileptic versus healthy hippocampi of kainate lesioned rats. When neural progenitors derived from an embryonic cell line were transplanted into the CA3 region, these cells formed tumors in a healthy hippocampus. In contrast, they did not form tumors and migrated longer distances toward the dentate gyrus in rat models of TLE (Carpentino *et al.*, 2008).

In addition to monitoring graft survival and spread, the impact of CA1 and CA3 transplants on the host epileptic brain has been examined. The hippocampi of TLE rodents and patients exhibit CA3 pyramidal cell and hilar interneuron loss as well as a reduction in GABAergic inhibition (see text in section *Acquired Models of Epilepsy*). Fetal CA3 cell transplants return the number of $GAD67^+$ and $calbindin^+$ interneurons in the TLE hippocampus toward that of control levels (Shetty & Turner, 2000; Shetty & Hattiangady, 2007b). However, it is currently unknown what causes this effect and whether an increase in GABAergic interneuron density translates to increased GABA-mediated inhibition in these animals.

Work from our lab has employed transplantations of the embryonic medial ganglionic eminence (MGE) into the newborn neocortex and hippocampus to understand how grafted cells behave in the host and affect host brain activity as assessed via single cell and cortical electrographic recordings (Alvarez-Dolado *et al.*, 2006; Baraban *et al.*, 2009). The MGE was chosen as the source of donor cells based on previous work from our collaborators and other laboratories featured in this special issue. An array of techniques including fluorescent tracing of MGE cells, *in utero* fate mapping and genetic models demonstrated that the MGE is the primary source of cortical interneurons (Lavdas *et al.*, 1999; Sussel *et al.*, 1999; Cobos *et al.*, 2001; Wichterle *et al.*, 2001). Further, grafting studies indicate the impressive migratory potential of MGE cells placed on cultured embryonic brain slices and transplanted into the adult striatum and thalamus *in vivo* (Wichterle *et al.*, 1999). In our studies, MGE cells derived from GFP^+ mice were transplanted into the neocortex and hippocampus of P2 wild-type mice (Figure 1). Thirty to sixty days after transplantation (DAT), immunohistochemistry, single cell electrophysiology, electron microscopy and cortical video-electrographic recording were used to assess a number of measures of both grafted-derived cells and the host brain. At 60 DAT, graft-derived cells had dispersed widely away from the injection site (up to 3 mm away in either direction) and had already started to migrate 3 days after injection. GFP^+ MGE cells developed the morphological characteristics of a variety of interneuron types (i.e. basket cells, chandelier cells, bipolar cells) and 69% of

these cells were $GABA^+$. We expect the number of GABAergic cells is an underestimate given the low signal produced by the GABA primary antibody and that we found no cells with pyramidal cell-like morphology and only a few oligodendrocytes (1.8%). At 30 DAT, graft-derived cells also expressed interneuron markers (e.g. PV, SOM, CR, CB, NPY) in the same ratios reported for native interneuron populations. Not only do graft-derived GFP^+ cells exhibit the morphological and neurochemical features of interneurons, they also fire like mature interneurons (e.g. fast-spiking, stuttering, regular spiking non-pyramidal cells). Single cell recordings of host pyramidal cells and interneurons have shown statistically significant increases in phasic and tonic GABAergic currents of grafted mice. Electron microscopy of the grafted brain demonstrated that GFP^+ cells form inhibitory synapses onto host pyramidal cells. Finally, in a test of the therapeutic potential of this approach, MGE cells were transplanted into the neocortex of a genetic model of epilepsy lacking a voltage activated K^+ channel, $Kv1.1^{-/-}$ mice. These mice were chosen because they exhibit a high frequency of behavioral and electrographic seizures and the age of seizure onset is consistent (Smart *et al.*, 1998; Wenzel *et al.*, 2007). We found that the total number of spontaneous seizures recorded in grafted Kv1.1 mutant animals was reduced by 86%; 2 of 8 MGE graft recipients exhibited no seizures during the recording period. For these assessments, we used dual digital cameras coupled to a cortical electroencephalographic recording system (Pinnacle Technology) and mice were monitored continuously for sessions up to 24 hr. Despite the promising results of these studies, they represent only the first step toward the use of interneuronal precursor transplantation in treating epilepsy.

In future studies, it is vital to test a more clinically relevant scenario in which cells are transplanted *after* a rodent exhibits spontaneous seizures. This type of protocol would more closely mimic the clinical condition in which epilepsy patients opt for more invasive procedures only after they have been experiencing recurrent seizures that are not controlled by available medications. To move toward this translational goal, first, MGE cells must be transplanted into the adult mouse brain and replicate the same successes with regard to migration, differentiation, and integration that were observed following neonatal transplants. Wichterle and colleagues have previously shown that MGE cells grafted into the adult brain can migrate long distances (~1.3 mm) away from the transplantation site (Wichterle *et al.*, 1999). Further studies are necessary to determine whether MGE cells transplanted into the adult brain differentiate into GABAergic interneurons that elevate inhibition in the host. Using the adult transplant protocol, MGE cells can then be transplanted into epileptic animals to assess the efficacy of graft-derived interneurons in reducing spontaneous behavioral and electrographic seizure activity in a variety of epilepsy models. Long-term assessment of potential tumorigenicity and evaluation of grafted animals using a battery of behavioral and cognitive tests is also recommended.

Recent work by Alvarez-Dolado and coworkers has utilized an adult transplantation protocol to demonstrate the therapeutic potential of MGE cell grafting in treating a mouse model of seizure susceptibility (Zipancic *et al.*, 2010). MGE cells transplanted into the adult hippocampus migrated, differentiated into GABAergic interneurons, increased synaptic inhibition in the host brain and survived months after grafting (~20% survival rate at 2 months, 4 months and 1 year post transplantation). Grafted MGE cells were able to reduce the frequency of severe, behaviorally monitored seizures that are induced by an injection of a seizure causing agent, pentylenetetrazol.

To examine whether MGE cells reduce the frequency of spontaneous seizures, preferably those that model a human form of epilepsy, we are characterizing MGE cells transplanted into the adult hippocampus. Preliminary recordings of GFP^+ graft-derived MGE cells transplanted into the adult hippocampus demonstrate that green cells receive both excitatory and inhibitory synaptic inputs and fire action potentials 47 DAT (Figure 2). It is also worth

noting, that we have never observed tumor formations in mice grafted with MGE interneuron progenitor cells (either early postnatal or adult) and no gross changes in behavior have been observed. The therapeutic promise of MGE cell transplantation is not limited to seizure suppression and may extend to a variety of neurological diseases. For example, MGE cells grafted into the adult striatum of Parkinsonian rats differentiate into GABAergic interneurons, receive synaptic inputs and ameliorate motor deficits (Martinez-Cerdeno *et al.*, 2010).

Conclusion

Our understanding of epilepsy has made tremendous progress since the disease was first described in 400 B.C. In ancient Grecian and in Biblical times, seizures were thought to be caused by demonic possession and “epileptics” were treated with magic and exorcism (Temkin, 1971). This ideology persisted for several hundreds of years, to the detriment of the treatment of patients and of scientific advancement. Finally in the mid 1800s, the first anticonvulsant medications, bromide salts, were administered followed by phenobarbital in 1912 (Porter, 1997). Our understanding of brain function and the causes of epilepsy continue to evolve and have led to more effective medications that help patients who would otherwise experience no relief from seizures. For example, recent work by Staley, Jensen and colleagues combined our knowledge of how Cl^- mediated transmission develops and seizures are generated to administer anti-seizure medications in newborn rats for subsequent use in newborn epileptic patients (Dzhala *et al.*, 2005; Kahle *et al.*, 2009). Given that frequent, severe seizures at a young age can interfere with brain development, treating pediatric epilepsy is of particular importance for cognitive development. Despite the benefits of anti-seizure medications, it is critical that alternative treatments are developed to increase therapeutic options for those patients who are experiencing inadequate relief from seizures. Gene therapy that inhibit surges of electrical brain activity and electrical devices that detect seizure onset are currently being explored (Shoeb *et al.*, 2004; Brooks-Kayal *et al.*, 2009; Foti, 2009; Shoeb *et al.*, 2009).

It is our hope that the transplantation of cells engineered to release GABA or interneuronal precursors with an endogenous ability to release GABA will effectively suppress seizures, first in rodent models then in patients. As we move forward in testing the therapeutic efficacy of cell transplantations, we must be rigorous in our scientific approach. Simply put, it is probably insufficient to transplant cells and assess the effect of grafting on visually monitored seizure-like behaviors. It would be better to examine how grafted cells behave in the host brain and how they affect host brain activity both on a cellular and network level. Network activity can be monitored via long-term video-EEG recordings of grafted animals to accurately assess effects on epilepsy. Such information will enable modifications to both grafted cells and the development of a transplantation protocol that may further enhance seizure suppression and allow us to anticipate or circumvent problems associated with grafting. As cell therapy in Parkinson’s disease has taught us, the road from successful transplantation in neonatal rodents to adult rodents to clinical trials is arduous and requires a clear and careful understanding of how grafted cells effect a recovery in brain function (Bjorklund & Lindvall, 2000; Dunnett *et al.*, 2001).

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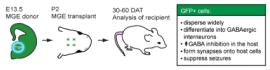

Figure 1.

A summary of the neonatal MGE cell transplantation protocol. GFP^+ MGE cells from E13.5 mice were transplanted into the P2 mouse neocortex. 30–60 days after transplantation (DAT), host mice were used for immunohistochemical, electrophysiological, electron microscopic, electroencephalographic and behavioral analysis. Primary findings are summarized in the text box (right)

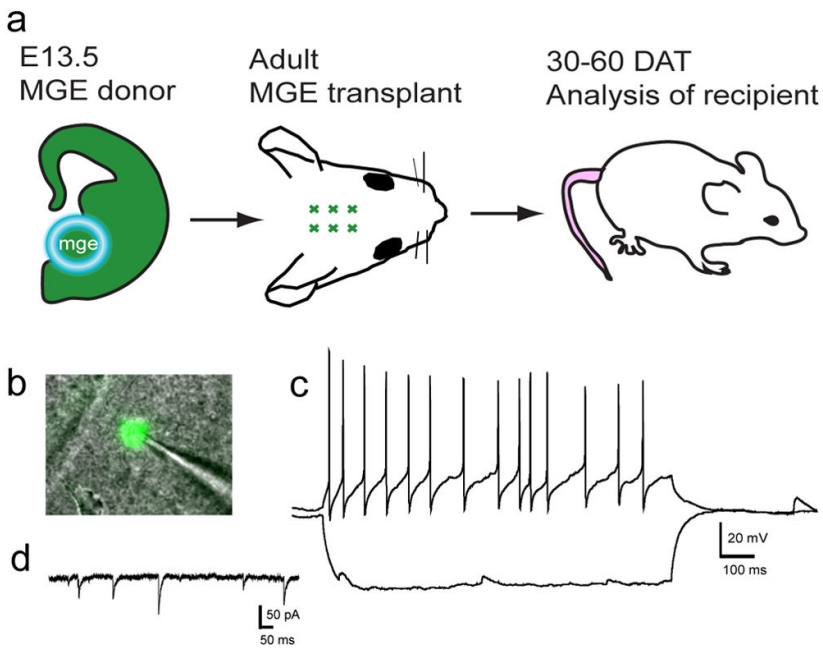

Figure 2.

Following adult hippocampal transplantation, GFP^+ graft-derived cells become functional neurons. A. An adult CD-1 mouse (P101) received a GFP^+ MGE cell graft and was sacrificed 47 DAT for electrophysiological analysis. B. Image of GFP+ cell for which the recordings are shown in C and D. C. Cell fired action potentials with fast afterhyperpolarizations that are characteristic of interneurons. Excitatory postsynaptic potentials (EPSPs) can be seen during and after the hyperpolarizing current step. D. Use of an internal solution containing KGluconate and KCl (Bacci *et al.*, 2003) allowed voltage clamp recordings from the same cell. Spontaneous inhibitory postsynaptic currents (IPSCs) recorded in the presence of glutamate receptor blockers demonstrate that GFP^+ cells receive inhibitory synaptic input. $V_{hold} = -60$ mV.