Chapter 9

GABAergic Synapse Dysfunction and Repair in Temporal Lobe Epilepsy

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Abstract

Severe medial temporal lobe epilepsy (mTLE) is often associated with pharmacoresistant seizures, impaired memory and mood disorders. In the hippocampus, GABAergic inhibitory interneuron dysfunction and other neural circuit abnormalities contribute to hyperexcitability, but the mechanisms are still not well understood. Experimental approaches aimed at correcting deficits in hippocampal circuits in mTLE include attempts to replace GABAergic interneurons through neural stem cell transplantation. Evidence from studies in rodent mTLE models indicates that transplanted GABAergic progenitor cells integrate into the hippocampus, form inhibitory synapses, reduce seizures and improve cognitive deficits. Here, we review current work in this field and describe potential molecular mechanisms underlying successful transplantation.

Keywords: GABA, temporal lobe, epilepsy, hippocampus, GABAergic, interneurons, neuroligin, neurexin, seizures, inhibition, gephyrin, collybistin, cognition, spatial memory, behaviour, transplantation, therapy, stem cells

1. Introduction

Epilepsy is a brain disorder characterized by a predisposition to generate epileptic seizures that may have subsequent neurological, cognitive, psychological and social effects. Many patients with severe medial temporal lobe epilepsy (mTLE) experience intractable seizures and degenerative changes in the temporal lobes of the brain, particularly the hippocampus [1]. Pharmacological treatments for these patients may become ineffective [2–5], and chronic severe pharmacoresistant seizures in mTLE patients can lead to memory impairments, anxiety and depression. While removing epileptogenic foci provides better seizure control in these patients, surgery may not be feasible if the seizures are generated bilaterally or at

multiple foci. Moreover, one of the challenges of treating mTLE is that seizures trigger neuroplastic changes in the adult hippocampus, including axonal sprouting, rewiring and abnormal migration and growth of new dentate granule cells (GCs). Which of these changes are necessary and sufficient for generating recurrent seizures that can be corrected through cell-replacement therapies is not well known.

A major focus of current research is developing rigorous protocols for deriving human neural stem cells from pluripotent stem cells (PSCs) and directing their differentiation into the specific types of neurons, including subtypes of GABAergic interneurons. Additional studies are focusing on the circuit-level and molecular mechanisms that regulate incorporation of transplanted mouse or human GABAergic interneuron progenitors into host brains. Studies of the functional impact of transplanting GABAergic interneurons into the brain and spinal cord in models of different neurological disorders are still in their infancy [6], and relatively little is known about mechanisms guiding the survival, differentiation and synaptic integration of transplanted GABAergic interneurons in the adult brain. This review focuses on current work in this field of regenerative medicine and new directions for regenerating neural circuits.

2. Pathology of medial temporal lobe epilepsy

Dentate gyrus (DG) reorganization has been extensively studied in rodent models of mTLE, particularly the chemoconvulsant models that employ kainic acid or pilocarpine injections to induce status epilepticus (SE). Prominent features of DG reorganization are the loss of glutamatergic mossy cells and subsets of GABAergic interneurons. Depletion of these neuronal populations results in loss of feed-forward inhibition of DG GCs [7–11]. Some of the principal cells of CA1 and CA3, as well as adult-generated GCs of the DG born around the time of SE, sprout excitatory axon collaterals, increasing recurrent excitatory drive between neighbouring neurons [12, 13]. Many somatostatin (SOM) -expressing GABAergic interneurons degenerate in the DG and CA1 of the hippocampus in mTLE, and some residual GABAergic interneurons form compensatory synaptic connections [10, 14–18]. Axonal sprouting by surviving hippocampal GABAergic interneurons increases the number of inhibitory synaptic puncta above control values in chronically epileptic rodents, although this response is insufficient to counter the development of spontaneous recurrent seizures typical of mTLE [15, 19]. Together, these studies suggest that replacing hippocampal GABAergic interneurons in pharmacoresistant mTLE may be a promising strategy for suppressing seizures (**Figure 1**).

GCs are a type of excitatory glutamatergic neuron in the granule cell layer (GCL) of the DG of the hippocampus, and studies suggest that they are relatively more resistant to seizure-induced injury than many other cell types in the hippocampus [32]. They form axons called the mossy fibres that project to CA3 pyramidal neurons and other cell types [1, 33–35]. GCs are generated throughout life [28, 36–41]. In rodent models of mTLE and human patients, many GCs, born around the time of SE, develop altered morphology, excitability and connectivity. These adult-generated GCs form recurrent axon collaterals in the inner molecular layer, a form of neuroplasticity termed mossy fibre sprouting (MFS) [26]. Overgrowth of mossy

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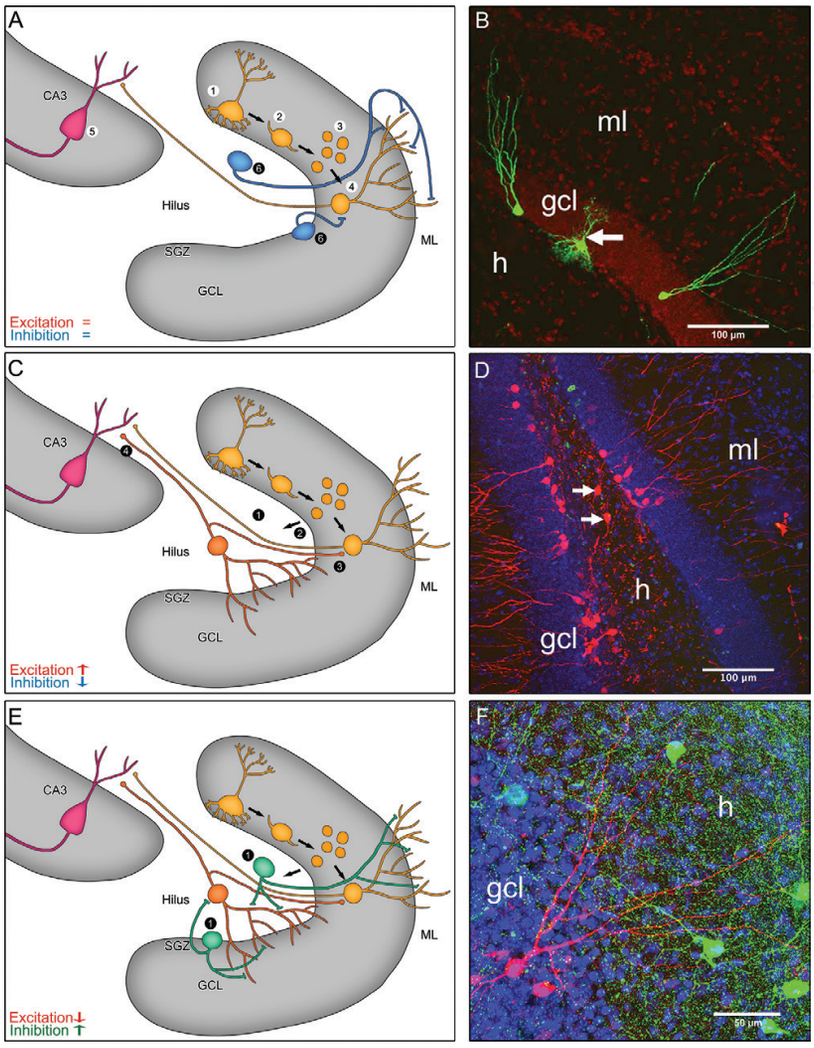

Figure 1. Studies of GABAergic interneuron transplantation are investigating whether it is feasible to replace populations of endogenous interneurons damaged by temporal lobe epilepsy. **(A)** In the non-epileptic mouse dentate gyrus (DG), self-renewing, quiescent Type 1 progenitor cells in the subgranular zone (SGZ) extend radial glial processes through the granule cell layer (GCL) (1). They divide asymmetrically to produce Type 2 progenitors (2) which further divide to generate pools of migratory Type 3 neuroblasts (3). As these neuroblasts mature, they differentiate into GCs, migrate into the GCL, extend their dendrites towards the molecular layer (ML)(4) and project axons to hilar interneurons and mossy cells and CA3 pyramidal cells (5). Inhibitory GABAergic interneurons (6) synapse with GCs and provide inhibition. GCs are shown in yellow, inhibitory interneurons in light blue and pyramidal cells in magenta. **(B)** High-resolution confocal image of retrovirally labelled GCs (green) and neuronal nuclei (NeuN, red) in the naïve mouse hippocampus. White arrow indicates a normal Type 1 progenitor cell in the SGZ. **(C)** In mTLE, some of the hilar GABAergic interneurons die, resulting in an overall loss of inhibition to GCs (1). Additionally, some adult-generated GCs undergo abnormal migration into the hilus, becoming ectopic. They typically form abnormal dendrites and sprout recurrent axonal collaterals, forming excitatory feedback projections onto other GCs (3) as well as abnormal excitatory projections to the CA3 pyramidal cells (4) [20–30]. GCs are shown in yellow; an abnormal, ectopic GC in orange; and pyramidal cells in magenta. **(D)** High-resolution confocal image of retrovirally labelled GCs (red) in the hippocampus of a mouse with mTLE. Nuclei are marked using a Nissl stain (blue). White arrows show ectopic GCs born after induction of epilepsy located in abnormal locations in the hilus. **(E)** Studies employing transplantation of GABAergic progenitors into either the normal or epileptic hippocampus show that they migrate away from the site of injection and form dense axonal arbors throughout the hilus, GCL and molecular layer. These interneurons appear to form functional synapses with hyperexcitable GCs, including those with aberrant morphologies (1), increasing synaptic inhibition in the epileptic circuit. GCs are shown in yellow; abnormal, ectopic GC in orange; transplanted GABAergic inhibitory interneurons in green; and pyramidal cells in magenta [31]. **(F)** High-resolution confocal image of a retrovirally labelled GC (red) receiving dense synaptic contacts from transplanted MGE-derived GABAergic progenitors (green). Nuclei are labelled using Nissl staining (blue) [31].

fibre recurrent collaterals onto GCs and pyramidal cells contributes to a hyperexcitable dentate environment [27, 29, 42–44].

As demonstrated by computer simulations, a few hubs of highly interconnected GCs are sufficient to create a hyperexcitable network [30, 45]. Additional epilepsy-induced neuroplastic changes to the DG include GC dispersion, formation of GC basal dendrites and ectopic migration of GCs into the hilus of the DG [23–25, 46–50]. Many adult-generated GCs born in epileptic rodents also have reduced dendritic spines and hypertrophic cell bodies [20, 21, 44, 51]. These cells often have higher baseline firing rates than normally positioned GCs in epileptic animals and non-epileptic controls and more depolarized resting membrane potentials, predisposing them to hyperexcitability [22]. Although increasing adult neurogenesis is not sufficient to cause seizures, it contributes to hyperexcitability [52, 53].

3. Cognitive changes in medial temporal lobe epilepsy

Severe mTLE is linked to a number of comorbidities including cognitive deficits, heightened anxiety, increased aggression and depression [54, 55]. Rodents with mTLE show decreased social recognition, greater preference for closed arms in the elevated zero or plus maze test for anxiety and longer periods of immobility in the forced swim test for depression [56]. Additionally, a number of studies demonstrated severe learning deficits in the Morris water maze test of spatial memory [57, 58] and other spatial memory tasks [59]. Human mTLE patients exposed to virtual environments that test spatial memory also showed memory deficits [60, 61].

Changes in the properties of hippocampal and entorhinal cortex circuits may be responsible for cognitive changes in mTLE, but the nature of these changes is not well understood. Both human and rodent spatial memory formation and recall are dependent on place cells in the hippocampus and grid cells in the entorhinal cortex. These important cells exhibit distinct, spatially specific firing patterns, forming a topographical memory map of an area as an individual moves through space [62–65]. Hippocampal inhibitory interneurons, similar to place cells, show distinct, spatially specific discharges, implicating a role in the formation and fine tuning of spatial memories [66, 67]. Studies suggest that impairments in receptive field properties of the grid and place cells may occur in mTLE [68–71].

The regulation by inhibitory interneurons of various brain rhythms may also become altered, as rodents with mTLE show distinctly lower frequency and power of theta rhythms correlated with poor performance in spatial memory tasks [72–74]. Although the exact alterations occurring in the grid-place cell network are not yet clear, it is evident that the hyperexcitable firing of GCs and the overall disinhibition of the network by loss of inhibitory interneurons severely disrupts spatial memory formation [72, 75–79]. The disinhibition of the hippocampal networks following epileptogenesis and the subsequent development of spatial memory deficits suggest that the loss of inhibitory interneurons may disrupt place fields, providing a further rationale for cell-based therapies aimed at GABAergic interneuron transplantation.

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4. Seizure suppression following transplantation of medial ganglionic eminence-derived neural progenitors

Initial studies established proof of concept for cell-based therapies for treating epilepsy by demonstrating that transplants of non-neural cells engineered to release GABA non-synaptically could increase seizure thresholds [80]. Increasingly, studies have aimed to identify the functional classes of interneurons that can migrate, integrate and suppress seizures in different models of epilepsy in rodents. The large variety of functional classes of cortical inhibitory interneurons and their sites of origin in the ventricular zones of the embryonic forebrain have been extensively studied. During development, forebrain GABAergic interneurons are born in the embryonic ventricular regions called the ganglionic eminences, including the medial, lateral and caudal ganglionic eminences (MGE, LGE, CGE). These transient proliferative zones lining the forebrain lateral ventricles generate different types of GABAergic interneuron progenitors, which then migrate to their final destinations in the forebrain, including the cerebral cortex, hippocampus and striatum [81–83]. Forebrain GABAergic progenitors expressing SOM or parvalbumin (PV) emerge from the MGE in early embryonic life and migrate tangentially into the cerebral cortex and hippocampus [84].

In naïve rodents and different epilepsy models, transplanted GABAergic interneuron progenitors from the embryonic MGE have been found to be highly migratory, a prerequisite for transplantation therapies aimed at repairing large brain areas. MGE-derived GABAergic progenitors transplanted into postnatal 3–4-day old mouse cerebral cortex differentiated into inhibitory interneurons expressing markers of mature GABAergic phenotypes, including PV, SOM, calretinin (CR) and neuropeptide Y (NPY), and displayed mature firing properties characteristic of inhibitory interneurons [85]. MGE-derived PV-positive interneurons transplanted into naïve postnatal 1–2-day old pups integrated into the endogenous circuitry and, upon maturation, displayed firing properties similar to endogenous PV-expressing interneurons and formed functional synapses onto pyramidal neurons [86]. In a mouse model of mTLE generated through neurotoxin-induced ablation of GABAergic interneurons, MGE transplantation significantly increased inhibitory postsynaptic currents (IPSCs) in CA1 pyramidal cells and reduced seizure frequency and severity [87]. These grafts contained high percentages of GABAergic interneurons that co-expressed PV, NPY or CR. Transplanting MGE cells into an epilepsy model caused by mutations of the Kv1.1 potassium channel also increased IPSCs in nearby endogenous pyramidal cells [88]. Additionally, MGE cell transplants into a cyclin D2 knockout model of hippocampal disinhibition restored lost inhibitory input and normalized hyperactivity and fear conditioning [89].

The efficacy of MGE cell transplantation for controlling seizures has also been studied in chemoconvulsant models of mTLE, including the kainic acid and pilocarpine (PILO) models. In an early ground-breaking study in the rat kainic acid model, Shetty and colleagues transplanted neurospheres derived from embryonic day-14 rat MGE progenitors and found that they reduced seizure duration, total time spent in seizures and seizure severity; however, these grafts failed to improve spatial memory deficits [90]. It is important to note that the

degree of cognitive impairment may differ between kainic acid or pilocarpine models, different species and even different strains of mice [91, 92].

The mouse PILO model shows a pattern of loss of hippocampal interneurons that is similar to human mTLE, making this model highly appropriate for preclinical studies investigating GABAergic interneuron transplantation [93]. Work from our laboratory showed that MGE cells transplanted into the hilus of the DG led to significant reductions in seizure frequency, duration and severity in the mouse PILO model [31]. The transplanted neurons matured into GABAergic interneurons that expressed CB, SOM or PV and formed dense networks of inhibitory synapses onto dentate GCs. Optogenetic experiments in hippocampal slices from these mice showed that light-induced depolarization of MGE transplants expressing channelrhodopsin (ChR2) triggered strong postsynaptic inhibitory currents in GCs, indicating that the transplanted neurons had integrated synaptically. These findings suggest that seizure suppression can be achieved with focal transplants into the DG. In this study, which employed continuous video-EEG recording for periods of up to 3 months, some of the mice show a reoccurrence of seizures several months after transplantation, suggesting that achieving enduring seizure suppression may require more widespread dispersion of the transplanted interneurons throughout different subfields of the hippocampus. Determining the optimal sites and cell types for permanent seizure suppression will be important for moving into clinical applications.

5. Transplantation therapy using human embryonic stem cell-derived progenitors

For treating patients with severe mTLE, sources of human interneurons are required. Previous work showed that differentiating human embryonic stem cells (hESCs) into GABAergic inhibitory interneuron progenitors can be achieved using specific combinations of signalling molecules and growth factors [94–100]. Carpentino et al. (2008) found that maturation of transplanted mouse or hESCs is highly dependent on the environment into which the cells are transplanted. For instance, in the mouse systemic kainic acid model, it was shown that ESC-derived neural progenitors transplanted in the CA3 area tended to migrate into the DG and differentiate into GCs, whereas those implanted into the fimbria tended to mature into astrocytes [101]. Lee et al. also transplanted undifferentiated hESCs into the CA3 region of the hippocampus in epileptic rats. Some of these differentiated into GABAergic interneurons (~21% of engrafted cells) and at 8 weeks post transplantation displayed immature morphology. Even with low numbers of GABAergic neurons, the animals with transplants showed reduced seizure frequency and seizure duration for 2–3 months. EEG recordings in these animals were limited to 60 hours per week, with a 2-week recording period, during daylight hours only. Additionally, when tested 3 months after transplantation, improvements in Morris water maze performance were not found [102]. More recent studies have focused on purified, fate-determined populations of hESCs for transplantation. Treating hESCs with the signalling molecule sonic hedgehog (SHH) or a sonic hedgehog agonist (SAG), in combination with modulating the WNT and FGF signalling pathways, can be used in vitro to induce ventral forebrain neural fates and MGE-like cell types [97–100, 103–106]. Ventralized hESC-derived progenitors have

identities similar to that of mouse MGE-derived GABAergic interneuron progenitors, potentially allowing the large-scale *in vitro* production of human cells for therapies to treat clinical disorders [94]. However, undifferentiated hESCs can cause teratomas, making it important to develop protocols for eliminating them prior to transplantation [107].

Evidence that fate-directed human GABAergic interneuron progenitors integrate into the epileptic circuitry of the hippocampus following transplantation into the hilus has emerged in several recent studies. To reduce immune rejection of cell grafts, human and mouse ESC transplantation studies generally use immunodeficient host animals. The nonobese diabetic (NOD)-severe combined immunodeficiency (SCID) mice are an immunodeficient mouse strain lacking mature T and B cells and with reduced natural killer (NK) cell activity. Another mouse strain, the Nod-scid-gamma (NSG) triple mutant, has a mutation at the interleukin-2 receptor (IL-2R) γ-chain locus. This strain shows the highest impairment in T-cell, B-cell and NK-cell development, resulting in low graft rejection [108]. Both strains have been used to study differentiation of ESC-derived GABAergic interneurons [109].

In a recent study in which hESC-derived progenitors were differentiated in vitro into MGE-like progenitors and transplanted into NSG mice, the transplanted cells differentiated into GABAergic neurons expressing SOM, PV, CB, CR or NPY after approximately 4 months. Additionally, optogenetic stimulation of the transplanted cells produced action potentials and resulted in IPSCs in endogenous hippocampal neurons, suggesting successful synaptic integration into the existing circuitry of the hippocampus. Video-EEG monitoring of these animals 3 months post-transplant showed reduced numbers of seizures in engrafted animals [110]. However, the EEG monitoring was only for short durations of 5–10 days, which is likely too brief a period to reliably evaluate seizures in rodent chemoconvulsant models, due to the clustered and periodic nature of the spontaneous recurrent seizures.

6. Ameliorating cognitive and behavioural abnormalities in epilepsy by transplantation of GABAergic interneurons

Inconsistent results regarding spatial memory improvement have been reported following GABAergic interneuron transplantation. In the Morris water maze test of spatial memory, C57BL/6 mice with PILO induced mTLE and received mouse MGE cell transplants showed significantly reduced escape latencies in training, significantly more platform crossings in the probe trial; improved path efficiency; and a greater amount of time spent in the target quadrant than epileptic controls [111]. In another study, rats with mTLE that MGE-derived stem cell grafts showed no improvements in the Morris water maze task 8 weeks post-engraftment relative to non-engrafted mTLE controls [90]. However, transplantation took place approximately 3 months following induction of epilepsy, a longer time interval than other studies. The lack of cognitive improvement at this later transplantation time point suggests a potentially limited time window in which transplanted GABAergic interneurons must integrate to confer cognitive improvements. In a third study in NSG mice with mTLE, engrafted hESC-derived GABAergic interneuron progenitors appeared to improve performance in the Y-maze test of spatial memory and memory in the novel recognition test [110].

Behavioural tests also suggested that mTLE mice receiving interneuron grafts were less hyperactive and aggressive, compared to mTLE controls with only intrahippocampal injections of media. In the handling test of aggression, in which mice are scored for aggressive reactions to a series of increasingly uncomfortable stimuli, TLE mice with hESC or foetal mouse MGE interneuron transplants scored significantly lower in aggression ratings than controls [109, 110]. These transplants also reduced hyperactive behaviour [110]. Taken together, these results suggest that both rodent and human GABAergic interneuron transplants may ameliorate some of the psychological comorbidities in rodents with mTLE. While the Morris water maze is currently one of the standard tests in the industry for spatial memory, rodents with mTLE often exhibit a phenomenon known as thigmotaxis, in which animals will locomote or swim adjacent to the walls of an apparatus or make repeated circles [91, 112]. In such animals, it is uncertain whether the data reflect poor spatial memory or an anxiety phenotype. Therefore, alternative spatial memory tests should be used to gain a more complete understanding of how GABAergic interneuron transplantation affects cognition. An alternative test of hippocampal-dependent spatial memory is a modification of the novel object recognition test in which animals must learn to recognize that a previously familiar object has changed location. This test, called novel object location task, takes advantage of the rodent preference for novelty and desire to explore changes in its environment [113, 114]. Another test of spatial memory is the Barnes maze, consisting of an elevated platform with closed holes around the circumference. One hole is available for escape into a dark box. Remaining on the platform is unpleasant to the rodent, due to bright lights, fans and/or loud ambient noise, encouraging a swift escape to the box. As this test measures a very natural desire to escape an unpleasant environment, it is considered an effective test of normal rodent behaviour and spatial memory [115]. The Barnes maze also has no walls, eliminating thigmotaxis, although care must be taken to prevent animals from falling from the raised platform. Additional tests of spatial memory include the Y-maze, T-maze and the radial arm maze, all of which measure the ability of a rodent to remember previously travelled areas [116–121]. This extensive array of spatial memory tests can provide a more complete picture of the behavioural improvements following GABAergic interneuron transplantation in rodents with mTLE.

Currently, most testing of aggression has been done using the handling test, which, while effective, is an unnatural stimulus to the rodent [110, 111]. In addition to the handling test, the resident-intruder test can be used to analyse the response of a rodent to more natural stimuli. Male rodents are territorial, and the resident-intruder test measures the aggressive reactions to a male rival within their space. Although care must be taken to avoid injury to animals, this test measures an innate animal response and can be an effective measure of aggression in mTLE animals with transplants [122].

Although heightened anxiety is a common and well-characterized comorbidity in rodent mTLE models and human patients, surprisingly little work has been done to examine the effects of GABAergic transplants on correcting anxiety phenotypes. As rodents with mTLE have a tendency to exhibit thigmotaxis, which skews results in tests such as the open field test or the Morris water maze [91, 112], paradigms such as the elevated plus maze, elevated zero maze or the light-dark box can be used to provide more accurate measures of anxiety in rodents with mTLE [123–128].

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7. GABAergic synapse formation and stability: potential mechanisms of transplanted cell integration

Relatively few studies have examined the molecular mechanisms responsible for guiding synaptic integration of transplanted cells into mature neural circuits. Previous findings suggest that cell-cell interactions mediate the formation and stabilization of both excitatory and inhibitory synapses [129–131]. The synaptic scaffolding complex between GABAergic interneurons and their postsynaptic targets in the developing brain may also guide recruitment and stabilization of the new synaptic connections formed by transplanted interneurons (**Figure 2**).

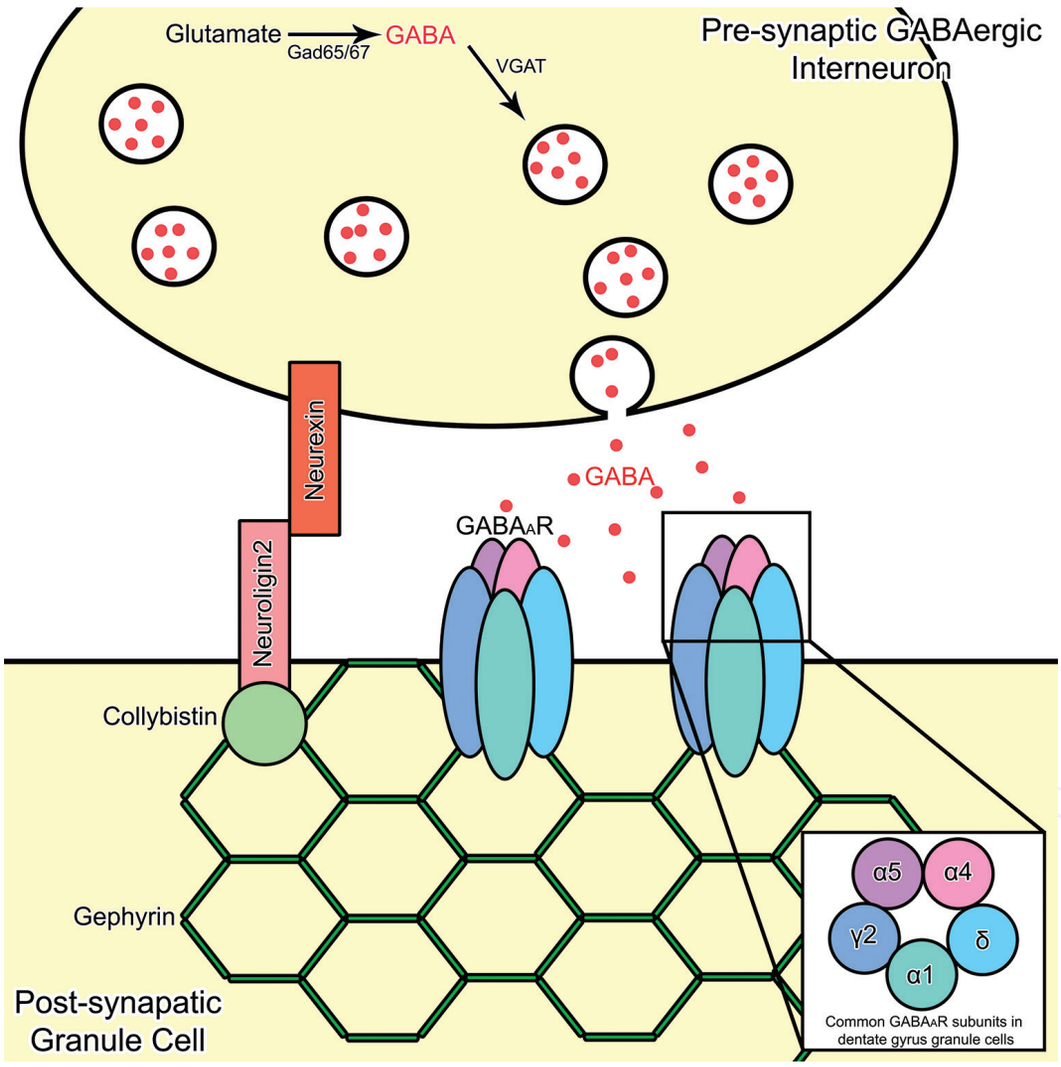

Figure 2. Interactions between cell surface molecules that are binding partners provide a potential mechanism for forming or stabilizing new synapses between transplanted GABAergic interneurons and endogenous neurons in the hippocampus. GABAergic synapse formation is coordinated by multiple molecules in the pre- and postsynaptic sites. Binding between presynaptic neurexin molecules and postsynaptic neuroligin2 (NLGN2) molecules may be important for initial formation or maintenance of GABAergic synapses. NLGN2 is associated with a postsynaptic complex containing collybistin, gephyrin and $GABA_AR$s, which are necessary in the formation of functional inhibitory circuitry. Collybistin, gephyrin, NLGN2 or $GABA_AR$ subunit γ2 deficiency results in impaired inhibitory synapses [132–141].

The synaptic scaffolding protein gephyrin is a tubulin-binding protein that forms a lattice-work structure of hexagonal trimers that regulate $GABA_A$ receptor clustering at synaptic sites [142, 143]. Gephyrin stabilizes inhibitory synapses and is required for proper function. Genetic reduction of the γ2 subunit of $GABA_A$ receptors, a primary binding partner of gephyrin in GABAergic synapses, also severely reduces gephyrin and $GABA_A$ receptor clustering required for functional inhibitory synapses [132]. Repression of gephyrin expression causes a similar loss of clustering, revealing an interdependent relationship between the two synaptic binding partners necessary for proper inhibitory synapse formation and function [132, 144, 145]. Increases in endogenous gephyrin in response to compensatory surviving interneuron sprouting may also make the epileptic hippocampus a more receptive environment for new inhibitory synapses to form [146]. Gephyrin is significantly decreased in the first few weeks post-SE followed by a significant increase back towards normal levels at around 1 month post-SE [147]. Following transplantation, a majority of engrafted GABAergic interneuron synaptic boutons were associated with postsynaptic gephyrin clusters, indicating that this vital synaptic scaffolding component may be recruited to sites of new GABAergic synapse formation in the adult hippocampus [31].

Collybistin, another GABAergic synaptic scaffolding component, binds to both gephyrin and Neuroligin 2 (NLGN2) and may facilitate gephyrin-mediated clustering of $GABA_A$ receptors. Collybistin is a GDP/GTP-exchange factor that interacts directly with gephyrin in the inhibitory synaptic scaffold [131, 133, 148–150]. Collybistin-deficient mice display reduced clustering of gephyrin and $GABA_A$ receptors, reduced synaptic inhibition and altered synaptic plasticity [131, 141].

NLGN2 is part of a family of cell adhesion molecules implicated in synapse formation and stability. NLGN2 localizes only to GABAergic inhibitory synapses, where it is associated with neurexin, its presynaptic binding partner [151–153]. NLGN2 is part of the molecular scaffolding complex that includes collybistin and gephyrin [133]. NLGN2-deficient mice show decreased inhibitory function, as well as a variety of cognitive and behavioural comorbidities, such as increased anxiety, aggression and disruptions in spatial memory formation, similar to those seen in mTLE and other neurological disorders [129, 136, 137, 154–157]. Various studies have shown that binding between NLGN2 and neurexin induces inhibitory synapse formation [130, 158] and stabilization [135, 159], even in non-neuronal cell types [160].

$GABA_A$ receptor subunit composition may also play a role in the integration and stabilizing influence of transplanted inhibitory interneurons. Composition of $GABA_A$ subunits is impacted by the pathological changes induced in mTLE [161–163]. DG GCs, which are significant propagators of hyperexcitability in mTLE, are particularly enriched in the δ subunit of $GABA_A$ receptors in the normal brain; these receptors have a very high affinity for GABA and are strongly involved in tonic inhibition [164–166] at extrasynaptic sites [167]. In general, hippocampal neurons express multiple subunits, including abundant α, β, δ and γ subunits, with δ primarily restricted to GCs of the DG, with additional expression of other subunits in the CA1 and CA3 areas [168]. As such, it is apparent that $GABA_A$ receptors in the hippocampus are composed of a diverse pool of subunits that regulate inhibitory input. In mTLE,

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the composition of $GABA_A$ subunits becomes altered. Similar to the upregulation of gephyrin during the chronic phase of mTLE in response to compensatory interneuron sprouting, the γ2 and α subunits also show increased expression in the hippocampus. Conversely, expression of the δ subunit decreases days after the initial epileptic event and remains depressed into the chronic stages of mTLE [169]. It is not known whether synapses formed by surviving inhibitory interneurons are capable of recruiting the necessary subunit composition for proper inhibition, considering the overall depletion of δ subunits compared to γ2 and α. Moreover, whether transplanted, healthy GABAergic inhibitory interneurons can recruit all of the normal subunits to inhibitory synapses is not known. Further investigation of subunit composition within the epileptic hippocampus post transplantation will be necessary to investigate whether transplantation normalizes $GABA_A$ receptor composition.

8. Conclusion

While safe and effective stem cell therapies for treating neurological disorders, including severe mTLE, may be years away from the clinic, recent work has increased scientific understanding of how to derive specific types of human neurons for transplantation and how to evaluate functional changes that result. Because human neuron maturation takes many months or years, transplantation studies in rodents are limited in the kinds of information they can provide about the potential therapeutic effects of these cells in clinical populations. Recent studies have utilized a wide range of experimental tools, including electrophysiology, immunohistochemistry, optogenetics, chemogenetics and behavioural assays to assess learning, memory, anxiety, social behaviour and depression. These approaches are aiding studies to evaluate synaptic integration and functionality of human neural stem cell transplants for treating epilepsy.

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