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·Review·

Dysfunction of hippocampal interneurons in epilepsy

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Gamma-amino-butyric acid (GABA)-containing interneurons are crucial to both development and function of the brain. Down-regulation of GABAergic inhibition may result in the generation of epileptiform activity. Loss, axonal sprouting, and dysfunction of interneurons are regarded as mechanisms involved in epileptogenesis. Recent evidence suggests that network connectivity and the properties of interneurons are responsible for excitatory-inhibitory neuronal circuits. The balance between excitation and inhibition in CA1 neuronal circuitry is considerably altered during epileptic changes. This review discusses interneuron diversity, the causes of interneuron dysfunction in epilepsy, and the possibility of using GABAergic neuronal progenitors for the treatment of epilepsy.

Keywords: interneuron diversity; therapy; GABA; progenitor cell

Introduction

The mammalian hippocampal circuit consists of two basic neuron types: excitatory principal cells and inhibitory interneurons. Typically, the input and output neurons are collectively referred to as principal cells, which mostly release glutamate as the neurotransmitter[1]. Generally, interneurons are neurons whose somata are located around excitatory principal cells, and their axons are confined to a single brain region where they regulate principal cell excitability[1, 2]. Because the majority of interneurons synthesize and release γ-amino-butyric acid (GABA), they are also referred to as GABAergic or inhibitory interneurons[1]. The balance between excitation and inhibition is crucial, and the maintenance of dynamic equilibrium involves many physiological mechanisms[3]. It has been hypothesized that an imbalance results in reduced GABAergic inhibition and increased excitation in epilepsy.

A small number of interneurons play an important role in maintaining the balance of excitation and inhibition in the nervous system, the generation of EEG oscillations, sleep, cognition, and other functions[4]. Abnormal numbers and dysfunction of interneurons are closely associated with certain nervous system/psychiatric disorders, such as epilepsy, schizophrenia, and autism[5]. Neuronal loss, altered excitation or inhibition, circuit rearrangement, and individual synaptic abnormalities have been associated with epileptogenesis and subsequent seizure expression[6-9]. Seizures are abnormal discharges in the cerebral cortex; they occur as systemic clonic and tonic seizures and in several epileptic syndromes. Epileptogenesis-induced hippocampal hypoxia can induce neuronal degeneration and necrosis, ultimately resulting in hippocampal sclerosis. Thus, analysis of the interneurons in the hippocampus and cerebral cortex could provide a wealth of information, adding to our understanding of the pathogenesis of neurological diseases, especially epilepsy.

This review summarizes advances in hippocampal interneuron research in seemingly disparate fields and

highlights the contributions of specific interneuron deficits to each unique pathophysiology. A better understanding of the properties of intrinsic interneurons and changes in specific brain circuits will ultimately facilitate our understanding of the roles of interneurons in shaping hippocampal function.

Classification of Interneurons

Comprehension of interneuron function in the normal brain may elucidate the role of abnormal interneurons in neurological diseases, but this is difficult because of the diversity of interneuron populations. Anatomically, interneurons represent diverse populations in the adult brain, and classifications based solely on anatomy tell us little about their functions. Here, we provide a brief summary of the complex classification of interneurons based on morphology, molecular expression, axon projection, and discharge pattern.

Morphological Classification

In the hippocampus, >20 classes of interneurons have been identified[1, 2, 4]. Based on morphology, they can be divided into basket cells, chandelier cells, Martinotti cells, double-bouquet cells, bitufted cells, and neurogliaform cells (Fig. 1)[2]. The basket cell, named after the basket-like appearance around pyramidal cell somata, is the most common in the cerebral cortex and hippocampus and targets the soma and dendrites of pyramidal neurons and interneurons. The chandelier cell is an axon-targeting interneuron, and has a characteristic axon termination that forms short vertical rows of boutons, resembling a chandelier[2]. The Martinotti cell, usually with multiple short dendritic branches and a small soma, is characterized by an axon distribution to the surface of the cerebral cortex and axon length depending on the location of the cell[10]. The double-bouquet cell usually has a bitufted dendritic morphology. Its special feature is the tendency of the axon to resemble a 'horse's tail'. The bitufted cell has an ovoid soma and the dendrites from opposite poles form a bitufted morphology. The neurogliaform cell is small, with a shape similar to that of neuroglia. These morphological features,

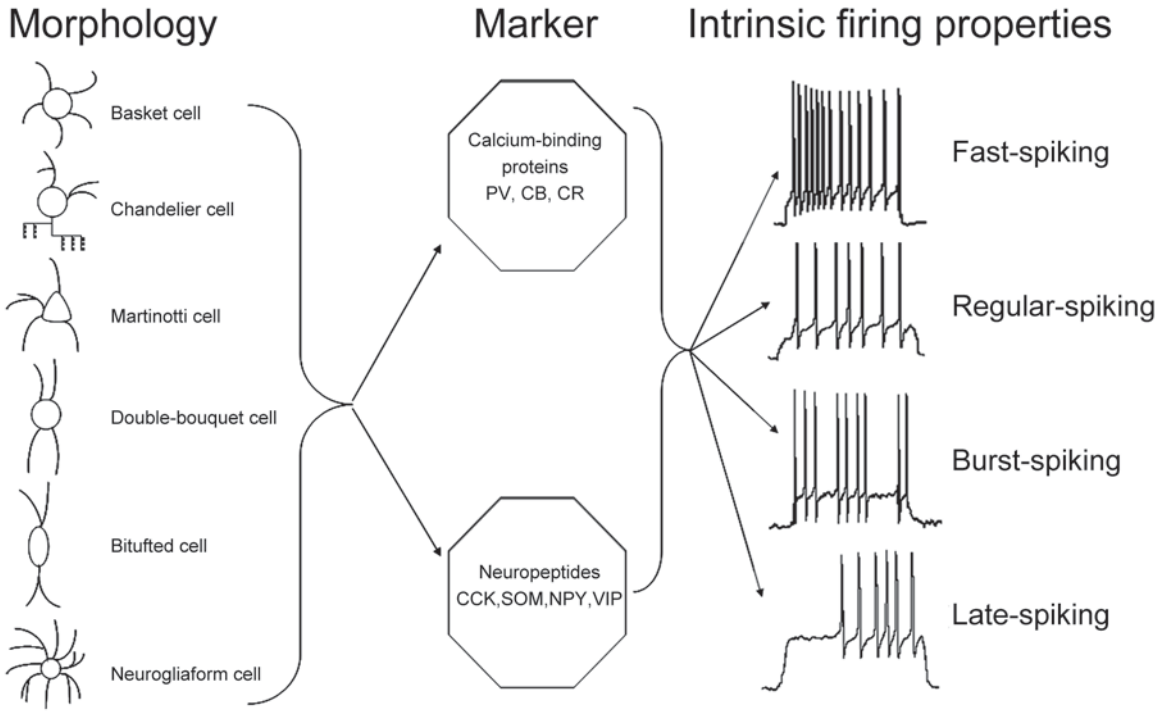

Fig. 1. Classification of interneurons. Classes of interneurons according to specific molecular makers: the calcium-binding proteins calbindin (CB), parvalbumin (PV), and calretinin (CR) and the neuropeptides neuropeptide Y (NPY), vasoactive intestinal peptide (VIP), somatostatin (SOM), and cholecystokinin (CCK), as well as morphological and electrophysiological features.

to a certain extent, reflect the functions of the different cell types.

Axon Projection Classification

Based on the axon projection domain, interneurons can be further divided into perisomatic, dendritic, interneuronal, and distant projection types[1]. Compared to the solely morphological classification, this classification better reflects the functions of interneurons and overcomes the shortcomings due to the fact that interneurons with different shapes can have similar functionality.

Molecular Marker Classification

The vast majority of interneurons are GABAergic. GABA is generated under the action of glutamic acid decarboxylase (GAD), of which there are two isoenzymes: 67-kDa glutamate decarboxylase (GAD67, also known as GAD1) and 65-kDa glutamate decarboxylase (GAD65, also GAD2)[11]. GAD65 is mainly distributed in synaptic terminals, whereas GAD67 is found in cell bodies, dendrites, and terminals[12]. Both GABA and GAD can be used as molecular markers of interneurons. GABAergic interneurons can also express other specific molecular markers that further identify various populations. The main specific molecular markers include Ca^{2+}-binding proteins such as parvalbumin (PV), calbindin (CB), and calretinin (CR), and neuropeptides such as cholecystokinin (CCK), somatostatin (SOM), neuropeptide Y (NPY), vasoactive intestinal peptide (VIP), and neuronal NO synthase (or NADPH-diaphorase) (Fig. 1)[13].

Generally, combining morphological and molecular markers facilitates the classification of interneuron functions. For example, the actions of CCK- and PV-containing basket cells differ in their responses to excitatory input and their functions in neuronal networks, as well as in the pathogenesis of epilepsy, which makes each particularly well-suited to performing different tasks in the regulation of principal cell output[14, 15]. PV-expressing basket cells generate trains of short-duration action potentials at high frequencies and provide fast, stable, and timed inhibitory output to their target cells (a highly synchronized GABA release which produce precisely timed inhibition), whereas CCK-expressing basket cells fire accommodating spike trains at moderate frequencies and generate an asynchronous, fluctuating, and less timed inhibitory output (action potentials with a longer half-duration that progressively broaden during repetitive activation, resulting in a less timed transduction of the signal from the input to the output site)[16] .

Classification by Action Potential Firing

In earlier studies, classical subdivisions were made based on action potential firing patterns, and cells were divided into fast-spiking (FS) cells (type I) and regular-spiking cells (type II)[17]. Type I cells have brief-duration action potentials and little or no frequency adaptation of spike discharge to depolarizing current pulses, whereas type II cells have long-duration action potentials and adaptation of spike discharge to depolarizing current pulses. Later, a "stuttering" pattern in cortex[18] and late- and burst-spiking in the hippocampus[19] (Fig. 1) were included in the primary physiological classes. Stuttering cells have high-frequency clusters of action potentials with little accommodation interspersed with periods of silence of unpredictable duration in response to depolarizing current pulses[20]. Late-spiking cells show spiking delayed for several seconds from the beginning of a current step and then demonstrate sustained firing during the remainder of current injection. Burst-spiking neurons exhibit two or more spikes with a short inter-spike interval in response to current injection[21].

To further identify interneuronal subtypes, transgenic mice that express fluorescent protein in GABAergic interneurons can be used and the interneuronal morphology, location, axon projection domain, and action potential firing pattern can be integrated. Since it has been reported that there are no marked differences in the interneuronal subtypes between cortex and hippocampus[1,4], we focus on those in the hippocampus. Multidisciplinary approaches applied to specific, anatomically identified interneuron populations might facilitate the understanding of their subtypes and the role of their connections[13].

Interneuron Fate and Functional Correlates in Epilepsy

Hippocampal GABAergic interneurons play an important role in epilepsy[22]. The loss of GABAergic interneurons and compensatory axonal sprouting are the main inhibitiory reasons for GABAergic neuron decrease, restoration and potentiation (Fig. 2A). GABAergic dysfunction in epilepsy may result in subtle alterations in inhibitory circuits[23, 24], and

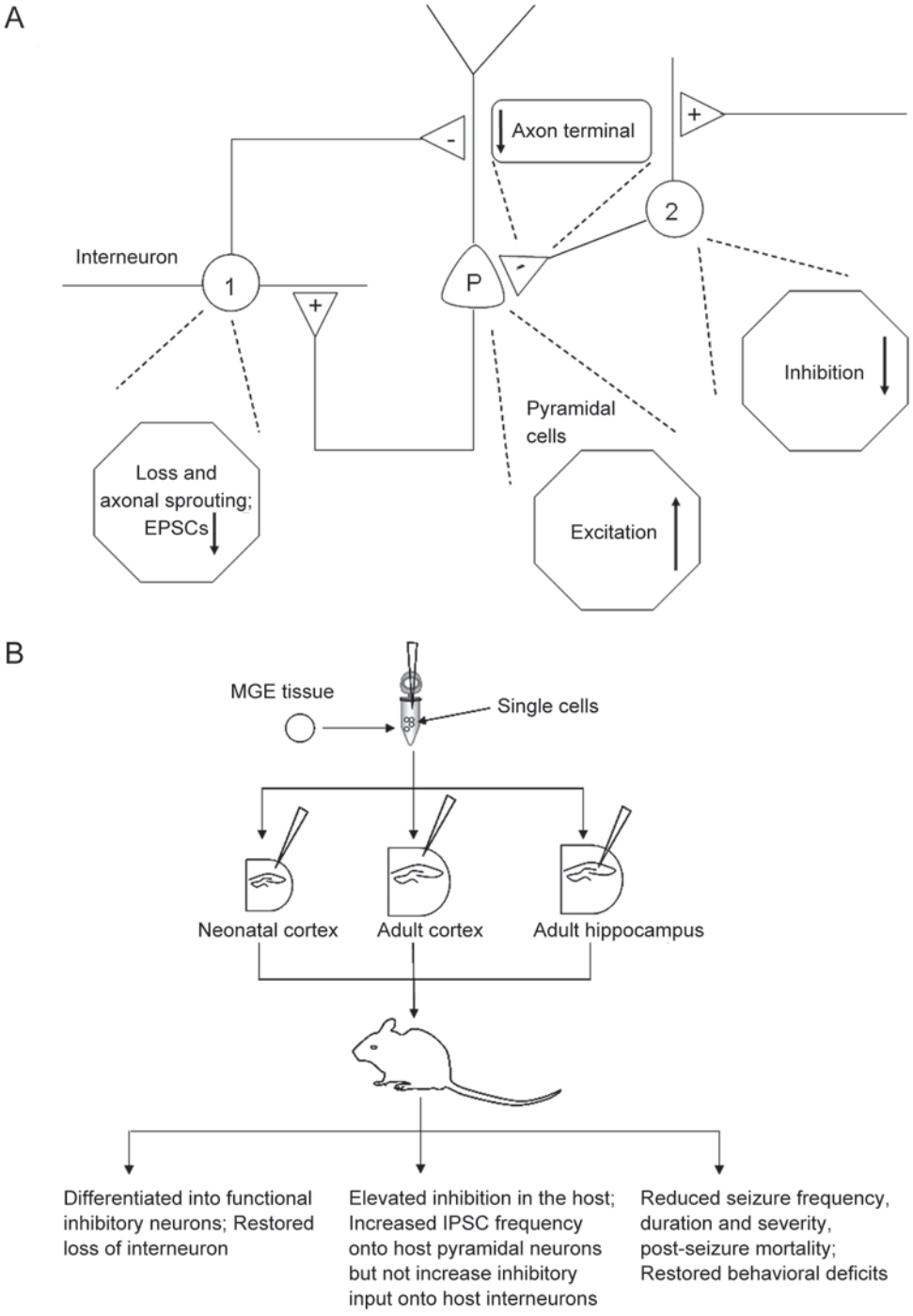

Fig. 2. Alterations in hippocampal circuitry and medial ganglionic eminence (MGE) transplants in the development of cell-based therapy for epilepsy. A. 1 and 2, interneurons; P, pyramidal neuron; (+), excitatory axon terminal; (-), inhibitory axon terminal. When interneuron 1 receives excitation from the pyramidal cells in the same circuit, the former inhibits the pyramidal cell by negative feedback. Furthermore, when a distant neuron excites interneuron 2, it inhibits other neurons including its target pyramidal cell. An imbalance between excitation and inhibition results in reduced GABAergic inhibition and increased glutamatergic excitation in epilepsy. Alterations in synaptic currents occur in specific classes of interneurons in epilepsy. B. The MGE is dissected out, re-suspended as single cells, and then injected into the desired region. These transplanted cells generate mature interneurons that integrate into the host circuitry, consequently ameliorating seizures.

the down-regulation of GABAergic inhibition may cause epileptiform activity[25]. In kainic acid (KA)-lesioned rats, the amplitude and conductance of both non-NMDA and NMDA components of excitatory postsynaptic currents (EPSCs) are significantly reduced in stratum lacunosum-moleculare interneurons, but the rise-time of EPSCs is not significantly changed[26]. These alterations occur in glutamatergic synaptic transmission. Moreover, the decay time-constant of EPSCs is significantly faster in interneurons located in the stratum oriens near the alveus. In addition, the conductance and amplitude of pharmacologically-isolated inhibitory postsynaptic currents (IPSCs), mediated by $GABA_A$ receptors, are not significantly changed in any cell type after KA treatment. However, the rise and decay time-constants of IPSCs are significantly faster in the pyramidal cells of KA-treated rats. These results suggest that alteration in synaptic currents occurs in specific classes of interneurons in the CA1 region after KA treatment[26]. In the medial entorhinal cortex of epileptic rats, the frequency and amplitude of sEPSCs in layer III interneurons are normal, while layer II stellate cells are hyperexcitable and receive a reduced frequency of spontaneous IPSCs and miniature IPSCs[8]. The inhibitory barrages in the pyramidal neuron (PyN) of the pair occur in coincidence with a burst in the PV-FS interneuron in both the 4-AP and the low Mg^{2+} models in temporal cortex slices from G42 mice[27].

Interneurons Containing Calcium-Binding Proteins and Epilepsy

Three Ca^{2+}-binding proteins are present in largely non-overlapping subsets of GABAergic interneurons: PV, CB, and CR.

PV-immunoreactive (PV-IR) interneurons are perisomatic inhibitory GABAergic neurons, including axo-axonic cells and basket cells, that mainly dominate the somata, proximal dendrites, and axon initial segments of principal cells[1]. Loss of PV-positive neurons, especially those of the hilus, has been reported in human patients and animal models of epilepsy[9, 28]. The loss of interneurons may lead to reduced inhibition of granule cells, thereby increasing the granule cell excitability and strengthening excitation in the dentate gyrus and other connected regions[29]. PV-IR interneurons are significantly decreased in the CA1 region, especially the superficial layers (e.g., stratum oriens), in epileptic patients and animal models[9, 29, 30]; the number of PV interneurons decreases slightly in the non-sclerotic epileptic CA1 region with mild cell loss, whereas in the sclerotic CA1 region, it dramatically decreases. However, the reductions in PV-IR may result from the decreased PV protein level itself rather than neuronal damage or degeneration. Preserved PV-positive inhibitory interneurons have been observed in temporal lobe epilepsy (TLE)[9, 31], indicating that the PV-positive neurons are resistant to excitotoxic damage. This loss or preservation may be due to a change of mRNA/protein or immunoreactivity. However, to date, little is known about the difference between the degree of decrease in PV-expressing neurons in the hippocampal formation and the neuronal loss observed in Nissl-stained sections.

Alterations in the expression of many voltage-gated potassium channels have been reported in epilepsies [32]. Recent evidence indicates that Kv1.6 protein expression on PV interneurons increases by >400% in kindling-induced epilepsy, which accounts for the increase in potassium currents and the change in firing patterns in these cells [33]. Kv3 channels are prominently expressed in neuronal populations including FS GABAergic interneurons in the neocortex and hippocampus, and selective blockade of Kv3 currents can impair high-frequency firing[34, 35]. Elimination of the Kv3.2 gene results in impairment of neocortical deep-layer FS neurons, supporting the idea that Kv3 channels play a critical role in high-frequency firing. In fact, Kv3.2 knock-out mice show an increased susceptibility to epileptic seizures and disturbed cortical rhythmic activity[34]. In a study of the relative contribution of inhibitory interneurons and excitatory pyramidal cells to SCN1A-derived epilepsy, Dutton found that the inactivation of one *Scn1a* allele in PV interneurons reduces the seizure threshold, whereas the threshold is unaltered following its inactivation in excitatory cells[36]. These results demonstrated that specific ion channels of interneurons play a significant role in epileptogenesis.

CR and CB neurons are Ca^{2+}-binding protein-containing interneurons, and changes in their functions and morphology are involved in the pathogenesis of cerebral ischemia, epilepsy, and chronic neurodegenerative diseases, mostly *via* interference with intracellular Ca^{2+} stability. CR is mainly expressed in interneurons in all layers and subfields of the hippocampus and dentate

gyrus, whereas CB is distributed in both principal cells and interneurons of the hippocampal formation and accounts for 10%–12% of GABAergic neurons[1]. In the epileptic dentate gyrus, CB-containing interneurons are maintained, but with longer and spiny dendrites, and occasionally spiny cell bodies[37]. The relative laminar distribution of CR-containing cells is not changed, but their number is considerably reduced[37]. Immunohistochemistry and microdensitometry reveal that the number of CR-positive neurons in the striatum significantly decreases 1, 3, and 6 days after a KA-induced seizure, whereas the numbers of CB- and PV-positive neurons do not change significantly[38]. The selective loss of CR-positive neurons after a seizure suggests that Ca^{2+}-binding proteins in the striatum have differential vulnerability to KA-induced seizures.

Other studies have demonstrated differences among these three Ca^{2+}-binding proteins in epileptic GABAergic interneurons. In the dentate hilus of epileptic patients with hippocampal sclerosis, most of the few surviving hilar neurons are CB-IR[39]. Studies have indicated that the density of inputs and the total number of afferent synapses are several times higher on PV cells than on CB or CR cells, whereas the ratio of inhibitory inputs is significantly higher on CB and CR cells[40], suggesting that PV-positive neurons receive more excitatory inputs than CB- and CR-positive neurons and thus are more vulnerable to excitotoxic damage. The AMPA receptor subunit GluR3 in PV-containing interneurons is highly expressed in the hippocampus and neocortex, whereas GluR2 is not observed, indicating that this is likely to contribute to the selective vulnerability of these interneurons to excitotoxicity[41].

Neuropeptide-Containing Interneurons and Epilepsy

Neuropeptides, including CCK, SOM, NPY, and VIP, are markers of interneurons and are specifically distributed in the hippocampus and the cerebral cortex.

CCK-IR GABAergic interneurons are located in the CA1, CA3 and the dentate gyrus regions and receive inputs from both the perforant path and local mossy fiber collaterals[1]. In animal models, CCK-IR fibers increase in the inner dentate molecular layer following KA treatment[42], and in the cerebral cortex, Ammon's horn and the molecular layer of the dentate gyrus in the ventral hippocampus, in rapidly-kindled and post-status epilepticus (post-SE) rats[43], indicating sprouting of CCK axons. Wyeth *et al.*[44] examined PV- and CCK-containing basket cell terminals in a mouse pilocarpine model of TLE, and found decreased CCK-labeled boutons in the pyramidal cell layer of CA1, whereas PV-containing boutons are conserved, indicating that the reduced CCK immunoreactivity is associated with degeneration of axon terminals soon after SE. One might hypothesize that the disappearance of CCK basket cells would increase the functional weight of PV basket cells [45].

SOM is the most specific marker of dendritic inhibitory interneurons. SOM-immunopositive neurons express GABA and NPY and mainly dominate the hippocampal dentate gyrus and primary cells (granulosa cells and pyramidal cells)[1]. Initial studies suggested that SOM interneurons do not contain GABA[46], but later, it was found that pre-prosomatostatin mRNA-containing neurons co-express GAD mRNA[47]. However, many GAD65 mRNA-labeled neurons do not contain pre-prosomatostatin mRNA, which suggests that those SOM neurons are GABAergic. The loss of SOM interneurons in the dentate gyrus after SE has been found in electrical stimulation models[31], KA models[48] and pilocarpine-induced epileptic rats[49]. In one study with the pilocarpine model, there was a 46% loss of SOM-containing interneurons in the stratum oriens of the CA1 area[50]. The loss of SOM-positive hilar neurons in TLE is likely to substantially reduce inhibitory synaptic input to granule cells. However, degeneration of SOM interneurons in the hilus has not been reported. Degenerating SOM terminals have not been found in the outer molecular layer, perhaps because the transport of SOM to the terminals is arrested in the early stages of neurodegeneration. Alternatively, SOM that is present in the terminals may be lost during SE[51].

Although SOM interneurons are clearly lost in the epileptic hippocampus, axonal sprouting may partially compensate for this loss. Greater SOM axon sprouting occurs in human TLE patients in the whole molecular layers[52]. Sprouting of SOM-positive fibers in the dentate gyrus mainly dominates in granule cell dendritic areas, enhances the inhibition of granule cells, and reduces their excitability, whereas SOM interneuron axonal sprouting in the CAl area not only controls pyramidal cell dendritic regions and reduces their excitability but also may dominate the dendrites of other inhibitory interneurons, resulting in a

potentially enhanced disinhibition that could increase the excitability of pyramidal cells[22].

NPY interneurons are dendritic GABAergic interneurons and mainly innervate the dendrites of principal cells, but with less specificity than SOM neurons[1, 22]. The loss and inhibition of NPY interneurons have been reported in the rapid kindling and electrical stimulation-induced epilepsy models, respectively[43, 51]. In addition, NPY increases in the hippocampus in KA-induced seizures, which suggests that the NPY-positive neurons are resistant to KA-induced seizures in the whole hippocampus, but NPY/NADPH-d-positive neurons have different sensitivities in its subregions[53]. This is contradictory to previous research[43, 51], and may be due to the different models and observation times used. In experiments comparing the survival of hippocampal GABAergic interneurons containing NPY or PV between young adult and aged rats with acute seizures, NPY-positive interneurons are relatively resistant to acute seizure activity in the aged hippocampus in comparison with the young adult hippocampus. However, PV-positive interneurons are highly susceptible to acute seizure activity in both age groups[54]. Moreover, there are much greater decreases in the NPY- and PV-positive interneurons in the hippocampus of aged rats after seizures. This is mainly because aging alone can substantially depletes these populations. In addition, NPY-IR interneurons are evidently lost in the hilus of the dentate gyrus but preserved in the granule cell layer in electrical stimulation-induced epilepsy[51]. Similar losses of NPY-IR interneurons have been reported in KA models[55].

The axonal sprouting of NPY-IR interneurons is similar to that of SOM-IR interneurons, and increased NPY-IR fibers are found in the dentate gyrus molecular layer of the human epileptic hippocampus, majorly in the inner molecular layer[52]. By comparing different TLE models, Schwarzer *et al.* found that NPY immunoreactivity is enhanced in the middle and outer molecular layers of the dentate gyrus in rapidly-kindled rats, and in the whole molecular layer in electrically-induced SE rats[43]. Dentate gyrus axonal sprouting of NPY may enhance the inhibition of granule cells, which may play a role in self-healing in epilepsy[6].

VIP interneurons are present in all layers of the dentate gyrus and the CA1 and CA3 subfields[1]. The distributions of VIP and its receptors were first reported in the hippocampus of patients with TLE[56], and showed an increase in VIP receptors but no changes in the distribution pattern of VIP-IR neurons in mesial TLE patients. In regard to the role of VIP in human TLE, there are three hypotheses that may account for these changes[56]. The first is that VIP plays a role in the hyperexcitability of neurons in the hippocampal seizure focus. The second is related to the role of VIP as a neurotrophic substance that protects neurons from excitotoxic injury. The third is that the increased VIP receptors reflect an increase in glycogenolysis in the mesial TLE hippocampus. These hypotheses provide good elucidation of the role of VIP in seizures. Earlier, specific interneuron populations with VIP-like immunoreactivity were found to be enhanced in epileptic mice, which is a model of hereditary sensory-precipitated TLE[57]. Subsequent studies have also found VIP-IR increases 3 days after injection of KA into the frontal cortex, but this decreases to control values at 10–60 days[58]. The transient rise in VIP following acute seizures may be due to the short-lasting overcompensation of VIP synthesis resulting in increases in neuropeptide release. Alternatively, this transient increase in VIP may be caused indirectly by complex neuropathological events (e.g., edema and anoxic-ischemic brain damage) that occur in limbic areas (e.g., amygdala) during the first days after KA injection[58].

Nitric Oxide Synthase and Epilepsy

NO is an important messenger in many physiological functions, including immune regulation, vasodilation, cell survival and death, synaptic transmission, and plasticity[59]. There are three NOS isoforms: neuronal (nNOS) localized in neurons, endothelial (eNOS), and inducible or immunological (iNOS)[60]. Studies have shown that nNOS is expressed in interneurons in different regions of the mouse brain, with the highest density in the dentate gyrus[61].

NO is involved in the pathophysiology of epilepsy, and the expression of nNOS in neurons is increased in epileptic patients and pilocarpine-induced animal models of epilepsy[62]. Systemic treatment with a highly selective nNOS inhibitor, L-NPA, reduces the severity and duration of seizures, the EEG power in the gamma band, and the frequency of epileptiform spikes during SE, suggesting that nNOS facilitates seizure generation and may be

important for the neurobiological changes associated with the development of chronic epilepsy, especially in the early stages[63]. In the human epileptic hippocampus, patients with hippocampal sclerosis display decreased hippocampal nNOS-IR neurons and increased nNOS-IR fibers in the fascia dentata[64]. Hippocampal NOS activity is not significantly changed during kainate-induced SE, but is inhibited by 7-nitroindazole (a relatively selective inhibitor of nNOS) after 1 h of SE and recovers to the basal level 24 h later[65]. Moreover, the hippocampal damage in the CA1 and CA3 layers is significantly decreased by 7-nitroindazole after 7 days. Increased numbers of nNOS-IR neurons in the stratum radiatum of the CA1 and CA3 subfields and the hilus of the dentate gyrus are seen after SE induced by perforant pathway stimulation, and the number of nNOS-IR neurons is not related to the neuronal damage, suggesting that the nNOS-expressing neurons are selectively resistant to excitotoxic damage[66]. It has been demonstrated that nNOS-positive interneurons also express CCK, VIP, PV, SOM, NPY, and CR[67]. However, it remains unclear whether nNOS is co-expressed with other molecular markers for interneurons, and if so, the differences in morphology, pattern of discharge, and axonal projection and their impact on postsynaptic cells, and their roles in epilepsy, need to be addressed.

Interneurons in Various Types of Epilepsy

Disorders of inhibitory interneurons have largely been demonstrated in different types of epilepsy, such as absence epilepsy, TLE, and SE. A general mechanism has been shown to involve the dysfunction of inhibitory GABAergic neurons. Absence epilepsy appears spontaneously, accompanied by characteristic spike-wave discharges (SWDs) in the EEG which reflect highly synchronized oscillations in the thalamocortical network[68]. The possibility that absence seizures are modulated by an inhibitory GABAergic neuron-dependent mechanism has been demonstrated, suggesting that an increase or decrease in the activity of interneurons can reduce or amplify, respectively, the occurrence of SWDs[69, 70]. TLE is a common form of epilepsy. One of its pathogenic features is the loss of inhibitory interneurons, which can lead to decreased feed-forward inhibition, relatively increased excitatory circuit activity, alteration of synaptic structure, and reduced threshold and increased vulnerability of seizures[51, 71]. SE exhibits seizure activity persisting for a sufficient length of time[72]. SE leads to the loss and structural reorganization of interneurons and weakened excitatory inputs to inhibitory interneurons[55, 73]. In other types of epilepsy, including complex partial epilepsy, myoclonic epilepsy, and generalized tonic clonic seizures, interneurons exhibit similar characteristics.

Summary

The different subclasses of interneurons sensitive to epilepsy-induced damage are influenced by various factors, including models, time-scale, and brain location (Table 1). Loss of inhibitory interneurons reduces the inhibitory control of excitability of the primary cells, which plays an important role in the promotion of epilepsy. Disinhibition is suggested to be involved in epileptogenesis. The loss of GABAergic interneurons may result in insufficient GABA release, and this leads to the disinhibition of principal cells thereby promoting the spread of seizure activity. This is supported by the decrease in paired-pulse inhibition reported *in vivo*[74]. However, paired-pulse inhibition recovers in the first week after kainate-induced SE[74], indicating that the surviving inhibitory neurons are still functional. Other mechanisms may also affect the disinhibition of principal neurons, including sprouting. An ultrastructural study indicates that synaptic vesicle recycling is accelerated in the mossy fibers in epileptic gerbils[75], thus the released GABA is relatively decreased, resulting in enhanced disinhibition. The axonal sprouting may form new inhibitory synapses that not only can control principal cells, reduce their excitability but also excessively inhibit other GABAergic interneurons, leaving principal cells inadequately inhibited. Therefore disinhibition occurs. The dendritic interneurons decrease partly because of neuronal degeneration and death, whereas the loss of perisomatic interneurons may be unrelated to these processes.

Potential Applications in the Treatment of Epilepsy

Epilepsy treatments include drug therapy, physical therapy, and cell therapy. Normally, antiepileptic drugs (AEDs) control seizures in most patients. The ultimate effects of AEDs involve modifying the bursting properties of neurons and reducing synchronization in localized

Table 1. Summary of alterations of interneurons in epilepsy

Interneuron type	Model of epilepsy	Salient features	References
PV	Epileptic patients/pilocarpine-induced	Decreased number of interneurons; synaptic coverage of axon initial segment of CA1 pyramidal cells significantly decreased; IR neurons preserved	20, 22-24
	KA treatment	Number of interneurons not significantly changed in striatum but reduced in hippocampus	28, 45
	Electrical stimulation	Number of IR basket cells unchanged	41
CB	Pilocarpine-induced/kindling	IR neurons preserved; dendrites longer and spiny; cell bodies occasionally spiny; number of interneurons reduced	27, 29
CR	KA treatment	Number of interneurons decreased in striatum	28
CCK	KA/rapid kindling/electrical stimulation	IR fibers increased; labeled boutons decreased; number of IR basket cells unchanged	34, 41
SOM	Pilocarpine/KA	Positive interneurons lost; axon sprouting	24, 38, 39, 42
	Electrical stimulation	IR neurons degenerated	41
NPY	Electrical stimulation/KA/rapid kindling	Positive neurons lost; IR fibers increased	33, 41, 46
	KA treatment	Neurons increased in young adult but reduced in aged rats	44, 45
VIP	Epileptic patients and mice	Receptors increased without change in pattern and distribution; IR enhanced	48, 49
	KA treatment	IR neurons increased at early stage but decreased to control level later	50
NOS	Epileptic patients/pilocarpine	Expression in neurons increased; decreased IR neurons and increased IR fibers in fascia dentata	54, 56
	KA treatment	Neuronal activity not significantly changed	57
	Electrical stimulation	Number of neurons increased	58

CB, calbindin; CCK, cholecystokinin; CR, calretinin; IR, immunoreactivity; KA, kainic acid; NOS, nitric oxide synthase; NPY, neuropeptide Y; PV, parvalbumin; SOM, somatostatin; VIP, vasoactive intestinal peptide.

neuronal ensembles[76]. Cell therapy can offer an alternative treatment. Here, we highlight drug therapy and cell therapy for epilepsy based on interneurons.

Drug Therapy

In a study of the effects of AEDs in patients with continuous spike-waves during slow-wave sleep, intravenous injection of diazepam (an agonist for the $GABA_A$ receptor in the GABAergic interneuron system) produced a longer-lasting effect on the intensity of spike-associated high-frequency oscillations than spike amplitudes during the recovery process, indicating that diazepam enhances the $GABA_A$ inhibition which is involved in the generation of pathologic high-frequency oscillations[77]. The AED topiramate has broad utility in epilepsy and acts on diverse ion channel targets such as voltage-gated Na^+ channels, Ca^{2+} channels, $GABA_A$ receptors, and non-NMDA receptors[78]. In a recent study, topiramate was shown to reduce the hyperexcitability in the basolateral amygdala by selectively inhibiting GluK1 (GluR5) kainate receptors on interneurons, enhancing GABAergic transmission in interneuron-to-pyramidal cell synapses, and directly enhancing $GABA_A$ receptor-mediated inhibitory currents[78]. In addition, Peng *et al*.[79, 80] concluded that the AEDs gabapentin and lamotrigine increase the hyperpolarization-activated cation current (I-H) in CA1 interneurons by decreasing EPSC frequency or increasing IPSC frequency, similar to I-H in pyramidal neurons and

I-H enhancement-increased interneuron excitability. Thus, these drugs indirectly increase the spontaneous inhibition of pyramidal neurons. In the pilocarpine-induced seizure model, rapamycin inhibits the mTOR signal pathway[81]. Buckmaster and colleagues tested whether rapamycin treatment for 2 months in GIN mice that express GFP in SOM interneurons, beginning at 12 h after pilocarpine-induced SE, affects axon reorganization[82]. They found that rapamycin suppresses axon sprouting by surviving SOM-positive interneurons, suggesting that sprouting might be partly due to activation of the mTOR signal pathway. The SOM-containing neurons are exceptionally vulnerable in experimental models of epilepsy and in human TLE. A high dose of vigabatrin, an irreversible inhibitor of GABA-transaminase, prevents the loss of hilar SOM-containing neurons and the development of interictal spiking activity[83]. It has been demonstrated that NO is involved in NMDA receptor-mediated neurotoxicity and convulsions. L-NAME, an inhibitor of NOS, suppresses the onset of PTZ- and strychnine-induced seizures, suggesting that NOS inhibitors can be used as AEDs[84]. Absence seizures are accompanied by SWDs and T-type Ca^{2+} currents (I_T) are involved in the pathophysiological oscillations that lead to absence seizures[85]. Recently, the effects of the T-type Ca^{2+} channel antagonists ethosuximide, valproate, and mibefradil on I_T in local circuit interneurons during SWDs have been elucidated. They all block the I_T and mibefradil attenuates intrathalamic oscillations as well as SWDs, indicating that I_T reduction is part of the mechanism of action of anti-absence drugs[85].

However, the mechanisms of action of AEDs in clinical development are currently unknown. Although current AEDs are effective in 60%–70% of individuals, they also have side-effects. Such side-effects vary depending on the medication, and are segregated into five distinct classes: cognition and coordination, mood and emotion, sleep, tegument and mucosa, and weight and cephalalgia[86]. Thus, there is an urgent need to develop new safe and effective AEDs, with reduced side-effects, to control epilepsy.

Cell Therapy

Defects in GABAergic function can cause epilepsy and cell-based therapies have attempted to correct these defects. Cell transplantation may repair neuronal circuits in the epileptic brain (Fig. 2B). Recently, some studies have demonstrated that bilateral transplantation of fetal interneuron precursors into early postnatal neocortex in animal models of epilepsy can ameliorate seizures in the following ways: (1) grafted cells generate mature GABAergic interneurons and are involved in the neuronal network in the host brain; (2) grafted cells significantly increase the IPSC mean frequency and tonic current onto the host pyramidal neurons but do not increase inhibitory input onto host interneurons; and (3) medial ganglionic eminence (MGE) cell grafts significantly reduce the duration and frequency of spontaneous electrographic seizures in epileptic mice lacking the Shaker-like K^+ channel[18]. Consistent with previous results, transplantation of inhibitory neurons into the hippocampus of adult epileptic mice also has a substantial therapeutic effect on seizures[19,87]. By 7 days after transplantation, MGE cells have moved away from the injection site and dispersed throughout hippocampal subfields. At 60 days, the grafted cells become mature interneurons which express interneuron markers (GAD, SOM, PV, nNOS, CB, CR, NPY, and CCK) in control and epileptic mice and differentiate into functional inhibitory neurons that receive excitatory synaptic input, indicating that these cells integrate into the hippocampal network. Moreover, in epileptic mice, MGE cells that move into the hippocampus reduce seizure frequency, electrographic events and behavioral severity, and restore behavioral deficits in spatial learning, hyperactivity, and the aggressive response to handling. However, MGE cells grafted into the basolateral amygdala have no effect on seizure activity and other abnormal behaviors except for reversing the hyperactivity deficit[19]. Human neural stem cells transplanted into the pilocarpine-induced rat model of TLE differentiate into GABA-IR interneurons in the damaged hippocampus. Such grafted cells also reduce generalized convulsive seizure frequency and severity[88]. Transplantation of fetal grafts containing CA3 cells into a lesioned CA3 region significantly restores the injury-induced loss of GAD- and CB-positive interneurons in the TLE hippocampus, likely *via* restitution of the disrupted circuitry[89, 90]. However, fetal CA1 cell grafts do not induce interneuron recovery. Recent work has demonstrated that MGE-derived cells transplanted into the normal brain migrate and differentiate into functional mature GABAergic

interneurons that increase inhibition in the host[19, 91, 92]. The above studies demonstrate the feasibility of cell therapy for epilepsy. However, how grafted cells behave in the host brain and how they affect host brain activity at both the cellular and network levels remain unknown. In addition, detailed experiments are still needed on various therapeutic aspects, including time-course, transplantation time-window, and adequate graft-cell dose.

Concluding Remarks

It is worth noting that alterations of GABAergic neurons during development do not simply involve the loss of a given type of inhibitory interneuron. Of particular interest is the use of interneuron progenitors to study interneurons in aspects of subgroup physiology, connectivity, and use in seizure treatment. However, preclinical and clinical studies are required to further investigate the exact pathophysiological mechanisms involving different classes of GABAergic interneurons in the etiology of epilepsy. In addition, the prospect of developing a new cell-based therapy based on transplantation of GABA progenitor cells is exciting and clearly merits further study.

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