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The Role of GABAergic Interneurons in the Cortex and Hippocampus in the Development of Epilepsy

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This review analyzes contemporary data on the possible roles of different classes of interneurons in the hippocampus and cortex in the pathogenesis of temporal epilepsy in humans – one of the commonest forms of epilepsy. Data obtained from humans (results of post mortem morphological investigation of patients' brain tissues and electrophysiological experiments on brain slices collected at neurosurgical procedures) are considered, along with results from studies of in vivo and in vitro animal models of temporal epilepsy. Systematic analysis of impairments to inhibitory processes in temporal epilepsy show that these result from the selective death of particular interneuron populations and from functional impairments to the operation of important interneurons. Understanding of the concrete roles of different classes of interneurons in epilepsy is required for the development of new and effective treatment methods for this disease.

Keywords: models of epilepsy, temporal epilepsy, epileptogenesis, hippocampus, cerebral cortex, GABAergic interneurons.

Paroxysmal, (convulsive, ictal) neuron activity is an anomalous form of hypersynchronization of brain activity. If this activity repeatedly arises spontaneously and spreads in the brain, this is a sign of the severe neurological disease epilepsy. It is important to note that the pathogenesis of epilepsy is based on an impairment to the balance between inhibitory and excitatory processes [18, 54]. Impairments to this balance can arise as a result of excessive activation of excitatory neurons or weakening of the functions of inhibitory neurons, or can be induced by impairments to the main types of interactions between neurons in micronetworks [58].

The healthy brain includes a number of reliable neural mechanisms preventing the generation and propagation of paroxysmal activity. The contemporary concept of the development of epilepsy suggests that the actions of adverse factors lead to partial loss of or impairment to these mechanisms. Epileptogenesis is divided into three main phases: 1) the action of the provocatory factor, triggering the process; 2) a latent period during which there are no spontaneous convulsions, but when rearrangements are taking place, weakening anticonvulsant mechanisms; 3) the chronic phase of epilepsy, when convulsive seizures can be seen or increased convulsive readiness develops [31]. Provocatory factors can be traumatic brain damage, tumors, strokes, or chemical actions. Convulsive states themselves are also important epileptogenic factors, so repeated convulsions exacerbate the disease [8].

The reorganization of the operation of neural networks in the cortex and hippocampus in epileptogenesis involves GABAergic interneurons, though the mechanisms of the rearrangements of neural networks, and the contributions of different types of interneuron, the functional correlates of ongoing changes are known only very approximately. The present review provides a critical analysis of current data on the possible roles of different classes of interneurons in the hippocampus and cortex in temporal epilepsy in humans – one of the commonest forms of epilepsy. Data obtained in humans are discussed, as are results from studies of animal models of temporal epilepsy. Analysis of impairments to inhibitory processes in temporal epilepsy shows that they are due to selective death of particular interneuron populations and to functional impairments to the operation of living in-

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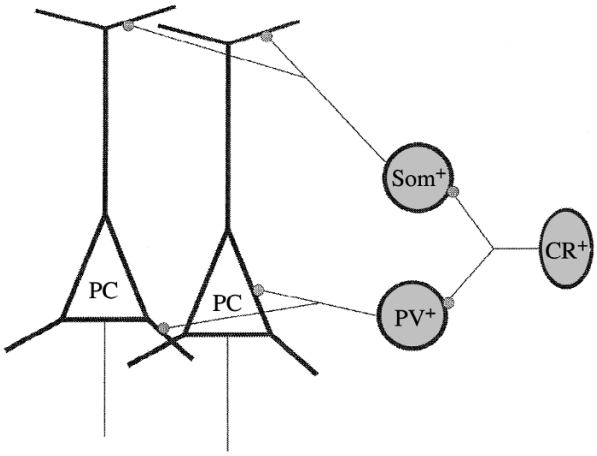

Fig. 1. Main types of neurons and inhibitory connections in the cortex. PC – glutamatergic pyramidal cell; PV^+ – parvalbumin-positive interneuron; Som^+ – somatostatin-positive neuron; CR^+ – calretinin-positive neuron. Thin lines show axons. GABAergic neurons are shaded in gray and excitatory neurons are left white.

terneurons. Understanding the concrete roles of different classes of interneurons is required for the development of new and effective methods of treating epilepsy.

An Integrated Morphofunctional Classification of Interneurons. All neurons in the cortex and hippocampus can be divided into two large classes: principal excitatory glutamatergic cells and inhibitory GABAergic interneurons [29, 51]. Interneurons in turn are divided into various groups on the basis of their morphological, electrophysiological, molecular, and functional properties [42, 51, 74, 75, 97]. This review is focused on three main groups of interneurons, which differ in terms of their functions and neural networks (Fig. 1).

Group 1 includes interneurons supporting perisomatic inhibition of principal cells. Most of these interneurons express the calcium-binding protein parvalbumin (PV). Morphologically, these constitute two main classes of cells: basket interneurons (PV-IN), which innervate the bodies and proximal dendrites of pyramidal cells, and candelabra cells, or axoaxonal cells (AAC), which form synaptic contacts with the initial axon segment [63]. The synaptic contacts of these cells are highly reliable and efficient, and their positions allow these interneurons to produce effective suppression of action potential generation in pyramidal cells. Because of the presence of a branched axon tree, these interneurons synchronize the operation of whole ensembles of pyramidal cells in the cortex and hippocampus [3].

In the cortex, excitation of PV-IN can be supported by the thalamic inputs [40, 79, 81]. On activation of the thalamic inputs, PV-IN reach the action potential generation threshold earlier in time and at a lower stimulation strength than the excitatory cells. Thus, PV-IN provide anticipatory disynaptic inhibition of their neighboring excitatory cells [40, 62, 96]. Anticipatory inhibition limits the time interval during which summation of excitatory thalamic inputs and action potential generation can occur in stellate and pyramidal cells; this provides time accuracy in the transmission of signals from the thalamus to the cortex [17, 40] and generally prevents overarousal in the cortex [79]. A similar mechanism has been seen for the hippocampus [28]. It has been suggested that anticipatory inhibition is one of the main factors in the reliable operation of the nervous system and that impairments to this process can lead to overloading and the production of epileptic activity [58]. At the same time, it should be stressed that the excitatory synaptic inputs to these neurons and their own inputs undergo marked transient synaptic depression, so the efficiency of inhibition decreases quickly during prolonged activation.

Group 2 consists of interneurons forming synapses on the distal dendrites of principal cells. This group of cells is very heterogenous in terms of morphology, neuropeptide content, and calcium-binding protein content in both the hippocampus [29] and the cortex [51]. Researchers' attention has focused on the more widely distributed type of interneurons of this group – somatostatin-containing Martinotti cells (MC) in the cortex [42] and the functionally analogous somatostatin- and NPY-containing interneurons of the hippocampus [49]. As compared with PV-containing interneurons, MC form small numbers of synapses on pyramidal cells [95]. The inhibitory effect of individual MC is weak because of the distal positioning of the synapses, though simultaneous actions of multiple MC produce effective inhibition. The excitatory inputs to MC are distinguished by strongly marked facilitation [56, 68], so these interneurons enter the aroused state more easily in conditions of high-frequency stimulation [72]. Simultaneous activation of MC is achieved if some subpopulation of pyramidal cells starts to discharge simultaneously. In this case, MC support recurrent inhibition to this subpopulation of pyramidal cells, leading simultaneously to lateral inhibition of neighboring pyramidal cells [72]. MC have been suggested to prevent the propagation of epileptic activity in the cortex more efficiently. In conditions of powerful activation, somatostatin-containing interneurons start to release not only GABA, but also somatostatin [11, 91]. Somatostatin, acting presynaptically, weakens glutamatergic neurotransmission in the hippocampus [13]. Recent studies have shown that somatostatin and agonists of SST_2 receptors effectively prevent or weaken pilocarpine seizures, suppressing glutamate release [46].

Group 3 includes interneurons forming contacts mainly but not exclusively with other GABAergic neurons and thus having disinhibitory effects. These interneurons generally contain calretinin (CR) and/or vasoactive intestinal peptide [33, 60]. This class of interneurons has been suggested to be responsible for synchronizing the operation of interneurons supporting dendritic inhibition of pyramidal cells. Thus, this class effectively controls the synaptic inputs and activity of pyramidal cells [86].

The Death of Interneurons of Different Classes in Epileptic Seizures. Studies of morphofunctional impairments and interneuron death in epilepsy need to address two questions: 1) how and when does interneuron death occur? Is interneuron death the cause of convulsive activity or do they die as a result of convulsive activity? 2) Do all types of interneuron suffer equally? If death is selective, which classes die more? [22]. Current data indicate that not all convulsive states lead to neuron death. For example, brief epileptic seizures, lasting no more than 5–10 sec do not lead to brain damage, while quite long-lasting and repeated seizures do lead to neuron death. The greatest level of neuron damage is seen in status epilepticus [23].

Hippocampal sclerosis is commonly seen in humans with temporal epilepsy and is accompanied by gliosis and neuron loss, while the temporal cortex shows lesser changes [22]. Morphological changes seen in different models of temporal epilepsy in rodents are frequently different from those seen in humans [18, 22], while the degree of degeneration of GABAergic interneurons differs in different models. For example, pentylenetetrazole kindling produces virtually no neuron death in the hippocampus [2] or of interneurons in the dentate gyrus in mice [92], while the lithium-pilocarpine model decreases the number of interneurons, especially in the hilus [92]. We will consider what is known of the death of neurons in different functional groups in more detail

Interneurons providing perisomatic inhibition. Data on selective death of PV-IN, which provide perisomatic inhibition, remain contradictory. Decreases in the numbers of PV-IN have been described in the epileptic human hippocampus [6, 94, 103]. However, electron microscopy data from studies of the bodies of pyramidal and granule neurons have shown that the number of perisomatic inhibitory contacts remains constant even in those areas in which the numbers of PV-IN and axon terminals are significantly decreased [6, 94]. Thus, loss of PV-immunoreactivity is not definitely evidence of the death of this particular type of neuron, but may be due to impaired PV synthesis or conformational changes in the protein due to excessive Ca^{2+} within the cell, with resultant changes in immunoreactivity [71].

In the damaged hippocampus, the number of synaptic contacts in the initial axon segment of granule cells forming AAC – another type of PV-positive interneuron – increases three-fold from the level in controls [94], i.e., there is a compensatory increase in the axons of surviving cells. It is interesting that excessive innervation of the initial axon segment of granule cells may increase the synchronization of their activity and can even lead to increases in epileptic activity [47, 94]. Thus, in some functional states, AAC can induce action potential generation in pyramidal cells [82]. This is linked with the fact that initial axon segments contain very little KCC2 potassium-chloride cotransporter, which in some cases leads to local increases in chloride ion contents, with the result that activation of chloride $GABA_A$ receptors induces membrane depolarization, leading to action potential generation [82]. However, the temporal cortex of epilepsy patients shows significant damage to AAC and the absence of axoaxonal synapses at the initial axon segment of pyramidal cells [22].

The use of a variety of models of epilepsy also fails to give an unambiguous answer regarding the death of interneurons of this group. In a model of traumatic temporal epilepsy, PV-IN death was apparent by a week, reaching 33–65% in different parts of the hippocampus and dental gyrus at 6–8 months [41, 99], PV-IN in field CA1 suffering less [99]. In a pilocarpine model of epilepsy, a significant reduction in the number of neurons was seen by 24 h after the development of status epilepticus [1, 5]. The death of PV-IN was more extensive in the pyramidal layer of the subiculum, while PV-positive neurons in the molecular layer of this same area were subject to less damage [20, 44]. PV-IN death was also seen in hippocampal field CA1, the hilus of the dentate gyrus, and the deep layers of the entorhinal, perirhinal, and insular cortex [5, 9, 14, 19].

It is interesting to note that a significant correlation between the frequency of developing spontaneous convulsions and the extent of PV-IN death was not seen even in a model of traumatic epilepsy or after status epilepticus induced by electrical stimulation of the amygdala for 30 min [41]. Furthermore, data have been reported providing evidence of an inverse relationship: at two weeks after administration of pilocarpine, in a group of rats with spontaneous convulsions, PV-IN death was less than in rats without spontaneous convulsions [5]. Comparison of different models with different levels of interneuron death also failed to lead to unambiguous conclusions regarding the roles of interneurons in the production of spontaneous convulsions. For example, there was a significantly greater level of interneuron death in a model of traumatic epilepsy than after status epilepticus induced by stimulation of the amygdala, though the frequency with which spontaneous convulsions developed was lower in this model [41].

Thus, it has now been demonstrated that convulsive states lead to damage to and, frequently, death of PV-IN in the hippocampus and, to a lesser extent, in the temporal cortex,, though there is insufficient evidence for the predominant death of this class of neuron over other cell types.

Interneurons supporting dendritic inhibition. Prolonged or repeated convulsions lead to damage to interneurons supporting dendritic inhibition. Somatostatin-positive and NPY-containing interneurons in the dentate gyrus and hippocampal fields CA1 and CA3 have been shown to have high susceptibility both in different models of temporal epilepsy [11, 73, 78] and in the epileptic human hippocampus [21, 80]. Data from immunohistochemical studies show that the hippocampus of temporal epilepsy patients shows selective death of somatostatin-positive neurons [21, 52], which is accompanied by significant growth of their axons. However, in situ hybridization has shown that the death of

somatostatin-containing neurons in the hilus of the hippocampus is essentially proportional to the total drop in the number of neurons, rather than being selective [80].

In animals, the vulnerability of somatostatin cells depends to a significant extent on the model used. In the post-traumatic model of epilepsy, less than half the number of somatostatin-positive neurons remained in the ipsilateral dentate gyrus one month after trauma, while after status epilepticus induced by electrical stimulation of the amygdala for 30 min, the maximum level of death of this type of neuron in different areas of the hippocampus was no more than 15% [41]. Status epilepticus induced by kainate administration led to the death of 80% of somatostatin-positive neurons in the hilus of the hippocampus [77] and up to 50% in the dentate gyrus [11, 15]. In the pilocarpine model of epilepsy, the death of somatostatin neurons in the hippocampus of GIN mice (somatostatin cells in animals of this strain express a green fluorescent protein) was around 40–50% [16, 101].

Surviving somatostatin cells showed an increase in the contents of somatostatin mRNA and protein. The detailed molecular mechanism of activation of somatostatin biosynthesis currently remains unknown, though it has been suggested that activation of NMDA receptors plays an important role in this process [11, 91]. Another important feature of surviving neurons is significant axon growth, with reorganization of axon branching and the appearance of new anomalous synaptic connections in the hippocampal fields, which in normal conditions are not innervated by somatostatin cells. For example, axons of somatostatin cells from the stratum oriens are usually restricted to the area of the stratum lacunosum-moleculare, while pilocarpine convulsions in mice are followed by axon growth reaching the molecular layer of the dentate gyrus [59]. This reorganization of the innervation system may promote the functional deficit of inhibition in epilepsy despite the presence of numerous GABAergic terminals [52, 59].

Interneurons providing inhibition of other interneurons. In hippocampal field CA1 in rats, CR-containing interneurons (CR-IN) terminate essentially selectively on calbindin- or VIP-containing interneurons [33]. In the human hippocampus, CR-IN are more diverse and innervate not only interneurons, but also principal cell dendrites [89], though CR is nonetheless used as a marker for interneurons providing inhibition of other interneurons. Initial data obtained on the hippocampus of patients with temporal epilepsy have shown that the number of CR-IN does not decrease; their axons extend [12], though later and deeper investigations identified reductions in the number of CR-IN, which correlated with the general loss of cells in the hippocampus [85]. The number of cells declines both in the dentate gyrus (especially in the hilus) and the sclerotic hippocampal field CA1, though nonsclerosed areas show no changes in cell number [85]. The morphology of surviving CR-IN is altered – their dendrites are shorter than normal, while the number of gap junctions between the dendrites of these interneurons is reduced. Electron microscopy studies have demonstrated that in the control group, CR-IN form 23% of the synapses on CR-positive dendrites, while the proportion of synapses of this type in the epileptic brain is decreased to 3–5% [85, 86]. All these points indicate impairments to the interactions of CR-IN with each other, probably degrading their synchronous operation [86].

In models of epilepsy, death and functional impairment of CR-IN have received relatively less study than other types of interneuron. Decreases in the number of CR-IN in the hippocampus of rodents have been seen in a traumatic model of epilepsy, though not after status epilepticus evoked by electrical stimulation of the amygdala for 30 min [41]. Even small doses of kainate given into hippocampal field CA3 evoked decreases in the number of CR-IN in the hilus of the dentate gyrus [48]. Significant death of CR-IN is seen after systemic administration of pilocarpine: by 30–45% in the hilus of the dentate gyrus, up to 70% in the pyramidal layer of CA3, 36% in the pyramidal layer of CA1, and up to 80% in the stratum oriens of CA1 [5]. The analysis reported by Huusko et al. [41] showed that the extent of CR-IN damage in different models of epilepsy increased in the following order: status epilepticus induced by electrical stimulation of the of the amygdala < traumatic model < status epilepticus induced by electrical stimulation of the hippocampus < pilocarpine model of epilepsy.

The death of CR-IN starts several hours after the development of status epilepticus [48] as a result of excitotoxic degeneration via the necrotic pathway [86]. Electron microscopy studies have identified degeneration of cytoplasmic organelles, degraded mitochondria, and numerous phagocytic vacuoles, suggesting overproduction of anomalous proteins and impairment to energy metabolism [85]. Although these cells contain the calcium-binding protein CR, they are extremely susceptible to increases in the cytosolic calcium concentration induced by epileptic activity in the brain. Some of the possible causes are: 1) a high interconnectedness between interneurons of this type with each other via numerous gap junctions between dendrites, such that the cells are activated simultaneously [34, 85]; 2) the cytoplasm has sparse organelles, so the energy reserves of these cells are small, making them vulnerable to stressors [37].

Functional Sequelae of Interneuron Death and/or Functional Impairment. The death of GABAergic interneurons due to convulsive activity and impairments to the functions of surviving interneurons may be significant epileptogenic factors. Several hypotheses for the induction of epilepsy in the brain due to degradation of the functions of GABAergic neurons have been proposed.

Hypothesis of disinhibition due to loss of individual types of GABAergic neurons. One of the first hypotheses was that of disinhibition due to loss of individual types of GABAergic neurons [38]. For example, the death of cells immunoreactive for PV or cholecystokinin weakens the perisomatic inhibition of hippocampal principal cells [6, 22]. Decreases in the numbers of interneurons immunoreac-

tive for somatostatin, NPY, or CR degrade the inhibition of the distal dendrites of principal cells and other inhibitory neurons [49, 52, 85]. Furthermore, a decrease in the number of presynaptic GABAergic terminals leads to decreased GABA release and the expression of GABA receptors with anomalous subunit composition in postsynaptic neurons, which also weakens postsynaptic inhibition [57, 100]. The axons of surviving GABAergic interneurons grow strongly, to compensate for insufficient inhibition, though they often form anomalous contacts [47, 101]. Such anomalous GABAergic innervation leads to additional impairments to the regulation of principal cell operation, with pathological synchronization in neural networks, which is apparent as impaired cognitive functions in epilepsy [43].

The disinhibition hypothesis remains very popular, though it provides no explanation for many important experimental facts – for example, there is as yet no convincing evidence that the relative death of any particular population of interneurons (except somatostatin-containing) exceeds the death of principal cells. The absence of any correlation between the frequency of spontaneous convulsions and the proportion of surviving interneurons determined in several studies [41] is also not explained by this hypothesis.

The non-active (dormant) basket cell hypothesis. Impairment to inhibition in epilepsy may be induced not only by the death of interneurons, but also by their functional inactivity. The non-active (dormant) basket cell hypothesis [7, 73] is widely accepted. This hypothesis provides an explanation for what was previously considered a paradox between morphological and physiological data: a significant decrease in the inhibitory action on principal cells by PV-IN, which, according to histological data, retain most of their inhibitory contacts with principal cells. Experimental studies on a kindling model of epilepsy evoked by electrical stimulation of the amygdala over periods of 2–5 months identified that hippocampal basket cells are preserved and are able to function normally, though they remain inactive because they deo not receive the necessary activatory excitation from mossy cells [7].

This popular hypothesis subsequently came to be doubted [10], as new experimental data did not fit within it. For example, a number of models of epilepsy have identified significant death of different classes of interneuron, including PV-IN and the link between the decrease in inhibitory innervation of principal cells and their elevated excitability was found to be beyond doubt [65]. In chronic models of epilepsy, pyramidal cells in the cerebral cortex may have large numbers of normally functioning inhibitory inputs; nonetheless, these cells are hyperexcitable [65]. On the other hand, studies in a number of models of temporal epilepsy, showed that several types of surviving hippocampal interneurons were not dormant, but, conversely, were more active than in control conditions [26, 35, 67].

Although the dormant basket cell hypothesis now has fewer adherents, experimental data have demonstrated the important functional role of this class of interneurons in epilepsy. Decreases in the activity of these cells as a result of a mutation in the *SCN1A* gene, which encodes the voltage-gated sodium channel $Na_v1.1$, lead to severe myoclonic epilepsy in early childhood (Dravet syndrome) and various forms of febrile convulsions [24, 25]. This type of sodium channel is found in most neurons, though the highest density is found on the initial axon segment on PV-IN [55], so mutations in the *SCN1A* gene lead to impaired spike generation in PV-IN, though they have no effect on pyramidal cell activity [55, 83]. Overexpression of the $Na_v1.1$ channel, conversely, decreases epileptiform activity in hAPP transgenic mice [90]. Mutations or manipulations to genes for the *KCNA1* and *KCNA2* voltage-gated potassium channels, which are expressed mainly on PV-IN, also lead to the development of epilepsy in humans and transgenic mice [27, 30, 69]. Generalized convulsions can also develop when GABA release is impaired in cortical PV-IN. As transmitter release in this class of cortical and hippocampal interneurons is mediated exclusively by P/Q-type calcium channels [36, 98], weakening of the functions of P/Q-type calcium channels due to various mutations leads to the occurrence of generalized convulsions in mice and humans [66, 70].

Thus, weakening of inhibitory innervation of principal cells by PV-IN is one of the main causes of impairments to the mechanism preventing convulsive activity in the brain. The causes of the weakening of innervation can be very diverse, so correction of this impairment may require fundamentally different approaches.

The neural network imbalance hypothesis. The causes of paroxysmal activity are currently regarded as including imbalance in neural networks [58]. As suggested by Paz and Huguenard, epilepsy is associated with impairment to the interaction between neurons in micronetworks. These authors identified four main types of interaction: feedforward and feedback inhibition, disinhibition (counter-inhibition), and recurrent inhibition. Interneurons are directly involved in the first three main types (Fig. 2). Impairments to the interaction of neurons in micronetworks lead to excessive synchronization of principal neurons and unpreventable propagation of excitation across the brain.

Impairments to the mechanism of feedforward inhibition. The anatomical connections and functional characteristics of PV-IN in the cortex and hippocampus allow them to play a leading role in mediating feedforward inhibition. This type of inhibition is highly effective in preventing the propagation of epileptic activity beyond the boundaries of the local generation focus, so PV-IN are regarded as one of the main obstacles on the pathway to the generation of convulsions [58]. A predominance of inhibition around the stimulated area of the cortex was described in the first in vivo experiments with intracellular recordings [64], which led to the concept of protective surround inhibition. Even when convulsive activity propagates across the brain, it is always preceded by a powerful front of feedforward inhi-

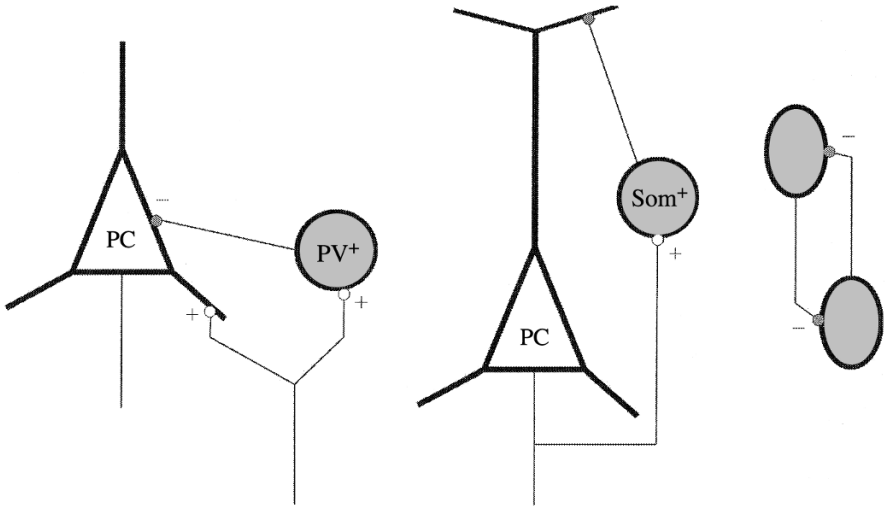

Fig. 2. Main types of interaction in neural networks involving inhibitory interneurons. *A*) Feedforward inhibition; *B*) feedback inhibition; *C*) disinhibition. For further details see caption to Fig. 1.

bition, slowing the spike generation activity of principal neurons [87]. This occurs because of the specific organization of excitatory and inhibitory inputs of different types of neurons: the bodies and proximal dendrites of pyramidal cells have only inhibitory synapses, while the bodies of GABAergic interneurons have both inhibitory and excitatory synapses [75]. As a result, pyramidal neurons close to the area of convulsive activity do not generate spikes for a long period of time when a majority of synapses and significant membrane depolarization are activated simultaneously because of the shunting effect of inhibitory synapses in the body. Thus, propagation of ictal activity in the brain slows [88]. In vitro experiments have shown that the first ictal events propagate across slices at a rate of < 1 mm/sec, though the rate increases to 25–100 mm/sec in the presence of GABA blockers [61, 87].

Feedforward inhibition is very susceptible and can be impaired by a number of factors: accumulation of intracellular Cl^- after convulsive activity, which leads to a change in the sign of the action of GABA from hyper- to depolarizing [8]; depletion of GABA and presynaptic inhibition [53, 84]. Thus, pharmacological actions on these factors can prevent the propagation of convulsive activity in the brain. In addition, if impairments to feedforward inhibition are the immediate cause of epilepsy, antiepileptic drugs must be directed to its restoration and must not under any circumstances suppress it [58].

Impairments to the mechanism of feedback inhibition. Feedback inhibition is mediated by many types of interneurons, the most numerous and best studied of which are somatostatin-positive interneurons in the cortex and hippocampus (for example, MC), as well as PV-positive AAC. Feedback inhibition in neural micronetworks develops as a result of excitation of neighboring neurons. As described above, an important feature of MC is that their excitatory inputs show marked facilitation [56, 68], so their effects are significantly enhanced when excitation in the micronetwork increases. Thus, MC can be very effective in preventing the occurrence of ictal activity, decreasing the local level of excitation.

Selective death of these neurons in epilepsy and the formation of anomalous synaptic connections lead to a deficiency in feedback inhibition [52, 59]. Studies have demonstrated that in the pilocarpine model of epilepsy in mice involves a compensatory increase in the number of excitatory synapses on somatostatin cells in the hippocampus, as well as various other changes increasing the excitability of these cells. For example, the following observations have been made: decreased membrane resting potential; increased membrane time constant and capacitance; increased frequency of spontaneous excitatory postsynaptic currents (EPSC); increased amplitude of evoked EPSC; increased frequency of spontaneous action potential generation in these cells. The factors increase the activity of surviving somatostatin-positive interneurons, providing partial compensation for reductions in their number in the hippocampus in epilepsy [35].

AAC are another important type of interneuron involved in mediating the mechanism of feedback inhibition. As described above, the temporal cortex of epilepsy patients shows significant damage to AAC and the absence of axo-axonal synapses on the initial axon segments of pyramidal cells [22]. In vivo experiments in rats have indicated that local application of the $GABA_A$ receptor bicuculline induced a 20-fold increase in the action potential frequency of AAC in the somatosensory cortex, which significantly ex-

ceeded the change in discharge frequency in any other type of neuron. This suggested that AAC play an important role in preventing epileptic activity, providing extreme inhibition of pyramidal cells and blocking action potential generation in the initial axon segment [58, 102].

Thus, feedback inhibition is an effective mechanism preventing hypersynchronization and the occurrence of paroxysmal activity in neural micronetworks.

Impairment to disinhibition and counter-inhibition. Interneurons often form chemical and electrical synapses with members of their class. There are also specialized types of interneuron, forming contacts mainly but not exclusively with other GABAergic neurons and thus having a disinhibitory action. Mutual inhibition of GABAergic interneurons may disinhibit principal cells, increasing their spike frequency; in addition, this aids the production of oscillatory activity. For example, synaptic interactions between PV-IN promote the appearance of γ-frequency oscillations [93]. Data from several studies have shown that before the occurrence of ictal discharges in temporal epilepsy in humans [39] and in the pilocarpine model of epilepsy in rats [32], the hippocampus shows a special type of synchronized activity – preictal discharges, due to the synchronized operation of interneurons but not pyramidal cells.

Conclusions: Potential for Selective Actions on Interneurons in Epilepsy. Significant progress has been made in our understanding of the pathophysiological mechanisms of epilepsy. We know much more about the roles of different types of interneuron in epilepsy and their critical importance to the generation and propagation of ictal activity across neural networks, so innovatory methods of treating epilepsy should take cognizance of this new information. Selective actions on target interneuron populations may be a potential approach to treating epilepsy. Given that different neuron populations differ significantly in terms of their receptor repertoire, the potential for pharmacological approaches is very high. A whole series of substances acting selectively on synaptic transmission between particular neuron classes or altering the excitability of individual interneuron classes has already been identified and synthesized [3]. However, the potential and efficacy of their use in clinical practice remain to be evaluated/

Experiments on the suppression of ictal activity have demonstrated that the optogenetic approach can be highly effective [45]. Lentivirus constructs can be used to express light-sensitive ion channels in defined interneuron populations, after which light of the required wavelength can be used to control the excitability of target populations of neurons. This method currently has a number of technical complexities, preventing its introduction into clinical practice, such as delivery of the genetic material and the light source. However, it should be noted that this method is very useful for studying the roles of different types of interneuron in epilepsy.

Another interesting research direction is the experimental treatment of cellular transplantation of interneurons [4, 50, 104]. Experimental results have now been obtained pointing to the significant potential of this approach. After transplantation, immature interneurons obtained from the ventral parts of the embryo telencephalon have the unique ability to migrate across significant distances in the cerebral cortex of neonatal and even adult animals, then integrating into neural networks [76]. Interneuron precursor cells were successfully transplanted into the brains of adult mice with temporal epilepsy and then migrated within the hippocampus and differentiated to form several classes of interneuron expressing different calcium-binding proteins and reminiscent of interneurons in normal brains in terms of their morphological and electrophysiological properties [50].

Undoubtedly, all these new approaches require significant additional studies before encouraging results from the treatment of epilepsy in rodents can be applied in clinical practice. In any case, these data allow us to hope that new and more effective methods of combating epilepsy will be developed in the foreseeable future.

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