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# Multiple facets of GABAergic neurons and synapses: multiple fates of GABA signalling in epilepsies

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**Because blocking GABAergic neurotransmission in control tissue generates seizures and because GABA boosters control epilepsy in many patients, studies on epilepsies have been dominated by the axiom that seizures are generated by a failure of GABA-mediated inhibition. However, GABAergic interneurons and synapses are heterogeneous and have many roles that go beyond the straightforward concept of 'inhibition of the target'. Operation of such a diversified system cannot be ascribed to a single mechanism. In epileptic tissue, GABAergic networks undergo complex rewiring at the anatomical, physiological and functional levels; GABAergic synapses are still operative but show unique features, including excitatory effects. Therefore, inhibition is not a uniform notion and the concept of 'failure' of inhibition in epilepsies must be reassessed. Seizures are not generated in a normal circuit in which GABA-mediated inhibition is simply impaired, but in a profoundly rewired network in which several properties of GABA function are altered. This review is part of the *TINS Interneuron Diversity* series.**

## Introduction

The starting point for conventional understanding of epileptic seizures is a simple model whereby inhibition and excitation have roles somewhat similar to those of the brakes and accelerator in an engine, respectively. Consequently, agents and conditions that reduce the former or augment the latter will inevitably favour the generation of seizures. In keeping with this, blockers of GABA-mediated transmission generate seizures in a wide range of preparations and in humans, suggesting that GABAergic inputs prevent this generation. Conversely, strong activation of glutamatergic synapses generates seizures. The consequence of this simplistic scheme is that agents that augment inhibition will have antiepileptic properties.

It is now clear that this message is oversimplified. First, the concept of GABA-mediated 'inhibition' must be re-evaluated. Recent data suggest that GABA neurotransmission can be excitatory in basal conditions, not only in immature but also in adult tissue. GABAergic synapses are indeed endowed with a unique and fundamental feature – resulting from their $Cl^-$ permeability – that enables them to shift from an inhibitory mode of operation to one that mainly excites. This feature is not shared by the cationic glutamate receptors, which do not shift to inhibition in pathological conditions. Second, the simple static view of 'inhibition of the target' is 'the tree that hides the forest'. One major function of GABA-mediated neurotransmission is to synchronize neuronal networks. In such dynamic perspective, the role of GABA extends well beyond mere 'excitation' and 'inhibition'. Third, studies on interneurons have unraveled an unsuspected heterogeneity of neuronal types that have very different roles. Such heterogeneity is an important parameter to consider when looking at the roles of GABAergic neurotransmission. Clearly, study of the fate of GABA-mediated functions in an epileptic neuronal network must take into account such complexity. The modifications that take place at various levels within GABAergic networks will be discussed in this review. But before addressing these issues, it is necessary to recall the *modus operandi* of GABA-mediated neurotransmission and interneuron heterogeneity in control tissue.

## Multiple actions of GABAergic synapses

Once opened, $GABA_A$ receptors allow $Cl^-$ and bicarbonate ions to flow through the membrane with a 4:1 ratio [1]. What are the physiological consequences of this flux of negative charges, assuming an average resting membrane potential (RMP) of $-70$ mV for the cell (Figure 1)? The estimated reversal potential for bicarbonate ions is much more depolarized than RMP ($E_{bicarbonate} = -10$ mV), which means that these ions always flow out of the cell, thus depolarizing the membrane. By contrast, the reversal potential for $Cl^-$ ($E_{Cl}$) is closer to RMP, which results in an age-, brain-structure- and context-dependent flow of ions. At early stages of development, $E_{Cl}$ is more depolarized than RMP and $Cl^-$ flows out of the cell, thus depolarizing the membrane [2] (Figure 1). In the adult, the situation is more complex as $E_{Cl}$ is close to RMP. Thus, in mature layer 5 pyramidal cells or cerebellar interneurons, $E_{Cl}$ is more depolarized than RMP and the resulting depolarizing GABA response increases the probability of action

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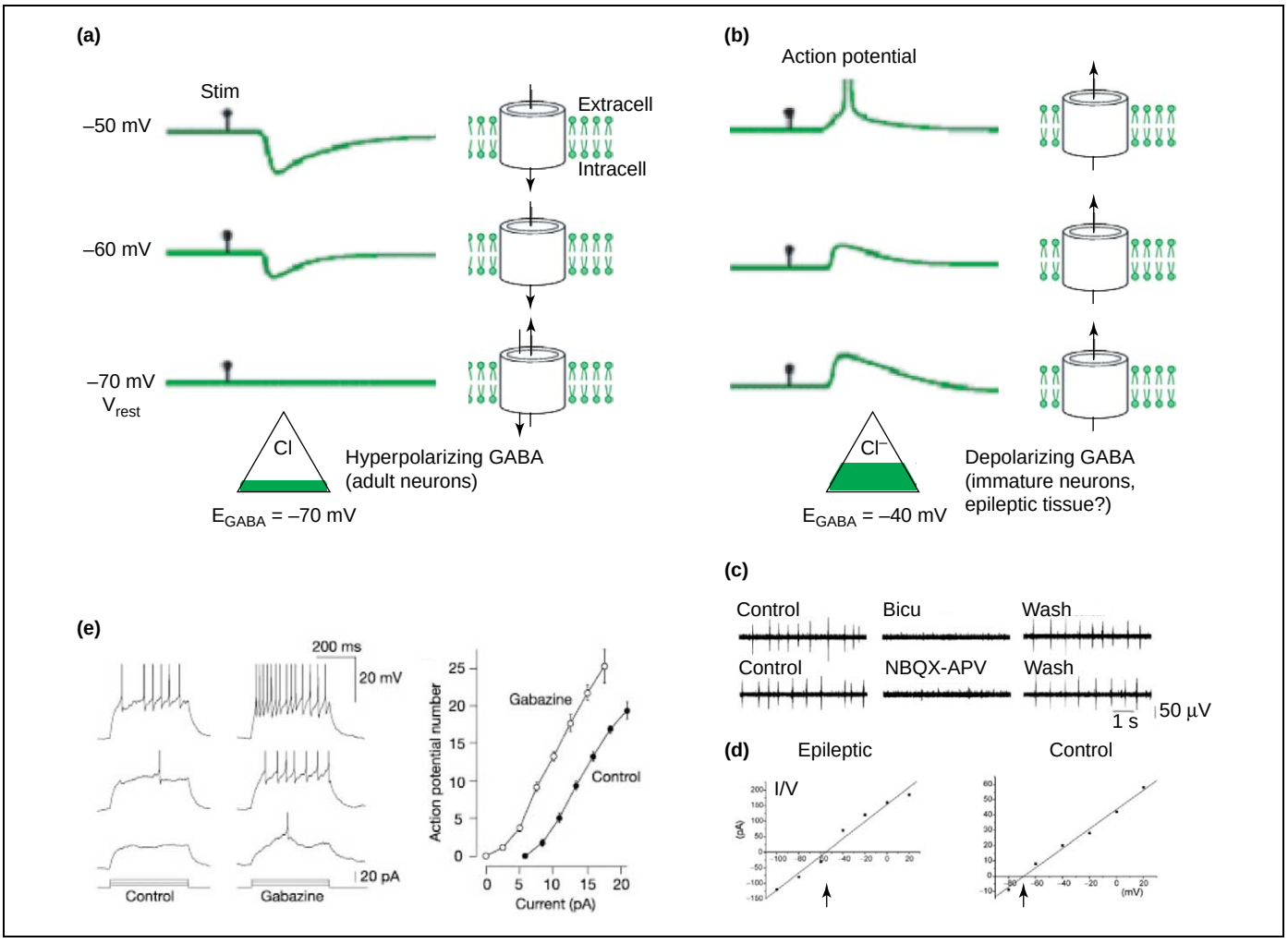


**Figure 1.** Multiple actions of GABAergic synapses. **(a)** The consequence of $GABA_A$ receptor activation ('stim'), according to the reversal potential of GABA currents. For a low concentration of $Cl^-$ in the cell, the reversal potential ($E_{GABA}$) is −70 mV (as in adult neurons). If the membrane potential is also −70 mV ($V_{rest}$) when $GABA_A$ channels open, the net flux of $Cl^-$ is null (because as many $Cl^-$ ions flow into the cell as out of it). If the membrane potential is −60 mV or −50 mV, $Cl^-$ flow into the cell, thus hyperpolarizing the membrane. **(b)** If $Cl^-$ accumulates in the cell with a reversal potential close to −40 mV (a situation encountered in immature tissue), $Cl^-$ flows out of the cell, thus depolarizing the membrane, eventually leading to action potential firing. This might be the case in epilepsy. Adapted from Ref. [75]. **(c)** In human epileptic tissue, spontaneous interictal activity is blocked in the presence of the $GABA_A$ receptor antagonist bicuculline, or in the presence of ionotropic glutamate receptor antagonists [6-nitro-7-sulfamoyl-benz(*f*)quinoxaline-2,3-dione (NBQX) and DL-2-amino-5-phosphonovaleric acid (APV)]. This suggests that interictal activity results from the synergistic actions of glutamate and GABA. Adapted from Ref. [5]. **(d)** A mirror focus develops *in vitro* in the contralateral hippocampus when the ipsilateral hippocampus receives repeated doses of the convulsive agent kainate. In the contralateral hippocampus, GABA has a depolarizing action because of a shift of $E_{GABA}$ (arrows) towards a more depolarized value. Adapted from Ref. [6]. **(e)** Blocking $GABA_A$ receptors with gabazine reduces the tonic GABAergic current, hence the shunt of the membrane, resulting in an increased firing probability in response to depolarizing current pulses of increasing amplitude. Adapted from Ref. [76].

potential firing [3,4]. Finally, $E_{Cl}$ can be dynamically regulated, with GABA switching from a hyperpolarizing to a depolarizing action, for example in pathological conditions, as will be discussed in this review [5–7].

Opening of $GABA_A$ receptors also shunts the membrane by decreasing its resistance, R (Figure 1). Following Ohm's law, AMPA receptors that are activated simultaneously with $GABA_A$ receptors will result in a lesser depolarization because of the drop in R. This shunt effect, which is efficient during the first half of the conductance change that occurs when $GABA_A$ receptors are synaptically activated [4,8], has a very strong impact on information processing [8–11].

Finally, $GABA_A$ receptor activation also affects active membrane properties. Neurons express a large variety of voltage-gated channels (VGCs). If $E_{Cl}$ is more depolarized than RMP, the resulting depolarizing postsynaptic potential may open low-threshold VGCs. Conversely, if $E_{Cl}$ is less depolarized than RMP, the resulting hyperpolarizing postsynaptic potential can open $I_h$ (a non-specific cationic channel activated by hyperpolarization) [12], decrease the probability of activation of low threshold VGCs, or de-inactivate previously inactivated low threshold VGCs. Thus, the consequences of $GABA_A$ receptor activation on active membrane properties is clearly context-specific, depending on the history of the membrane (the ratio of activated to inactivated to closed VGCs at the time of $GABA_A$ receptor activation) and the spatial location of $GABA_A$ receptors and the distribution of VGCs along the somatodendritic axis [13]. There are therefore multiple facets to GABA-mediated neurotransmission and all of these – ionic flux, shunt and interaction with VGCs – have to be encompassed in a dynamic perspective.

## Multiple types of interneurons

The diversity of interneurons needs to be taken into account to achieve a reliable picture of the reorganized

epileptic network. It is now commonly accepted that the GABAergic interneuron population cannot be studied in the same way as its glutamatergic counterpart because the biophysical, electrophysiological and neurochemical properties measured might be selective for a specific morphological type of interneuron, if not for the recorded cell only. Several studies suggest that these parameters might even not give a constant description of a given cell, as they can vary dynamically according to the brain state [14]. Besides, the variability in physiological and morphological parameters inside a given cell class might alone carry a specific function, because theoretical studies have shown that this variability can influence the inhibitory control of pyramidal cells and be altered in hyperexcitable tissues [15].

A comprehensive review of different types of interneurons will not be included here as there is not even an agreed taxonomy for these cells [16,17]. This heterogeneity probably reflects a division of labor inside a population serving multiple functions, ranging from the basic prevention of action potential firing to coincidence detection and signal integration [18,19], synaptic plasticity [17,20–23], network oscillations and epileptic synchronization [24–26]. Probably the most meaningful description of the functional variety of hippocampal interneurons, regarding their role in the generation of synchronous network activities and their fate in remodeled epileptic circuits, is based on their axonal wiring [27,28]. Four major GABAergic interneuron families can be distinguished in the hippocampus (Figure 2):

(i) Interneurons with a dense local axonal arbor that targets the perisomatic domain of principal cells; they control action potential generation in principal cells [23], provide temporal fidelity and show correlated activity during gamma oscillations and high-frequency ripples [25,29,30].

(ii) Interneurons with a dense local axonal arbor that targets the distal dendrites of principal cells; they control the synaptic inputs from the entorhinal cortex and are thus designed to pace the rhythmic theta excitation of hippocampal distal dendrites [31]. They show anti-phase activity with principal cells during theta waves [25].

(iii) Interneurons with an extended bistratified axonal arborization that targets the dendritic tree of principal cells. They control signal integration and $Ca^{2+}$ spike initiation at the dendrite [23,32], show correlated activity in phase with principal cells during theta oscillations and are major contributors to the sharp wave-associated ripple episodes [33].

(iv) Long-range interneurons with a dispersed axonal arborization extending to the medial septum. These interneurons are likely to coordinate interneuron assemblies and seem to be spared in animal models of temporal lobe epilepsy (TLE) [27,34,35].

There are therefore multiple types of GABAergic cells in the hippocampus. Given the fact that these cells are differentially affected during epileptogenesis, it is very likely that the rewired epileptic GABAergic circuit will produce aberrant network activities that should lead to ictogenesis [36].

## Multiple fates of GABAergic components in epilepsy

Modifications within the GABAergic system can occur at all levels of integration, from $GABA_A$ receptors to interneuron networks.

### *When GABA receptors change subunits after seizures*

$GABA_A$ receptors can be assembled from a large number of different subunits. Different subunit compositions allow receptors to have different properties in terms of affinity for GABA, allosteric modulation, interaction with intracellular proteins, probability of channel opening, kinetics and conductance. This issue is particularly worth considering as the function of the neuronal network can be modified following a change in subunit composition [37,38]. There is now a large body of evidence indicating that $GABA_A$ receptor function is altered in TLE in humans [39,40]. These alterations include modifications in subunit composition, for example the upregulation of $\alpha 1$ and $\alpha 2$ subunits [41], which could be responsible for changes in allosteric modulations by compounds such as benzodiazepine [42]. Animal models enable more detailed analysis of the dynamics with which $GABA_A$ receptor numbers and subunit composition are modified. Animal models of epilepsy usually involve three main phases: the induction phase (drug-induced or electrically induced status epilepticus), the latent period (during which the animal does not display spontaneous seizures) and the chronic phase. The $GABA_A$ receptor subunit composition is differentially modified in dentate gyrus granule cells

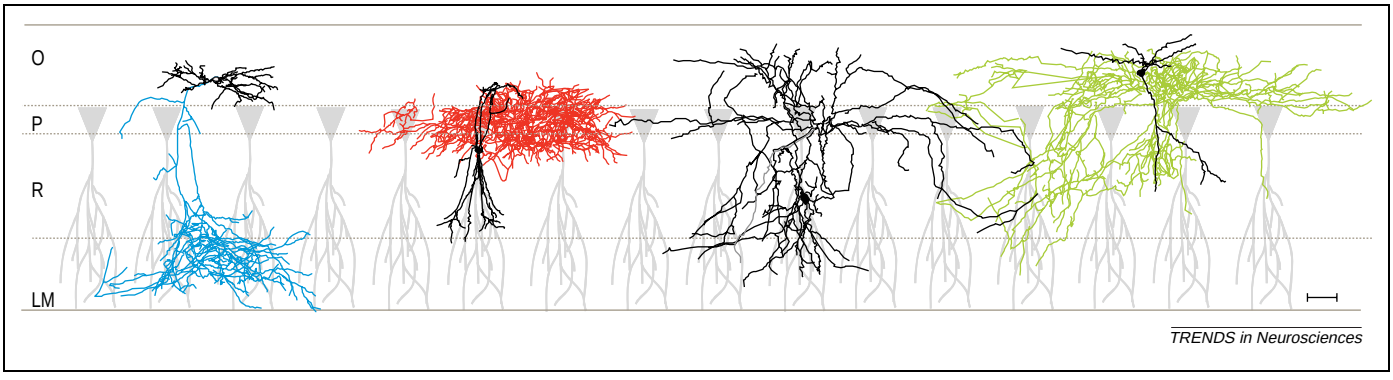


**Figure 2.** Different types of interneurons. Four major types of rat CA1 hippocampal interneurons, characterized by their laminar axonal distribution Neurolucida drawings of biocytin-filled neurons; axon are in color, dendrites are in black and pyramidal neurons are represented in gray. (R. Cossart. M. Esclapez *et al.* unpublished.) Scale bar, 100 μm. Abbreviations: LM, stratum lacunosum moleculare; O, stratum oriens; P, stratum pyramidale; R, stratum radiatum.

according to the phase, indicating that the process is dynamic [43–46]. The number of receptors is modified [47], and the change in subunit composition results in increased sensitivity to GABA and $Zn^{2+}$ and in decreased sensitivity to the benzodiazepine-type site-1 modulator, zolpidem [45,48,49]. By contrast, the sensitivity to GABA is decreased in pyramidal cells of the CA1 hippocampus, indicating that the modifications are region-specific. These modifications most likely involve synaptic receptors. Downregulation of the $\alpha 5$ subunit, a constituent of extrasynaptic receptors in CA1 pyramidal cells [50], could have a profound impact on information processing in the cell [51]. The functional consequences of all these modifications remain to be established, although a change in subunit composition appears to be linked to seizure susceptibility [52,53]. Finally, modifications other than a change in subunit composition might alter $GABA_A$-receptor-mediated responses. Intracellular factors, such as phosphorylation processes [54] or anchoring of the receptors by gephyrin, GABA-receptor-associated protein (GABARAP) and other proteins, can change $GABA_A$ receptor function.

### *When $Cl^-$ accumulates and GABA depolarizes neurons*

It has long been suspected that regulation of intracellular $Cl^-$ concentration ($[Cl^-]_i$), in particular following intense activity of GABAergic synapses, is time-, activity- and context-specific [7,55]. It is also age-dependent, as there is now a general agreement that $[Cl^-]_i$ is higher in the immature brain than in adults in all species and brain structures studied [2]. Removal of $Cl^-$ is regulated by the $K^+$–$Cl^-$ cotransporter KCC2, which is expressed later in development [56]. Interestingly, there is a significant shift of the reversal potential of GABA-mediated currents in slices obtained form epileptic patients [5] (Figure 1). Application of a GABA receptor antagonist blocked ongoing activity, instead of generating epileptic activity as is observed in control conditions. This inhibitory-to-excitatory shift of GABA actions suggests that this modification recapitulates ontogenesis. GABA-mediated depolarization could be a major contributor to ictogenesis, although this issue remains to be addressed. Do the alterations described here take place rapidly following a few seizures? Is there a continuum of changes that occur at various delays after the initial insult? How do GABAergic synapses alter their mode of operation after brief seizures that are not associated with cell loss or new synapse formation? These questions have been addressed by a recent study in which seizures were generated by application of kainate to an intact hippocampus *in vitro* and the contralateral hippocampus, which had not been submitted to the drug, was analyzed [6] (Figure 1). After repeated application of kainate, a powerful mirror focus was generated in the naïve hippocampus via an LTP-like NMDA-dependent process [57]. Most interestingly, GABA action switched permanently from inhibitory to excitatory in the mirror focus, and GABA antagonists blocked seizures [6] (Figure 1). These observations indicate that alterations occur rapidly, become long-lasting (most likely after a few seizures) and do not involve neuronal damage.

### *When some neurons die fast and others survive well*

The fate of the hippocampal GABAergic neurons after the epileptogenic insult in animal models, as well as in human patients, is characterized by the restricted vulnerability of select cellular subgroups (Figure 3). Several studies pointed out the somatostatin-containing subpopulation as one of the most vulnerable in different brain regions, in different models of TLE and in human patients [34,58–62]. Hence, the degeneration of somatostatin-containing interneurons accounts for 83% of the total GABAergic cell loss in the hilus [58] and ~50% in the stratum oriens of CA1 [60]. Furthermore, ultrastructural and electrophysiological studies indicate that these cells correspond to interneurons that innervate the distal region of pyramidal cell dendrites [34,61,63]. Another vulnerable population shared by different brain regions and models is that of the parvalbumin-containing interneurons that project to the axon initial segment of pyramidal cells [34,61,64–66] Decreased expression of other markers, such as neuropeptide Y, calretinin or cholecystokinin, has been reported in a few studies but has not been associated with loss of a specific type of GABA-mediated innervation [66,67]. Finally, a few isolated studies suggested a possible sprouting of GABAergic fibers [68] (Figure 3). In animal models, the death of selective interneuron populations occurs relatively quickly (a few hours after the insult), before the animal presents spontaneous seizures [60]. This indicates that interneuron death participates in network reorganization but is not sufficient for seizure generation.

The differential fate of interneurons in epileptic tissue is likely to be the immediate consequence of their biophysical and neurochemical heterogeneity rather than their network embedment. For example, somatostatin-containing oriens neurons projecting to the stratum lacunosum moleculare (O–LM cells) and septum-projecting interneurons receive similar glutamatergic inputs [69], yet only O–LM cells degenerate in the epileptic tissue [34]. The selective loss of O–LM cells might result from their specific expression of postsynaptic receptors such as kainate [70], their neurochemical content, or the dynamic properties of their synaptic inputs. All these parameters might contribute to a different $Ca^{2+}$ economy for distinct interneuron cell types [71]. However, the content of $Ca^{2+}$-binding proteins cannot explain the differential vulnerability of interneurons [43]. It will be essential to determine the cause of this selective vulnerability. An additional major factor to consider is the reactive plasticity that takes place after an episode of status epilepticus or recurrent seizures.

### *When cell bodies and dendrites of neurons speak different languages*

Functional consequence of the rearrangement of interneuron networks can be directly measured at the level of the different postsynaptic domains targeted by GABAergic axons. Schematically, interneurons that contact the soma of principal cells control their output (i.e. action potential generation), whereas distally, interneurons that contact the dendrites control the input of principal cells and the propagation of $Ca^{2+}$ currents from the dendrite to the

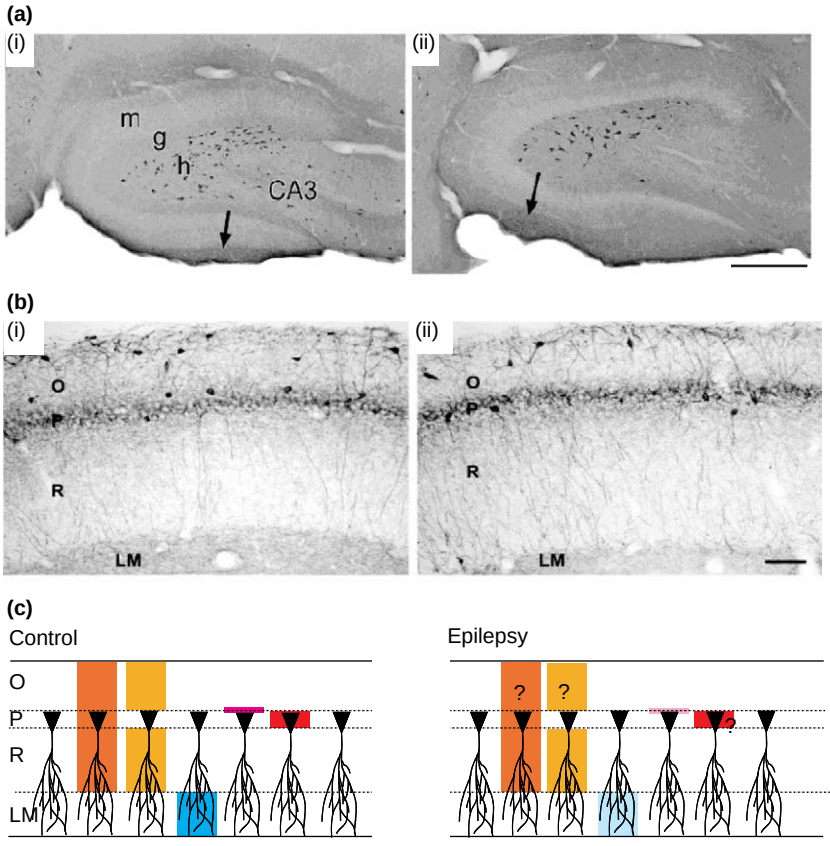


**Figure 3.** Loss of interneurons from epileptic tissue. **(a)** Loss of hilar somatostatin-immunoreactive interneurons in the kainic acid model (ii) as compared with a control rat (i). The number of cells is decreased but the immunoreactivity of the surviving ones is increased. Arrows indicate the somatostatin-immunoreactive fiber plexus in the outer molecular layer. Scale bar, 500 μm. Adapted from Ref. [77]. **(b)** Loss of parvalbumin-containing interneurons in the stratum oriens of the CA1 region in the pilocarpine model (i) as compared with a control rat (ii). Scale bar, 100 μm. Adapted from Ref. [60]. **(c)** Reorganization of the different interneuron networks distinguished according to the projection zone of their axons on their pyramidal cell targets. Until now, only axo-axonic GABAergic synapses (pink) and GABAergic synapses located in the stratum lacunosum moleculare (blue) have been clearly established as affected in the epileptic tissue (lighter shading). Question marks indicate that sprouting and/or loss of GABAergic fibers remains to be assessed for GABAergic synapses contacting the soma (red) or the proximal dendrites (orange and yellow) of principal cells. Abbreviations: g, granule cell layer; h, hilus; LM, stratum lacunosum moleculare; m, molecular layer; O, stratum oriens; P, stratum pyramidale; R, stratum radiatum.

soma [23]. Hence, in principal cells, although the somatic innervation is relatively preserved and even increased owing to maintenance and hyperactivity of interneurons that contact the cell body area [34,72], there is a selective decrease of distal dendritic GABA-mediated transmission resulting from the loss of O–LM interneurons. The physiological consequence of this alteration in the dendrites is measured experimentally as a permissiveness of the CA1 hippocampal network to the excitatory input of the entorhinal cortex [34]. Theoretical studies predict that this impairment of dendritic inhibition might directly drive ictogenesis [36]. Furthermore, the loss of O–LM cells should have direct implications in the generation of theta-frequency oscillations in the hippocampus [31]. Finally, an additional feature to consider is the loss of tetrodotoxin-independent miniature GABA currents in epileptic hippocampus [72], suggesting a deficiency in GABA release mechanisms in epilepsies.

### *When the GABA-mediated transmission is enhanced*

Several studies report that epilepsy can be associated with a paradoxical increase in GABA-mediated transmission. In different models of epilepsy, potentiation of the GABAergic synapses onto dentate granule cells has been reported [45,47,73] and linked to upregulation in the number of synaptic $GABA_A$ receptors in the kindling model [47,73]. Likewise, as mentioned in the previous paragraph, CA1 perisomatic GABAergic interneurons discharge at a higher frequency in the pilocarpine model of TLE than do their dendritic equivalents [34]. This results in enhancement of the GABAergic input to CA1 principal cell somata. Such changes in GABAergic function can be viewed either as possible compensatory changes or, if associated with an excitation shift of the postsynaptic effect of $GABA_A$-receptor activation (see the section 'When $Cl^-$ accumulates and GABA depolarizes neurons'), as direct sources for network hyperexcitability [12,74].

## Discussion

The take-home message is the inadequacy of 'inhibition' to describe GABA-mediated neurotransmission in general. The concept is too volatile to base epilepsy research on the hypothesis that GABA-mediated inhibition is decreased. The multiple facets of GABA mechanisms that act on neuronal excitability, network-driven activity, generation of patterns and oscillations, and inhibition of excitatory

**Box 1. GABAergic inhibition is neither dormant nor hyperactive!**

Several unifying hypotheses on the fate of inhibition have been proposed. Perhaps the most influential was that seizures are generated because basket cells, which exert a major role on principal cells excitability [23], are dormant [78,79]. This hypothesis was proposed to account for the *in vivo* observations that after intense perforant path stimulation, paired pulse inhibition (PPI) appeared decreased in the CA1 region upon activation of fibers ipsilateral to the stimulated side, but that PPI was present upon activation of fibers contralateral to the stimulated side. The central idea is that 'despite malfunction, inhibitory systems remain intact in "epileptic" tissue and are capable of functioning if appropriately activated' [79]. However, the mechanisms underlying PPI are unknown and the causal relationship between the loss of PPI in epileptic tissue and a decrease in inhibitory function has not been established [78]. Furthermore, if dentate gyrus basket cells are partially de-afferented following the loss of mossy cells (reactive synaptogenesis was not tested) [62], their loss results in a decrease of dentate granule cell excitability [80], not in an increase as implied by the hypothesis. Perhaps most importantly, GABAergic synapses are operative in epilepsies [81] and their activation is even needed for the generation of epileptic activity [5,6] (Khalilov *et al.*, personal communication).

In a more recent development, Sloviter proposed an opposite hypothesis: inhibition in the epileptic network is now suggested to be so efficient that seizures do not propagate to the hippocampus – a sort of hyperactive inhibition [82]. Surprisingly, this suggestion is in complete disagreement with the large list of studies showing that the hippocampus is the trigger zone for major epileptic attacks in patients as well as in animal models. Clearly, more subtle changes occur in inhibition than a complete loss, or massive gain, of function of GABA-mediated transmission.

Modern research on interneurons points to a set of behaviours that are brain-state-dependent and context-dependent [23,25], rather than to a single specific behavior. The behavior of basket cells is indeed modified in epileptic tissue as they become hyperexcitable [81,83] and receive an increased excitatory drive *in vitro* [34]. Finally, it must be recalled that, because GABA-mediated neurotransmission can be excitatory in control [3,4] and in epileptic tissue [5,6], 'hypofunctionality' of a GABAergic pathway could in reality decrease the global excitability of the network.

inputs, but that also contribute to generation of action potentials in certain conditions, cannot follow a single decremental curve during seizures (Box 1). In fact, presently available observations already suggest that some of these features are increased or even reversed and that this step is instrumental in the generation of seizures. Present interest has moved towards gaining a better understanding of the mechanisms that underlie the inhibitory-to-excitatory shift of GABA actions and, in a more general perspective, the function of this device that enables GABA to change the direction of $Cl^-$ fluxes. What are the dynamics of $Cl^-$ movements? Do these dynamics signal the recent history of the neuron in terms of its activity? And how does that alter the generation of network events? Why does the post-epileptic network seem to return to an immature one, and how is that related to the well-established unique susceptibility of developing networks to generate seizures? Undoubtedly, combined studies, on the multiple facets of GABAergic synapses and interneurons during development and during episodes of hyperactivity, are warranted. They will considerably improve our understanding of the relationship between activity and brain operation in health and disease.


**References**

1 Kaila, K. (1994) Ionic basis of $GABA_A$ receptor channel function in the nervous system. *Prog. Neurobiol.* 42, 489–537
2 Ben Ari, Y. (2002) Excitatory actions of GABA during development: the nature of the nurture. *Nat. Rev. Neurosci.* 3, 728–739
3 Chavas, J. and Marty, A. (2003) Coexistence of excitatory and inhibitory GABA synapses in the cerebellar interneuron network. *J. Neurosci.* 23, 2019–2031
4 Gulledge, A.T. and Stuart, G.J. (2003) Excitatory actions of GABA in the cortex. *Neuron* 37, 299–309
5 Cohen, I. *et al.* (2002) On the origin of interictal activity in human temporal lobe epilepsy *in vitro*. *Science* 298, 1418–1421
6 Khalilov, I. *et al.* (2003) *In vitro* formation of a secondary epileptogenic mirror focus by interhippocampal propagation of seizures. *Nat. Neurosci.* 6, 1079–1085
7 Staley, K.J. *et al.* (1995) Ionic mechanisms of neuronal excitation by inhibitory $GABA_A$ receptors. *Nature*, 977–981
8 Liu, G. (2004) Local structural balance and functional interaction of excitatory and inhibitory synapses in hippocampal dendrites. *Nat. Neurosci.* 7, 373–379
9 Chen, W.R. *et al.* (1997) Forward and backward propagation of dendritic impulses and their synaptic control in mitral cells. *Science* 278, 463–467
10 Mitchell, S.J. and Silver, R.A. (2003) Shunting inhibition modulates neuronal gain during synaptic excitation. *Neuron* 38, 433–445
11 Pare, D. *et al.* (1998) Inhibitory control of somatodendritic interactions underlying action potentials in neocortical pyramidal neurons *in vivo*: an intracellular and computational study. *Neuroscience* 84, 377–402
12 Chen, K. *et al.* (2001) Persistently modified h-channels after complex febrile seizures convert the seizure-induced enhancement of inhibition to hyperexcitability. *Nat. Med.* 7, 331–337
13 Johnston, D. *et al.* (2003) Active dendrites, potassium channels and synaptic plasticity. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 358, 667–674
14 Steriade, M. (2004) Neocortical cell classes are flexible entities. *Nat. Rev. Neurosci.* 5, 121–134
15 Aradi, I. and Soltesz, I. (2002) Modulation of network behaviour by changes in variance in interneuronal properties. *J. Physiol.* 538, 227–251
16 Maccaferri, G. and Lacaille, J.C. (2003) *Interneuron Diversity series*: Hippocampal interneuron classifications–making things as simple as possible, not simpler. *Trends Neurosci.* 26, 564–571
17 McBain, C.J. and Fisahn, A. (2001) Interneurons unbound. *Nat. Rev. Neurosci.* 2, 11–23
18 Jonas, P. *et al.* (2004) *Interneuron Diversity series*: Fast in, fast out – temporal and spatial signal processing in hippocampal interneurons. *Trends Neurosci.* 27, 30–40
19 Pouille, F. and Scanziani, M. (2001) Enforcement of temporal fidelity in pyramidal cells by somatic feed-forward inhibition. *Science* 293, 1159–1163
20 Cohen, I. and Miles, R. (2000) Contributions of intrinsic and synaptic activities to the generation of neuronal discharges in *in vitro* hippocampus. *J. Physiol.* 524, 485–502
21 Freund, T.F. and Buzsáki, G. (1996) Interneurons of the hippocampus. *Hippocampus* 6, 347–470
22 Hoffman, D.A. *et al.* (1997) $K^+$ channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. *Nature* 387, 869–875
23 Miles, R. *et al.* (1996) Differences between somatic and dendritic inhibition in the hippocampus. *Neuron* 16, 815–823
24 Cobb, S.R. *et al.* (1995) Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature* 378, 75–78
25 Klausberger, T. *et al.* (2003) Brain-state- and cell-type-specific firing of hippocampal interneurons *in vivo*. *Nature* 421, 844–848
26 Whittington, M.A. *et al.* (1997) Spatiotemporal patterns of gamma frequency oscillations tetanically induced in the rat hippocampal slice. *J. Physiol.* 502, 591–607
27 Buzsaki, G. *et al.* (2004) *Interneuron Diversity series*: Circuit complexity and axon wiring economy of cortical interneurons. *Trends Neurosci.* 27, 186–193
28 Nelson, S. (2002) Cortical microcircuits: diverse or canonical? *Neuron* 36, 19–27

29 Csicsvari, J. *et al*. (2003) Mechanisms of gamma oscillations in the hippocampus of the behaving rat. *Neuron* 37, 311–322
30 Penttonen, M. *et al*. (1998) Gamma frequency oscillation in the hippocampus of the rat: intracellular analysis *in vivo*. *Eur. J. Neurosci.* 10, 718–728
31 Buzsaki, G. (2002) Theta oscillations in the hippocampus. *Neuron* 33, 325–340
32 Pouille, F. and Scanziani, M. (2004) Routing of spike series by dynamic circuits in the hippocampus. *Nature* 429, 717–723
33 Klausberger, T. *et al*. (2004) Spike timing of dendrite-targeting bistratified cells during hippocampal network oscillations *in vivo*. *Nat. Neurosci.* 7, 41–47
34 Cossart, R. *et al*. (2001) Dendritic but not somatic GABAergic inhibition is decreased in experimental epilepsy. *Nat. Neurosci.* 4, 52–62
35 Gulyas, A.I. *et al*. (2003) Interneurons are the local targets of hippocampal inhibitory cells which project to the medial septum. *Eur. J. Neurosci.* 17, 1861–1872
36 Wendling, F. *et al*. (2002) Epileptic fast activity can be explained by a model of impaired GABAergic dendritic inhibition. *Eur. J. Neurosci.* 15, 1499–1508
37 Traub, R.D. *et al*. (1996) Analysis of gamma rhythms in the rat hippocampus *in vitro* and *in vivo*. *J. Physiol.* 493, 471–484
38 Wang, X.J. and Buzsaki, G. (1996) Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *J. Neurosci.* 16, 6402–6413
39 Isokawa, M. (1996) Decrement of $GABA_A$ receptor-mediated inhibitory postsynaptic currents in dentate granule cells in epileptic hippocampus. *J. Neurophysiol.* 75, 1901–1908
40 Shumate, M.D. *et al*. (1998) $GABA_A$ receptor function in epileptic human dentate granule cells: comparison to epileptic and control rat. *Epilepsy Res.* 32, 114–128
41 Loup, F. *et al*. (2000) Selective alterations in $GABA_A$ receptor subtypes in human temporal lobe epilepsy. *J. Neurosci.* 20, 5401–5419
42 Koepp, M.J. *et al*. (1996) Cerebral benzodiazepine receptors in hippocampal sclerosis. An objective *in vivo* analysis. *Brain* 119, 1677–1687
43 Bouilleret, V. *et al*. (2000) Early loss of interneurons and delayed subunit-specific changes in $GABA_A$-receptor expression in a mouse model of medial temporal lobe epilepsy. *Hippocampus* 10, 305–324
44 Fritschy, J.M. *et al*. (1999) GABAergic neurons and $GABA_A$ receptors in temporal lobe epilepsy. *Neurochem. Int.* 34, 435–445
45 Gibbs, J.W. *et al*. (1997) Differential epilepsy-associated alterations in postsynaptic $GABA_A$ receptor function in dentate granule cells and CA1 neurons. *J. Neurophysiol.* 77, 1924–1938
46 Schwarzer, C. *et al*. (1997) $GABA_A$ receptor subunits in the rat hippocampus II: altered distribution in kainic acid-induced temporal lobe epilepsy. *Neuroscience* 80, 1001–1017
47 Nusser, Z. *et al*. (1998) Increased number of synaptic $GABA_A$ receptors underlies potentiation at hippocampal inhibitory synapses. *Nature* 395, 172–177
48 Brooks-Kayal, A.R. *et al*. (1998) Selective changes in single cell $GABA_A$ receptor subunit expression and function in temporal lobe epilepsy. *Nat. Med.* 4, 1166–1172
49 Buhl, E. *et al*. (1996) Zinc-induced collapse of augmented inhibition by GABA in a temporal lobe epilepsy model. *Science* 271, 369–373
50 Mody, I. (2001) Distinguishing between $GABA_A$ receptors responsible for tonic and phasic conductances. *Neurochem. Res.* 26, 907–913
51 Semyanov, A. *et al*. (2004) Tonically active $GABA_A$ receptors: modulating gain and maintaining the tone. *Trends Neurosci.* 27, 262–269
52 McIntyre, D.C. *et al*. (2002) Divergent $GABA_A$ receptor-mediated synaptic transmission in genetically seizure-prone and seizure-resistant rats. *J. Neurosci.* 22, 9922–9931
53 Poulter, M.O. *et al*. (1999) Differential expression of $\alpha1$, $\alpha2$, $\alpha3$, and $\alpha5$ $GABA_A$ receptor subunits in seizure-prone and seizure-resistant rat models of temporal lobe epilepsy. *J. Neurosci.* 19, 4654–4661
54 Palma, E. *et al*. (2004) Phosphatase inhibitors remove the run-down of gamma-aminobutyric acid type A receptors in the human epileptic brain. *Proc. Natl. Acad. Sci. U. S. A.* 101, 10183–10188
55 Ben Ari, Y. *et al*. (1980) Lability of synaptic inhibition of hippocampal pyramidal cells. *J. Physiol.* 298, 36P–37P
56 Rivera, C. *et al*. (1999) The $K^+/Cl^-$ co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. *Nature* 397, 251–255
57 Ben-Ari, Y. and Gho, M. (1988) Long-lasting modification of the synaptic properties of rat CA3 hippocampal neurones induced by kainic acid. *J. Physiol.* 404, 365–384
58 Buckmaster, P.S. and Jongen-Relo, A.L. (1999) Highly specific neuron loss preserves lateral inhibitory circuits in the dentate gyrus of kainate-induced epileptic rats. *J. Neurosci.* 19, 9519–9529
59 DeLanerolle, N. *et al*. (1989) Hippocampal interneuron loss and plasticity in human temporal lobe epilepsy. *Brain Res.* 495, 387–395
60 Dinocourt, C. *et al*. (2003) Loss of interneurons innervating pyramidal cell dendrites and axon initial segments in the CA1 region of the hippocampus following pilocarpine-induced seizures. *J. Comp. Neurol.* 459, 407–425
61 Kobayashi, M. and Buckmaster, P.S. (2003) Reduced inhibition of dentate granule cells in a model of temporal lobe epilepsy. *J. Neurosci.* 23, 2440–2452
62 Wittner, L. *et al*. (2001) Preservation of perisomatic inhibitory input of granule cells in the epileptic human dentate gyrus. *Neuroscience* 108, 587–600
63 Sloviter, R.S. *et al*. (2003) 'Dormant basket cell' hypothesis revisited: relative vulnerabilities of dentate gyrus mossy cells and inhibitory interneurons after hippocampal status epilepticus in the rat. *J. Comp. Neurol.* 459, 44–76
64 DeFelipe, J. (1999) Chandelier cells and epilepsy. *Brain* 122, 1807–1822
65 Sayin, U. *et al*. (2003) Spontaneous seizures and loss of axo-axonic and axo-somatic inhibition induced by repeated brief seizures in kindled rats. *J. Neurosci.* 23, 2759–2768
66 van Vliet, E.A. *et al*. (2004) Progression of temporal lobe epilepsy in the rat is associated with immunocytochemical changes in inhibitory interneurons in specific regions of the hippocampal formation. *Exp. Neurol.* 187, 367–379
67 de Lanerolle, N.C. *et al*. (1989) Hippocampal interneuron loss and plasticity in human temporal lobe epilepsy. *Brain Res.* 495, 387–395
68 Arellano, J.I. *et al*. (2004) Histopathology and reorganization of chandelier cells in the human epileptic sclerotic hippocampus. *Brain* 127, 45–64
69 Blasco-Ibanez, J.M. and Freund, T.F. (1995) Synaptic input of horizontal interneurons in stratum oriens of the hippocampal CA1 subfield: structural basis of feed-back activation. *Eur. J. Neurosci.* 7, 2170–2180
70 Cossart, R. *et al*. (2002) Quantal release of glutamate generates pure kainate and mixed AMPA/kainate EPSCs in hippocampal neurons. *Neuron* 35, 147–159
71 Goldberg, J.H. *et al*. (2003) $Ca^{2+}$ imaging of mouse neocortical interneurone dendrites: contribution of $Ca^{2+}$-permeable AMPA and NMDA receptors to subthreshold $Ca^{2+}$ dynamics. *J. Physiol.* 551, 67–78
72 Hirsch, J.C. *et al*. (1999) Deficit of quantal release of GABA in experimental temporal lobe epilepsy. *Nat. Neurosci.* 2, 499–500
73 Otis, T.S. *et al*. (1994) Lasting potentiation of inhibition is associated with an increased number of gamma-aminobutyric acid type A receptors activated during miniature inhibitory postsynaptic currents. *Proc. Natl. Acad. Sci. U. S. A.* 91, 7698–7702
74 Chen, K. *et al*. (1999) Febrile seizures in the developing brain result in persistent modification of neuronal excitability in limbic circuits. *Nat. Med.* 5, 888–894
75 Hammond, C. (2001) *Cellular and Molecular Neurobiology*, Academic Press
76 Chadderton, P. *et al*. (2004) Integration of quanta in cerebellar granule cells during sensory processing. *Nature* 428, 856–860
77 Buckmaster, P.S. and Dudek, F.E. (1997) Neuron loss, granule cell axon reorganization, and functional changes in the dentate gyrus of epileptic kainate-treated rats. *J. Comp. Neurol.* 385, 385–404
78 Bernard, C. *et al*. (1998) Interneurones are not so dormant in temporal lobe epilepsy: a critical reappraisal of the dormant basket cell hypothesis. *Epilepsy Res.* 32, 93–103
79 Sloviter, R.S. (1991) Permanently altered hippocampal structure, excitability, and inhibition after experimental status epilepticus in the rat: the 'dormant basket cell' hypothesis and its relevance to temporal lobe epilepsy. *Hippocampus* 1, 41–66

80 Ratzliff, A.H. *et al*. (2004) Rapid deletion of mossy cells does not result in a hyperexcitable dentate gyrus: implications for epileptogenesis. *J. Neurosci.* 24, 2259–2269
81 Esclapez, M. *et al*. (1997) Operative GABAergic inhibition in hippocampal CA1 pyramidal neurons in experimental epilepsy. *Proc. Natl. Acad. Sci. U. S. A.* 94, 12151–12156
82 Harvey, B.D. and Sloviter, R. (2003) Dentate granule cell quiescence and inhibitory interneuron activation during spontaneous seizures in awake, chronically epileptic, pilocarpine-treated. In *2003 Abstract Viewer and Itinerary Planner*, Program 303.5., Society for Neuroscience Online
83 Rempe, D.A. *et al*. (1997) Interneurons in area CA1 stratum radiatum and stratum oriens remain functionally connected to excitatory synaptic input in chronically epileptic animals. *J. Neurophysiol.* 78, 1504–1515