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Alterations in synaptic function in epilepsy

Christophe Bernard[1]

Temporal Lobe Epilepsy (TLE) is often triggered by a brain insult (meningitis, brain trauma, etc.). The insult induces network modifications during epileptogenesis (the process leading to epilepsy), and when seizures are recurrent. Since these modifications are extremely diverse, it is essential to determine their causal relationship with respect to the construction of epileptic networks. These issues have been addressed in animal models of TLE. In this chapter we present the state of our current knowledge regarding the time-dependent reorganizations of GABAergic and glutamatergic circuits - at the synaptic level - during epileptogenesis. We will discuss the possible functional consequences of these alterations. We will focus particularly on the fate of GABAergic circuits. Does the loss of interneurons many days before the first occurrence of a spontaneous seizure suggest that decreased inhibition is not pro-epileptic per se? We will discuss the role of interneuron loss in the construction of epileptic circuits. Synaptic reorganizations at GABAergic and glutamatergic synapses not only enable seizure occurrence, they also modify the normal information processing performed by these networks. We will also discuss how modifications in GABAergic and glutamatergic circuits can negatively impact cognitive functions. Strategies have been designed to prevent these reorganizations or to repair the circuitry; their efficiency is discussed.

Epilepsy is characterized by the occurrence of seizures and by the presence of co-morbidities, e.g. cognitive deficits. Their underlying mechanisms remain unknown. Since seizures and cognition usually involve large networks of networks of millions of neurons, it is difficult to formulate working hypotheses regarding potential mechanisms. The activity of these networks is controlled by numerous parameters. Hence, why should a given parameter (or a set of parameters) be considered to play a more important role than any other? Further, some parameter changes may be crucial for epilepsy, while others may be central for the associated co-morbidities. Which parameters are common to both issues, and which ones are specific to the various aspects of epilepsy? Since we do not have a comprehensive understanding of how the brain works, it is very difficult to generate a sound hypothesis-driven research strategy to uncover the mechanisms of epileptogenesis. Our strategy must rely simply upon correlations and comparisons with "normal" circuits. Since one major locus for the transfer of information/activity is the synapse, it seems reasonable to propose that synaptic modifications may be involved in epilepsy and associated co-morbidities.

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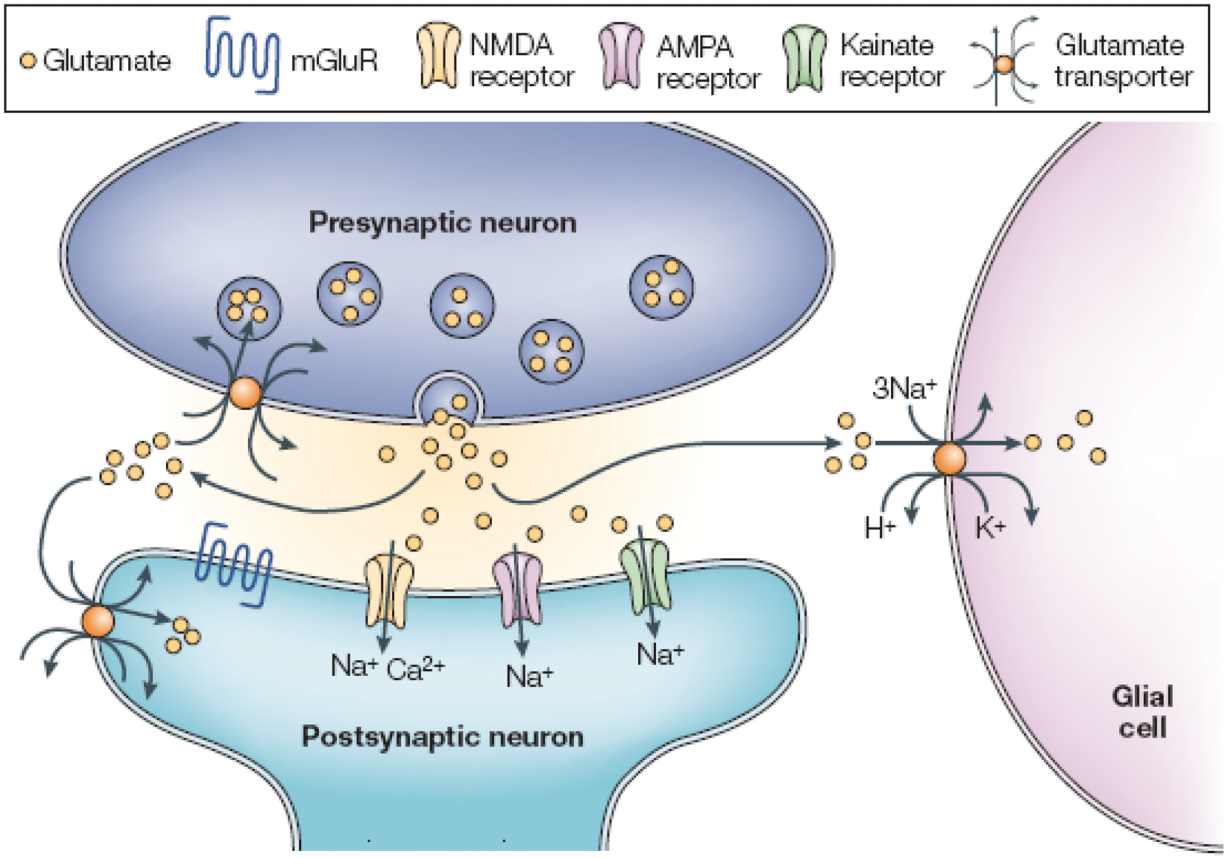

Figure 1. Schematic drawing of a glutamatergic synapse, with postsynaptic AMPA, NMDA, KA and metabotropic receptors. Glutamate transporters are present on the presynaptic and postsynaptic sites, as well as on the nearby glial cell process (from Attwell and Gibb, Nature Reviews Neuroscience, 2005).

What do we mean by the phrase "synaptic modifications"? A synapse involves three compartments: the presynaptic terminal, the postsynaptic site, and the glial cell processes surrounding them. The extrasynaptic space will not be considered, although it is known to play a central role in controlling synaptic transmission. A simplified scheme of the transfer of information between two neurons involves the release of neurotransmitters by a presynaptic terminal, the activation of postsynaptic receptors, and the uptake of the neurotransmitters (Figure 1). Many features of the synapse can be modified. The number of synapses established by a given neuron on its targets can decrease ("pruning, " or death of the presynaptic neuron) or increase (sprouting, neosynaptogenesis). The properties of the presynaptic terminal can be changed (release probability, neurotransmitter concentration in vesicles, control by presynaptic receptors). On the postsynaptic site, the number, subunit composition, and function (e.g., phosphorylation, anchoring) of the receptors can be changed. Finally, alterations at the glial cell level may affect the environment of the synapse and its function (neurotransmitter uptake, energy supply to neurons, etc.).

How do alterations in synaptic function relate to seizures and their co-morbidities? This question has been particularly difficult to address since epilepsy is often a time-dependent disorder, involving (for example) an initial insult (which may involve genetic alterations, meningitis, brain trauma etc.) and the subsequent trigger of a number of network modifications. Ultimately, some of these modifications may be directly linked to seizure generation and/or co-morbidities. It is therefore important to understand the time-course of these changes. This issue has been extensively investigated in experimental models of temporal lobe epilepsy, which are characterized by a latent, seizure-free period, of about two weeks, following the initial insult (usually a period of

status epilepticus). We will use these models to describe synaptic remodeling and its possible functional consequences in the adult brain, focusing on the hippocampus.

PRESYNAPTIC MODIFICATIONS

Neurons receive information from different sources; information from other neurons is generally transmitted at the level of the synapse. The transfer of information starts with the release of neurotransmitter from the presynaptic terminal. The transfer of information ends with the transformation of this chemical signal into an electro-chemical one (the flux of ions via the opening of ionotropic receptors and/or the activation of second messengers via metabotropic receptors).

There are multiple ways to change the transfer of information at the presynaptic level between two neurons. These changes can involve the disappearance of the presynaptic terminals themselves, a modification of the neurotransmitter content in the vesicles, and an alteration in control of the release machinery. Several of these modifications have been described in epilepsy. They are presented below, starting with the most drastic one, the loss of the presynaptic terminals.

Cell Death

The loss of the presynaptic terminal can result from the death of the source neuron. Early work demonstrated the rapid loss of glutamatergic synapses on CA1 pyramidal cells due to the death of CA3 pyramidal cells following kainic acid injection in adult animals. [1–3] Similarly, GABAergic synapses disappear due to the death of interneurons soon after status epilepticus. [4–6] Interestingly, interneuron loss is cell-type specific and an early event. For example, it affects axo-axonic cells and O-LM interneurons, which project to initial segment and the distal part of the dendritic tree of pyramidal cells, respectively (Figure 2). [5, 6]

How does neuron loss affect the network/system? Certainly, neuronal death should change the way these networks process information. For example, the loss of O-LM interneurons is associated with a decreased GABAergic drive in the distal dendrites of CA1 pyramidal cells, and with a large facilitation of entorhinal inputs (which O-LM cells "control" under normal conditions) [6] This reorganization occurs soon after the initial status epilepticus, during the latent period, days before the first spontaneous seizure. [7] Clearly, such a loss of neurons and synapses is not sufficient, in itself, to facilitate/trigger seizures. Using a theoretical approach, we have proposed that the decreased GABAergic drive provides sufficient conditions for the emergence of interictal activity, [7] which appears soon after the status epilepticus and which is predictive of epileptogenesis. [7–10] We have also proposed that this reorganization would be causally linked to the degradation of theta rhythm and spatial memory found soon after status epilepticus in these models. [11]

Another example is provided by the loss of cholecystokinin (CCK) basket cells. [12] Basket cells target the soma and proximal dendrites of CA1 pyramidal cells. Two major classes of basket cells can be distinguished based on their neurochemical content: CCK and parvalbumin (PV). [13] CCK basket cells appear to degenerate soon after status epilepticus, [12] further supporting the idea that the loss of GABAergic cells is not sufficient to trigger seizures. CCK basket cells carry type1 cannabinoid (CB1) receptors on their presynaptic terminals. [14] The activation of CB1 receptors decreases the release of neurotransmitter, in particular GABA from CCK basket cells. [14] The functional consequence of the loss of such a regulatory pathway remains to be investigated. One might hypothesize that the disappearance of CCK basket cells would increase the functional weight of PV basket cells. Since the latter appear to play a key role in synchronizing large sets of neurons to produce oscillations, an increased PV basket cell contribution may increase the ability of the network to synchronize in a pathological manner. [12, 13] It is important to note that the number of CB1 containing GABAergic terminals is not modified in the dentate gyrus from epileptic patients [15] and so it is unclear if this subpopulation of GABAergic neurons is selectively lost in human brain. A change in CCK/PV basket cell ratio may be species- and/or brain region-dependent.

Finally, the loss of interneurons does not only affect GABAergic cells that target principal cells, but also calretinin GABAergic interneurons that contact other interneurons. [16] Such reorganization would remove an inhibitory drive onto interneurons, which may in turn contribute to their hyperexcitability in epileptic animals. [6] Since calretinin interneurons may play a central role in synchronizing large ensembles of interneurons, their loss may hamper the capacities of the networks to generate/propagate physiological oscillations [16] – which may help explain the observed decrease in theta rhythm and associated cognitive deficits in epilepsy. [11] Whether the loss of calretinin interneurons increases synchronization associated with seizures remain to be investigated.

This functional scheme, as intuitively simple as it seems, is based upon what we think we know about brain function. It is in fact simplistic. Losing GABAergic function is generally considered to be "bad" for the system. But is it? Mutations in the α7 and β2 neuronal nicotinic acetylcholine receptor subunit genes result in epilepsy (i.e. GEFS+). Yet, mouse models of such mutations are characterized by *increased* GABAergic activity, and spontaneous seizures are abolished by the injection of low doses of the $GABA_A$ receptor antagonist picrotoxin. [17] Similarly, we know that the activation of GABAergic axo-axonic cells can directly excite their targets; GABA has an excitatory action in the initial segment due to the low level of expression of the KCC2 transporter at this site. [18] It could therefore be argued that losing axo-axonic synapses in epilepsy [5, 19] would in fact be protective, by removing a powerful excitatory and synchronization mechanism. These two examples clearly show that it is very difficult to interpret the observations made in a pathological tissue, if only because we lack a conceptual framework in that accounts for the various physiological components of the system.

The loss of neurons can be seen as a drastic modification of the architecture of the network. However, new synapses can be generated, perhaps as a direct consequence of the loss of neurons.

Neosynaptogenesis

Axonal sprouting of glutamatergic neurons has been identified in all hippocampal subfields, including dentate gyrus (mossy fibers), Schaffer collaterals, and CA1 pyramidal cell collaterals. [1, 2, 20–23] In the CA1 region, the sprouting of CA1 pyramidal cell axon can clearly be identified during the chronic period (i.e. when animals have spontaneous seizures), [22, 23] although its time-course after the initial insult remains to be established. Interestingly, in the chronically epileptic animal, CA1 axon collaterals innervate the stratum radiatum (Figure 3) (a region rarely contacted by CA1 collaterals in normal control animals [23]) and extend further into the subiculum. [24]

The targeting of new regions has also been established for mossy fibers [25]. This collateralization of this system appears to depend upon the activation of a serine/threonine kinase (mTOR) that controls protein synthesis linked to cell growth. [26, 27] Sprouting is associated with the formation of new synapses [1, 2, 21, 25] which appear to be functional. [23, 28] The functional consequence of this neosynaptogenesis include increased connectivity between principal cells and increased glutamatergic drive. [23, 28] Although glutamatergic neosynaptogenesis onto GABAergic cells remains to be established, indirect evidence based upon the measure of the frequency of glutamatergic currents received by the surviving interneurons suggests that the sprouting of excitatory axons also targets interneurons. [6] Early work on the Schaffer collateral pathway led to the hypothesis that the loss of synapses due to presynaptic neuronal death would trigger sprouting and reactive synaptogenesis. [1, 2] Whether the death of interneurons following the initial insult also triggers a similar mechanism remains to be clearly established. If it does, it does not fully compensate for the initial loss, since the number of GABAergic synapses on principal cells remains decreased in epileptic animals as compared to controls. [5] However, a class of GABAergic cells located in the hilus, and containing somatostatin, displays axonal sprouting and establishes more synaptic contacts with granule cells in epileptic animals. [29] It has been argued that such sprouting may act as a mechanism to compensate for some of the GABAergic neurotransmission that is lost after the death of vulnerable populations of GABAergic interneurons. [29] It will be important to determine the time course of this sprouting after the initial insult in order to relate it to epileptogenesis.

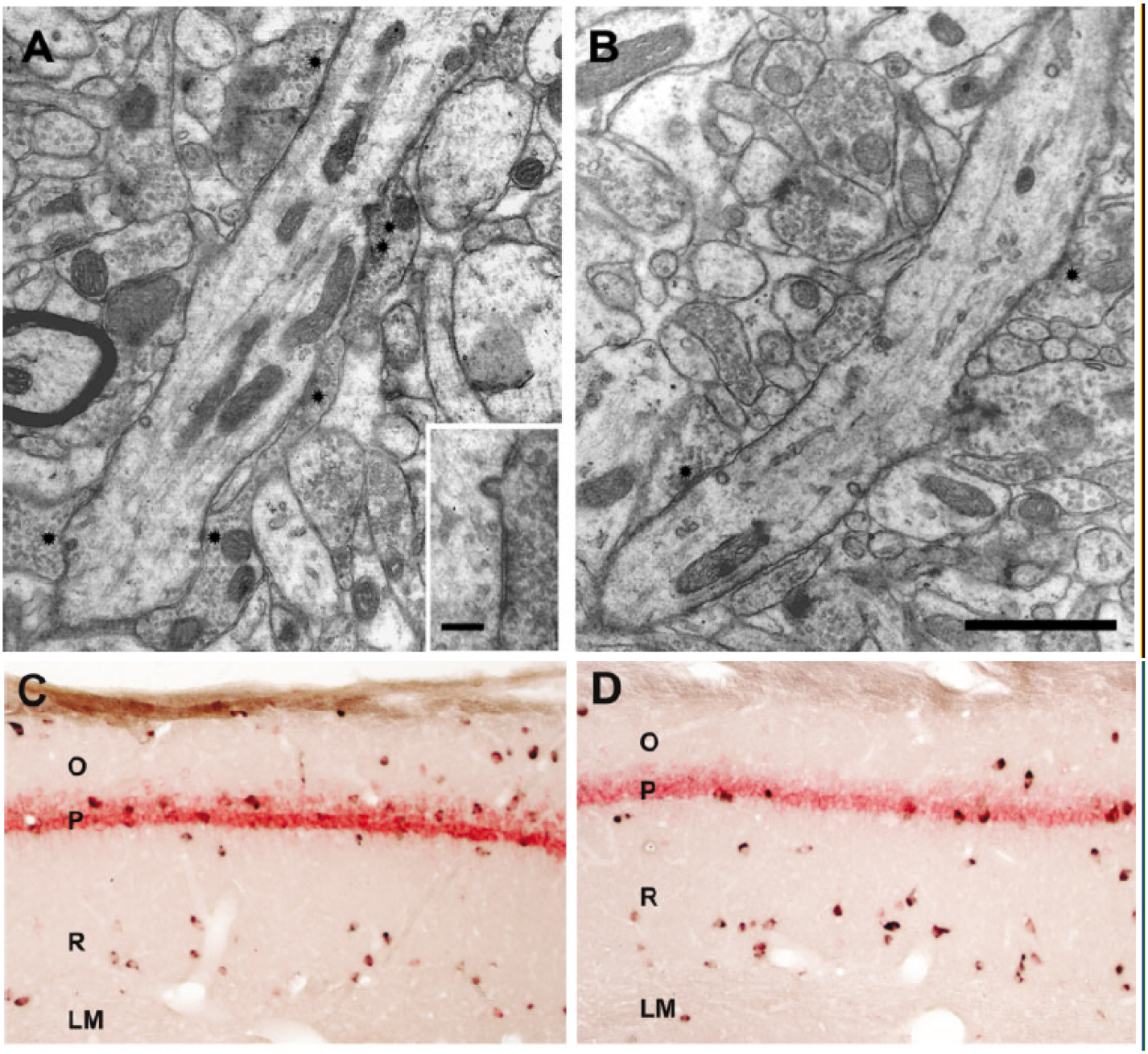

Figure 2. Loss of GABAergic synapses. Photomicrograph showing the loss of coverage by symmetrical (GABAergic) synapses (*) of the initial segment of the axon of CA1 pyramidal cells in pilocarpine-treated rats (B) as compared to control (A). Scale bar, 0.5 μm. (C) In a control animal, many NeuN- (red) and GAD65 mRNA- (dark) containing neurons can be seen in CA1 stratum oriens (O). Many of these neurons are lost in pilocarpine-treated animals (D). They include O-LM interneurons. Adapted from Dinocourt et al. J Comp Neurol 2003.

Available information indicates that sprouting of glutamatergic and GABAergic fibers is not an early event. It is tempting to propose that it is causally related to the occurrence of seizures, i.e. that increased connectivity is necessary for seizure genesis and propagation. According to this hypothesis, sprouting in the dentate gyrus would create hub cells, which could favor seizure genesis. [30, 31] At present, we can only propose a correlation, not causality.

In addition to a morphological reorganization (loss of terminals and neosynaptogenesis), presynaptic terminals function is modified in epileptic tissue.

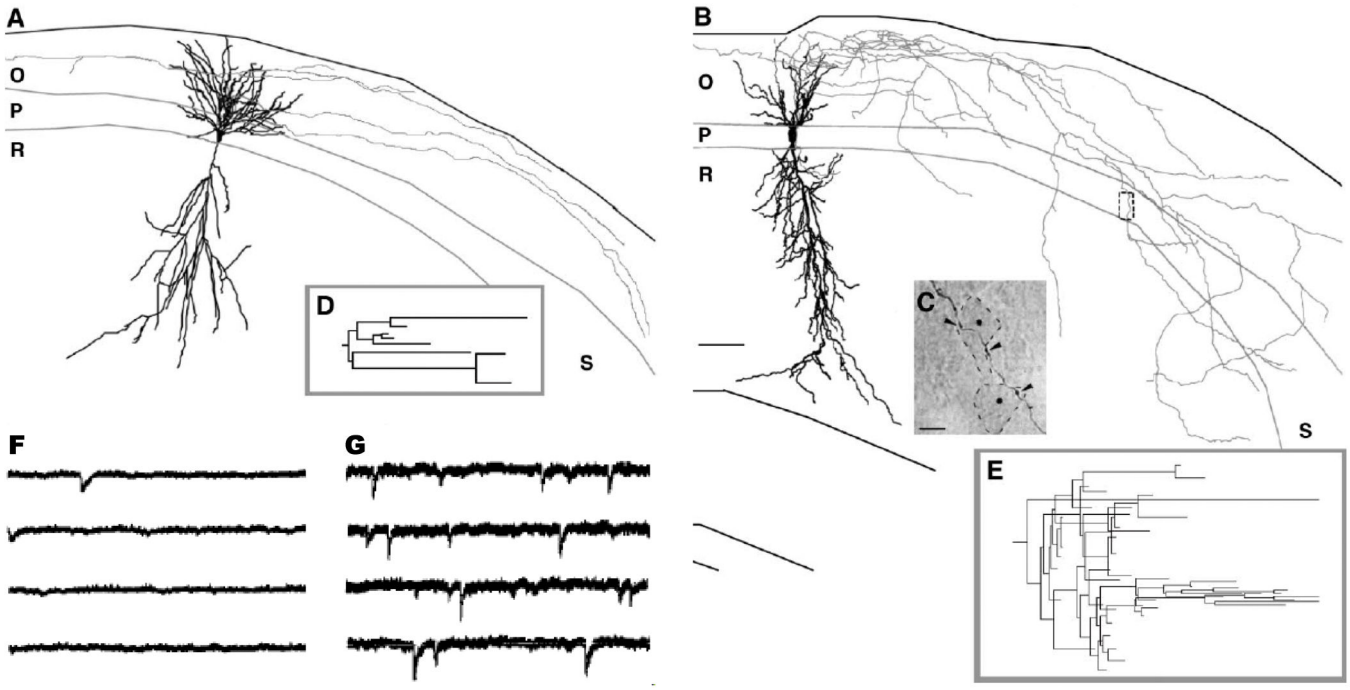

Figure 3. Sprouting of CA1 pyramidal cell axon in epileptic animals and increased glutamatergic activity received by pyramidal cells. (A) Tridimensional reconstruction of a CA1 pyramidal cell in a control animal. Note that the axon (light grey) emits few branches in stratum oriens (O), as shown on the axogram (D panel). (B) Tridimensional reconstruction of a CA1 pyramidal cell in an epileptic animal. Note that the axon (light grey) displays profuse branching, as shown on the axogram (E panel). Axonal branches cross the pyramidal cell layer (P)(C panel) and enter stratum radiatum (R), which rarely occurs in control animals. (F) Patch clamp recording of the control cell. The downward deflections represent spontaneous AMPA receptor-mediated currents. These glutamatergic events are rare. In contrast, in an epileptic animal, the frequency of these events is considerably increased, as a consequence of sprouting (G). Adapted from Esclapez et al., J Comp Neurol, 1999.

Presynaptic terminal

One key function of presynaptic terminals is the release of neurotransmitter, a process that involves a complex machinery regulated by numerous proteins, including presynaptic receptors. There are numerous ways to affect neurotransmitter release, many of which could play a role in epileptogenesis and seizure genesis/propagation. The end product of such modifications is the modulation of amount of neurotransmitter that is released. The filling of vesicles can be dynamically modulated. For example, the filling of glutamate vesicles requires an allosteric activation by Cl^{-}.[32] Ketone bodies compete with Cl^{-} for this allosteric activation and reduce glutamate content in the vesicle, which may contribute to the anti-epileptic affect of the ketogenic diet. [32] The filling of GABAergic vesicles can also be modulated. Reactive astrocytosis induces a downregulation of glutamine synthetase, which results in decreased GABA synthesis and GABA content in synaptic vesicles (cf. the glial section below in this chapter). [33] Inflammation, reactive astrocytosis and decreased glutamine synthetase activity occur soon after the initial insult, and are maintained during epileptogenesis. [34, 35] These changes should result in decreased GABA content in vesicles. Since there is currently no direct way to measure precisely neurotransmitter content in vesicles, one must rely on the amplitude distribution of miniature inhibitory postsynaptic currents (mIPSCs) for an indication. In CA1 pyramidal cells, the amplitude of mIPSCs is decreased in epileptic animals, lending support to this hypothesis. [36] In contrast, the amplitude of mIPSCs is increased in dentate granule cells [37] (but see [38]). Since the amplitude of mIPSC depends upon many factors (including the subunit composition, the number of receptors, their phosphorylation state, etc), it is difficult to draw strong conclusions regarding synaptic filling based on mIPSC analysis (it only provides indirect arguments).

In addition to altered vesicle filling, defects in neurotransmitter release may alter synaptic transmission. A decrease in the reserve pool of GABA-containing vesicles in presynaptic terminals contacting CA1 pyramidal cells may explain a decreased in mIPSC frequency, [36] since miniature events appear to reflect release of the reserve pool rather than release from the immediate releasable pool, at least in glutamatergic terminals. [39] Paired recordings between basket cells and dentate granule cells revealed a decreased probability of release despite a larger size of the immediate releasable pool. [40] Changes in the release machinery (e.g., in presynaptic Ca^{2+} channels) or a different tonic control by presynaptic receptors (e.g., by $GABA_B$, mGluRs, CB1 etc.) may explain these modifications.

For example, there is a downregulation of CB1 receptors and of the endocannabinoid machinery in human epileptic tissue. [41] Interestingly, CB1 downregulation affects glutamatergic, but not GABAergic terminals, which would remove an important regulatory component of glutamate (excitatory neurotransmitter) release, and act as a pro-epileptic factor. [14, 42]

The presynaptic terminal is a complex unit of signal integration with multiple control pathways. There are thus countless ways to alter synaptic transmission, many/all of which may be brain state-dependent, since the transmission of information between pre and postsynaptic elements depends upon the frequency and duration of presynaptic signals. At present, it is not possible to provide a clear picture of the real functional consequences of these reorganizations.

Once neurotransmitters are released, they activate postsynaptic receptors. As is the case for the presynaptic terminal, there are countless ways to change the transfer of information by altering component of the postsynaptic site.

POSTSYNAPTIC MODIFICATIONS

The mechanisms which are known control to $GABA_A$ receptors will be used below as a typical example of how postsynaptic receptors might be modulated; similar considerations could be developed for ionotropic and metabotropic glutamate receptors). These mechanisms are described in the legend of Figure 4.

One key point about this synapse is that $GABA_A$ receptor trafficking is very fast (5 minutes for subunit assembly, 20 minutes for cycling). Although many mechanisms and interacting proteins remain to be identified, the schemes presented in Figure 4 clearly show the diversity of the postsynaptic control systems of GABAergic neurotransmission. These various mechanisms reflect the many parameters that can be altered in epilepsy.

Trafficking of $GABA_A$ receptors in epilepsy

After a status epilepticus, $GABA_A$ receptors are internalized. [43, 44] The resulting loss of postsynaptic $GABA_A$ receptors may explain why status epilepticus may become pharmacoresistant, at least in response to drugs targeting $GABA_A$ receptors such as benzodiazepines. [43, 44] The underlying mechanism involves the dephosphorylation of the β3 subunit, which enables the association between clathrin adaptor 2 (AP2) and β3, and internalization (Figure 4). [45] As might be predicted, blocking this pathway restores GABAergic activity. [45] In addition to internalization, network hyperexcitability increases the lateral diffusion of receptors, which naturally occurs in physiological conditions (Figure 4). As a result, fewer $GABA_A$ receptors are present postsynaptically in hyperexcitable brain, decreasing the amplitude of mIPSCs. [46] These two mechanisms – receptor internalization and receptor diffusion – constitute two examples of a fast removal of $GABA_A$ receptors from the postsynaptic site. Whether increased lateral diffusion and endocytosis occur after a spontaneous seizure, and whether they constitute a stable feature during epileptogenesis and the chronic period, remain to be investigated.

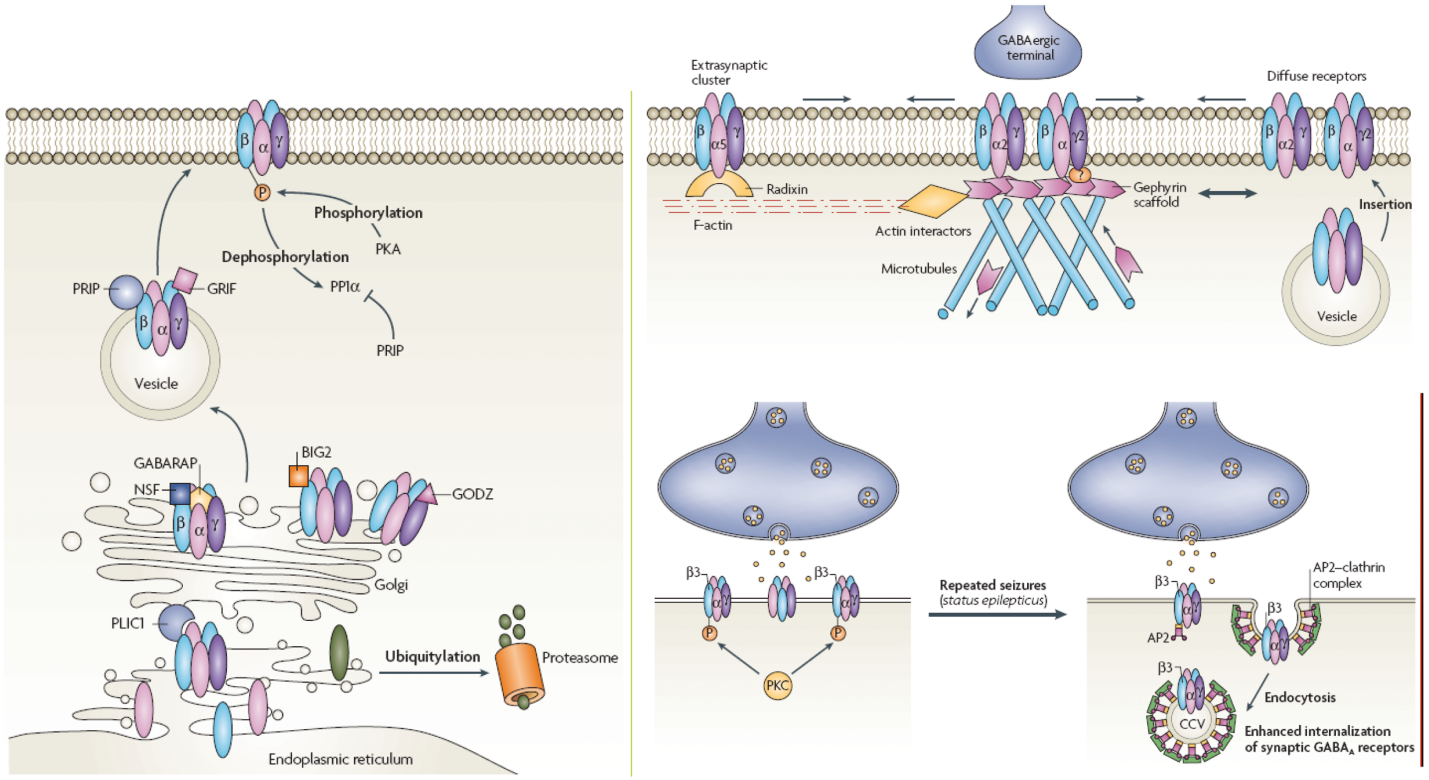

Figure 4. GABA$_A$ receptor trafficking. Left panel. GABA$_A$ receptors have a pentameric structure usually made of two α, two β and one γ subunit. These subunits are assembled in the endoplasmic reticulum to form the receptor. Some of these are ubiquitinated to be degraded by the ubiquitin-proteasome system. The ubiquitin-like protein PLIC1 prevents this degradation. Exit from the Golgi apparatus is facilitated by a number of proteins, which can associate with β subunits including GABARAP (GABA$_A$ receptor-associated protein), NSF (N-ethylmaleimide-sensitive factor), BIG2 (brefeldin-A-inhibited GDP/GTP exchange factor 2), and γ2 subunits such as GODZ (palmitoyltransferase Golgi-specific DHHC zinc-finger-domain protein). The receptors are then trafficked to the membrane in vesicles, a process that depends upon other proteins such as PRIP (phospholipase-C-related catalytically inactive protein) and GRIF (GABA$_A$ receptor-interacting factor protein). Once inserted, GABA$_A$ receptor properties can be modulated by phosphorylation and dephosphorylation processes. Right top panel. Mobility of GABA$_A$ receptors. Postsynaptic receptors are anchored to microtubules via the interaction between α2 subunits and gephyrin. Gephyrin is also associated with γ2 subunits via an unknown interacting protein. GABA$_A$ receptors can diffuse in and out the synapse (lateral diffusion). In addition to postsynaptic clusters of receptors, extrasynaptic GABA$_A$ receptors can also be identified. They contain the α5 subunit, which links them to radixin, which is bound to F-actin. These receptors participate in the tonic current. Right bottom panel. Internalization of GABA$_A$ receptors during status epilepticus. A status epilepticus leads to the dephosphorylation of β3 subunits (usually phosphorylated by protein kinase C – PKC). As a consequence, AP2 (clathrin-adaptor protein 2) can associate with GABA$_A$ receptors, leading to clathrin-dependent endocytosis. Adapted from Jacob et al., Nat Rev Neurosci. 2008.

Changes in subunit composition

A straightforward way to change GABAergic function (in a permanent fashion) is to alter the subunit composition of the receptors. [47] Such modifications constitute a hallmark of human epileptic tissue. [48, 49] The modifications observed in human tissue are very similar to those reported in experimental animal models. [50] These changes are area-specific; for example, GABA$_A$ receptors appear upregulated in the dentate gyrus but are downregulated in CA1. 50 A detailed analysis in the dentate gyrus revealed a change in subunit composition, which appears early during epileptogenesis and persists during the chronic phase. [51] This reorganization is associated with increased GABAergic currents, decreased sensitivity to zolpidem (a nonbenzodiazepine that can potentiate GABA$_A$ receptors), and increased inhibition by Zn^{2+}. [51] Since network function may depend upon the kinetics of receptors, alterations in GABA$_A$ receptor kinetics may potentially lead to altered network dynamics. The functional impact of these changes remains to be addressed.

As displayed in Figure 4, $GABA_A$ receptor clusters can also be formed extrasynaptically. They are responsible for the presence of a tonic GABAergic current, which represents more than 75% of the total (transient and tonic) GABAergic current received by principal cells. [52] The subunit composition of extrasynaptic receptors is also modified after the initial insult. [53, 54] In particular, there is a decreased expression of the δ subunit, which results in a decreased sensitivity of the tonic current to neurosteroids. [55] Despite the loss of, δ subunit containing receptors, the magnitude of the tonic current is not modified in epileptic animals, suggesting the presence of compensatory mechanisms. [54] A redistribution of the γ2 subunit to the perisynaptic domain may also participate in the decrease of the amplitude of synaptic GABAergic currents in epileptic tissue. [54]

Alterations in chloride homeostasis

Two main ions can transit via the channel opened by $GABA_A$ receptors: Cl^- and bicarbonate. Bicarbonate leaves the cell, but the direction of Cl^- flux critically depends upon the intracellular concentration of Cl^-.[56] If it is low, Cl^- enters the cell, which hyperpolarizes the membrane. It it is high, Cl^- leaves the cell, which depolarizes the membrane. The internal concentration of Cl^- depends upon various transporters (e.g. KCC2, which extrudes Cl^-, and NKCC1, which pumps Cl^- in the cell) and chloride channels (e.g. ClC2). These systems can be dynamically regulated. For example, GABA appears to have an inhibitory action in physiological conditions in the immature intact hippocampus in vitro, [57] and also *in vivo* in the cerebellum, [58] but shifts to a depolarizing action after several seizures due to a hyperactivity of NKCC1. [57] This result may explain why seizures become resistant to drugs potentiating $GABA_A$ receptors at early developmental stages in human. Counteracting NKCC1 with the diuretic, bumetanide, restores the inhibitory action of GABA and renders seizures sensitive to drugs potentiating $GABA_A$ receptors. [57]

In adult human epilepsy, 20% of subicular cells are depolarized by GABA [59] due to the downregulation of the KCC2 transporter in these cells. [60] A shift to a depolarizing action in a minority of cells may be sufficient to favor the occurrence of interictal spikes. [59]

GLIAL MODIFICATIONS

Astrocytes play crucial roles in regulating numerous functions, from blood flow to neuronal activity. In addition to controlling extracellular levels of K^+ and neurotransmitters (e.g. glutamate), they can respond to various neurotransmitters and hormones, and release several factors such as glutamate, ATP etc. [61, 62] Alterations in astrocytic function in epilepsy may directly alter synaptic function. Several important modifications have been reported. [62] Only changes that could change synaptic function are described below.

The first obvious change is morphological. Epileptic tissue is characterized by the presence of reactive astrocytes, as assessed by the overexpression of glial fibrillary acidic protein (GFAP). What could be the functional consequences of this reaction? Astrocytes possess an extensive network of processes. One astrocytic domain can cover approximately 150, 000 synapses, a volume that does not overlap with that of neighboring astrocytes in normal conditions. This organization is lost in experimental epilepsy where there is a 10-fold increase in overlap. [63] The functional consequence of such reorganization is not known, but it has been suggested to be linked to the parallel increase in dendritic spines. [63]

Increased overlap of astrocytic domains could facilitate neuronal synchronization. Astrocytes can release glutamate (or D-serine), producing NMDA receptor-dependent slow inward currents in neurons, which in turn may facilitate neuronal synchronization. [64] Such a scheme has been proposed to play a central role in seizure genesis, [65] although the issue remains controversial. [66] Furthermore, the release of glutamate appears to be increased in astrocytes in epilepsy. [62, 67–69] Reactive astrocytes and microglia release tumor necrosis factor α (TNFα), a cytokine which can act on TNFR1 receptors. The activation of TNFR1 increases the production of prostaglandin 2, which in turn can amplify glutamate release. If such a mechanism is at play in epilepsy, there should be an increase of slow inward currents in neurons, which remains to be tested experimentally. Another

important cytokine released by reactive astrocytes is interleukin 1β (IL-1β). IL-1β can boost NMDA receptor responses via the activation of Src tyrosine kinases and subsequent NR2A/B subunit phosphorylation, which could favor hyperexcitability. [70]

Under physiological conditions, NMDA receptors are most of the time blocked by Mg^{2+}, i.e. they are not conducting any current when activated by glutamate. In contrast, in the epileptic hippocampus, NMDA receptors contribute directly to glutamatergic neurotransmission and produce a long-lasting depolarization of neurons. [71] The origin of such an increase in NMDA contribution has remained elusive, although a change in the redox state of NMDA recetors has been proposed as an important contributing factor. [72]

Other changes in astrocytic function may increase the likelihood of neuronal synchronization. Astrocytes play an active role in regulating the extracellular concentration of glutamate, K^+ and water content. [62] Epileptogenesis is associated with changes in gene expression in astrocytes. [73] A marked downregulation of two genes coding for two astrocytic glutamate transporters results in reduced astrocytic glutamate uptake. Current data suggest that the functional consequence of this change is marginal, and only seen during high (>100 Hz) frequency stimulation. [73] In addition to glutamate transporters, there is a marked reduction in the expression of the inwardly rectifying K^+ channel, Kir4.1, in astrocytes, resulting in decreased K^+ buffering capacities, and facilitation of glutamatergic synaptic responses. [73]

It is important to note that Kir1.4 acts in concert with acquaporin 4 (AQP4) to regulate K^+ and water levels in the extracellular space. Seizure genesis leads to cell swelling, reducing the extracellular space and favoring hyperexcitability. [74] The downregulation of APQ4 and its redistribution away from the astrocytic endfeet in epilepsy [75, 76] may further impair K^+ buffering and favor hyperexcitability.

In addition to postsynaptic/extrasynaptic consequences, as described above, astrocytic dysfunction may have pro-epileptic effects at presynaptic sites. Synaptic function critically depends upon the glutamate-glutamine cycle. Glutamate transported into astrocytes is transformed into glutamine by the glutamine synthetase. Glutamine is then exported to neurons where it is transformed into glutamate by the mitochondrial glutaminase. Glutamate in then reused as such, or transformed into GABA. Inhibition of glutamine synthesis results in a specific downregulation of GABAergic neurotransmission, involving a presynaptic mechanism (decreased vesicular GABA content). [77] Reactive astrocytosis reduces GABAergic neurotransmission, [33] perhaps since there is a downregulation of glutamine synthetase in epileptic tissue. [73] Depleted GABAergic terminals may favor the occurrence of paroxysmal discharges.

FUNCTIONAL CONSEQUENCES OF THESE MODIFICATIONS

The reorganizations occurring around the synapse are extremely diverse and complex. What could be the functional consequences? The hypotheses are admittedly very speculative, since we do not know the role of each parameter under physiological conditions. Very importantly, a drastic alteration of one parameter (e.g., the loss of GABAergic inhibition, or its transformation into excitation) may be without any functional impact. This is a key concept derived from Eve Marder's work, [78] summarized below. Simply put, Marder's work, performed in the stomatogastric system of the lobster, has lead to the concept that there are multiple solutions to a given biological problem. The stomatogastric system, which generates a rhythm vital for the animal, is composed of three nuclei connected to each other via different neurotransmitter systems. Knowing the types of channels expressed by the neurons in each nuclei and the type of connections, the researchers built a computer model in which each parameter (amplitude of the ionic current, strength of the connection) could take any biologically realistic value. They varied all the parameters, and selected the sets of parameters that produced the same rhythm recorded *in vivo*. They found that there are countless possible solutions, which produce the same behavior at the network level. [78] Importantly, they also found that the system is "resistant" even if one type of channel is not expressed, or if a connection between two nuclei is missing. Further, the values taken by a given parameter (among the sets of solutions) match the biological variability. [79, 80] That is, the variability of a given

parameter measured in a biological system (e.g. amplitude of $GABA_A$ receptor-mediated currents) may just reflect the different solutions that enable networks to function adequately. One might therefore consider that all the modifications occurring in epileptic networks (including those described above) may simply constitute the expression of another set of "solutions" to perform normal physiological function. Seizures are, after all, very infrequent events - which suggests that most of the time the system can cope with various parameters permutations without engaging in abnormal activity.

Nevertheless, important functional changes in epilepsy appear to stem from some of the synaptic modifications identified so far. We'll consider interictal activity and cognitive deficits.

Interictal activity

Interictal-like activity appears very early after the initial insult in experimental models, and precedes (by days) and even predicts the appearance of the chronic phase of epilepsy defined by recurrent seizures. [7, 8, 81] Using a crude model of hippocampal circuitry, we have tried to determine the conditions sufficient for the genesis of interictal spikes. [7] Many different solutions exist, which include decreased dendritic GABAergic inhibition and increased glutamatergic excitation, [7] in a range of values found experimentally. [6, 7] This model does not explain why interictal activity is not permanent *in vivo*, but suggests clues regarding its underlying mechanisms. Since interictal activity is rarely encountered in non-epileptic individuals, it has been proposed that it is pathological. Studies performed *in vitro* suggest that interictal-like activity can produce long-term potentiation of synapses, thus contributing to the construction of hyperexcitable networks. [82] The presence of interictal-like activity during the earliest stages of epileptogenesis may not only constitute biomarkers for at-risk patients, but also one core mechanism of epileptogenesis. [7, 8, 81] One study performed in patients with temporal lobe epilepsy suggests that the size of the epileptogenic zone increases with the duration of epilepsy. [83] The brain regions outside the epileptogenic zone (i.e. the irritative zone) are often characterized by the presence of interictal spikes. Some of these regions become part of the epileptogenic zone as epilepsy evolves in time. [83] It is therefore tempting to propose that interictal spikes participate in the transformation of the irritative regions into epileptic ones.

Cognitive deficits

Interictal spikes may have other deleterious consequences, in particular for learning and memory processes. Interictal spikes correspond to a more-or-less synchronous firing of large populations of cells. [84, 85] In physiological conditions, groups of hippocampal cells fire in a coordinated and precisely timed fashion, in particular during replay for the storage of information or its transfer. [86] In keeping with this scheme, interictal spikes have deleterious cognitive consequences during memory retrieval in experimental epilepsy. [87]

Cognitive deficits are consistently found in epileptic patients, but their underlying basis is yet to be determined. Since hippocampal circuitry is drastically modified after the initial insult in experimental animals, it is tempting to propose that the normal physiological functions performed by these circuits are altered. Consistent with this prediction, spatial memory performance is decreased soon after the initial insult. [11] This type of memory depends upon the hippocampus (which is considerably reorganized);.in contrast, non spatial memory, hippocampus-independent, is preserved during epileptogenesis and the chronic period. [11] The same study showed that theta rhythm (4–12 Hz), which plays a key role in numerous cognitive processes, [86] is altered soon after the initial insult, and that spatial performance is proportional to the power of theta rhythm. [11] These results are consistent with the proposal that an altered circuitry should result in dysfunctions. However, they are only correlative; causality has not been demonstrated.

REPAIR STRATEGIES

Several biomarkers have been proposed to predict the construction of an epileptic brain, including inflammatory factors, interictal spikes, and cognitive deficits. [7, 11, 81, 88] Validation of these markers in prospective studies in

at-risk patients would open the way to preventive treatments. Since the circuitry is modified soon after the initial insult, it is important to determine the mechanisms responsible for these reorganizations. Alternatively, one could simply try to repair the circuits (without knowledge of the pathological mechanisms). As mentioned above, cell death is a hallmark of epilepsy. It is also an early event. Interestingly, the delivery of viral vectors to supply fibroblast growth factor-2 (FGF-2) and brain-derived neurotrophic factor (BDNF) after the initial insult, increased neurogenesis, limited cell damage, and reduced the severity of epilepsy in an experimental model. [89] These findings suggest that the circuitry may be repaired, even partially, after the damage has been done.

Is it possible to act upstream to prevent these changes? To do so would require understanding the mechanisms responsible for the reorganization of the circuitry. Key aspects of the early processes triggered by the initial insult are now under investigation, and include the rupture of the brain blood barrier, oxidative stress, and inflammation. [34, 35, 90, 91] Experimental studies have shown that acting on these parameters can be disease-modifying (i.e., may decrease the damage and/or the severity of epilepsy), although none have managed to stop the occurrence of spontaneous seizures. [34, 35, 90, 91]

CONCLUSION

The previous considerations clearly demonstrate that considerable reorganization takes place at the synaptic level soon after an initial epileptogenic insult. Whether these reorganizations play a role in epileptogenesis, seizure genesis/propagation, or cognitive deficits remains an open question. All our studies are correlative. None can show causality since we do not know the role of each parameter under physiological conditions.

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