U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Prince DA, Parada I, Graber K. Traumatic Brain Injury and Posttraumatic Epilepsy. In: Noebels JL, Avoli M, Rogawski MA, et al., editors. Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition. Bethesda (MD): National Center for Biotechnology Information (US); 2012.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Traumatic Brain Injury and Posttraumatic Epilepsy

David A. Prince, Isabel Parada, and Kevin Graber*.[1]

Enhanced excitatory connectivity and decreases in GABAergic inhibition are important mechanisms underlying injury-induced epileptogenesis in many animal models and in humans. Sprouting of excitatory axons and establishment of new synapses is a ubiquitous epileptogenic response to cortical injury. In the rodent chronic partial isolation (undercut) model of posttraumatic epilepsy, tetrodotoxin treatment of undercut cortex during a critical period decreases this axonal response to injury and blocks epileptogenesis. Gabapentin, an agonist that competes with glial-derived thrombospondins at the α2δ-1 calcium subunit receptor, is antiepileptogenic in neocortical slices from undercut rats and decreases injury-induced excitatory synapse formation, cell death, and neurofilament immunoreactivity. GABAergic interneurons become atrophic and dysfunctional in undercuts, resulting in decreases in inhibitory connectivity and the strength of inhibition on pyramidal cells. A potential underlying mechanism is loss of trophic support from brain derived neurotrophic factor (BDNF) released by pyramidal neurons acting on interneuronal TrkB receptors. Treatment of undercut rats after injury with agents that mimic activation of TrkB receptors by BDNF may reduce signs of injury and dysfunction of interneurons and provide a second promising antiepileptogenic approach. A focus on limiting new excitatory connectivity and providing trophic support for injured GABAergic interneurons may allow development of effective prophylactic measures for posttraumatic epilepsy.

The epidemiology of posttraumatic epilepsy (PTE) has been extensively analyzed and reviewed in a number of studies of both civilian and military brain injuries[1,2]; reviewed in[3]. Several conclusions from this research are relevant to considerations of the potential mechanisms and prophylaxis of PTE. Results clearly show that the incidence of PTE is related to the severity of injury, and is therefore significantly higher in the military during wartime than in the civilian population, ranging up to 53 % with penetrating wounds[1,2]; reviewed in[3]. Both the increased incidence at older ages, and the potential development of PTE by the large number of individuals who have survived severe concussive injury during recent conflicts, suggest that the size of the affected population will increase in coming years, emphasizing the need for understanding the underlying pathophysiological processes and the development of prophylactic strategies.[4,5] Although initial seizures in those who develop epilepsy most commonly have a focal origin in neocortex, both partial neocortical and temporal lobe epilepsy can follow traumatic brain injury (TBI) in man[6]. One remarkable feature of PTE is the variable, often very

Author Affiliation: 1 Stanford University School of Medicine.

* Corresponding author: David Prince, M.D., Pimley Professor of Neurology and Neurological Sciences, Stanford University School of Medicine, 300 Pasteur Dr., Room M016, Stanford CA 94305. daprince@stanford.edu.

prolonged latency from injury to epilepsy which can range from weeks to years[1,2,6]. This provides a possible window for prophylactic intervention, once more information regarding the underlying pathophysiological processes and strategies for modifying them is available. However the long latency also represents a potential therapeutic problem, particularly in the absence of reliable biomarkers of "epileptogenesis in progress". This chapter will focus on examples of aberrant excitatory and inhibitory processes in injured epileptogenic cortex and potential approaches to prevention of epileptogenesis that are focused on these pathophysiological mechanisms. Some of the challenges for development of prophylactic therapies are also discussed. Readers are referred to a number of reviews and papers published very recently that deal with various aspects of the basic mechanisms, pathogenesis and potential prophylaxis of PTE, and complement the areas covered in this chapter[6–18].

Spectrum of potential epileptogenic mechanisms induced by traumatic brain injury

A large number of alterations in gene expression[19] and a variety of pathophysiological processes occur in parallel following a brain injury[20–22], reviewed in[7,23], making it unlikely that an intervention focused on any one of these, in isolation, will emerge as a prophylactic "silver bullet". The situation is further complicated by the likelihood that variables such as the level of brain maturation, site and distribution of injury (focal vs. multifocal vs. diffuse), type of trauma (e.g. concussive versus penetrating), presence or absence of significant bleeding, and other factors may affect the underlying type and sequence of epileptogenic events and the optimal timing of a potentially successful intervention in a given individual. Do different combinations of pathophysiological mechanisms underlie human epileptogenesis that follows different types of cortical injuries such as those due to stroke with cortical infarction, penetrating vs. closed concussive head injuries, focal infections or other etiologies? The same question is relevant to potential similarities or differences in events underlying chronic epileptogenesis in various models of TBI such as fluid percussion injury[24] versus controlled cortical impact[25] versus neocortical partial isolation or "undercut"[26]. Are underlying mechanisms in these models in neocortex the same as those in posttraumatic temporal lobe epilepsy models, or when hippocampal damage is induced by status epilepticus rather than direct trauma? These are critical questions because they bear on potential prophylactic therapies and, unfortunately, the detailed data required for answers are incomplete.

A survey of the limited cellular results from neocortical injury models, and from animals whose temporal lobes are injured in the course of experimental status epilepticus, as well as from available human material, indicates that two pathophysiological processes are prominent in focal epileptogenesis, namely, enhanced excitatory connectivity[10,27–34], and alterations in GABAergic inhibitory mechanisms[33,35–40]. But even within these broad categories, different types of abnormalities may be present that will require different prophylactic or therapeutic approaches. For example, disinhibition might involve alterations in gamma-aminobutyric acid A ($GABA_A$) receptor subunits[41,42], decreases in voltage dependent calcium channels[40] or Na+/K+ adenosine triphosphatase (ATPase) at inhibitory terminals[43,44], shifts in the chloride gradient due to changes in expression of chloride transporters KCC2 or NKCC[45–47], loss of inhibitory connectivity due to structural changes in interneurons[16,48] or actual loss of interneurons of various subtypes[36,38].

Subsets of abnormalities can also affect the mechanisms controlling excitation, such as alterations in the probability of release (Pr) at terminals[49], burst firing in axons[50], reviewed in[51], receptor efficacy or number[52–56], and dysfunction of ion or transmitter transport[57–62]. In addition to alterations in inhibitory efficacy and enhanced excitation, many other potentially epileptogenic changes are present following injury such as alterations in voltage dependent ion channels[63–67], blood brain barrier disturbances[68], inflammatory responses and release of cytokines[21,69], alterations in glia[70,71], and so on. In terms of evaluation of therapeutic trials of potential prophylactic agents, this plethora of abnormalities raises a difficult issue: a single agent may fail to prevent PTE, even though it is effective at its intended target, that is a false negative result may be obtained due to the presence of other epileptogenic mechanisms acting in parallel.

Choice of models for research on posttraumatic epilepsy

There is no perfect model of human posttraumatic epilepsy. The advantages and disadvantages of acute and chronic models of epilepsy have recently been reviewed in detail[72]. Fluid percussion injury, controlled cortical impact and undercut models each have their place in advancing our understanding of PTE. Valuable information has also been obtained from status epilepticus temporal lobe injury models, although direct traumatic injury is not present and the resulting epileptogenesis represents a different epilepsy syndrome that may involve a somewhat different spectrum of underlying mechanisms. Discussions about the merits of one model versus another thus are only useful in the context of the particular pathophysiological process or event to be investigated. Obviously, to determine whether a drug will be prophylactic against seizures *in vivo*, a model in which there might be extensive injury and an expected high incidence of electrographic and behavioral posttraumatic seizures at relatively short latency after injury (i.e. high throughput), would be most practical and desirable.[73–75] However, this might not be the model of choice for investigation of the details of functional or structural alterations in neocortical GABAergic interneurons or pyramidal cells that occur at a site of stereotyped restricted epileptogenic focal injury, and the potential prophylactic effects induced by the same drug on these alterations. Such a question would be better addressed with a more reductionistic approach using a model that would facilitate detailed cellular *in vitro* experiments and avoid the complications of widespread damage and variability.[30,32,76] Both kinds of experiments are critical for progress, and fitting the preparation used to the question posed is certainly not a new concept in neurobiological research. There is no one best approach to unraveling the mechanisms underlying the pathogenesis and prophylaxis of PTE.

Partial neocortical isolation ("undercut") model

The authors' familiarity with this model, the significant amount of anatomical and cellular electrophysiological data available (references below and in[77]) and the fact that this is the first case in which prophylaxis of epileptogenesis after local cortical injury has been demonstrated (discussion below), has lead us to focus on the undercut model in this review. The advantages of this model have been detailed elsewhere.[77] Most important is the relatively short interval between injury and epileptiform activity that is present in a high proportion of neocortical slices cut through the damaged area and maintained in vitro [78–80] (Figure 1C,D). This has allowed the detailed examination of epileptogenic cellular structural and functional alterations in pyramidal (Pyr) cells and GABAergic interneurons detailed below. We have also obtained in vivo video/electroencephalographic (EEG) recordings that show electrographic and behavioral seizures beginning with focal discharge in the undercut cortex, spreading across the cortex on the injured side and propagating contralaterally (Figure 2 in[77]).

Partially isolated neocortical islands with intact pial circulation ("undercuts" below) are an established *in vivo* and *in vitro* model for development of chronic post-traumatic hyperexcitability and epileptogenesis[32,78,79,81,82], and partially isolated neocortex is also epileptogenic in man[83]; Figure 1A). The undercut cortex retains normal laminations (Figure 1B), although it becomes thinner with modest cell loss and obvious structural alterations in deep lying pyramidal (Pyr) cells[78,84], (K Graber and DA Prince, unpublished). Disinhibition, increases in neuronal membrane excitability, and increases in excitatory synaptic coupling have been suggested as potential mechanisms in this chronic epilepsy model.[32,78,85–87] The undercut cortex becomes progressively more epileptogenic over several weeks[82,88], and spontaneous interictal discharges can persist for at least 1 year in the monkey[26]. The time of onset of *epileptogenesis*, or the "critical period" in rats occurs during the first 3 days after injury[89] and recent data suggest that epileptogenic activity is already present at 3 days after the undercut (DK Takahashi and DA Prince, unpublished results). Isolated islands of neocortical gray matter, with neuropathological evidence of substantial axonal reorganization, are also present in postmortem specimens from epileptic children who developed extensive underlying white matter lesions as infants[90]. Interictal epileptiform activity can be recorded within partially isolated cortex of anesthetized rats, and c-fos immunoreactivity (IR) is increased for weeks in the injured cortex, suggesting ongoing abnormal activity[91]. Behavioral and electrographic

seizures occur in *in vivo* experiments on monkey, cat and rodents in this model (see above and references in[77]). Areas of partially isolated cortex with underlying loss of white matter are also present in the cortical contusion (Figure 2 in[25] and fluid percussion injury models (Figure 1D in[23]), although it is not clear whether seizure activity originates from the cortex above these sites. Of interest are reports of chronic electrographic and clinical seizures in humans as a complication of psychosurgery in which connections from portions of frontal lobes were severed, essentially producing large partially isolated neocortical slabs [92,93] (Figure 1A).

Abnormalities in excitatory mechanisms in the undercut cortex

The capacity of injured brain to make new connections has been known since the groundbreaking anatomical studies of Cajal[94] who described sprouting of injured Pyr cell axons in neocortex. Maladaptive axonal sprouting and establishment of new excitatory connections occur in mature undercut neocortex[32] and as early as 2 days after injury in isolated immature neocortex[95]. Excitatory sprouting also occurs following injury to the hippocampus in other animal models of epileptogenesis[27,28,96–102]; and in epileptic human temporal lobes[103–107]. The ubiquitous nature of this phenomenon is shown by its occurrence in other models of cortical trauma such as stroke[108,109], thermo-ischemic lesions[110] and fluid percussion injury[111], where it may begin hours after the trauma[112]. The onset of an axonal reaction and sprouting, as signaled by increases in immunoreactivity for growth-associated protein (GAP)43, may begin in as early as 12h after lesions in culture and these alterations are well established by 3 days after injury[30,113]. Sprouting occurs 3-4 days after injury to dissociated neocortical neurons in culture[114]. Hyperexcitability due to synaptic innervation by sprouted axons has been shown in experiments in hippocampus[29,30,76] and neocortex[34]. Activation of brain-derived neurotrophic factor (BDNF) may be an important mechanism underlying injury-induced sprouting and hyperactivity in hippocampus.[115,116]

Results from whole cell recordings of layer V pyramidal (Pyr) neurons done 2–3 weeks after injury in the undercut cortex model support the conclusion that there is enhanced synaptic excitatory connectivity by showing (1) an increased frequency of miniature (m) excitatory postsynaptic currents (EPSCs); (2) a steeper input/output relationship for evoked EPSCs; and (3) an increased probability of release of glutamate from excitatory terminals[33,49]. The latter finding suggests intrinsic abnormalities in the terminals of Pyr cells. In addition, anatomical studies of biocytin-filled layer V Pyr cell axons showed evidence of significant sprouting, mainly in layer V[32], where the epileptogenic field potentials were initiated[78,79]. These functional and structural abnormalities presumably contribute to the large polysynaptic excitatory currents in Pyr cells that occur synchronously with field potential epileptiform bursts (Figure 1D) and propagate across the cortex (Figure 1C).

More recently, laser scanning photostimulation of caged glutamate in epileptogenic slices from undercuts allowed detailed mapping of excitatory and inhibitory connectivity[34,48]. Results showed that the excitatory "map" was significantly expanded, particularly in layer V, and that both Pyr cells and fast-spiking inhibitory interneurons were targets of presumed sprouted axons and terminals from other nearby Pyr neurons[32]. These alterations in excitatory synaptic connectivity and strength, together with abnormalities in inhibitory circuits discussed below may contribute to the development and increased conduction of epileptiform activity across cortex in the *in vivo* undercut model in cat[117] (reviewed in[118]).

It is interesting that hyperexcitability closely resembling that recorded in layer V of undercut cortex has also been shown in neocortical slices from the fluid percussion injury model. Rats from both models have epileptiform seizures in vivo[77,119], and there is also a similarity in the morphology of field potentials that are evoked or occur spontaneously in slices versus those in *in vivo* EEG recordings in these two models. Also, recent recordings from another TBI model studied *in vitro* clearly show repetitive bursts of EPSCs that coincide with epileptiform field potentials which would be termed "ictal" EEG discharges if they occurred *in vivo*[10].

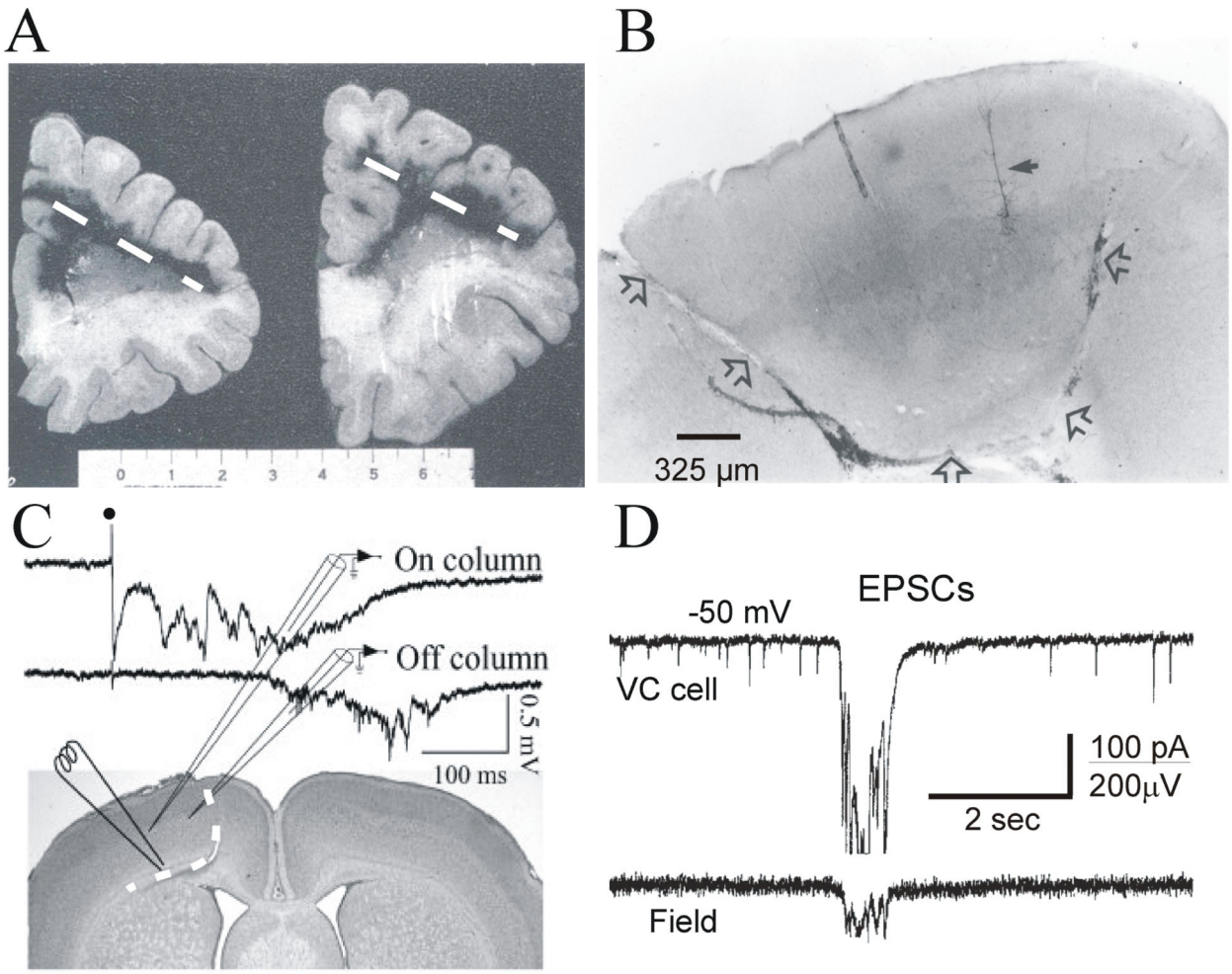

Figure 1. Undercut cortex in rats and humans. A: Coronal section of human brain in patient who underwent undercutting surgery of right frontal lobe for intractable pain. Dashed white lines drawn through the undercut here and in C. (Modified from Scoville WB. Selective cortical undercutting as a means of modifying and studying frontal lobe function in man; preliminary report of 43 operative cases. J Neurosurg 1949; 6:65, with permission.) **B:** Fixed coronal section cut through rat sensorimotor cortex containing a partial cortical isolation made 3 wks earlier. Black arrow points to layer V pyramidal cell filled with biocytin. Open arrows mark edge of undercut that extends from pial surface to white matter. **C:** Upper: Evoked epileptiform field potentials recorded simultaneously by 2 electrodes (On column, Off column) in layer V of an in vitro slice 3 wks after partial isolation. Lower: Nissl stained section from the same slice showing approximate site of undercut lesion and electrode positions. Stim: stimulation electrode. All-or-none prolonged polyphasic epileptiform activity was evoked by stimulus in layer VI/whitematter just above undercut margin. Epileptiform burst was initiated by on-column stimulation and propagated across cortex to off-column electrode. From Graber KD, Prince DA. A critical period for prevention of posttraumatic neocortical hyperexcitability in rats. Ann Neurol 55(6):860, 2004, with permission. **D:** Representative voltage clamp recording (upper trace) from layer V pyramidal cell in undercut during a spontaneous epileptiform event. Vhold: −50 mV, close to E_{Cl}; inward current downward. Random EPSCs are followed by large spontaneous epileptiform event consisting of summed polysynaptic EPSCs coincident with epileptiform field potential burst in bottom trace. Field: negativity down; current peak clipped). Evoked epileptiform field potential and cell recording were similar to those evoked by extracellular stimuli (not shown). Slice perfused with standard ACSF. From Salin P, Tseng GF, Hoffman S, Parada I, Prince DA. Axonal sprouting in layer V pyramidal neurons of chronically injured cerebral cortex. J Neurosci 15:8234, 1995, with permission.

Abnormalities in GABAergic inhibitory mechanisms in undercut cortex

A variety of structural and electrophysiological evidence shows that GABAergic inhibition is compromised in undercut cortex. Recent experiments in the cat suggest that glutamic acid decarboxylase (GAD-) or GABA-positive neocortical interneurons are selectively and progressively reduced in density in cat undercut cortex[84]. Although our initial cell counts in undercut rat cortex have not shown a selective decrease in density of

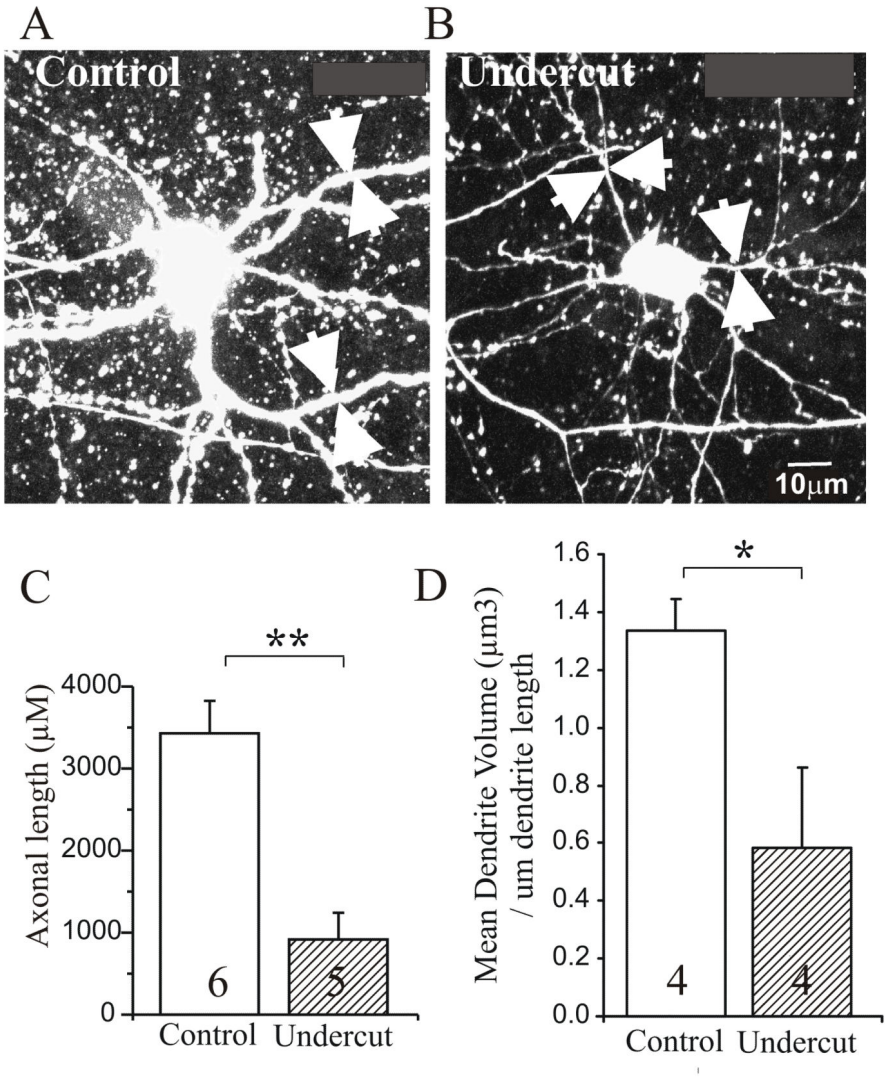

Figure 2. Structural alterations in fast-spiking interneurons in undercut cortex. A,B: Images of single layer V fast-spiking interneurons filled with biocytin and processed in control (A) and undercut slice (B). The cell from the undercut has thinner dendrites (arrows) and a less dense axonal arbor. Calibration in B: 10 μm for A, B. **C–D:** Graphs show significant decreases in axonal length (C) and mean dendritic volume (D) in undercut (hatched bars) vs. control cells (white bars). Numbers of cells analyzed shown in each column. Measurements obtained from stacks of confocal images. Mean ± SD axonal length for control: 3429.8 ± 968.1 μm and for undercut: 726.9 ± 325.1 μm. **p < 0.001; *p<.01. A–B,D: from I Parada, DA Prince, unpublished. C: modified from Prince DA, Parada I, Scalise K, Graber K, Jin X, Shen F. Epilepsy following cortical injury: cellular and molecular mechanisms as targets for potential prophylaxis. Epilepsia 50, Suppl 2:30, 2009, with permission.

parvalbumin (PV)-immunoreactive interneurons[120], we have found significant structural changes in biocytin-filled fast-spiking PV-containing cells, including marked decreases in axonal lengths and dendritic volume (Figure 2), giving them an appearance similar to that seen in immature PV interneurons (cf Figure 3A of[121] with Figure 2B). Further, the axons of these interneurons in the undercut cortex have a significant increase in the proportion of small (<1 um in diameter) boutons and a decrease in numbers of larger (>1 um in diameter) boutons (see Figure 5 in[16]), changes that would be associated with altered pre- and postsynaptic structures at GABAergic synapses and with less effective inhibitory transmission[122,123].

Results of several electrophysiological experiments confirm a decreased efficacy of GABAergic inhibitory transmission in the undercut cortex. Whole cell recordings in rat undercut slices showed a decreased frequency of mIPSCs in Pyr cells[33], and quantitative electronmicroscopic experiments confirmed a decreased density of

symmetrical (inhibitory) synapses on somata of layer V Pyr cells (J. Wenzel, PA Schwartzkroin and DA Prince, unpublished results) as one potential mechanism for decreased miniature inhibitory postsynaptic current (mIPSC) frequency. More recently, we have also shown that the axonal terminals of layer V interneurons in undercuts are abnormal in that they have a decreased probability of GABA release and increased failure rate[40] due in part to a downregulation of N-type calcium channels in terminals.[123a] Dual recordings from synaptically coupled FS-Pyr or FS-spiny stellate pairs in layer IV of undercuts showed a decrease in Pr, a large reduction in the amplitude of unitary IPSCs, increased coefficient of variation and increased failures, indicating alterations in presynaptic terminals of the largest subgroup of GABAergic neurons in cortex, FS cells [123b]. Neuronal injury can also decrease the efficacy of postsynaptic inhibition by decreasing expression of KCC2 and impairing outward chloride transport[124,125]. In the undercut, there are also decreases in KCC2 and in the outward transport of chloride in postsynaptic Pyr cells that would make GABAergic inhibition less effective at times of high frequency activity[126]. Recent results, obtained with laser scanning photostimulation of caged glutamate in combination with whole cell recordings, have shown that the net effects of some of the above-mentioned anatomical and electrophysiological abnormalities are to reduce the spatial extent of inhibitory inputs onto both Pyr cells and FS interneurons in the chronic undercut[127].

Fast-spiking interneurons in neocortex normally have a high density of Na^+-K^+ ATPase ("sodium pump") in their membranes[44] and particularly in their axonal terminals surrounding Pyr cell somata[43,128]; (Figure 3A). Sodium pump activation would be important in fast-firing neurons to prevent excessive increases in $[Na^+]_i$ that might depolarize terminals and decrease GABA release. There is a significant loss of Na pump immunoreactivity in undercut cortex surrounding Pyr cells (Figure 3B), similar to that previously found in the freeze-microgyrus model of epileptogenesis[43], suggesting another potential mechanism that would lead to terminal dysfunction and decreased GABA release.

When does posttraumatic epileptogenesis begin?

Answers to this critical question would influence decisions about the timing of potential antiepileptogenic treatment. From the available data, it appears likely that processes eventually leading to hyperexcitability in cortical networks and to seizures may be set into motion at the time of the TBI, although the latency to the first behavioral spontaneous seizure is highly variable. Seizures in the first week after injury are usually not followed by epilepsy in man; however they are associated with an increased statistical risk of subsequent epilepsy[3], indicating that, at least in some individuals, an epileptogenic process is initiated early. Epileptiform activity may be initially undetectable by surface EEG, making this an unreliable marker of the onset of epileptogenesis[129]. There is evidence for early emergence of epileptogenesis in a variety of experimental data. In models of acute neocortical trauma, epileptiform activity may develop within minutes or hours after injury in vitro[130,131] and results from acute partial isolation experiments done under ketamine anesthesia in cats do show that acute epileptiform discharges are generated in cortex near the isolation[132]. However the underlying mechanisms in these early seizures may be different from those in more chronic models in that they might involve acute alterations such as release of excitatory amino acids[131], spreading depression, large increases in $[K^+]_o$ and blood-brain barrier disruption.

Recently we recorded *in vitro* from undercut slices obtained 3 days after the injury and found that they generate robust prolonged spontaneous and evoked epileptiform field potentials associated with large amplitude EPSCs. Confocal images obtained after immunocytochemical processing for GAP43, vesicular glutamate transporter 1 (vGLUT1) and postsynaptic density (PSD)95 have suggested that there is significant sprouting of excitatory axons onto pyramidal somata within days after the undercut is placed. Other electrophysiological data suggest that these sprouted terminals are functional and contribute to epileptogenesis (D.K. Takahashi and D.A. Prince, unpublished).

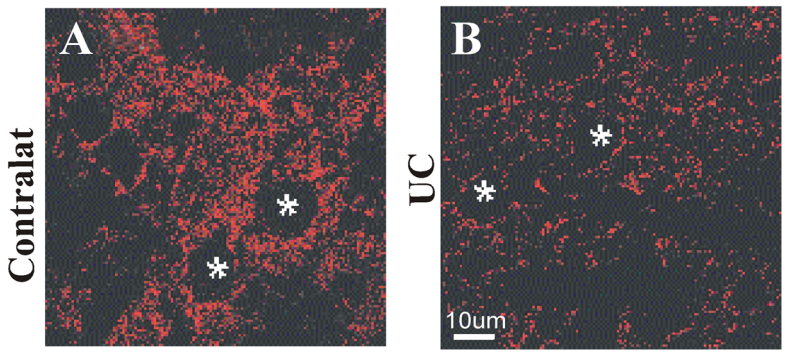

Figure 3. Loss of perisomatic α3Na+K+ ATPase in undercut cortex. A: Immumoreactivity (IR) for α3Na+K+ATPase in layer V of control cortex contralateral and homotopic to undercut on rat 21d after lesion. IR is localized around the somata of pyramidal cells (asterisks in A,B), suggesting that it is in terminals of FS interneurons that target somata. Dual staining with GAD65 (not shown) confirmed this conclusion[43].

B: Undercut side from animal of A shows significant downregulation of α3Na+K+ATPase-IR. From[128].

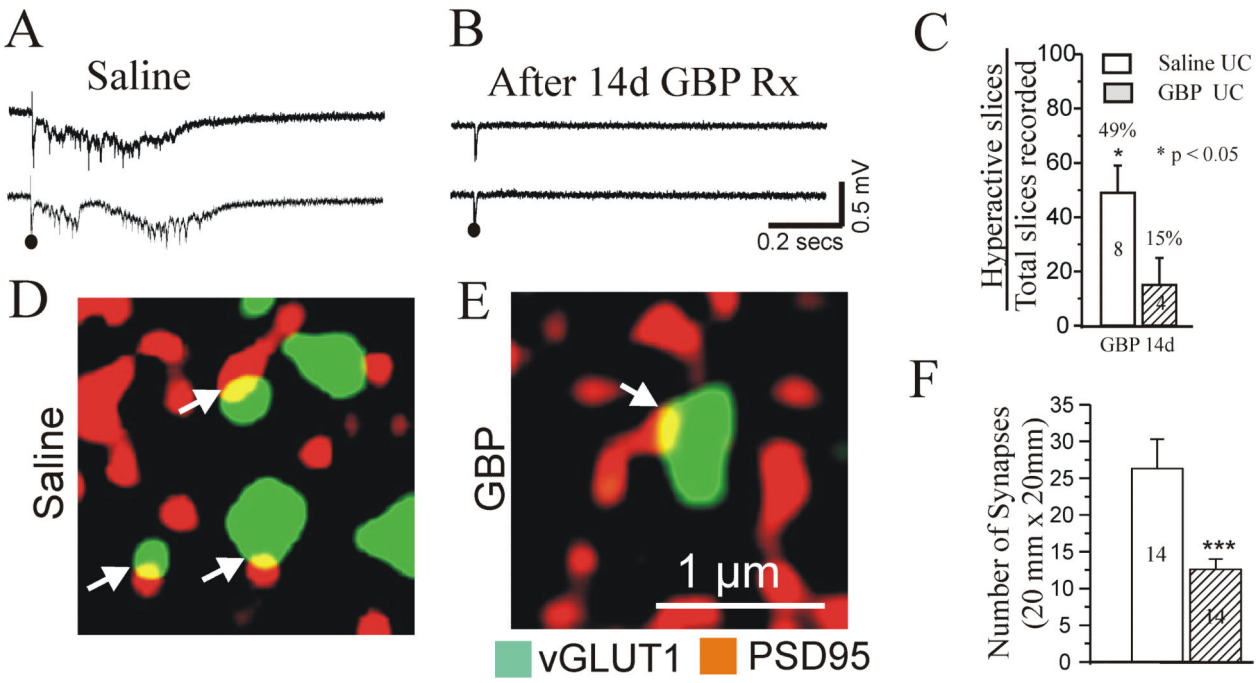

Figure 5. Gabapentin (GBP) in vivo reduces epileptogenesis and excitatory synapse density in undercut slices. A–B: Field potentials evoked in layer V of undercut slice by stimuli in partial cortical isolations 14 d after injury. **A:** Rat was treated with i.p. infusion of saline for 14d, followed by slice experiment. Single stimuli within isolation evoke typical epileptiform discharges consisting of slow potentials lasting ~400–500 ms with superimposed extracellular unit bursts. **B:** Representative non-epileptiform responses to stimulation of slice from rat treated ×14d with an ip infusion of ~8 mg/d GBP via Alzet pump. Recordings done 1d after termination of GBP infusion. **C:** Group data showing percentage of epileptogenic slices 14 d after undercuts in GBP- vs. saline-treated animals. UC: undercut in both groups. Numbers in bars: numbers of animals. Average of 4.3 slices/rat. GBP significantly reduced epileptogenesis in these experiments. **D–E:** Confocal images of neocortical layer V from undercut rats treated with ip saline (D) or GBP (E; ~8 mg/kg × 7d) after undercut. Sections were immunoreacted with antibodies for postsynaptic (PSD95, red) and presynaptic markers (vGlut1, green). Sites of putative synapses shown by close appositions (yellow; arrows) were fewer in sections from GBP-treated rats (E vs. D). **F:** Group data from saline (white bar) and GBP-treated animals (hatched bar). Numbers in bars: total number of sections examined. Three images were taken from each section and 2–3 sections from each of 5 rats in each group. ***: p<001. From H Li, KD Graber, DA Prince, unpublished.

Axonal sprouting and excitatory synapse formation occur in parallel with a number of other pathophysiological events following TBI (e.g. alterations in GABAergic inhibition discussed above, intrinsic changes in membrane excitability[78]), so it is difficult to determine whether hyperconnectivity alone would be sufficient to induce posttraumatic epileptogenesis. A potential answer to this question comes from recent results in C1q knockout mice that have behavioral and electrographic seizures resulting from failure to prune excitatory cortical synapses during development.[133] *In vitro* slices from these animals are epileptogenic due to increased excitatory connectivity without apparent alterations in inhibitory events.

In experiments using controlled cortical impact (CCI), epileptiform activity and electrographic seizures are present in vitro at the first week after injury[10] and appear to progress with generation of "ictal" discharges lasting for many seconds by the second week. In other experiments such as those involving kainate kindling, epileptogenic activity is present early in hippocampus but goes undetected in *in vivo* recordings from the usual skull electrodes[134]. Our previous results in the undercut model provided the first proof-in principle that posttraumatic epileptogenesis, as gauged by the occurrence of epileptiform activity in *in vitro* slices, begins shortly after injury and can be prevented[80]. However this prophylaxis was only effective if the treatment, namely topical exposure of the injured cortex to tetrodotoxin (TTX) in a slow release resin, was administered for the first 3 days after injury. Later applications were ineffective at limiting the proportion of slices that were epileptogenic[89]. Thus the results revealed a brief critical period of a few days beginning after the partial isolation when the seeds for subsequent epileptogenesis are sown in the undercut cortex model. Tetrodotoxin has also been effective in decreasing axonal sprouting and rhythmic neocortical burst discharges that begin by the second day after thermocoagulation lesions in rat neocortex, although the relationship to later epileptogenesis is unclear.[110] These results with TTX appear contrary to the hypothesis that the enhanced excitability and epileptogenesis in the undercut may be due to activation of homeostatic increases in excitatory neurotransmission due to deafferentation[118,135]. It is possible that homeostatic compensatory increases in alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors do occur, but are offset by decreases in innervation of postsynaptic targets induced by the TTX treatment. Immunocytochemical analysis of undercut cortex shows that TTX blockade of activity down-regulates anatomical markers of the axonal and terminal sprouting response that are evident as early as 3 days after injury (Figure 4A–C) and are long-lasting (Figure 4D–F). Other as yet unexplored results of silencing injured cortex may account for the blockade of hyperexcitability in the undercut that outlasts the TTX treatment by many months (K.D. Graber and D.A. Prince, unpublished results). It is important to note that TTX may produce quite different (opposite) effects on epileptogenesis when given during early development in hippocampus[136], a result that emphasizes the difficulty of generalizing results from one model to another in terms of potential prophylactic approaches.

Prophylaxis of posttraumatic epileptogenesis

Potential approaches to modification of the increased excitatory sprouting and synapse formation and decreased GABAergic interneuronal structure/function, are suggested by results of experiments dealing with normal development of excitatory synapses and interneurons.

Limiting excitatory connectivity

Reactive astrogliosis is a ubiquitous pathological finding following TBI and is present in all of the models discussed above, including the undercut. Release of thrombospondins (TSPs) by astrocytes provides an important signal for excitatory synapse formation early in development[137,138] and following injury to the mature central nervous system (CNS).[139,140] The α2δ-1 voltage-gated calcium channel subunit, that is up-regulated in peripheral pain models and after brain injury, is the receptor for the antiallodynic/antiepileptic drug gabapentin (GBP)[141,142], reviewed in[143,144] and is also the receptor for TSPs[137]. GBP can block excitatory synapse formation in the developing retinogeniculate pathway by interfering with TSP actions[137]. The increased axonal sprouting and synapse formation are reduced in TSP knockout animals in a stroke model, leading to the

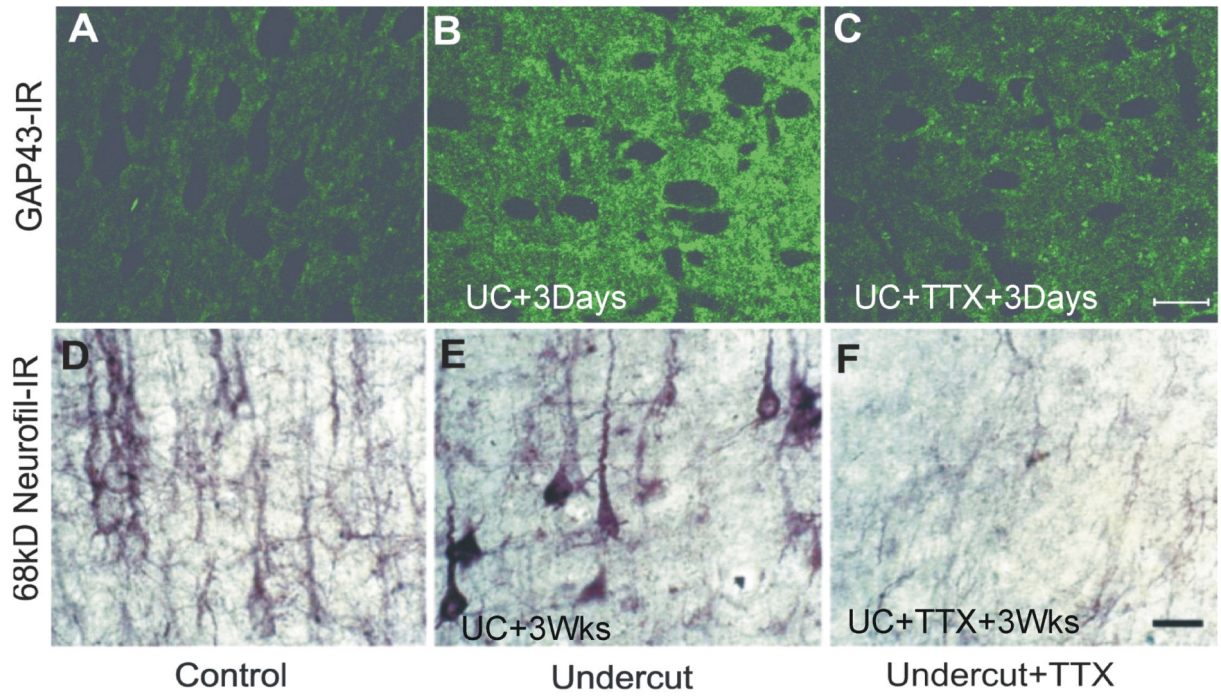

Figure 4. Immunoreactivity (IR) of axons and terminals in partially isolated neocortex. A–C: Sections through layer V of rat sensorimotor cortex reacted with growth-associated protein (GAP) 43 antibody. **D–F:** Comparable sections from rats reacted with antibody for 68-kDa neurofilaments. **A,D:** Control from layer V of hemisphere contralateral to the undercut. **B,E:** GAP43-IR (B) and 68-kDa neurofilament-IR (E) in layer V of undercuts made 3 days earlier, contralateral to A and D, respectively. **C,F:** Representative sections from undercuts of two other rats in which Elvax impregnated with tetrodotoxin was placed subdurally over the undercut area at the time of surgery. Immunocytochemistry was done after 3 days in A–C and after 3 weeks in D–F. Tetrodotoxin (TTX) treatment reduced IR for both GAP43 and neurofilament in the undercuts. Calibrations in C and F: 50 μm for A–C and D–F, respectively. From Prince DA, Parada I, Scalise K, Graber K, Jin X, Shen F. Epilepsy following cortical injury: cellular and molecular mechanisms as targets for potential prophylaxis. Epilepsia; 50 Suppl 2:30, 2009, with permission.

hypothesis that GBP would have similar actions and might be an antiepileptogenic agent in the undercut model. In recent experiments, GBP, given by sc infusion or ip for 2-3d up to 14d following the day of the undercut, decreased the proportion of slices that subsequently generated evoked epileptiform activity (Figure 5A–C; H Li, KD Graber, DA Prince. Soc Neurosci abstr, 2009). In addition, dual immunocytochemical processing of sections from the animals treated with GBP showed significantly fewer presumptive excitatory synapses (i.e. close appositions between pre- [vGLUT1] and postsynaptic markers [PSD95] (Figure 5D–F)). GBP also reduced expression of 200 kD neurofilament-IR and the numbers of neurons stained with fluorojade C (not shown), suggesting potential neuroprotective effects.

Preventing structural/functional alterations in GABAergic interneurons

The above structural changes in FS interneurons gave them an appearance that resembled, in some respects, that seen in immature GABAergic cells[121], prompting us to assess expression of BDNF in neurons of the undercut, as this trophic factor is a key molecule in regulating development and maintenance of both interneuronal and Pyr cell structure and function[121,135,145–147], reviewed in[145]. Immunoreactivity for BDNF in Pyr cells and its TrkB receptor on parvalbumin-containing interneurons and the associated mRNAs were significantly down-regulated as early as 3d after the undercut, suggesting that supplying this or another trophic factor after injury might be an approach to prevention of trauma-induced alterations in these cells (Figure 6 in[16]; see also[17]. BDNF has many potential actions including *both* enhancement of network excitation and inhibition[150,151], so that it is unclear whether the net effect of BDNF or other TrkB receptor agonists will be anti- or pro-epileptogenic at this time.

Variables such as dose level and timing or choice of mimetic molecule might allow differentiation of beneficial vs. detrimental effects.

Important unresolved issues affecting application of antiepileptogenic therapies for PTE

1. The question of adaptive vs. maladaptive changes in connectivity following injury is a key one that must be considered in approaching potential preventative treatments that decrease epileptogenic sprouting. A number of reports implicate axonal sprouting and new connections as major adaptive plastic events in recovery of function after cortical lesions[108,109]. In recent experiments in a stroke model where middle cerebral artery occlusion induces expression of TSPs in astrocytes, TSP1–2 knock-out mice showed significant defects in the axonal sprouting and synaptic density compared to wild type animals, together with defects in functional recovery[140]. The post-stroke incidence of epilepsy was not studied in these experiments; however the results, and those in the above references, provide a cautionary note.
2. A number of pathophysiological processes occur in parallel after a serious epileptogenic brain injury. Although any one of these in isolation might not induce seizure activity, in combination their effects on excitability would summate and epileptogenesis could result. Thus, a single prophylactic approach might be ineffective and a "prophylactic cocktail" might be required.
3. Two key elements in developing epileptogenesis in a variety of injury models are reductions in functional GABAergic inhibition and enhanced new excitatory connectivity. Although attempts to reverse such alterations may be effective, the relationships between both excitatory and inhibitory circuit function, circuit repair and epileptiform activity are complex. GABAergic synchronization of cortical networks occurs in epileptogenic cortical lesions[152], and in both acute[153] and genetic models of epileptiform discharge[154]. Also, depolarizing GABA responses due to altered chloride gradients occur in excitatory cells during development[155] and after injury[125,156]. These factors make the net effect of enhanced interneuronal output hard to predict. Antiepileptogenesis, through decreases in excitatory circuit activities might also have obverse effects such as decreased activation of interneurons[157]; but see[158–160] or reduced activity-dependent axonal sprouting, pathfinding and circuit repair[110,161,162].
4. As more becomes known about processes controlling excitation and inhibition during cortical development or following injury, it is possible that prophylactic therapies selectively affecting maladaptive processes might be applied. One important obstacle at this time is the unavailability of a reliable biological marker that would select for individuals who will go on to develop post-traumatic epilepsy, although it is clear that the incidence increases with the severity of brain injury (reviewed in[163]).
5. We know little about the temporal extent of critical periods in man when prophylactic intervention would be effective, or how to identify epileptogenesis "in progress". The latent period may be very long between injury and expression of behavioral seizures[1]; however the critical period for intervention could closely follow injury[89,164].
6. Finally, multiple offsetting potential effects of a given intervention are possible, such as both enhancement of excitatory connectivity together with "rescue" of inhibitory interneurons by TrkB receptor agonists (e.g. [165,166]).

The chapters in this volume suggest that significant progress is being made in understanding the basic mechanisms leading to epilepsy, and that we may have potential prophylactic therapies available in the years to come, providing that some of the issues mentioned above are settled by detailed basic and clinical investigations.

Acknowledgements

Supported by NIH grants NS12151, NS39579 and NS06477 from the NINDS and a grant from Citizens United for Research in Epilepsy.

Reference List

1. Salazar AM, Jabbari B, Vance SC, Grafman J, Amin D, Dillon JD. Epilepsy after penetrating head injury. I. Clinical correlates: a report of the Vietnam Head Injury Study. Neurology. 1985;35:1406–1414. PubMed PMID: 3929158.
2. Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. N Engl J Med. 1998;338:20–24. PubMed PMID: 9414327.
3. Frey LC. Epidemiology of posttraumatic epilepsy: a critical review. Epilepsia. 2003;44(Suppl 10):11–17.
4. Garga N, Lowenstein DH. Posttraumatic epilepsy: a major problem in desperate need of major advances. Epilepsy Curr. 2006;6(1):1–5. PubMed PMID: 16477313.
5. Dichter MA. Posttraumatic epilepsy: the challenge of translating discoveries in the laboratory to pathways to a cure. Epilepsia. 2009;50(Suppl 2):41–45.
6. Raymont V, Salazar AM, Lipsky R, Goldman D, Tasick G, Grafman J. Correlates of posttraumatic epilepsy 35 years following combat brain injury. Neurology. 2010;75(3):224–229. PubMed PMID: 20644150.
7. Giblin KA, Blumenfeld H. Is epilepsy a preventable disorder? New evidence from animal models. Neuroscientist. 2010;16(3):253–275. PubMed PMID: 20479472.
8. Hunt RF, Scheff SW, Smith BN. Regionally localized recurrent excitation in the dentate gyrus of a cortical contusion model of posttraumatic epilepsy. J Neurophysiol. 2010;103(3):1490–1500. PubMed PMID: 20089815.
9. Kharatishvili I, Pitkanen A. Posttraumatic epilepsy. Curr Opin Neurol. 2010;23(2):183–188. PubMed PMID: 20125011.
10. Yang L, Afroz S, Michelson HB, Goodman JH, Valsamis HA, Ling DS. Spontaneous epileptiform activity in rat neocortex after controlled cortical impact injury. J Neurotrauma. 2010;27(8):1541–1548. PubMed PMID: 20504156.
11. D'Ambrosio R, Hakimian S, Stewart T, Verley DR, Fender JS, Eastman CL, et al. Functional definition of seizure provides new insight into post-traumatic epileptogenesis. Brain. 2009;132(Pt 10):2805–2821. PubMed PMID: 19755519.
12. Dichter MA. Emerging concepts in the pathogenesis of epilepsy and epileptogenesis. Arch Neurol. 2009;66(4):443–447. PubMed PMID: 19364928.
13. Israelsson C, Wang Y, Kylberg A, Pick CG, Hoffer B, Ebendal T. Closed head injury in a mouse model results in molecular changes indicating inflammatory responses. J Neurotrauma. 2009.
14. Lowenstein DH. Epilepsy after head injury: an overview. Epilepsia. 2009;50(Suppl 2):4–9.
15. Pitkanen A, Lukasiuk K. Molecular and cellular basis of epileptogenesis in symptomatic epilepsy. Epilepsy Behav. 2009;14(Suppl 1):16–25. PubMed PMID: 18835369.
16. Prince DA, Parada I, Scalise K, Graber K, Jin X, Shen F. Epilepsy following cortical injury: cellular and molecular mechanisms as targets for potential prophylaxis. Epilepsia. 2009;50(Suppl 2):30–40.
17. Paradiso B, Marconi P, Zucchini S, Berto E, Binaschi A, Bozac A, et al. Localized delivery of fibroblast growth factor-2 and brain-derived neurotrophic factor reduces spontaneous seizures in an epilepsy model. Proc Natl Acad Sci U S A. 2009;106(17):7191–7196. PubMed PMID: 19366663.
18. Temkin NR. Preventing and treating posttraumatic seizures: the human experience. Epilepsia. 2009;50(Suppl 2):10–13.
19. Raghavendra RV, Dhodda VK, Song G, Bowen KK, Dempsey RJ. Traumatic brain injury-induced acute gene expression changes in rat cerebral cortex identified by GeneChip analysis, J Neurosci Res. 2003;:208–219.
20. David Y, Cacheaux LP, Ivens S, Lapilover E, Heinemann U, Kaufer D, et al. Astrocytic Dysfunction in Epileptogenesis: Consequence of Altered Potassium and Glutamate Homeostasis. J Neurosci. 2009;29:10588–10599. PubMed PMID: 19710312.
21. Vezzani A. Innate immunity and inflammation in temporal lobe epilepsy: new emphasis on the role of complement activation. Epilepsy Curr. 2008;8(3):75–77. PubMed PMID: 18488060.

22. Hicks RR, Martin VB, Zhang L, Seroogy KB. Mild experimental brain injury differentially alters the expression of neurotrophin and neurotrophin receptor mRNAs in the hippocampus. Exp Neurol. 1999;160(2):469–478. PubMed PMID: 10619564.
23. Pitkanen A, Immonen RJ, Grohn OH, Kharatishvili I. From traumatic brain injury to posttraumatic epilepsy: what animal models tell us about the process and treatment options. Epilepsia. 2009;50(Suppl 2):21–29.
24. McIntosh TK, Vink R, Yamakami I, Faden AI. Magnesium protects against neurological deficit after brain injury. Brain Res. 1989;482(2):252–260. PubMed PMID: 2784989.
25. Feeney DM, Boyeson MG, Linn RT, Murray HM, Dail WG. Responses to Cortical Injury: I. Methodology and Local Effects of Contusions in the Rat. Brain Res. 1981;211:67–77. PubMed PMID: 7225844.
26. Echlin FA, Battista A. Epileptiform seizures from chronic isolated cortex. Arch Neurol. 1963;9:154–170. PubMed PMID: 14048164.
27. Tauck DL, Nadler JV. Evidence of functional mossy fiber sprouting in hippocampal formation of kainic acid treated rats. J Neurosci. 1985;5:1016–1022. PubMed PMID: 3981241.
28. Cronin J, Dudek FE. Chronic seizures and collateral sprouting of dentate mossy fibers after kainic acid treatment in rats. Brain Res. 1988;474(1):181–184. PubMed PMID: 3214710.
29. Molnar P, Nadler JV. Mossy fiber-granule cell synapses in the normal and epileptic rat dentate gyrus studied with minimal laser photostimulation. J Neurophysiol. 1999;82(4):1883–1894. PubMed PMID: 10515977.
30. McKinney RA, Debanne D, Gahwiler BH, Thompson SM. Lesion-induced axonal sprouting and hyperexcitability in the hippocampus in vitro: implications for the genesis of post-traumatic epilepsy. Nature Med. 1997;3:990–996. PubMed PMID: 9288725.
31. Esclapez M, Hirsch JC, Ben Ari Y, Bernard C. Newly formed excitatory pathways provide a substrate for hyperexcitability in experimental temporal lobe epilepsy. J Comp Neurol. 1999;408(4):449–460. PubMed PMID: 10340497.
32. Salin P, Tseng GF, Hoffman S, Parada I, Prince DA. Axonal sprouting in layer V pyramidal neurons of chronically injured cerebral cortex. J Neurosci. 1995;15:8234–8245. PubMed PMID: 8613757.
33. Li H, Prince DA. Synaptic activity in chronically injured, epileptogenic sensory-motor neocortex. J Neurophysiol. 2002;88(1):2–12. PubMed PMID: 12091528.
34. Jin X, Prince DA, Huguenard JR. Enhanced excitatory synaptic connectivity in layer v pyramidal neurons of chronically injured epileptogenic neocortex in rats. J Neurosci. 2006;26(18):4891–4900. PubMed PMID: 16672663.
35. Ribak CE, Bradburne M, Harris AB. A preferential loss of GABAergic, symmetric synapses in epileptic foci: a quantitative ultrastructural analysis of monkey neocortex. J Neurosci. 1982;2:1725–1735. PubMed PMID: 6815309.
36. Cossart R, Dinocourt C, Hirsch JC, Merchan-Perez A, De Felipe J, Ben Ari Y, et al. Dendritic but not somatic GABAergic inhibition is decreased in experimental epilepsy. Nat Neurosci. 2001;4(1):52–62. PubMed PMID: 11135645.
37. Magloczky Z, Freund TF. Impaired and repaired inhibitory circuits in the epileptic human hippocampus. Trends Neurosci. 2005;28:334–340. PubMed PMID: 15927690.
38. Rosen GD, Jacobs KM, Prince DA. Effects of neonatal freeze lesions on expression of parvalbumin in rat neocortex. Cereb Cortex. 1998;8(8):753–761. PubMed PMID: 9863702.
39. Kumar SS, Buckmaster PS. Hyperexcitability, interneurons, and loss of GABAergic synapses in entorhinal cortex in a model of temporal lobe epilepsy. J Neurosci. 2006;26(17):4613–4623. PubMed PMID: 16641241.
40. Faria LC, Prince DA. Presynaptic inhibitory terminals are functionally abnormal in a rat model of posttraumatic epilepsy. J Neurophysiol. 2010;104(1):280–290. PubMed PMID: 20484536.
41. Kharlamov EA, Downey KL, Jukkola PI, Grayson DR, Kelly KM. Expression of GABA A receptor alpha1 subunit mRNA and protein in rat neocortex following photothrombotic infarction. Brain Res. 2008;1210:29–38. PubMed PMID: 18407248.

42. Brooks-Kayal AR, Shumate MD, Jin H, Rikhter TY, Coulter DA. Selective changes in single cell $GABA_A$ receptor subunit expression and function in temporal lobe epilepsy. Nature Med. 1998;4:1166–1172. PubMed PMID: 9771750.
43. Chu Y, Parada I, Prince DA. Temporal and topographic alterations in expression of the alpha3 isoform of Na+, K(+)-ATPase in the rat freeze lesion model of microgyria and epileptogenesis. Neuroscience. 2009;162(2):339–348. PubMed PMID: 19362129.
44. Anderson TR, Huguenard JR, Prince DA. Differential effects of Na^+/K^+ATPase blockade on cortical layer V neurons. J Physiol (Lond). 2010;588.22:4401–4414. PubMed PMID: 20819946.
45. Aronica E, Boer K, Redeker S, Spliet WG, van Rijen PC, Troost D, et al. Differential expression patterns of chloride transporters, Na+-K+-2Cl--cotransporter and K+-Cl--cotransporter, in epilepsy-associated malformations of cortical development. Neuroscience. 2007;145(1):185–196. PubMed PMID: 17207578.
46. Dzhala VI, Talos DM, Sdrulla DA, Brumback AC, Mathews GC, Benke TA, et al. NKCC1 transporter facilitates seizures in the developing brain. Nat Med. 2005;11(11):1205–1213. PubMed PMID: 16227993.
47. Shimizu-Okabe C, Okabe A, Kilb W, Sato K, Luhmann HJ, Fukuda A. Changes in the expression of cation-Cl- cotransporters, NKCC1 and KCC2, during cortical malformation induced by neonatal freeze-lesion. Neurosci Res. 2007;59(3):288–295. PubMed PMID: 17904674.
48. Jin X, Huguenard JR, Prince DA. Reorganization of Inhibitory Synaptic Circuits in Rodent Chronically Injured Epileptogenic Neocortex. Cereb Cortex.
49. Li H, Bandrowski AE, Prince DA. Cortical injury affects short-term plasticity of evoked excitatory synaptic currents. J Neurophysiol. 2005;93(1):146–156. PubMed PMID: 15342719.
50. Gutnick MJ, Prince DA. Thalamocortical relay neurons: antidromic invasion of spikes from cortical epileptogenic focus. Science. 1972;176:424–426. PubMed PMID: 4337289.
51. Pinault D. Backpropagation of action potentials generated at ectopic axonal loci: Hypothesis that axon terminals integrate local environmental signals. Brain Res Reviews.
52. De Lanerolle NC, Eid T, Von Campe G, Kovacs I, Spencer DD, Brines M. Glutamate receptor subunits GluR1 and GluR2/3 distribution shows reorganization in the human epileptogenic hippocampus. Eur J Neurosci. 1998;10(5):1687–1703. PubMed PMID: 9751141.
53. Blumcke I, Beck H, Scheffler B, Hof PR, Morrison JH, Wolf HK, et al. Altered distribution of the alpha-amino-3-hydroxy-5-methyl-4- isoxazole propionate receptor subunit GluR2(4) and the N-methyl-D-aspartate receptor subunit NMDAR1 in the hippocampus of patients with temporal lobe epilepsy. Acta Neuropathol (Berl). 1996;92:576–587. PubMed PMID: 8960315.
54. Chen HX, Xiang H, Roper SN. Impaired Developmental Switch of Short-term Plasticity in Pyramidal Cells of Dysplastic Cortex. Epilepsia. 2007;48(1):141–148. PubMed PMID: 17241221.
55. Wong RK, Bianchi R, Taylor GW, Merlin LR. Role of metabotropic glutamate receptors in epilepsy. Adv Neurol. 1999;79:685–698. PubMed PMID: 10514855.
56. Gold SJ, Hennegriff M, Lynch G, Gall CM. Relative concentrations and seizure-induced changes in mRNAs encoding three AMPA receptor subunits in hippocampus and cortex. J Comp Neurol. 1996;365:541–555. PubMed PMID: 8742301.
57. Tanaka K, Watase K, Manabe T, Yamada K, Watanabe M, Takahashi K, et al. Epilepsy and exacerbation of brain injury in mice lacking the glutamate transporter GLT-1. Science. 1997;276:1699–1702. PubMed PMID: 9180080.
58. Campbell SL, Hablitz JJ. Decreased glutamate transport enhances excitability in a rat model of cortical dysplasia. Neurobiol Dis. 2008;32(2):254–261. PubMed PMID: 18674619.
59. Boulland JL, Ferhat L, Tallak ST, Ferrand N, Chaudhry FA, Storm-Mathisen J, et al. Changes in vesicular transporters for gamma-aminobutyric acid and glutamate reveal vulnerability and reorganization of hippocampal neurons following pilocarpine-induced seizures. J Comp Neurol. 2007;503(3):466–485. PubMed PMID: 17503488.
60. Brines ML, Tabuteau H, Sundaresan S, Kim J, Spencer DD, De Lanerolle N. Regional distributions of hippocampal Na+,K(+)-ATPase, cytochrome oxidase, and total protein in temporal lobe epilepsy. Epilepsia. 1995;36(4):371–383. PubMed PMID: 7607116.

61. Grisar T. Glial and neuronal Na+-K+ pump in epilepsy. Ann Neurol. 1984;16(Suppl):S128–134. PubMed PMID: 6095737.
62. Vaillend C, Mason SE, Cuttle MF, Alger BE. Mechanisms of neuronal hyperexcitability caused by partial inhibition of Na+-K+-ATPases in the rat CA1 hippocampal region. J Neurophysiol. 2002;88(6):2963–2978. PubMed PMID: 12466422.
63. Chen K, Aradi I, Thon N, Eghbal-Ahmadi M, Baram TZ, Soltesz I. Persistently modified h-channels after complex febrile seizures convert the seizure-induced enhancement of inhibition to hyperexcitability. Nat Med. 2001;7(3):331–337. PubMed PMID: 11231632.
64. Beck H, Steffens R, Elger CE, Heinemann U. Voltage-dependent Ca2+ currents in epilepsy. Epilepsy Res. 1998;32(1–2):321–332. PubMed PMID: 9761331.
65. Kohling R. Voltage-gated sodium channels in epilepsy. Epilepsia. 2002;43(11):1278–1295. PubMed PMID: 12423377.
66. Biervert C, Schroeder BC, Kubisch C, Berkovic SF, Propping P, Jentsch TJ, et al. A potassium channel mutation in neonatal human epilepsy. Science. 1998;279:403–406. PubMed PMID: 9430594.
67. Smart SL, Lopantsev V, Zhang CL, Robbins CA, Wang H, Chiu SY, et al. Deletion of the K(V)1.1 potassium channel causes epilepsy in mice. J Physiol (Lond). 1998;20:809–819.
68. Ivens S, Kaufer D, Flores LP, Bechmann I, Zumsteg D, Tomkins O, et al. TGF-beta receptor-mediated albumin uptake into astrocytes is involved in neocortical epileptogenesis. Brain. 2007;130:535–547. PubMed PMID: 17121744.
69. Marcon J, Gagliardi B, Balosso S, Maroso M, Noe F, Morin M, et al. Age-dependent vascular changes induced by status epilepticus in rat forebrain: implications for epileptogenesis. Neurobiol Dis. 2009;34(1):121–132. PubMed PMID: 19320047.
70. Takahashi DK, Vargas JR, Wilcox KS. Increased coupling and altered glutamate transport currents in astrocytes following kainic-acid-induced status epilepticus. Neurobiol Dis. 2010.
71. Tian GF, Azmi H, Takano T, Xu Q, Peng W, Lin J, et al. An astrocytic basis of epilepsy. Nat Med. 2005;11:973–981. PubMed PMID: 16116433.
72. Pitkanen A, McIntosh TK. Animal models of post-traumatic epilepsy. J Neurotrauma. 2006;23(2):241–261. PubMed PMID: 16503807.
73. Kharatishvili I, Nissinen JP, McIntosh TK, Pitkanen A. A model of posttraumatic epilepsy induced by lateral fluid-percussion brain injury in rats. Neuroscience. 2006;140(2):685–697. PubMed PMID: 16650603.
74. Kharlamov EA, Jukkola PI, Schmitt KL, Kelly KM. Electrobehavioral characteristics of epileptic rats following photothrombotic brain infarction. Epilepsy Res. 2003;56(2–3):185–203. PubMed PMID: 14643003.
75. D'Ambrosio R, Fender JS, Fairbanks JP, Simon EA, Born DE, Doyle DL, et al. Progression from frontal-parietal to mesial-temporal epilepsy after fluid percussion injury in the rat. Brain. 2005;128(Pt 1):174–188. PubMed PMID: 15563512.
76. Dudek FE, Staley KJ. Laser scanning photostimulation: new evidence for enhanced recurrent excitation in a model of posttraumatic epilepsy. Epilepsy Curr. 2006;6(6):215–216. PubMed PMID: 17260064.
77. Graber KD, PD. Chronic partial cortical isolation. In: Pitkanen ASPaMS, editor. Models of Seizures and Epilepsy. San Diego: Elsevier Academic Press; 2006. pp. 477–493.
78. Prince DA, Tseng GF. Epileptogenesis in chronically injured cortex: in vitro studies. J Neurophysiol. 1993;69:1276–1291. PubMed PMID: 8492163.
79. Hoffman SN, Salin PA, Prince DA. Chronic neocortical epileptogenesis in vitro. J Neurophysiol. 1994;71:1762–1773. PubMed PMID: 8064347.
80. Graber KD, Prince DA. Tetrodotoxin prevents posttraumatic epileptogenesis in rats. Ann Neurol. 1999;46(2):234–242. PubMed PMID: 10443889.
81. Halpern LM. Chronically isolated aggregates of mammalian cerebral cortical neurons studied in situ. In: Purpura DP, Penry JK, Tower D, Woodbury DM, Walter R, editors. Experimental models of epilepsy--a manual for the laboratory worker. New York: Raven; 1972. pp. 197–221.

82. Sharpless SK, Halpern LM. The electrical excitability of chronically isolated cortex studied by means of permanently implanted electrodes. Electroenceph clin Neurophysiol. 1962;14:244–255. PubMed PMID: 13911417.
83. Echlin FA, Arnett V, Zoll J. Paroxysmal high-voltage and rhythmic low-voltage discharges from isolated and partially isolated human cortex. AMA Arch Neurol Psychiatry. 1952;67(5):692–693. PubMed PMID: 14914253.
84. Avramescu S, Nita DA, Timofeev I. Neocortical post-traumatic epileptogenesis is associated with loss of GABAergic neurons. J Neurotrauma. 2009;26(5):799–812. PubMed PMID: 19422294.
85. Ribak CE, Reiffenstein RJ. Selective inhibitory synapse loss in chronic cortical slabs: a morphological basis for epileptic susceptibility. Can J Physiol Pharmacol. 1982;60(6):864–870. PubMed PMID: 7116231.
86. Bush PC, Prince DA, Miller KD. Increased pyramidal excitability and NMDA conductance can explain posttraumatic epileptogenesis without disinhibition: a model. J Neurophysiol. 1999;82(4):1748–1758. PubMed PMID: 10515964.
87. Prince DA. Epileptogenic neurons and circuits. Adv Neurol. 1999;79:665–684. PubMed PMID: 10514854.
88. Grafstein B, Sastry P. Some preliminary electrophysiological studies on chronically neuronally isolated cerebral cortex. Electroencephalogr Clin Neurophysiol. 1957;9:723–725. PubMed PMID: 13480247.
89. Graber KD, Prince DA. A critical period for prevention of posttraumatic neocortical hyperexcitability in rats. Ann Neurol. 2004;55(6):860–870. PubMed PMID: 15174021.
90. Marin-Padilla M. Developmental neuropathology and impact of perinatal brain damage. II: white matter lesions of the neocortex. J Neuropathol Exp Neurol. 1997;56(3):219–235. PubMed PMID: 9056536.
91. Jacobs KM. PIPD. Enhanced c-fos staining in two post-lesional models of cortical hyperexcitability: neonatal freeze lesions and partial cortical isolations. Epilepsia. 2001;42(Suppl 7):221. Ref Type: Abstract.
92. Scoville WB. Selective cortical undercutting as a means of modifying and studying frontal lobe function in man; preliminary report of 43 operative cases. J Neurosurg. 1949;6(1):65–73. PubMed PMID: 18106833.
93. Scoville WB. Late results of orbital undercutting. Report of 76 patients undergoing quantitative selective lobotomies. Am J Psychiatry. 1960;117:525–532. PubMed PMID: 13749417.
94. Cajal SRy. Study of traumatic degeneration in the cerebral cortex. In: May RM, editor. Degeneration and regeneration of the nervous system. London: Oxford Univ. Press; 1928. pp. 656–692.
95. Purpura DP, Housepian EM. Morphological and physiological properties of chronically isolated immature neocortex. Exp Neurol. 1961;4:377–401. PubMed PMID: 14037425.
96. Sutula T, He XX, Cavazos J, Scott G. Synaptic reorganization in the hippocampus induced by abnormal functional activity. Science. 1988;239:1147–1150. PubMed PMID: 2449733.
97. Mello LE, Cavalheiro EA, Tan AM, Kupfer WR, Pretorius JK, Babb TL, et al. Circuit mechanisms of seizures in the pilocarpine model of chronic epilepsy: cell loss and mossy fiber sprouting. Epilepsia. 1993;34:985–995. PubMed PMID: 7694849.
98. Represa A, Jorquera I, Le Gal La, Salle G, Ben-Ari Y. Epilepsy induced collateral sprouting of hippocampal mossy fibers: does it induce the development of ectopic synapses with granule cell dendrites. Hippocampus. 1993;3:257–268.
99. Perez Y, Morin F, Beaulieu C, Lacaille JC. Axonal sprouting of CA1 pyramidal cells in hyperexcitable hippocampal slices of kainate-treated rats. Eur J Neurosci. 1996;8:736–748. PubMed PMID: 9081625.
100. Buckmaster PS, Zhang GF, Yamawaki R. Axon sprouting in a model of temporal lobe epilepsy creates a predominantly excitatory feedback circuit. J Neurosci. 2002;22(15):6650–6658. PubMed PMID: 12151544.
101. Buckmaster PS, Dudek FE. Neuron loss, granule cell axon reorganization, and functional changes in the dentate gyrus of epileptic kainate-treated rats. J Comp Neurol. 1997;385(3):385–404. PubMed PMID: 9300766.
102. Smith BN, Dudek FE. Network Interactions Mediated by New Excitatory Connections Between CA1 Pyramidal Cells in Rats With Kainate-Induced Epilepsy. J Neurophysiol. 2002;87(3):1655–1658. PubMed PMID: 11877537.
103. Babb TL, Kupfer WR, Pretorius JK, Crandall PH, Levesque MF. Synaptic reorganization by mossy fibers in human epileptic fascia dentata. Neuroscience. 1991;42:351–363. PubMed PMID: 1716744.

104. Babb TL, Pretorius JK, Kupfer WR, Mathern GW, Crandall PH, Levesque MF. Aberrant synaptic reorganization in human epileptic hippocampus: evidence for feedforward excitation. Dendron. 1992;1:7–25.
105. Masukawa LM, Uruno K, Sperling M, O'Connor MJ, Burdette LJ. The functional relationship between antidromically evoked field responses of the dentate gyrus and mossy fiber reorganization in temporal lobe epileptic patients. Brain Res. 1992;579:119–127. PubMed PMID: 1623399.
106. Isokawa M, Levesque MF, Babb TL, Engel J Jr. Single mossy fiber axonal systems of human dentate granule cells studied in hippocampal slices from patients with temporal lobe epilepsy. J Neurosci. 1993;13:1511–1522. PubMed PMID: 8463831.
107. Marco P, DeFelipe J. Altered synaptic circuitry in the human temporal neocortex removed from epileptic patients. Exp Brain Res. 1997;114:1–10. PubMed PMID: 9125446.
108. Dancause N, Barbay S, Frost SB, Plautz EJ, Chen D, Zoubina EV, et al. Extensive cortical rewiring after brain injury. J Neurosci. 2005;25(44):10167–10179. PubMed PMID: 16267224.
109. Lee JK, Kim JE, Sivula M, Strittmatter SM. Nogo receptor antagonism promotes stroke recovery by enhancing axonal plasticity. J Neurosci. 2004;24(27):6209–6217. PubMed PMID: 15240813.
110. Carmichael ST, Chesselet MF. Synchronous neuronal activity is a signal for axonal sprouting after cortical lesions in the adult. J Neurosci. 2002;22:6062–6070. PubMed PMID: 12122067.
111. Christman CW, Salvant JB Jr, Walker SA, Povlishock JT. Characterization of a prolonged regenerative attempt by diffusely injured axons following traumatic brain injury in adult cat: a light and electron microscopic immunocytochemical study. Acta Neuropathol (Berl). 1997;94:329–337. PubMed PMID: 9341933.
112. Povlishock JT, Kontos HA. Continuing axonal and vascular change following experimental brain trauma. Cent Nerv Syst Trauma. 1985;2(4):285–298. PubMed PMID: 3836013.
113. Dickson TC, Adlard PA, Vickers JC. Sequence of cellular changes following localized axotomy to cortical neurons in glia-free culture. J Neurotrauma. 2000;17(11):1095–1103. PubMed PMID: 11101211.
114. Chuckowree JA, Vickers JC. Cytoskeletal and morphological alterations underlying axonal sprouting after localized transection of cortical neuron Axons in vitro. J Neurosci. 2003;23:3715–3725. PubMed PMID: 12736342.
115. Dinocourt C, Gallagher SE, Thompson SM. Injury-induced axonal sprouting in the hippocampus is initiated by activation of trkB receptors. Eur J Neurosci. 2006;24(7):1857–1866. PubMed PMID: 17040478.
116. Scharfman HE, Goodman JH, Sollas AL, Croll SD. Spontaneous limbic seizures after intrahippocampal infusion of brain-derived neurotrophic factor. Exp Neurol. 2002;174(2):201–214. PubMed PMID: 11922662.
117. Nita DA, Cisse Y, Timofeev I, Steriade M. Waking-sleep modulation of paroxysmal activities induced by partial cortical deafferentation. Cereb Cortex. 2007;17(2):272–283. PubMed PMID: 16495431.
118. Timofeev I, Bazhenov M, Avramescu S, Nita DA. Posttraumatic epilepsy: the roles of synaptic plasticity. Neuroscientist. 2010;16(1):19–27. PubMed PMID: 19359668.
119. D'Ambrosio R, Perucca E. Epilepsy after head injury. CURRENT OPINION IN NEUROLOGY. 2004;17:731–735. PubMed PMID: 15542983.
120. Graber KDKVNPIaPDA. Parvalbumin-containing interneurons are spared in the undercut model of posttraumatic epileptogenesis., 1999. Epilepsia. 1999;40(Suppl 7):31. Ref Type: Abstract. PubMed PMID: 10487171.
121. Jin X, Hu H, Mathers PH, Agmon A. Brain-derived neurotrophic factor mediates activity-dependent dendritic growth in nonpyramidal neocortical interneurons in developing organotypic cultures. J Neurosci. 2003;23(13):5662–5673. PubMed PMID: 12843269.
122. Harris KM, Sultan P. Variation in the number, location and size of synaptic vesicles provides an anatomical basis for the nonuniform probability of release at hippocampal CA1 synapses. Can J Physiol Pharmacol. 1995;34(11):1387–1395.
123. Pierce JP, Lewin GR. An ultrastructural size principle. Neuroscience. 1994;58(3):441–446. PubMed PMID: 8170532.

123a. Faria LC, Parada I, Prince DA. Interneuronal calcium channel abnormalities in posttraumatic epileptogenic neocortex. Neurobiol. Dis. 2012;45:821–828. PubMed PMID: 22172650.
123b. Ma Y, Prince DA. Functional alterations in GABAergic fast-spiking interneurons in chronically injured epileptogenic neocortex. Neurobiol. Dis. 2012. doi:10.1016/j.nbd.2012.03.027. Epub.
124. Nabekura J, Ueno T, Okabe A, Furuta A, Iwaki T, Shimizu-Okabe C, et al. Reduction of KCC2 expression and GABAA receptor-mediated excitation after in vivo axonal injury. J Neurosci. 2002;22(11):4412–4417. PubMed PMID: 12040048.
125. van den Pol AN, Obrietan K, Chen G. Excitatory actions of GABA after neuronal trauma. J Neurosci. 1996;16:4283–4292. PubMed PMID: 8753889.
126. Jin XM, Huguenard JR, Prince DA. Impaired Cl- extrusion in layer V pyramidal neurons of chronically injured epileptogenic neocortex. J Neurophysiol. 2005;93:2117–2126. PubMed PMID: 15774713.
127. Jin X, Huguenard JR, Prince DA. Reorganization of Inhibitory Synaptic Circuits in Rodent Chronically Injured Epileptogenic Neocortex. Cereb Cortex. 2010 Sep 20. [Epub ahead of print]. PubMed PMID: 20855494.
128. Lee L, Parada I, Prince DA. Downregulation of the α3 subunit of NA+K+ ATPAse in a model of post-traumatic epileptogenesis. Epilepsia. 2006;47:3.058.
129. Spencer SS, Sperling MRSDAKP. Intracranial electrodes. In: Engel T, JraTAP, editors. Epilepsy, a comprehensive textbook. Philadelphia: Lippencott, Williams & Wilkins; 2010. pp. 1791–1815.
130. Yang L, Benardo LS. Epileptogenesis following neocortical trauma from two sources of disinhibition. J Neurophysiol. 1997;78:2804–2810. PubMed PMID: 9356429.
131. Nilsson P, Ronne-Engström E, Flink R, Ungerstedt U, Carlson H, Hillered L. Epileptic seizure activity in the acute phase following cortical impact trauma in rat. Brain Res. 1994;637:227–232. PubMed PMID: 8180800.
132. Topolnik L, Steriade M, Timofeev I. Partial cortical deafferentation promotes development of paroxysmal activity. Cereb Cortex. 2003;13(8):883–893. PubMed PMID: 12853375.
133. Chu Y, Jin X, Parada I, Pesic A, Stevens B, Barres B, et al. Enhanced synaptic connectivity and epilepsy in C1q knockout mice. Proc Natl Acad Sci U S A. 2010;107(17):7975–7980. PubMed PMID: 20375278.
134. Hellier JL, Patrylo PR, Dou P, Nett M, Rose GM, Dudek FE. Assessment of inhibition and epileptiform activity in the septal dentate gyrus of freely behaving rats during the first week after kainate treatment. J Neurosci. 1999;19(22):10053–10064. PubMed PMID: 10559413.
135. Turrigiano GG. Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same. Trends Neurosci. 1999;22:221–227. PubMed PMID: 10322495.
136. Galvan CD, Hrachovy RA, Smith KL, Swann JW. Blockade of neuronal activity during hippocampal development produces a chronic focal epilepsy in the rat. J Neurosci. 2000;20:2904–2916. PubMed PMID: 10751443.
137. Eroglu C, Allen NJ, Susman MW, O'Rourke NA, Park CY, Ozkan E, et al. Gabapentin receptor alpha2delta-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis. Cell. 2009;139(2):380–392. PubMed PMID: 19818485.
138. Christopherson KS, Ullian EM, Stokes CCA, Mullowney CE, Hell JW, Agah A, et al. Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis. Cell. 2005;120(3):421–433. PubMed PMID: 15707899.
139. Lin TN, Kim GM, Chen JJ, Cheung WM, He YY, Hsu CY. Differential regulation of thrombospondin-1 and thrombospondin-2 after focal cerebral ischemia/reperfusion. Stroke. 2003;34(1):177–186. PubMed PMID: 12511771.
140. Liauw J, Hoang S, Choi M, Eroglu C, Choi M, Sun GH, et al. Thrombospondins 1 and 2 are necessary for synaptic plasticity and functional recovery after stroke. J Cereb Blood Flow Metab. 2008;28(10):1722–1732. PubMed PMID: 18594557.
141. Luo ZD, Chaplan SR, Higuera ES, Sorkin LS, Stauderman KA, Williams ME, et al. Upregulation of dorsal root ganglion (alpha)2(delta) calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. J Neurosci. 2001;21(6):1868–1875. PubMed PMID: 11245671.

142. Luo ZD, Calcutt NA, Higuera ES, Valder CR, Song YH, Svensson CI, et al. Injury type-specific calcium channel alpha 2 delta-1 subunit up-regulation in rat neuropathic pain models correlates with antiallodynic effects of gabapentin. J Pharmacol Exp Ther. 2002;303(3):1199–1205. PubMed PMID: 12438544.
143. Maneuf YP, Luo ZD, Lee K. alpha2delta and the mechanism of action of gabapentin in the treatment of pain. Semin Cell Dev Biol. 2006;17(5):565–570. PubMed PMID: 17067834.
144. Field MJ, Cox PJ, Stott E, Melrose H, Offord J, Su TZ, et al. Identification of the alpha2-delta-1 subunit of voltage-dependent calcium channels as a molecular target for pain mediating the analgesic actions of pregabalin. Proc Natl Acad Sci U S A. 2006;103(46):17537–17542. PubMed PMID: 17088553.
145. McAllister AK, Katz LC, Lo DC. Neurotrophins and synaptic plasticity. Annu Rev Neurosci. 1999;22:295–318. PubMed PMID: 10202541.
146. Marty S, Berzaghi M, Berninger B. Neurotrophins and activity-dependent plasticity of cortical interneurons. Trends Neurosci. 1997;20(5):198–202. PubMed PMID: 9141194.
147. Croll SD, Wiegand SJ, Anderson KD, Lindsay RM, Nawa H. Regulation of neuropeptides in adult rat forebrain by the neurotrophins BDNF and NGF. Eur J Neurosci. 1994;6:1343–1353. PubMed PMID: 7981876.
148. Burkhalter J, Fiumelli H, Allaman I, Chatton JY, Martin JL. Brain-derived neurotrophic factor stimulates energy metabolism in developing cortical neurons. J Neurosci. 2003;23(23):8212–8220. PubMed PMID: 12967982.
149. Massa SM, Yang T, Xie Y, Shi J, Bilgen M, Joyce JN, et al. Small molecule BDNF mimetics activate TrkB signaling and prevent neuronal degeneration in rodents. J Clin Invest. 2010;120(5):1774–1785. PubMed PMID: 20407211.
150. Danzer SC, McNamara JO. Localization of brain-derived neurotrophic factor to distinct terminals of mossy fiber axons implies regulation of both excitation and feedforward inhibition of CA3 pyramidal cells. J Neurosci. 2004;24(50):11346–11355. PubMed PMID: 15601941.
151. Koyama R, Ikegaya Y. To BDNF or not to BDNF: that is the epileptic hippocampus. Neuroscientist. 2005;11(4):282–287. PubMed PMID: 16061515.
152. D'Antuono M, Louvel J, Kohling R, Mattia D, Bernasconi A, Olivier A, et al. GABAA receptor-dependent synchronization leads to ictogenesis in the human dysplastic cortex. Brain. 2004;127(Pt 7):1626–1640. PubMed PMID: 15175227.
153. Marchionni I, Maccaferri G. Quantitative dynamics and spatial profile of perisomatic GABAergic input during epileptiform synchronization in the CA1 hippocampus. J Physiol. 2009;587(Pt 23):5691–5708. PubMed PMID: 19840998.
154. Klaassen A, Glykys J, Maguire J, Labarca C, Mody I, Boulter J. Seizures and enhanced cortical GABAergic inhibition in two mouse models of human autosomal dominant nocturnal frontal lobe epilepsy. Proc Natl Acad Sci U S A. 2006;103(50):19152–19157. PubMed PMID: 17146052.
155. Tyzio R, Minlebaev M, Rheims S, Ivanov A, Jorquera I, Holmes GL, et al. Postnatal changes in somatic gamma-aminobutyric acid signalling in the rat hippocampus. Eur J Neurosci. 2008;27(10):2515–2528. PubMed PMID: 18547241.
156. Pathak HR, Weissinger F, Terunuma M, Carlson GC, Hsu FC, Moss SJ, et al. Disrupted dentate granule cell chloride regulation enhances synaptic excitability during development of temporal lobe epilepsy. J Neurosci. 2007;27(51):14012–14022. PubMed PMID: 18094240.
157. Sloviter RS. Permanently altered hippocampal structure, excitability, and inhibition after experimental status epilepticus in the rat: the "dormant basket cell" hypothesis and its possible relevance to temporal lobe epilepsy. Hippocampus. 1991;1:41–66. PubMed PMID: 1688284.
158. Zhang W, Yamawaki R, Wen X, Uhl J, Diaz J, Prince DA, et al. Surviving hilar somatostatin interneurons enlarge, sprout axons, and form new synapses with granule cells in a mouse model of temporal lobe epilepsy. J Neurosci. 2009;29(45):14247–14256. PubMed PMID: 19906972.
159. Halabisky B, Parada I, Buckmaster PS, Prince DA. Excitatory Input onto Hilar Somatostatin Interneurons is Increased in a Chronic Model of Epilepsy. J Neurophysiol. 2010.

160. Sloviter RS, Zappone CA, Harvey BD, Bumanglag AV, Bender RA, Frotscher M. “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. 2003;459(1):44–76. PubMed PMID: 12629666.
161. Katz LC, Shatz CJ. Synaptic activity and the construction of cortical circuits. Science. 1996;274(5290):1133–1138. PubMed PMID: 8895456.
162. Ming G, Henley J, Tessier-Lavigne M, Song H, Poo M. Electrical activity modulates growth cone guidance by diffusible factors. J Physiol (Lond). 2001;29(2):441–452.
163. Chen JW, Ruff RL, Eavey R, Wasterlain CG. Posttraumatic epilepsy and treatment. J Rehabil Res Dev. 2009;46(6):685–696. PubMed PMID: 20104398.
164. Yang L, Benardo LS. Valproate prevents epileptiform activity after trauma in an in vitro model in neocortical slices. Epilepsia. 2000;41(12):1507–1513. PubMed PMID: 11114207.
165. Binder DK, Croll SD, Gall CM, Scharfman HE. BDNF and epilepsy: too much of a good thing. Trends Neurosci. 2001;24:47–53. PubMed PMID: 11163887.
166. Reibel S, Depaulis A, Larmet Y. BDNF and epilepsy--the bad could turn out to be good. Trends Neurosci. 2001;24(6):318–319. PubMed PMID: 11421232.

License