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POSTTRAUMATIC EPILEPSY

From traumatic brain injury to posttraumatic epilepsy: What animal models tell us about the process and treatment options

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Summary

A large number of animal models of traumatic brain injury (TBI) are already available for studies on mechanisms and experimental treatments of TBI. Immediate and early seizures have been described in many of these models with focal or mixed type (both gray and white matter damage) injury. Recent long-term video-electroencephalography (EEG) monitoring studies have demonstrated that TBI produced by lateral fluid-percussion injury in rats results in the development of late seizures, that is, epilepsy. These animals develop hippocampal alterations that are well described in status epilepticus–induced spontaneous seizure models and human posttraumatic epilepsy (PTE). In addition, these rats have damage ipsilaterally in the cortical injury site and thalamus. Although studies in the trauma field provide a large amount of information about the molecular and cellular alterations corresponding to the immediate and early phases of PTE, chronic studies relevant to the epileptogenesis phase are sparse. Moreover, despite the multiple preclinical pharmacologic and cell therapy trials, there is no information available describing whether these therapeutic approaches aimed at improving posttraumatic recovery would also affect the development of lowered seizure threshold and epilepsy. To make progress, there is an obvious need for information exchange between the trauma and epilepsy fields. In addition, the inclusion of epilepsy as an outcome measure in preclinical trials aiming at improving somatomotor and cognitive recovery after TBI would provide valuable information about possible new avenues for antiepileptogenic interventions and disease modification after TBI.

KEY WORDS: Antiepileptic drug, Epileptogenesis, Fluid-percussion injury, Recovery, Surrogate marker.

Heterogeneity of TBI in Humans—A Challenge for Animal Model Development

Traumatic brain injury (TBI) in humans is a heterogeneous disorder that can differ in the type of injury, distribution of damage, or mechanisms of damage (Gennarelli & Graham, 2005). Regarding the type of injury, TBI can be classified into those injuries that result from a direct mechanical force to the head occurring at the time of injury (primary TBI, Table 1), or those that result from nonmechanically induced secondary complications that were or were not initiated by the primary damage (secondary TBI, Table 1). The extent and distribution of damage can vary from focal to diffuse, comprising a variety of different types of lesions (Table 1). Mechanisms of damage can vary from the direct impact to the skull/brain (e.g., a fall) to the acceleration/deceleration type of injury (e.g., rapid head rotation in a car accident) (Table 1). This variability challenges not only modelers of TBI, but in particular those who wish to develop models for posttraumatic epilepsy (PTE). This relates to the fact that information about the risk factors for PTE originates mostly from retrospective epidemiologic studies rather than prospective

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Table 1. Classification of traumatic brain injury, type of damage, and mechanisms of damage according to Gennarelli and Graham (2005)

Traumatic brain injury
Primary
Injury to scalp
Skull fracture
Surface contusion/laceration
Intracranial hematoma
Diffuse axonal injury
Diffuse vascular injury
Injury to cranial nerves and pituitary stalk
Secondary
Hypoxia–ischemia
Swelling/edema
Raised intracranial pressure and associated vascular changes
Meningitis/abscess
Damage after brain injury
Focal
Injury to scalp
Skull fracture
Surface contusion/laceration
Intracranial hematoma
Raised intracranial pressure and associated vascular changes
Diffuse (multifocal)
Diffuse axonal injury
Hypoxic–ischemic damage
Meningitis
Vascular injury
Mechanisms of damage
Contact
Injury to scalp
Fracture of skull with or without an associated extradural hematoma
Surface contusions and lacerations and associated intracerebral hematomas
Acceleration/deceleration
Tearing of bridging veins with formation of subdural hematoma
Diffuse axonal injury, tissue tears, and associated intracerebral hematomas
Diffuse vascular injury

studies that would have carefully characterized the details of injury type, distribution, or the mechanisms of damage associated with subsequent epileptogenesis using novel imaging and other methodologies (see Pitkänen & McIntosh, 2006).

Currently available TBI models can be divided into focal models of TBI, diffuse brain injury models, mixed models of focal and diffuse brain injury, combined injury models, experimental models of coma, and models of repetitive concussive injury (Cernak, 2005; Morales et al., 2005). Most of these models are performed in rodents and utilize a direct impact on the epidural space or the brain tissue (Cernak, 2005). Acceleration models resulting in widespread white matter damage (diffuse axonal injury, DAI) have been successfully applied in primates and miniature swine that have a larger amount of white matter than rodents (Gennarelli et al., 1981; Smith et al., 1997a). Although none of the TBI models recapitulates fully the human syndrome, it is well acknowledged that these models are useful for understanding the molecular mechanisms of TBI and testing the efficacy of novel treatments for TBI (Cernak, 2005; Morales et al., 2005). Therefore, there are plenty of possibilities when planning to use TBI models as a starting point for modeling PTE.

Using TBI Models for Modeling PTE

A PubMed search in April 2008 for the term ''TBI model'' yielded approximately 900 references, whereas the search for the term ''post-traumatic epilepsy model'' resulted in only around 40 references. In most of these models, PTE has been triggered by iron injection to the cortex or the amygdala, or by cortical undercut (Willmore et al., 1978; see Prince et al., 2009). Only recently, models developed in the trauma field to investigate human TBI have been used to assess the development of lowered seizure threshold and epilepsy (Table 2). The large majority of these studies have used lateral fluid-percussion (LFP) or central fluid-percussion (CFP) TBI models that produce both gray matter and white matter damage (Fig. 1). Other models used include weight drop, controlled cortical impact, or penetrating ballistic injury models (see Table 2). All of these models belong to mixed type or focal models of TBI (Morales et al., 2005).

In Table 2, we have divided the observations made about the posttraumatic brain excitability into immediate (within 24 h postinjury), early (between 24 h and 1 week postinjury), and late changes (>1 week postinjury) (Frey, 2003). At the immediate phase, a subpopulation of animals that experienced either weight drop or LFP-induced TBI were reported to experience spontaneous postinjury seizures (Nilsson et al., 1994; Kharatishvili et al., 2006). In addition, seizure threshold for induced seizures was reduced (Roncati Zanier et al., 2003) and in vitro studies demonstrated hyperexcitability in the CA1 subfield of the hippocampus (Reeves et al., 2000; Griesemer & Mautes, 2007). In addition, during the first week after TBI (early phase, between 24 h and 1 week postinjury), spontaneous, presumably injury-related seizures can still occur as reported by Williams and coworkers in the new penetrating ballistic-like injury (Williams et al., 2005, 2006). At this later phase, most of the in vitro electrophysiologic studies have demonstrated increased excitability not only in the CA1 (Reeves et al., 1997; Akasu et al., 2002) but also in the dentate gyrus (Lowenstein et al., 1992; Coulter et al., 1996; Reeves et al., 1997; Toth et al., 1997; Santhakumar et al., 2001; Witgen et al., 2005; Tran et al., 2006). In addition to changes in local excitability, Baker et al. (2002) reported an axonal conductance defect in the

Table 2. Summary of studies that have investigated changes in brain excitability after traumatic brain injury

Injury type	Postinjury assessment	Preparation	Change in excitability	Reference
Immediate phase (<24 h)				
Weight drop	0–2 h post-TBI	In vivo	82% of rats had electrographic generalized seizures	Nilsson et al. (1994)
LFP	1 h post-TBI	Hippocampal slice	Increased duration of evoked presynaptic volleys in CA1	Reeves et al. (2000)
LFP	1–4 h post-TBI	Hippocampal slice	Depolarizing shift in the resting membrane potential of dentate interneurons (recovers in 4 days)	Ross & Soltesz (2000)
LFP	1 h post-TBI	In vivo	Lowered threshold for kainate-induced behavioral seizures	Roncati Zanier et al. (2003)
LFP	0–24 h post-TBI	In vivo	Up to 30% of rats had behavioral clonic seizures	Kharatishvili et al. (2006)
Weight drop	2 h and 24 h post-TBI	Hippocampal slice	CA1 pyramidal cell hyperexcitability (not detected in CA3). Normalized within 3 days	Griesemer & Mautes (2007)
Early phase (≤1 week)				
LFP	1 week post-TBI	In vivo	Increased granule cell hyperexcitability	Lowenstein et al. (1992)
LFP	1 week post-TBI	Hippocampal-entorhinal slices	Increased stimulus-induced afterdischarge duration and self-sustained epileptic activity in dentate gyrus	Coulter et al. (1996)
LFP	2 days post-TBI	In vivo	Decreased inhibition in CA1 Increased inhibition in dentate gyrus	Reeves et al. (1997)
LFP	1 week post-TBI	Hippocampal slice	Decreased feed-forward $GABA_A$ receptor-mediated inhibition of granule cells	Toth et al. (1997)
LFP	1 week post-TBI	Hippocampal slice	Mossy cell and granule cell hyperexcitability	Santhakumar et al. (2000)
LFP	1 week post-TBI	Hippocampal slice	Dentate gyrus hyperexcitability to low-frequency stimulation (recovers in 1 month)	Santhakumar et al. (2001)
LFP	1 week post-TBI	Hippocampal slice	CA1 hyperexcitability	Akasu et al. (2002)
CFP	3 h–7 days post-TBI	Coronal slice with corpus callosum	Axonal conductance defect in corpus callosum	Baker et al. (2002)
LFP (mice)	6–8 days post-TBI	Hippocampal slice	Enhanced inhibition in CA1 Reduced inhibition in the dentate gyrus	Witgen et al. (2005)
Penetrating ballistic-like injury	0–72 h	In vivo	Seizures in 14% of animals	Williams et al. (2006)
LFP (mice)	7 days post-TBI	Hippocampal slice	Bilateral dentate gyrus hyperexcitability	Tran et al. (2006)
Late Phase (>1 week)				
CFP	PTZ kindling started 24 h after TBI	In vivo	No difference in kindling rate as compared to controls	Hamm et al. (1995)
LFP	15 days post-TBI	In vivo	Increased inhibition in dentate gyrus	Reeves et al. (1997)
LFP	3 months post-TBI	Hippocampal - entorhinal slice	Decrease in the threshold for generation of self-sustaining epileptiform activity to high-frequency stimulation in CA1	Santhakumar et al. (2001)
Weight drop	3 weeks post-TBI	Hippocampal slice	Bilateral hyperexcitability of the granule cell and molecular layers of dentate gyrus	Golarai et al. (2001)
Weight drop	15 weeks post-TBI	In vivo Hippocampal slice	Increased susceptibility to PTZ-induced seizures Bilateral hyperexcitability of the granule cell and molecular layers of dentate gyrus	Golarai et al. (2001)

Continued

Table 2. Continued

Injury type	Postinjury assessment	Preparation	Change in excitability	Reference
LFP	8–10 weeks post-TBI	Cortical slice	Cortical hyperexcitability	D'Ambrosio et al. (2004)
LFP	2–16 weeks post-TBI	In vivo	Spontaneous seizures originating in the frontoparietal cortex	D'Ambrosio et al. (2004)
rpFPI	Up to 7 months post-TBI	In vivo	Spontaneous hippocampal seizures in addition to cortical seizures	D'Ambrosio et al. (2005)
LFP	Up to 1 year post-TBI	In vivo	Up to 50% of rats have electrographic seizures clonic seizures	Kharatishvili et al. (2006)
LFP (mice)	30 days post-TBI	Hippocampal slice	Dentate gyrus hyperexcitability ipsilaterally but not contralaterally	Tran et al. (2006)
LFP	Up to 1 year post-TBI	In vivo	Epileptiform electrographic interictal spiking in 80% of rats	Kharatishvili et al. (2007)
CCI (P16-18)	2 weeks post-TBI (P34–40)	In vivo	No change in limbic, hindbrain or forebrain seizure threshold	Statler et al. (2008)
	6 weeks post-TBI (P60–63)		Decreased forebrain (minimal clonic seizure) threshold	

CCI, controlled cortical impact; CFP, central fluid-percussion traumatic brain injury (TBI); GABA, γ-amino butyric acid; LFP, lateral fluid-percussion TBI; P, postnatal day; PTZ, pentylenetetrazol; rpFPI, rostral parasagittal fluid-percussion injury. All experiments were performed in rats unless otherwise indicated.

Table 3. Comparison of epilepsy phenotypes in posttraumatic and post–status epilepticus models

Epilepsy phenotype	TBI Lateral fluid-percussion Kharatishvili et al. (2006)	SE Amygdala stimulation Nissinen et al. (2000)
Epileptogenesis		
Duration of latency	Several months	Days–1 month
% of rats with seizures	50%	80–100%
Epilepsy		
Mean seizure frequency	0.3/day	8/day
Maximal seizure frequency	Up to 1/day	Up to 30/day
Mean seizure duration	104 s	49 s
Day–night cycle	44% lights on	57% lights on
Response to AEDs	No data	Yes
Comorbidities		
Memory impairment	Yes	Yes
Sensorimotor impairment	Yes	No data
Drug-refractoriness	No data	Yes

AED, antiepileptic drug; SE, status epilepticus; TBI, traumatic brain injury.

corpus callosum. Whether it has an effect on seizure spread at later stages remains to be studied.

A survey of conventional animal models in the trauma field indicates that late spontaneous seizures or epilepsy have consistently been reported only in the rat fluid-percussion TBI model, which is the most commonly used model of human closed head TBI (D'Ambrosio et al., 2004, 2005; Kharatishvili et al., 2006). Interestingly, as compared to the most commonly used epileptogenesis models that are induced by status epilepticus (SE), in PTE induced by LFP injury the epileptogenesis phase is longer, seizure frequency is substantially lower, and most of the seizures are secondarily generalized rather than partial (Table 3; Nissinen et al., 2000; Kharatishvili et al., 2006). In the rat weight-drop model the threshold for pentylenetetrazol (PTZ)–induced seizures is reduced but no spontaneous seizures have been reported (Golarai et al., 2001). Recently, Statler et al. (2008) reported lowered minimal clonic seizure threshold in the mouse controlled cortical impact (CCI) model. Although reports about the occurrence of spontaneous seizures have been sparse, which may partly relate to low seizure frequency, observations available from in vitro slice studies support the idea that cortical and hippocampal excitability are chronically increased in a variety of TBI models (Table 2).

There are several caveats to consider when interpreting the experimental data available. A large majority of the studies characterizing post-TBI changes in excitability have investigated rats with focal or mixed type TBI, that is, models in which white matter damage is not the dominant pathologic feature. This may impose limitations on data interpretation, in particular when assessing the

association of type of damage with risk of epileptogenesis (e.g., focal gray matter damage vs. DAI). In addition, little information is available about the development of epilepsy in mice with TBI, although such information would be valuable in guiding the use of genetically modified mice in search of risk genes for PTE. Furthermore, very little information is available about the excitability change after TBI in immature animals, even though childhood PTE is not uncommon (Statler, 2006). Moreover, combining TBI with other factors such as hypoxia, hyperthermia, intracerebral bleeding, infection, or SE that compromise the outcome in the clinical setting could provide useful information about the mechanisms and conditions that increase the risk of PTE. We will focus next on the fluid-percussion TBI model, the only model, so far, where the occurrence of spontaneous seizures has been consistently demonstrated.

Epileptogenesis versus Recovery

LFP injury causes both primary and secondary damage to the brain. The primary damage is caused by the impact itself, and it initiates ionic, molecular, and cellular alterations within seconds. This is followed by secondary damage that is composed of neurodegeneration, neurogenesis, astrocytosis, microgliosis, axonal and myelin injury, axonal sprouting, vascular damage, and angiogenesis (see Reilly, 2001; Thompson et al., 2005; Pitkänen & McIntosh, 2006). Previous histologic analyses of the LFP injury model demonstrated that these alterations can happen in the injured cortex, perifocal area, underlying hippocampus, and/or thalamus (Thompson et al., 2005). Most of the data concerning the progression of damage have been collected during the first 1–2 months postinjury, which corresponds also to the time period when most of the electrophysiologic alterations implying increased excitability of injured tissue have been performed (Thompson et al., 2005). Very few studies have addressed the dynamics of molecular and cellular alterations at the later stages when the spontaneous seizures appear (Kharatishvili et al., 2006). The application of MRI in the analysis of cellular and pathway alterations will likely provide useful information about the association of cellular pathology with epileptogenesis, and help to understand why epileptogenesis is seen only in a subpopulation of animals (Kharatishvili et al., 2007).

Well-documented functional consequences of LFP-induced injury include somatomotor and cognitive impairment (Thompson et al., 2005). Interestingly, somatomotor impairment is partly recoverable within the few weeks or months postinjury. This is associated with regenerative cellular processes in the brain such as axonal sprouting and revascularization. It is important to bear in mind that epileptogenesis is underway in parallel to the physical recovery of animals, at least in subpopulations of animals (Fig. 2).

Preclinical Trials in Experimental Models of TBI—Do They Pave the Way for Finding Antiepileptogenic or Disease-Modifying Treatments for PTE?

A large number of different treatments have been tested to enhance posttraumatic recovery. Pharmacologic approaches include use of compounds reducing excitotoxicity, calcium channel blockage, free radical scavengers, antiinflammatory agents, neurotrophic factors, caspase inhibitors, calpain inhibitors, hormonal treatments, augmentation of various neurotransmitter systems, anticoagulants, poly (ADP-ribose) polymerase (PARP) inhibitors, and antiepileptic drugs (AEDs) (for a comprehensive review, see Marklund et al., 2006). More recently, cell transplantation including genetically manipulated cell types have been tested as a recovery-enhancing treatment option (see Pitkänen et al., 2006).

Both in pharmacologic and cell therapy studies, outcome measures have included the effects of treatments on the edema development, volume of cortical lesions, severity and extent of hippocampal neurodegeneration, axonal injury, somatomotor function, and learning and memory. Although positive effects have been obtained in several experimental trials, treatments have not yet been translated to clinical practice. From the epileptogenesis point of view it is, however, conspicuous that the development of late spontaneous seizures has never been an outcome measure in preclinical TBI trials. This creates a question: whether some of these treatments were actually antiepileptogenic or disease-modifying, if epilepsy would have been analyzed as an outcome measure.

Use of AEDs at Early Postinjury Phase—Any Harm?

As discussed by Temkin (see the present volume), there is no evidence that any of the AEDs, when administered after TBI, would have any antiepileptogenic or disease-modifying effects on the development of PTE in humans. Conversely: do AEDs compromise the postinjury recovery?

Table 4 summarizes the effects of AEDs on posttraumatic recovery in animal models. So far, remacemide, topiramate, talampanel, lacosamide, and carisbamate have been investigated. No major harmful or beneficial effects have been reported. However, studies in which AEDs had been administered for a longer period after TBI and in which outcome measures had been assessed months later are not available.

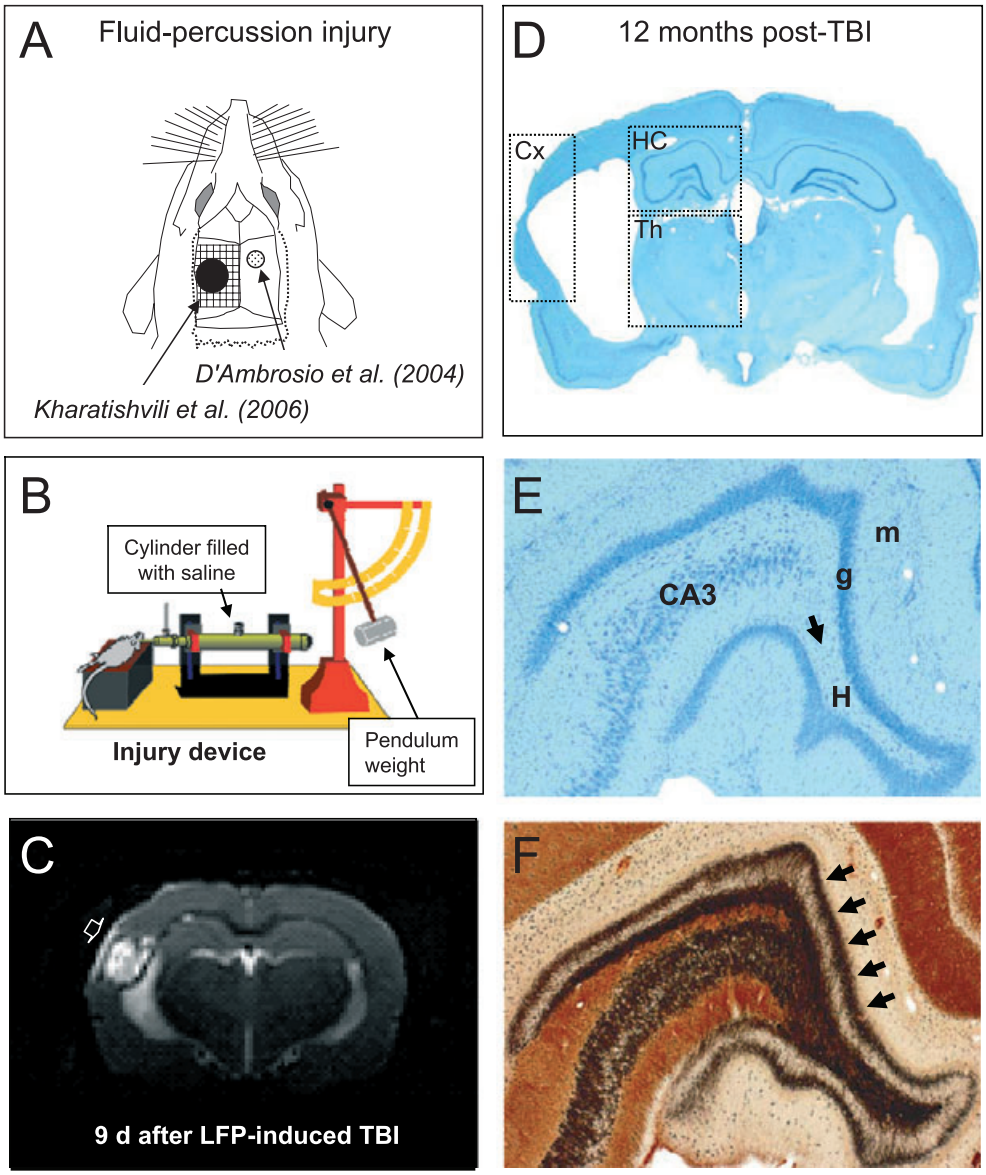

Figure 1.
(**A**) Location of craniectomy in a model of fluid-percussion (FP) traumatic brain injury (TBI) in the two laboratories that have shown the development of epilepsy in this model of TBI. (**B**) Injury device that is used for induction of FP injury. The strength of the injury is adjusted by pendulum height. After release, the pendulum hits the cork piston, sealing one end of the saline-filled cylinder that transmits the liquid pulse to the epidural space. (**C**) The injury develops gradually (see also Fig. 2). Here the location and extent of injury is shown in a T_2-weighted image (open arrow) at 9 days after lateral FP injury. (**D**) A thionin-stained coronal section from the brain of a rat subjected to lateral FP (LFP) brain injury. The animal had been followed for 12 months postinjury and had a total of 11 seizures during seven video-EEG (electroencephalography) monitoring sessions (63 recording days). The first spontaneous seizure was recorded 3 months after injury. Seventy-one percent of seizures were secondarily generalized. In addition to the injury site in the cortex, structural alterations are clear ipsilaterally in the hippocampus (HC) and thalamus (Th). (**E**) Higher magnification photomicrograph from a thionin-stained hippocampus from a rat with LFP injury–induced posttraumatic epilepsy (PTE). Note the loss of hilar cells (indicated with an arrow). (**F**) Timm-stained hippocampal section from the rat with PTE demonstrating mossy fiber sprouting in the inner molecular layer (arrows). CA3, CA3 pyramidal cell layer of the hippocampus; g, granule cell layer; f, the dentate gyrus; H, hilus; m, molecular layer.

Table 4. Effects of administration of antiepileptic drugs on posttraumatic recovery in experimental models

AED	Beginning and duration of treatment	Outcome measures (time of analysis)	Effect	Reference
Remacemide	15 min postinjury	Cortical lesion (48 h postinjury)	⇩	Smith et al. (1997b)
	Rx single dose	Learning and memory (48 h postinjury)	⇔	
Topiramate	30 min postinjury	Edema (48 h postinjury)	⇔	Hoover et al. (2004)
	Rx for 32 h	Neurodegeneration (48 h postinjury)	⇔	
		Memory (48 h postinjury)	⇔	
		Learning (4 weeks postinjury)	⇩	
		Motor recovery (4 weeks postinjury)	⇧	
		Rotating pole (4 weeks postinjury)	⇧	
Talampanel	30 min postinjury	Cortical lesion (7 days postinjury)	⇩	Belayev et al. (2001)
	Rx for 3 day	CA1 degeneration (7 days postinjury)	⇩	
Lacosamide	30 min postinjury	Lesion severity (2 weeks postinjury)	⇔	Nissinen et al. (2006)
	Rx for 3 day	Motor function (2 weeks postinjury)	⇔	
		Learning and memory (2 weeks postinjury)	⇔	
Carisbamate (RWJ-333369)	15 min postinjury	Edema (48 h postinjury)	⇔	Keck et al. (2007)
	Rx for 1 day	Lesion size (4 week postinjury)	⇔	
		Motor function (up to 4 week postinjury)	⇔	
		Learning (4 week postinjury)	⇔	

AED, antiepileptic drug.

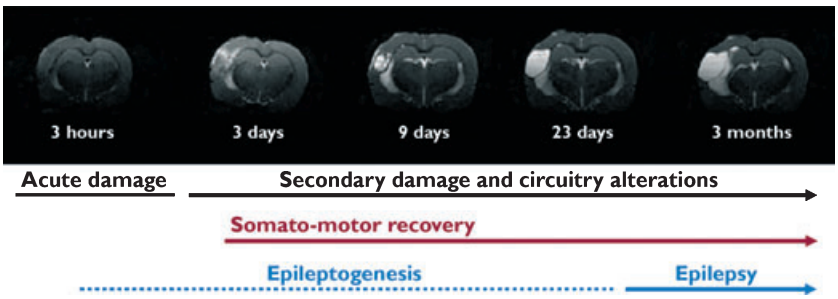

Figure 2.
The brain faces many challenges after traumatic brain injury (TBI). Acute damage related to the primary impact is followed by a myriad of secondary molecular and cellular changes, including delayed neurodegeneration, neurogenesis, axonal injury, axonal sprouting, gliosis, and angiogenesis. Many of these alterations are apparently needed for successful recovery that occurs over the weeks and months postinjury. In parallel to the recovery process, a subpopulation of animals undergo epileptogenesis, culminating in the occurrence of spontaneous seizures. The great challenge is to differentiate those mechanisms that lead to favorable and unfavorable recovery.
Epilepsia © ILAE

Future Challenges

We already have plenty of information on postinjury neurogenesis, synaptogenesis, and revascularization, which presumably contribute to the repair process. This raises a question: Is epilepsy a concomitant of an effective recovery process, a by-product of aberrant recovery, or a complication that hampers good clinical outcome? Furthermore, would the best recovery enhancements also modify the epileptogenic process? To find the answers it will be necessary to differentiate the molecular mechanisms that lead to favorable recovery from those that compromise it. Data available also show that modeling of PTE is laborious. Therefore, there is an urgent need for development of bio/surrogate markers that would predict epileptogenesis after different types of brain injuries and could be used for selection of animals for studies aimed at understanding the mechanisms of posttraumatic epileptogenesis, preclinical trials testing novel treatments, and also for the follow-up of treatment efficacy.

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