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REVIEW

Epilepsy Related to Traumatic Brain Injury

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Abstract Post-traumatic epilepsy accounts for 10–20 % of symptomatic epilepsy in the general population and 5 % of all epilepsy. During the last decade, an increasing number of laboratories have investigated the molecular and cellular mechanisms of post-traumatic epileptogenesis in experimental models. However, identification of critical molecular, cellular, and network mechanisms that would be specific for post-traumatic epileptogenesis remains a challenge. Despite of that, 7 of 9 proof-of-concept antiepileptogenesis studies have demonstrated some effect on seizure susceptibility after experimental traumatic brain injury, even though none of them has progressed to clinic. Moreover, there has been some promise that new clinically translatable imaging approaches can identify biomarkers for post-traumatic epileptogenesis. Even though the progress in combating post-traumatic epileptogenesis happens in small steps, recent discoveries kindle hope for identification of treatment strategies to prevent post-traumatic epilepsy in at-risk patients.

Keywords Biomarker · Controlled cortical impact · Epileptogenesis · Epigenetics · Lateral fluid-percussion · Magnetic resonance imaging · microRNA · Traumatic brain injury

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Introduction

Traumatic brain injury (TBI) refers to a brain injury caused by an external mechanical force such as a blow to the head, concussive forces, acceleration–deceleration forces, blast injury, or a projectile missile, such as a bullet [1]. TBI is recognized as a critical public health problem worldwide [1, 2]. According to the World Health Organization, TBI will surpass many other diseases as the major cause of death and disability by the year 2020 [3]. Though the problems experienced by those suffering TBI are often not visible (e.g., impairments in memory or cognition), the disease is often referred to as the "silent epidemic" [4].

TBI can be classified based on the injury mechanism [5]. Depending on the characteristics of the mechanical force (amplitude, duration, velocity, acceleration), injury can be static or dynamic. The severity of brain injury is commonly rated using the 15-point Glasgow Coma Scale (GCS), which assesses 3 major parameters: verbal, motor, and eye-opening reactions to stimuli [6]. In mild TBI, the GCS score is ≥13, in moderate TBI it is 9–12, and in severe TBI it is ≤8. Importantly, the same injury severity may represent different pathological and clinical endophenotypes that depend on the injury mechanism (e.g., static *vs* dynamic) or distribution and type of damage (e.g., gray *vs* white matter) (see [7]). In some endophenotypes, post-traumatic epilepsy (PTE) is a significant life-compromising component [8].

In this review we will summarize the concepts and mechanisms proposed to be associated with the development of PTE, existing animal data, and key questions that remain open.

From TBI to PTE

Process of Epileptogenesis in Humans

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the

neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one unprovoked seizure [9]. Depending on the time delay from the TBI to the occurrence of the first seizure, post-TBI seizures have been categorized into immediate (<24 h), early (1–7 days), or late seizures (>1 week after TBI) [8]. Thus, when TBI is associated with one unprovoked late seizure it qualifies for diagnosis of PTE.

PTE accounts for 10–20 % of symptomatic epilepsy in the general population and 5 % of all epilepsy [10, 11]. Based on epidemiologic studies on civilian or military populations, most of which were conducted before modern imaging era, the risk factors for PTE include old age, penetrating injuries, injury severity (GCS<10), biparietal or multiple contusions, intracranial hemorrhage, frontal or temporal location of the lesion, >5 mm brain midline shift, duration of coma >24 h, loss of consciousness >24 h, prolonged length of post-traumatic amnesia, multiple intracranial procedures, and the occurrence of early post-traumatic seizures [10, 12–17]. Related to methodology, many of the identified risk factors directly or indirectly reflect the severity of brain injury, and strengthen the view that the risk for PTE increases with the severity of TBI.

The latency from the TBI to the occurrence of the first seizure can vary largely. Epidemiologic studies show that a 30-year cumulative incidence of epilepsy is 2.1 % for mild, 4.2 % for moderate, and 16.7 % for severe injuries [8, 18]. After the first late seizure, 86 % of patients have been reported to develop a second seizure within 2 years, suggesting the establishment of an epileptogenic process [19]. Moreover, the risk of developing epilepsy remains higher for a longer period of time after severe than moderate TBI (10 *vs* 30 years) [8]. Further, recent magnetoencephalography studies have revealed that some patients without reported seizures after mild TBI have epileptiform spikes when assessed at 12–140 months after TBI [20].

Information on genetic risk factors for outcome from TBI are emerging, but few studies have assessed the linkage of genes to PTE [21]. One study found that the ApoE4 allele is associated with a 2.4-fold increased risk of late post-traumatic seizures after moderate-to-severe TBI [22]. This was not, however, confirmed by another study [23, 24]. The study by Anderson et al. [24] also did not reveal any association between PTE and polymorphism in HP2-2. Wagner et al. [25] found two single nucleotide polymorphisms in the adenosine A1 receptor that were associated with later seizures in civilian population of patients with severe TBI. More recently, they reported that polymorphisms in the *GAD1* gene (but not in *GAD2*) were associated with the occurrence of late post-traumatic seizures [26]. One study found an association between variation in a gene encoding methylenetetrahydrofolate reductase and the risk of PTE in a military population [27].

The detailed information about the endophenotypes of patients that associate with the highest risk of PTE would be of great value for attempts to model PTE in clinically relevant ways. Such information would also guide the search of mechanisms and biomarkers (or surrogate markers) for epileptogenesis.

Process of Epileptogenesis in Experimental Models

Data from several laboratories are now available to demonstrate that several models commonly used to investigate the molecular and cellular mechanisms of TBI have chronically lowered seizure threshold or even spontaneous seizures (Table 1). Chronically increased seizure susceptibility to chemoconvulsants or electroshock has been demonstrated in weight-drop, fluid-percussion (FP), controlled cortical impact (CCI), and closed skull models of TBI (Table 1). Chronic spontaneous seizures were reported after FP- and CCI-induced TBI, both in rats and mice. Acute epileptiform activity/seizures (up to 3 days after injury) has been reported in a rat model of penetrating ballistic injury [28–31] and blast injury [32], but whether late spontaneous seizures develop after these injury mechanisms remains to be studied. So far, studies have not found acute/late seizures after repeated mild concussive TBI [33]. We will next focus on models in which spontaneous seizures develop after TBI.

Epilepsy in the FP Model

Lateral FP-induced TBI produces both focal and diffuse (mixed) brain injury [34]. It reproduces several aspects of human TBI, including focal contusion, petechial intraparenchymal and subarachnoid hemorrhages, tissue tears, and traumatic axonal injury. The sequelae include blood–brain-barrier disruption, white matter damage, neuronal loss, gliosis, altered cerebral metabolism, altered cerebral blood flow, and altered brain electrical activity. The damage appears most severe in the ipsilateral cortex, hippocampus, and thalamus, but milder lesions can also be detected contralaterally. More chronic network alterations include neurogenesis with axonal and dendritic plasticity. The molecular and cellular changes can continue for weeks and months, and they associate with behavioral impairments and cognitive comorbidities [35].

Kharatishvili et al. [36] monitored adult Sprague–Dawley rats with lateral FP injury (FPI) over a period of 12 months with periodic 24/7 video electroencephalography (EEG), and demonstrated that 50 % of rats developed PTE. The seizures were partial or secondarily generalized, and lasted for about 60–110 s. A substantial proportion of animals had lowered seizure thresholds. These data have now been reproduced by several laboratories (Table 1). Rostral parasagittal FP was also reported to trigger epileptogenesis and the occurrence of

Table 1 Summary of *in vivo* recorded changes in excitability in different models of traumatic brain injury. Only the data that were collected at least 1 week after injury are included

Model	Species, age, strain, preparation	Seizure susceptibility *in vivo*	Epilepsy					Reference
			Animals with epilepsy (%)	Latency to spontaneous seizure	Seizure frequency	Seizure duration (s)	Epileptiform spiking or EDs in EEG	
Weight-drop (Feeney)	Rat, adult	increased susceptibility to PTZ-induced seizures, 15 weeks post-TBI	n.d.	n.d.	n.d.	n.d.	n.d.	[83]
Weight-drop (Marmarou)	Mouse, adult	Increased seizure susceptibility to ECS-induced seizures, 7 days post-TBI	n.d.	n.d.	n.d.	n.d.	n.d.	[71]
Central FPI	Rat, adult	No difference in PTZ-kindling, started 24 h post-TBI	n.d.	n.d.	n.d.	n.d.	n.d.	[51]
Parasagittal FPI	Rat, P32-35	n.d.	100 % (follow-up: 7 months)	~2 weeks	Up to 7 seizures/h	Ictal episodes ≤10 s (up to 99 s)	n.d.	[37, 38, 75]
	Rat, adult	Increased susceptibility to PTZ-induced seizures, 12 weeks post-TBI	n.d.	n.d.	n.d.	n.d.	n.d.	[74]
	Rat, adult	Increased susceptibility to PTZ-induced seizures, 2 weeks post-TBI	No	n.d.	n.d.	n.d.	n.d.	[50]
Lateral FPI	Rat, adult	Granule cell hyperexcitability, 1 week post-TBI	n.d.	n.d.	n.d.	n.d.	n.d.	[84]
	Rat, adult	Increased inhibition in dentate gyrus, 15 days post-TBI	n.d.	n.d.	n.d.	n.d.	n.d.	[85]
	Rat, P19	No change in PTZ-seizure threshold, 20 weeks post-TBI	0 % (behavioral observation)	n.d.	n.d.	n.d.	n.d.	[86]
	Rat, adult	Increased susceptibility to PTZ-induced seizures, 12 months post-TBI	50 % (follow-up: 12 months)	4–11 weeks	0.3/day	104	80 %	[36, 65]
	Rat, P21-22	Increased susceptibility to kainate-induced seizures, 6 weeks post-TBI	n.d.	n.d.	n.d.	n.d.	n.d.	[70]
	Rat, adult	No change in susceptibility to fluorothyl-induced seizures, 3 and 6 weeks post-TBI	n.d.	n.d.	n.d.	n.d.	n.d.	[72]
	Mouse, adult	Increased susceptibility to PTZ-induced seizures, 6 months post-TBI	6 % (follow-up: 9 months)	n.d.	0.1/d	91	yes	[39]
	Rat, adult	n.d.	52 % spontaneous seizures (30 %) or ED (22 %)	n.d.	6.3/2 week	53	11.5/2 week	[67]
	Mouse, adult	Increased susceptibility to PTZ-induced seizures, 30 days post-TBI	n.d.	n.d.	n.d.	n.d.	n.d.	[60]
CCI	Rat, P16-18	Unchanged threshold for tonic hindlimb extension or minimal clonic seizures in electroconvulsive seizure threshold test, testing on P34-40 Reduced threshold for minimal clonic seizures, testing on P60-63	n.d.	n.d.	n.d.	n.d.	n.d.	[87]

Table 1 (continued)

Model	Species, age, strain, preparation	Seizure susceptibility *in vivo*	Epilepsy		Seizure frequency	Seizure duration (s)		Reference
			Animals with epilepsy (%)	Latency to spontaneous seizure			Epileptiform spiking or EDs in EEG	
	Rat, P17	n.d.	1 of 8 (13 %) (follow-up: 11 months)	n.d.	n.d.	45–60 s	88 % had epileptiform spiking	[44]
	Mouse, adult	n.d.	20 % (mild) – 36 % (severe injury)	n.d. (monitoring 42–71 days post-TBI)	n.d	~90 s (behavioral assessment)	n.d.	[41]
	Mouse, adult	n.d.	40 %	6.5±1.3 weeks	n.d.	n.d.	n.d.	[42]
	Mouse, adult	Increased susceptibility to PTZ-induced seizures, 6 months	9 % (follow-up: 9 months)	n.d.	0.2/day	50	Yes	[39]
	Mouse, adult	post-TBI	50 % of vehicle* treated animals	82.3±10.2 days	0.55±0.16/day	35.5±2.8	Rare	[43]

ED = epileptiform discharges; EEG = electroencephalography; FPI = fluid-percussion injury; CCI = controlled cortical impact; PTZ = pentylenetetrazol; ECS = electroconvulsive shock; n.d. = no data

*Data from vehicle-treated mice that were included in rapamycin treatment study.

spontaneous seizures [37, 38]. Data from several laboratories show that lateral FP can trigger increased seizure susceptibility, which can be detected after administration of pentylenetetrazol (PTZ) or kainate. Lateral FPI also triggers susceptibility to seizures induced by PTZ as well as spontaneous seizures in mice [39, 40].

Epilepsy in the CCI Model

CCI injury to the lateral cortex causes a focal brain injury that is associated with a spectrum of contusion injuries, including intraparenchymal petechial hemorrhages that are accompanied by epidural and subdural hematomas. Histologic analysis reveals widespread cortical gray matter damage, as well as axonal injury in the adjacent white matter, corpus callosum, and capsula interna. Degeneration is present not only in the cortex, but also in the hippocampus and thalamus.These anatomical changes associate with a spectrum of cognitive and motor deficits [34]. Recently, elegant studies from Hunt et al. [41, 42] demonstrated that CCI-induced TBI in the lateral cortex triggers the development of PTE in CD1 mice. Behavioral seizures were observed in 20 % of animals with mild injury and in 36 % with severe injury when observed 42–71 days after injury. Guo et al. [43] complemented these data by showing that up to 50 % of CD1 mice developed epilepsy by 4 months after CCI (impact depth=2 mm) when continuously monitored by video-EEG. Our data show also increased susceptibility to PTZ-induced seizures and the occurrence of electrographic spontaneous seizures after lateral CCI injury in C57BL/6J mice [39]. Statler et al. [44] monitored rats with lateral CCI at postnatal day 17 with video-EEG over a period of 4–11 months after TBI. They reported that 88 % of rats developed epileptiform spiking, and 13 % of animals (1 of 8) had spontaneous recurrent seizures. Recently, Yang et al. [45] recorded spontaneous epileptiform activity in cortical slices that were taken from rats that had experienced CCI injury 14–16 days earlier at postnatal day 24.

Mechanisms of PTE

The aftermath of TBI consist of several phases, including primary injury, evolution of the primary injury, secondary injury, and regeneration [46, 47]. Primary injury occurs at the moment of TBI and is accompanied by massive disturbance of the cellular ion homeostasis, release of the excitatory neurotransmitters, and exacerbation of excitotoxicity. The secondary injury occurs in the hours and days after the primary injury, and is an indirect result of the insult. It includes a complex set of molecular changes and cellular processes, some of which may also be relevant to post-traumatic epileptogenesis. However, few reports have specifically

linked the observed post-injury molecular changes with epileptogenesis. Further, little is known of whether the alterations contributing to epileptogenesis are separate or overlapping compared with those relevant to post-injury recovery [46, 48, 49]. For example, PTZ (30 mg/kg)-induced seizures in rats that had experienced lateral FPI 2 weeks earlier exacerbated cortical damage [50]. Another report, however, suggests that exposure of rats with moderate central FPI to PTZ kindling (once daily injections of 25 mg/kg) beginning at 24 h post-injury improved performance in the Morris water-maze when tested at 25–29 days after TBI [51].

Even though data from human PTE is meager, available studies show hippocampal neurodegeneration, as well as mossy fiber sprouting [52]. Approximately 53 % of patients with post-traumatic temporal lobe epilepsy have mesial temporal lobe sclerosis on magnetic resonance imaging (MRI). It is, however, important to note that it is not uncommon that TBI results in multifocal pathology [53, 54]. Moreover, Vespa et al. [55] suggest that hippocampal atrophy detected at the chronic post-injury phase could be caused by (prolonged) seizures at the acute post-TBI phase. Tomkins et al. [56] pointed out the possible role of BBB damage in PTE by showing that cortical BBB permeability was higher in TBI patients with epilepsy than those without, whereas the size of cortical lesion did not differ. Interestingly, a recent analysis of the resected pericontusional cortex demonstrated remarkable degeneration of subpopulations of inhibitory neurons, but no information was available about whether any of these patients developed epilepsy in follow-up [57, 58].

What are the molecular changes underlying circuitry reorganization during epileptogenesis? We recently conducted a meta-analysis of published gene array data after TBI and status epilepticus (SE) [59]. When the lists of genes regulated during post-TBI and post-SE epileptogenesis were compared, only 46 out of 624 regulated genes were found to have abnormal regulation in more than one study. Seventeen of 46 genes (40 %) were regulated in both SE and TBI models, indicating similarity in molecular events during epileptogenesis between different etiologies. The genes regulated by both SE and TBI were *CALM3*, *CAMK2B*, *CTSB*, *CTSS*, *DBI*, *DNAJC3*, *DNAJC5*, *GABRD*, *GFAP*, *GRN*, *HPCA*, *IL6R*, *NPC2*, *NPTX2*, *PTPN6*, *S100B*, and *SPARC*. One interesting subcategory of molecular reorganization is the development of various types of channelopathies, which, to

Table 2 Effect of traumatic brain injury (TBI) on histone modifications, DNA methylation, and levels of microRNAs (miRNA) in experimental models and in humans

Model	Species	Tissue	Timing	Finding	Reference
Histone modification or DNA methylation					
CCI	Rat (P17)	HC	<72 h	H3 acetylation ⇩, H3 methylation ⇩	[88]
Weight-drop	Rat	Cx	<96 h	Methylation ⇩	[89]
Weight-drop	Rat	Cx	≤14 days	Dnmt1 localization in astrocytes	[90]
CCI	Mouse	HC	≥ 4 weeks	H3 acetylation ±0	[91]
CCI	Rat (P17)	HC	≤14 days	Methylation of IGF-1B promoter ⇧ Increase in H3 activation marks at promoter and exon 5 region of IGF-1B	[92]
microRNAs					
Parasagittal FPI	Rat	Cx	<72 h	Altogether: 5⇩, 19⇧ miR-21 ⇧ at all time points	[93]
CCI	Rat	HC	3 and 24 h	Altogether: 50⇩, 35⇧ (of 444) 8 verified (signal transduction, transcriptional regulation, proliferation, differentiation)	[94]
Severe TBI	Human (n=47)	Plasma	ASAP	Altogether: 33⇩, 19⇧ (of 875) 8 miRNAs in TBI only (miR-16, miR-92a, miR-765)	[95]
CCI	Rat	HC	<15 days	miR-21 (enzyme-linked receptor signaling, transcriptional regulation, developmental processes)	[96]
Parasagittal FPI	Rat	Cx	<24 h	Altogether: 8⇩, 7⇧ (of 388) Modified by therapeutic hypothermia	[97]
Mild TBI	Human (n=9)	PBMC	?	18 regulated (of 1500) 3 diagnostic for mTBI	[98]
Blast injury	Mouse	Cerebellum	6 h	miR-132⇩ cholinergic anti-inflammatory signaling	[99]

CCI = controlled cortical impact; FPI = fluid-percussion injury; HC = hippocampus; Cx = cortex; PBMC = peripheral blood mononuclear cells; ASAP = as soon as possible; Dnmt1 = DNA methyl transferase 1; IGF-1B = insulin-like growth factor 1B

date, have been demonstrated to affect both gamma aminobutyric acid$_A$ receptors and sodium and potassium channels (see [60]). Further studies are needed to reveal whether any of these genes form a target to combat post-traumatic epileptogenesis.

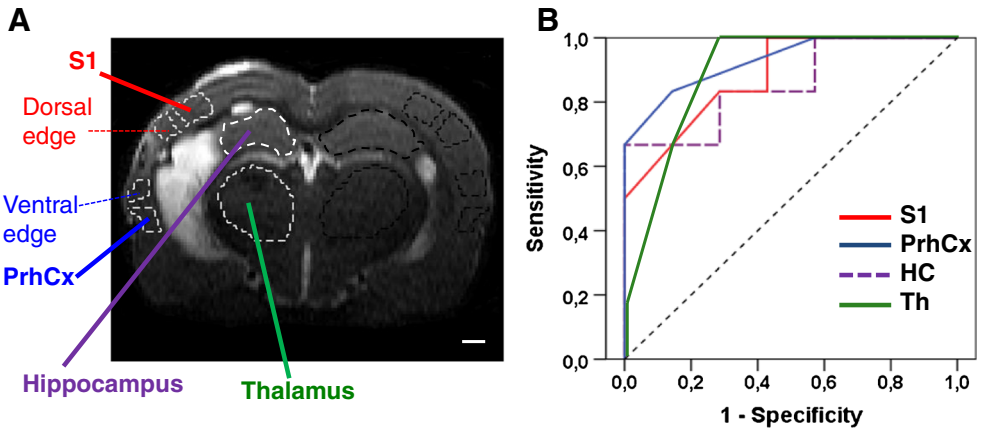
In addition to changes in transcription, post-translational modifications and epigenetic changes have been described after TBI (Table 2 and references therein). In most of the studies assessing histone modifications, DNA methylation, or microRNAs the analysis has been done within 72 h of TBI, and none of the reports has specifically addressed the contribution of changes to epileptogenesis. As only two studies have been conducted for human TBIs, the data available do not allow any comparisons of experimental and clinical findings.

Biomarkers for Epileptogenesis After Brain Injury

Currently, we have no biomarkers to identify patients at risk for PTE. Also, studies available on candidate biomarkers that can possibly be used to diagnose TBI and predict post-injury functional outcome provide no information on whether the TBI biomarkers could be used as PTE biomarkers [61, 62].

The most promising data related to biomarking epileptogenesis come from imaging studies. Long-term MRI studies have indicated that the progression of pathology has a different temporal course in the cortex, hippocampus, and thalamus [63, 64]. In addition to apparent neurodegeneration, long-term alterations include changes in axons/myelin, as well as in the vasculature [65, 66]. Importantly, not only epileptogenesis, but also the extent and temporal progression of neuropathologic changes, vary among animals [63].

So far, correlations have been found between increased seizure susceptibility and diffusion changes or hypometabolism by arterial spin-labeling in MRI in the hippocampus [65, 66]. Recently, Schultz et al. [67] reported that abnormalities in the surface morphology of the ipsilateral hippocampus present at 1 week after lateral FPI predicted the occurrence of epilepsy 6 months after TBI [67]. We recently investigated whether quantitative T2, T1ρ, and diffusion (Dav) assessed with MRI at 9 days, 23 days, or 2 months after TBI in the peri-lesional cortex, thalamus, and hippocampus would predict seizure susceptibility in the PTZ test at 12 months after TBI [68]. Our data showed that the highest predictive value for the development of seizure susceptibility at 12 months post-TBI was achieved by co-assessment of the Dav in the peri-lesional cortex and the thalamus 2 months after TBI. Importantly, assessment of individual MRI parameters in the peri-lesional cortex or the thalamus at 9 days after TBI also provided high sensitivity and specificity for the prediction of increased seizure susceptibility at 12 months after TBI (Fig. 1).



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MRI	ROI	AUC	Sensitivity at 90% Specificity
T1σ	S1 cortex	0.881*	63%
T1σ	Perirhinal cortex	0.929**	80%
T2	Thalamus	0.893*	77%
T1σ	Hippocampus	0.857*	67%

Fig. 1 (**a**) Coronal T2-weighted image from a rat with lateral fluid-percussion-induced TBI 23 days earlier, demonstrating the regions of interests (dashed lines), from which T2 and T1σ (**c**) were analyzed. (**b**) Receiver–operating characteristics for parameters in (**c**). Note that including data from the hippocampus (HC) for the calculation of the area under curve (AUC) did not increase sensitivity. (**c**) Summary of parameters with the highest sensitivity at 90 % specificity 9 days after TBI regarding prediction of seizure susceptibility 12 months after TBI. *$P \leq 0.05$, **$P \leq 0.01$ AUC compared with the area under diagonal line. For details, see [68]. PrhCx = perirhinal cortex; S1 = somatosensory cortex 1, Th=thalamus

Table 3 Disease-modifying effects of different treatments after traumatic brain injury (TBI) in experimental models

Drug	Mechanism	Model	Disease-modifying effect		Reference
			Antiepileptogenesis	Comorbidity modification*	
SR141716A	CB1 receptor antagonist	Lateral FPI-induced TBI in rats	Seizure susceptibility to kainate ⇩	n.d.	[70]
Minozac	Reduction of pro-inflammatory cytokine production by activated glia	Closed skull TBI (CD1 mouse)	Seizure susceptibility to PTZ and electroshock ⇩	Yes	[71]
Ketogenic diet	Multiple	Lateral FPI-induced TBI in rats	No effect on fluorothyl-induced seizures	n.d.	[72]
Hypothermia	Multiple	Parasagittal FPI-induced TBI in rats	Seizure susceptibility to PTZ ⇩	n.d.	[74]
Focal passive cooling	Multiple	Parasagittal FPI-induced TBI in rats	Yes	n.d.	[75]
Creatine	Reduction of oxidative stress	Parasagittal FPI-induced TBI in rats	No effect on seizure susceptibility to PTZ	Yes	[76]
Ceftriaxone	Stimulation of glutamate transporter in astrocytes	Lateral FPI-induced TBI in rats	Yes	Yes	[78]
Rapamycin	mTOR inhibition	Controlled cortical impact in CD1 mice	Yes	Yes	[43]
Treadmill exercise	Reduction of oxidative stress	Parasagittal FPI-induced TBI in rats	Seizure susceptibility to PTZ ⇩	Yes	[80]

mTOR = mammalian target of rapamycin; FPI = fluid percussion injury; PTZ = pentylenetetrazol; n.d. = no data

*Included change in biochemical or structural pathology

Taken together, studies from different laboratories provide great hope that it will be possible to follow specific molecular or network changes related to epileptogenesis, and that the first applications of MRI biomarkers could become available for preclinical use.

Proof-of-Concept Antiepileptogenesis Studies After TBI

A large number of preclinical trials have been conducted to improve motor and cognitive recovery from TBI, but none of these studies has assessed seizure susceptibility or epilepsy as an outcome measure [59, 69]. Recently, however, 9 studies have made attempts to modify post-traumatic epileptogenesis in experimental models (Table 3). The first was the study conducted by Echegoyen et al. [70], who induced epileptogenesis by lateral FP-induced TBI, and administered the cannabinoid receptor 1 antagonist, SR141716A (Rimonabant) as a single injection 2 mins after injury. The threshold for kainate-induced seizures was assessed at 6 weeks after TBI. The TBI-associated reduction in the latency to kainate-induced seizures was prevented by SR141716A. Also, the total time spent in seizures after kainate administration was reduced in the SR141716A group compared with the vehicle group. Importantly, no positive effect of treatment was found if SR141716A was administered 20 mins after TBI.

Chrzaszcz et al. [71] used the closed-skull midline impact model of TBI in mice and administered minozac, a small molecule that suppressed the increased production of pro-inflammatory cytokines in glial cultures, at 3 or 6 h after injury. One week after TBI, minozac-treated mice showed less susceptibility to electroconvulsive shock-induced seizures

Table 4 Summary of clinical trials including development of seizures after traumatic brain injury as primary or secondary outcome. Data were collected from www.clinicaltrials.gov

Study	Identifier	Status	PTE
Seizure prophylaxis with lacosamide	NCT01110187	Terminated	Secondary outcome
Levetiracetam to prevent PTE	NCT01463033	Completed and reported [100–102]	Secondary outcome
Preventing epilepsy after TBI with topiramate	NCT00598923	Unknown	Secondary outcome
Use of biperiden for the prevention of PTE	NCT01048138	Not yet recruiting	Secondary outcome
Allopregnanolone for the treatment of TBI	NCT01673828	Recruiting	Secondary outcome
Prevention of post-traumatic seizures with levetiracetam	NCT00566046	Terminated	Secondary outcome
Effects of huperzine A in treatment of moderate-to-severe TBI	NCT01676311	Not yet recruiting	Secondary outcome

PTE = post-traumatic epilepsy; TBI = traumatic brain injury

than sham-operated rats. Whether minozac treatment prevents long-term increase in seizure susceptibility and the occurrence of late seizures remains to be explored.

Schwartzkroin et al. [72] triggered lateral FPI to 8-week-old rats and administered a ketogenic diet for 3 weeks after injury. Seizure susceptibility to flurothyl was no different from that in rats on a standard diet when assessed 3 and 6 weeks after discontinuation of the ketogenic diet. It should be noted, however, that TBI had no effect on seizure susceptibility to flurothyl (seizure threshold, seizure duration) when injured and sham-operated animals on a standard diet were compared.

Hypothermia is considered to be a promising therapy that improves structural and functional outcome measures after experimental and clinical TBI [73]. Atkins et al. [74] induced moderate parasagittal FPI in adult rats. Animals were kept under normothermic or moderate hypothermic temperatures for 4 h starting 30 mins after injury. Susceptibility to PTZ-induced seizures was tested 12 weeks after TBI. Behavioral analysis of data indicated a reduced number of induced seizures during the 60-min period after PTZ injection. The behavioral severity of seizures was not affected. Recently, D'Ambrosio et al. [75] started a 5.5-week focal passive cooling of the peri-lesional cortex 3 days after TBI, causing a 2 °C decrease in the temperature of the peri-lesional cortex. They found a remarkable reduction in the number and duration (from 9.1 s to 3.2 s) of electrographic ictal episodes (for a description, please see [75]), which lasted beyond the cooling treatment, that is, for >10 weeks after TBI [75].

Saraiva et al. [76] induced parasagittal FPI in adult Wistar rats. At 30 mins after TBI, they initiated a treatment with creatine (300 mg/kg, once per day, p.o.) for up to 4 or 7 days in order to reduce oxidative stress and gain neuroprotection. One day after the end of creatine administration (i.e., 4 or 8 days after TBI), a PTZ seizure susceptibility test was performed under EEG. The data obtained did not reveal any effect of creatine treatment on seizure susceptibility.

Ceftriaxone is a β-lactam antibiotic with good BBB penetration. It is a potent stimulator of glutamate transporter 1 expression in astrocytes [77]. Goodrich et al. [78] induced lateral FPI in adult Long–Evans rats and started cetriaxone treatment (200 mg/kg, once a day, i.p.) 30 mins after TBI for 7 days. At 12 weeks post-TBI, the occurrence of epileptiform activity was assessed using a 24-h EEG recording. They found a remarkable decrease in peri-lesional astrocytosis and restoration of the decreased post-TBI glutamate transporter 1 expression. The seizure frequency was lower in the ceftriaxone-treated animals than in controls (151 seizures/24 h *vs* 47 seizures/24 h). Also, seizure duration was shorter in the ceftriaxone group than in controls (from 22.7 s to 18.5 s).

Rapamycin, a mammalian target of rapamycin inhibitor, has shown disease-modifying effects in several genetic and acquired epilepsy models, even though there are also contradicting results (see [79]). Guo *et al*. [43] induced CCI in adult CD1 mice. Rapamycin treatment (6 mg/kg, once a day, i.p.) was started 60 mins after TBI and continued for 4 weeks. Mice were continuously monitored by video-EEG. Rapamycin reversed the hyperactivation of mTORC1 pathway, reduced neurodegeneration, and reduced the rate of development of PTE and decreased seizure frequency. However, it did not affect the latency to the occurrence of the first spontaneous seizure after TBI or seizure duration.

Silva et al. [80] investigated the effect of physical exercise on the development of epilepsy after TBI. Treadmill exercise (5 mins + 5 mins + 20 mins each day) was started 7 d after induction of parasagittal TBI in adult male Wistar rats, and continued for 4 weeks (5 days a week). A PTZ seizure susceptibility test performed 3 days after the end of the exercise period showed reduced seizure susceptibility. Histologic analysis of brain tissue did not reveal evidence of neuroprotection. However, favorable effects were observed on markers of oxidative stress.

Taken together, proof-of-concept studies in experimental models have shown that post-TBI seizure susceptibility can be modified by treatments affecting different targets, which is in line with the complexity of molecular and cellular changes underlying post-traumatic epileptogenesis. There are also several previous, recently completed, or new studies that aim to prevent epilepsy after TBI in humans ([81]; Table 4). Interestingly, however, there is no overlap between treatments applied in preclinical laboratories and in the clinic. The challenge is how to harmonize the antiepileptogenesis efforts made in laboratories and clinics to take favorable proof-of-concept studies to clinical practice. The roadmap prepared by the International League Against Epilepsy/American Epilepsy Society task force was recently provided to guide such efforts [82].

Conclusions

Recent advances in model development provide a platform for studies that aim at a better understanding of the molecular and cellular mechanisms leading to PTE. Experimental imaging studies have offered encouraging results to maintain a spirit that discovery of biomarkers that can be used to predict and diagnose post-traumatic epileptogenesis is possible. Finally, several proof-of-concept studies have already had favorable results, suggesting that post-TBI seizure susceptibility can be modified. Even though the progress happens in small steps, prevention of PTE appears as a feasible goal.

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