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REVIEW

Novel Approaches to Prevent Epileptogenesis After Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is defined as an alteration in brain function or other evidence of brain pathology caused by an external force. When epilepsy develops following TBI, it is known as post-traumatic epilepsy (PTE). PTE occurs in a subset of patients suffering from different types and severities of TBI, occurs more commonly following severe injury, and greatly impacts the quality of life for patients recovering from TBI. Similar to other types of epilepsy, PTE is often refractory to drug treatment with standard anti-seizure drugs. No therapeutic approaches have proven successful in the clinic to prevent the development of PTE. Therefore, novel treatment strategies are needed to stop the development of PTE and improve the quality of life for patients after TBI. Interestingly, TBI represents an excellent clinical opportunity for intervention to prevent epileptogenesis as typically the time of initiation of epileptogenesis (i.e., TBI) is known, the population of at-risk patients is large, and animal models for preclinical studies of mechanisms and treatment targets are available. If properly identified and treated, there is a true opportunity to prevent epileptogenesis after TBI and stop seizures from ever happening. With that goal in mind, here we review previous attempts to prevent PTE both in animal studies and in humans, we examine how biomarkers could enable better-targeted therapeutics, and we discuss how genetic variation may predispose individuals to PTE. Finally, we highlight exciting new advances in the field that suggest that there may be novel approaches to prevent PTE that should be considered for further clinical development.

Keywords Anti-epileptogenesis · Biomarker · Epileptogenesis · Post-traumatic epilepsy · Treatment

Introduction

Globally, an estimated 2.4 million people are diagnosed with epilepsy each year. Thus, a new person is diagnosed with epilepsy every 13 s [1]. Epileptogenesis refers to the development and extension of tissue capable of generating spontaneous seizures, resulting in (a) the development of an epileptic condition and/or (b) progression of epilepsy *after* it is established [2]. In 60% of those affected, epileptogenesis is initiated by structural causes such as traumatic brain injury (TBI) [3, 4]. Recent epidemiologic data indicate that approximately 2.5 million people experience TBI annually, both in Europe and the USA. The risk of epileptogenesis increases according to the severity of TBI: about two- to four-fold after mild, eight-fold after moderate, and 16-fold after severe TBI [5, 6]. Up to 53% of patients with penetrating TBI develop epilepsy [7, 8]. Post-traumatic epilepsy (PTE) is estimated to account for approximately 5% of all epilepsies and 20% of structural epilepsies [9]. Mild TBI comprises over 90% of all TBI [10], and thus the total number of patients developing epilepsy after mild TBI can be expected to be greater than that of patients developing epilepsy after severe TBI, which has been the focus of experimental and clinical PTE studies (Fig. 1).

TBI refers to an alteration in brain function, or other evidence of brain pathology, caused by an external force [11]. Seizures after TBI have been classically categorized into immediate (seizures ≤ 24 h post-TBI), early (≤ 7 days), or late (> 7 days) seizures. A person with PTE suffers repeated unprovoked seizures that result from TBI and occur more than a week after the initial injury [12]. According to the

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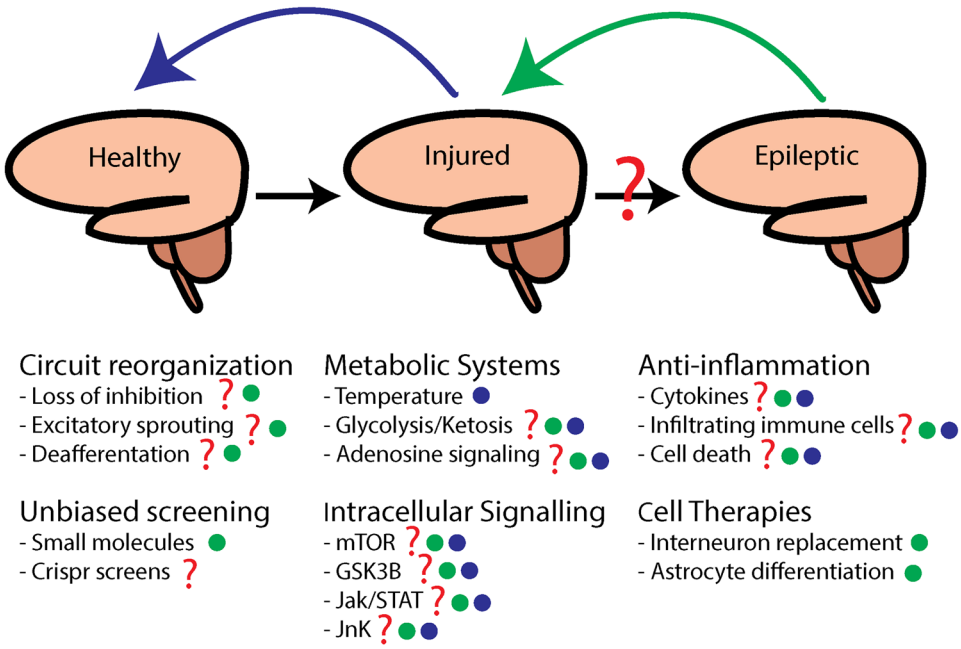

Fig. 1 Potential mechanisms and therapeutic strategies to treat post-traumatic epilepsy. A schematic of the healthy, injured, and epileptic brain. Mechanisms that have been implicated in post-traumatic epileptogenesis are indicated with a red question mark. Mechanisms that may be targeted to reduce brain injury are indicated in blue. Mechanisms that may be targeted to reverse or prevent epileptogenesis are indicated in green. We also point out that small molecule and genetic screens may be able to identify novel mechanisms and treatment strategies

current International league Against Epilepsy definitions, PTE belongs to structural epilepsies, and is diagnosed if the subject experiences one unprovoked seizure > 7 days post-TBI [3, 12, 13]. Approximately 80% of TBI patients who eventually develop epilepsy will receive a PTE diagnosis within 2 years after the TBI [5, 15]. Both clinical and basic science studies have investigated a wide range of biological processes that may be involved in the transition from an injured brain to an epileptic brain. Changes occurring with TBI, including neuroinflammation, neuronal cell death, and changes in synaptic abundance and function, just to name a few, have been studied for their role in PTE [16–18]. While there are diverse cellular, molecular, metabolic, and circuit-level changes, we have not been able to identify a causative molecular or cellular event and its temporal relation to the occurrence of PTE. Innovation in both clinical care and basic science suggests that we may be closer than ever to identifying novel therapeutic approaches to prevent PTE. In this review, we examine past failures in preventing PTE, consider diagnostic and genetic information that could guide targeted interventions, and highlight exciting new approaches with may help reduce the prevalence and impact of PTE.

Old and New Strategies for Prevention of Epilepsy After TBI—Still No Treatments in Clinic

In a review of pharmacologic prophylaxis for PTE, Rapport II and Penry [19] cite the first anti-epileptogenesis studies conducted in head-injured patients using diphenylhydantoin [20, 21]. Since then, the concept of using compounds designed to suppress epileptic seizures (anti-seizure drugs) to prevent the complex molecular and cellular processes that drive epileptogenesis [anti-epileptogenic drugs (AEGs)] was expanded to carbamazepine, phenobarbital and valproic acid (for review, see [22]). According to ClinicalTrials.gov, initial studies on PTE are also planned using the third-generation anti-seizure drugs lacosamide (NCT01110187), levetiracetam (NCT01463033, NCT02631759, NCT00566046), and topiramate (NCT00598923). In addition, a study using acetylcholinesterase inhibitor, huperzine A (NCT01676311) was planned but is now discontinued. Biperiden, a cholinergic antagonist acting in the muscarinic receptor, is still under investigation (biperiden (NCT01048138)) [23]. So far, the use of anti-seizure drugs has not resulted in favorable anti-epileptogenic effects, and their use has been recommended only for the first post-injury week to suppress immediate and early seizures (Brain Trauma Foundation Guidelines) [24].

The recent rapid progress in modeling PTE provides an opportunity to vigorously assess preclinical candidate treatments in different clinically relevant epileptogenic injuries, mimicking the heterogeneity of TBI in humans with PTE (Table 1). Long-term video-electroencephalogram (EEG) monitoring studies have shown that epileptogenesis can be triggered in different strains of rats and mice by various injury types, including focal (*e.g.,* controlled cortical impact-induced TBI, CCI), diffuse (repetitive weight-drop), mixed type injury (*e.g.,* lateral-fluid percussion TBI), and blast injury. Although gaps in animal models remain, including epileptogenesis in females and younger animals, currently available animal models have identified candidate

Table 1 Summary of in vivo recorded changes in excitability in different models of traumatic brain injury. Only the data that was collected at least 1 week post-injury is included

Model	Species Strain Sex Age/weight Anesthesia[#]	Seizure susceptibility in vivo	Epilepsy					Reference
			Animals with epilepsy (%)	Latency to spontaneous sz	Sz frequency	Average Sz duration (s)	Epileptiform spiking or EDs in EEG	
Weight drop (Feeney)	Rat Sprague–Dawley Male 250–400 g Halothane	Increased susceptibility to PTZ-induced seizures, 15 wk post-TBI	n.d	n.d	n.d	n.d	n.d	[25] Golarai et al.
Weight drop (Marmarou)	Mouse CD-1 Male Adult 20–25 g Isoflurane	Increased seizure susceptibility to ECS-induced seizures, 7 d post-TBI	n.d	n.d	n.d	n.d	n.d	[26] Chrzaszcz et al.
Weight drop (modified)	Rat Wistar 230–300 g Ketamine:xylazine	Increased susceptibility to PTZ-induced seizures, 15 wk post-TBI	n.d	n.d	n.d	n.d	n.d	[27] Ghadiri et al.
Central FPI	Rat Sprague–Dawley Male 300–350 g Isoflurane	No difference in PTZ-kindling, started 24 h post-TBI	n.d	n.d	n.d	n.d	n.d	[28] Hamm et al.
Parasagittal FPI	Rat Sprague–Dawley Male P32–35 Halothane	n.d	100% (follow-up: 7 months)	~2 weeks	Up to 7 seizures/h	Ictal episodes ≤ 10 s (up to 99 s)	n.d	[29–31] D'Ambrosio et al.
	Rat Sprague–Dawley Male 270–320 g Halothane	Increased susceptibility to PTZ-induced seizures, 12 wk post-TBI	n.d	n.d	n.d	n.d	n.d	[32] Atkins et al.
	Rat Sprague–Dawley Male Adult 294–384 g Isoflurane	Increased susceptibility to PTZ-induced seizures, 2 wk post-TBI	No	n.d	n.d	n.d	n.d	[33] Bao et al.

Table 1 (continued)

Model	Species Strain Sex Age/weight Anesthesia[#]	Seizure susceptibility in vivo	Epilepsy					Reference
			Animals with epilepsy (%)	Latency to spontaneous sz	Sz frequency	Average Sz duration (s)	Epileptiform spiking or EDs in EEG	
	Rat Spraque-Dawley with MAM-induced cortical dysplasia (CD) Male P55 Isoflurane	n.d	TBI only 25% TBI + CD 55%		TBI only 2.8/wk TBI + CD 4.7/wk	TBI only 67 s TBI + CD 47 s	TBI only 58% TBI + CD 100%	[34] Nemes et al.
Lateral FPI	Rat Spraque-Dawley Sex—n.d Adult 350–450 g Pentobarbital or isoflurane	Granule cell hyperexcitability, 1 wk post-TBI	n.d	n.d	n.d	n.d	n.d	[35] Lowenstein et al.
	Rat Spraque-Dawley Male 250–300 g Pentobarbital	Increased inhibition in dentate gyrus, 15 d post-TBI	n.d	n.d	n.d	n.d	n.d	[36] Reeves et al.
	Rat Sprague–Dawley Male P19 34–58 g Isoflurane	No change in PTZ-seizure threshold, 20 wk post-TBI	0% (behavioral observation)	n.d	n.d	n.d	n.d	[37] Gurkoff et al.
	Rat Sprague–Dawley Male Adult 325 g Pentobarbital-based cocktail	Increased susceptibility to PTZ-induced seizures, 12 month post-TBI	50% (follow-up: 12 months)	4–11 weeks	0.3/day	104	80%	[38, 39] Kharatishvili et al.
	Rat Wistar Sex—n.d P21–22 35–50 g Anesthesia—n.d	Increased susceptibility to kainate-induced seizures, 6 wk post-TBI	n.d	n.d	n.d	n.d	n.d	[40] Echegoyen et al.

Table 1 (continued)

Model	Species Strain Sex Age/weight Anesthesia[#]	Seizure susceptibility in vivo	Epilepsy					Reference
			Animals with epilepsy (%)	Latency to spontaneous sz	Sz frequency	Average Sz duration (s)	Epileptiform spiking or EDs in EEG	
	Rat Sprague–Dawley Male 8 wk Isoflurane	No change in susceptibility to fluorothyl-induced seizures, 3 and 6 wk post-TBI	n.d	n.d	n.d	n.d	n.d	[41] Schwarztkroin et al.
	Mouse C57BL/6JOlaHsd Male 10–11 wk 22–26 g Pentobarbital	Increased susceptibility to PTZ-induced seizures, 6 month post-TBI	6% (follow-up: 9 months)	n.d	0.1/d	91	Yes	[42] Bolkvadze et al.
	Rat Wistar Male 8–12 wk Isoflurane	n.d	30% had spontaneous seizures (6 months post-TBI)	n.d	6.3/2 wk	53	11.5/2 wk	[43] Schultz et al.
	Mouse C57Bl6 Male 23–28 g Isoflurane	Increased susceptibility to PTZ-induced seizures, 30 d post-TBI	n.d	n.d	n.d	n.d	n.d	[44] Mukherjee et al.
	Rat Long-Evans Male 8–9 wk Isoflurane	n.d	100% (EEG monitoring started at 12 wk post-TBI)	n.d	151/24 h	23	n.d	[45, 46] Goodrich et al. Hameed et al.
	Rat Spraque-Dawley Male 90 d Isoflurane	n.d	0% at 5 wk Non-convulsive sz[&] in 94% and convulsive sz in 18% at 12 wk after TBI	n.d	Non-convulsive sz 7/h convulsive 0.05/h	14 (non-convulsive) 95 (convulsive)	n.d	[47] Campbell et al.
	Rat Spraque-Dawley Male Adult Chloral hydrate	Increased susceptibility to PTZ-induced seizures, 6 wk post-TBI	n.d	n.d	n.d	n.d	n.d	[48] Wang et al.

Table 1 (continued)

Model	Species Strain Sex Age/weight Anesthesia[#]	Seizure susceptibility in vivo	Epilepsy					Reference
			Animals with epilepsy (%)	Latency to spontaneous sz	Sz frequency	Average Sz duration (s)	Epileptiform spiking or EDs in EEG	
	Rat Spraque-Dawley Male 65 d old Isoflurane	n.d	50% (follow-up up to 52 wk)	n.d	n.d	Variable depending on TBI severity	10/14 rats with epilepsy had repeated high-frequency oscillations	[49] Reid et al.
	Rat Spraque-Dawley Male 65 d old Chloral hydrate	nd	55% (12 months follow-up)	6 sz/rat during follow-up	n.d	n.d	n.d	[50] Wang et al.
CCI	Rat Sprague–Dawley Sex—n.d P17 Isoflurane	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	[51] Statler et al.
	Rat Sprague–Dawley Sex—n.d P16–18 Isoflurane	n.d	1 of 8 (13%) (follow-up: 11 months)	n.d	n.d	45–60	88% had epileptiform spiking	[51] Statler et al.
	Mouse CD-1 Sex—n.d Adult 25–30 g Isoflurane	n.d	20% (mild) –36% (severe injury)	n.d. (monitoring 42–71 d post-TBI)	n.d	~90 (behavioral assessment)	n.d	[52] Hunt et al.
	Mouse CD-1 Male 7–8 wk 28–35 g Isoflurane	n.d	40%	6.5 ± 1.3 wk	n.d	n.d	n.d	[53] Hunt et al.
	Mouse C57BL/6JOlaHsd Male 10–11 wk 22–26 g Pentobarbital	Increased susceptibility to PTZ-induced seizures, 6 month post-TBI	9% (follow-up: 9 months)	n.d	0.2/d	50	Yes	[42] Bolkvadze et al.

Table 1 (continued)

Model	Species Strain Sex Age/weight Anesthesia[#]	Seizure susceptibility in vivo	Epilepsy					Reference
			Animals with epilepsy (%)	Latency to spontaneous sz	Sz frequency	Average Sz duration (s)	Epileptiform spiking or EDs in EEG	
	Mouse CD-1 Male 8 wk Isoflurane		50% of vehicle* treated animals	82.3 ± 10.2 d	0.55 ± 0.16/d	35.5 ± 2.8	Rare	[54] Guo et al.
	Mouse CD-1 Sex—n.d 6–8 wk Isoflurane	n.d	40% (behavioral seizures; weeks 6–10 post-TBI)			> 30		[55] Butler et al.
	Rat Spraque-Dawley Male 2–3 months Isoflurane	n.d	20% (follow-up for up to 619 d)	n.d	n.d	Non-convulsive 32 ± 3 convulsive 91 ± 12	n.d	[56] Kelly et al.
	Mouse C57BL6 Male 2 months Ketamine/xylazine	Increased firing frequency of LV pyramidal cells within 1–2 mm from the lesion core at 14 d post-TBI	n.d	n.d	n.d	n.d	n.d	[57] Ping and Yin
	Rat Wistar Male Adult 250–280 g Chloral hydrate	Facilitate PTZ-kindling started at 24 h post-TBI and rapid electrical kindling started at 1 wk after TBI	n.d	n.d	n.d	n.d	n.d	[58] Eslami et al.
	Plau -/- mouse C57BL/6 J Male Adult 12–14 wk Pentobarbital	Similar increase in susceptibility to PTZ-induced seizures as in wild type mice with CCI	0% Wt w/CCI 0% *Plau w/CCI*	n.d	n.d	n.d	n.d	[59] Bolkvadze et al.
	Plaur mouse C57BL/6 J Male Adult 12–14 wk Pentobarbital	Similar increase in susceptibility to PTZ-induced seizures as in Wt mice with CCI	15% Wt w/CCI 0% *Plaur w/CCI*	n.d	n.d	n.d	n.d	[60] Bolkvadze et al.

Table 1 (continued)

Model	Species Strain Sex Age/weight Anesthesia[#]	Seizure susceptibility in vivo	Epilepsy					Reference
			Animals with epilepsy (%)	Latency to spontaneous sz	Sz frequency	Average Sz duration (s)	Epileptiform spiking or EDs in EEG	
	APP/PS1 mouse C57BL/6 J × C3H hybrid Male Adult 13–15 wk Pentobarbital	n.d	88% APP/PS1 w/ CCI 11% Wt w/CCI 50% APP/PS1 without CCI	n.d	0.47/d	35	n.d	[61] Miszczuk et al.
Repetetive (3x) blast injury	Mouse C57BL/6 J Male Adult 10 wk Ketamine-dexmedetomidine		46%					[62] Bugay et al.

CCI controlled cortical impact; *ECS* electroconvulsive shock; *FPI* flud-percussion injury; *n.d.* no data; *P* post-natal day; *PTZ* pentylenetetrazol; *sz* seizure; *TBI* traumatic brain injury; # anesthesia preceding or at the time of induction of impact; * data from vehicle-treated mice that were included in rapamycin treatment study; & non-convulsive seizures could be interrupted with sudden changes in lightning or noise

molecular, cellular, and network epileptogenic mechanisms that will pave the way for the discovery of novel treatments for PTE.

Table 2 summarizes the current in vivo treatment studies on epileptogenesis in relevant animal models. Most of them have administered small molecules with a variety of mechanisms of action as a monotherapy. Commonly targeted mechanisms include oxidative stress, neuroinflammation, neuroprotection, and restoration of inhibitory GABAergic function. Unlike in status epilepticus-induced epileptogenesis models, gene therapy, administration of monoclonal antibodies, or treatments targeting DNA or RNA have not yet been tested in PTE models. Some laboratories have applied ketogenic diet, hypothermia, focal passive cooling, treadmill exercise, or transplantation of GABAergic progenitors (Table 2). These pharmacological treatments have typically been initiated within hours after the injury. Studies delivering anti-epileptogenic interventions at later time points would also greatly inform future clinical studies and would complement the development of biomarkers to identify high-risk patients at later timepoints. Ex vivo analysis of tissue excitability or in vivo analysis of seizure susceptibility, incidence of epilepsy, or characteristics of epilepsy phenotype (seizure frequency, duration or behavioral severity of seizures) have been used as outcome measures. Assessment of a 50% responder rate has been challenging as it would require large animal numbers as typically 25–50% of animals with TBI develop epilepsy within the 4–6 months follow-up (Table 2). So far, none of the treatments except the transplantation of GABAergic progenitors has been able to prevent the development of epilepsy.

Advancing Biomarkers from Basic and Clinical Studies

One of the biggest challenges in preventing post-traumatic epilepsy is identifying patients who are at the greatest risk following injury. Only a fraction of those who suffer a traumatic brain injury will go on to develop epilepsy. Clinicians are often hesitant to use aggressive or experimental interventions when there is little certainty that a patient is at significant risk of developing PTE. Therefore, developing biomarkers that are predictive of PTE would be extremely useful in stratifying patients into those that have a low probability of developing epilepsy from those that are at significantly higher risk. For patients at high risk, targeted interventions may slow or prevent the development of PTE. With this goal in mind, much work has been devoted, both in clinical and basic epilepsy research, to identifying useful biomarkers predictive of the later development of PTE (Table 3).

A biomarker is a characteristic that can be objectively measured as an indicator of normal biologic processes,

Table 2 Preclinical proof-of-concept studies in animal models of traumatic brain injury (TBI). Only the studies with treatment initiated after the TBI have been included. Studies are in chronological order

Treatment	Proposed mechanisms	Model (species)	Disease-modifying effect		*Reference*
			Anti-epileptogenesis	**Co-morbidity modification***	
Small molecules					
SR141716A (Rimonabant)	CB1 receptor antagonist	Lateral FPI (P21–22 Wistar rat, sex unknown)	**Start:** within 2 min or 20 min post-TBI **Monitoring:** hippocampal EEG **Outcome:** seizure susceptibility to kainate ⇩ at 6 wk post-TBI	Behavioral and/or cognitive outcome: n.d Structural outcome: n.d	[40] Echegoyen et al.
		Lateral FPI (adult male Sprque-Dawley rats)	**Start:** within 5 min after TBI **Monitoring:** observation **Outcome:** seizure susceptibility to PTZ ⇩ at 6 wk after TBI	Behavioral and/or cognitive outcome: n.d Structural outcome: n.d	[50] Wang et al.
		Lateral FPI (rat) (adult male Spraque-Dawley rats)	**Start:** 2 min once or 30 min after TBI for 9 wk **Monitoring:** video-EEG **Outcome:** PTZ test; unprovoked seizures—no effect	Behavioral and/or cognitive outcome: n.d Structural outcome: n.d	[63] Nissinen et al.
Minozac®	Reduction of proinflammatory cytokine production by activated glia	Midline closed skull TBI (adult male CD1 mouse)	**Start:** Two doses; at 3 h and 6 h post-TBI **Monitoring:** video **Outcome:** seizure susceptibility to electroshock ⇩ at 7 d post-TBI	Behavioral and/or cognitive outcome: improved performance in Barns maze Structural outcome: suppression of glial activation	[26] Chrzaszcz et al.
Creatine	Reduction of oxidative stress	Lateral FPI (adult male Wistar rats)	**Start:** 30 min post-TBI for 3 or 7 d, once a day **Monitoring:** observation & EEG, PTZ seizure susceptibility test **Outcome:** no effect on seizure susceptibility to PTZ 4 d or 8 d post-TBI	Behavioral and/or cognitive outcome: n.d Structural outcome: n.d	[64] Saraiva et al.
		Lateral FPI (90-d old male Wistar rat)	**Start:** 1 wk after TBI for 4 wk **Monitoring:** EEG and observation (5 wk or 6 wk post-TBI) **Outcome:** PTZ seizure susceptibility ⇩	Behavioral and/or cognitive outcome: n.d Structural outcome: neuroprotection	[65] Gerbatin et al.
Ceftriaxone	Stimulation of glutamate transporter in astrocytes	Lateral FPI (adult male Long-Evans rats)	**Start:** daily for 7 d after verum TBI **Monitoring:** EEG 12 wk post-TBI **Outcome:** seizure frequency ⇩	Behavioral and/or cognitive outcome: n.d Structural outcome: neuroprotection	[45] Goodrich et al.

Table 2 (continued)

Treatment	Proposed mechanisms	Model (species)	Disease-modifying effect		*Reference*
			Anti-epileptogenesis	**Co-morbidity modification***	
Rapamycin	mTOR inhibition	Controlled cortical impact (8 wk old male CD1 mice)	**Start:** 1 h post-injury for 4 wk (once7d) **Monitoring:** Video-EEG for 16 wk post-TBI **Outcome:** Reduced incidence of epilepsy and seizure frequency	Behavioral and/or cognitive outcome: n.d Structural outcome: neuroprotection	[54] Guo et al.
	mTOR inhibition	Controlled cortical impact (6–8 wk old CD1 mice, sex unknown)	**Start:** 20–30 min after TBI, continued till analysis **Monitoring:** observation between weeks 6–10 post-TBI (6 h/wk) **Outcome:** a trend towards reduction in seizure frequency (> 2 Racine's scale)	Behavioral and/or cognitive outcome: n.d Structural outcome: no protection of hilar neurons	[55] Butler et al.
Tacrolimus (FK-506)	Calcineurin inhibitor	Lateral FPI (adult male Spraque-Dawley rat)	**Start:** 1 h post-TBI (single injection) **Monitoring:** video-EEG (for 51 h/8 d) **Outcome:** reduction of non-convulsive seizures at 33 wk	Behavioral and/or cognitive outcome: n.d Structural outcome: no effect on cortical lesion size	[47] Campbell et al.
WP1066	JAK/STAT inhibitor	CCI (adult male CD1 mice)	**Start:** 30 and 90 min after TBI **Monitoring:** video-EEG for 6 wk starting 8 or 10 wk post-TBI **Outcome:** no effect on % of mice epileptic	Behavioral improvement Lesion size: no effect	[66] Raible et al.
Sodium selenate	Protein phosphatase 2A activator	Lateral FPI (adult male Long-Evans rats)	**Start:** after injury for 12 wk (minipump) **Monitoring:** video-EEG for 2 wk during Rx and for 2 wk after 2-wk washout **Outcome:** seizure frequency ⇩; seizure duration ⇩	Behavioral and/or cognitive outcome: n.d Structural outcome: n.d	[67] Liu et al.
Atipamezole	α2-adrenergic receptor antagonist	Lateral FPI (male Spraque-Dawley rat)	**Start:** 30 min or 7 d after TBI for 9 wk **Monitoring:** video-EEG **Outcome:** reduced susceptibility to TBI induced sz at 14 wk post-TBI (7 d Rx group); no effect on prevalence of epilepsy	Improvement in beam-walking and neuroscore but not in MWM No neuroprotection	[63] Nissinen et al.

Table 2 (continued)

Treatment	Proposed mechanisms	Model (species)	Disease-modifying effect		*Reference*
			Anti-epileptogenesis	**Co-morbidity modification***	
SU1498	VEGFR2 antagonist	Lateral FPI (juvenile 23–25 d old male Wistar rats)	**Start:** 2 h after TBI (lateral ventricle) **Monitoring:** **Outcome:** (1) granule cell population spike amplitude normalized in hippocampal slices 7–9 d post-TBI; (2) prolongation of latency to KA-induced sz under video EEG 30–31 d post-TBI		[68] Neuberger et al.
Progesterone	progesterone receptor	Weight drop (adult male Wistar rats)	**Start:** 30 min, 6 h and then daily for 2 wk **Monitoring:** EEG and observation **Outcome:** seizure susceptibility in PTZ test ⇩ on D15 post-TBI	Behavioral and/or cognitive outcome: n.d Structural outcome: neuroprotection	[27] Ghadiri et al.
KPT-350	Selective inhibitor of nuclear export	CCI (adult male C57BL/6 mice)	**Start:** 1 h after TBI for 3 wk (3x/wk) **Monitoring:** cortical slice electrophysiology after drug discontinuation **Outcome:** reduced excitability	Behavioral and/or cognitive outcome: n.d Structural outcome: preservation of cortical PARV + neurons	[69] Cantu et al.
Levetiracetam	SV2A	CCI (P21–32 male and female Spraque-Dawley rats)	**Start**: < 2 min post-TBI, single injection **Monitoring:** (a) perilesional cortical slices; (2) **Outcome:** Reduced cortical excitability at 2–3 wk post-TBI	Behavioral and/or cognitive outcome: n.d Structural outcome: n.d	[70] Yang et al.
Other					
Ketogenic diet	Multiple	Lateral FPI (8 wk old male Spaque-Dawley rats)	**Start:** after TBI for 4 wk **Monitoring: observation** **Outcome:** no effect on fluorothyl-induced seizure susceptibility	Behavioral and/or cognitive outcome: n.d no HC neuroprotection	[41] Schwartzkroin et al.
Hypothermia	Inflammation ⇩ Pro-survival signaling ⇧	Parasagittal FPI (adult male Spraque-Dawley rats)	**Start:** 30 min post-TBI for 4 h **Monitoring:** Observation and EEG **Outcome:** 12 weeks post-TBI seizure susceptibility to PTZ ⇩	Behavioral and/or cognitive outcome: n.d Structural outcome: neuroprotection	[32] Atkins et al.

Table 2 (continued)

Treatment	Proposed mechanisms	Model (species)	Disease-modifying effect		Reference
			Anti-epileptogenesis	Co-morbidity modification*	
Focal passive cooling	Multiple	Parasagittal FPI (32–36 d old male Sprague-Dawley rats)	**Start:** 3 d post-TBI for 5.5 wk **Monitoring:** video-EEG **Outcome:** Suppression of ictal activity > 10 wk post-TBI (up to 16 wk)	Behavioral and/or cognitive outcome: n.d Structural outcome: n.d	[31] D'Ambrosio et al.
Treadmill exercise	Reduction of oxidative stress	Parasagittal FPI (adult male Wistar rats)	**Start:** 1 wk after TBI for 4 weeks **Monitoring:** Observation and EEG **Outcome:** 5 weeks post-TBI seizure susceptibility to PTZ ⇩	Behavioral and/or cognitive outcome: n.d Structural outcome: neuroprotection	[71] Silva et al.
GABAergic progenitor transplantation	Restoration of post-TBI decrease in hippocampal synaptic inhibition	CCI (adult male CD1 mice)	**Start:** Transplantation 7 d post-TBI **Monitoring:** Video-EEG **Outcome:** Seizure-freedom at 4–5 months post-TBI	Memory improvement	[72] Zhu et al.

CCI controlled cortical impact; *FPI* fluid-percussion injury; *n.d.* no data; *PTE* post-traumatic epilepsy; *PTZ* pentylenetetrazol; *TBI* traumatic brain injury; ±0 no effect; * behavioral/cognitive performance (B/C) or change in biochemical or structural pathology (S)

pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Biomarker modalities include molecular, histologic, radiographic, or physiologic characteristics. To improve the understanding and use of biomarker terminology in biomedical research, clinical practice, and medical product development, the FDA-NIH Joint Leadership Council developed the BEST Resource (*B*iomarkers, *E*ndpoint*S*, and other *T*ools). The seven BEST biomarker categories include (a) susceptibility/risk biomarkers, (b) diagnostic biomarkers, (c) monitoring biomarkers, (d) prognostic biomarkers, (e) predictive biomarkers, (f) pharmacodynamic/response biomarkers, and (g) safety biomarkers.

The current status of biomarker development in PTE field is summarized in Table 3. Many types of biomarkers have been examined to predict the development of epilepsy after different epileptogenic etiologies (for recent review see [88]), including molecular biomarkers (serum proteins, non-coding RNAs, cerebrospinal fluid (CSF)), imaging biomarkers (MRI, PET), and EEG based biomarkers. Unfortunately, no useful clinical biomarkers have been rigorously validated using sufficient patient populations. That said, there are a few exciting studies that suggest clinical biomarkers of PTE may be not that far down the road. A study of 256 Caucasian adults showed that high levels of the inflammatory cytokine IL-1β in the CSF, relative to levels in the serum, were associated with an increased risk of developing PTE over time [73]. While quite promising, this study had a small sample size and did not include statistical analysis of the predictive value of IL-1β CSF/serum ratios in PTE. None the less, this is an exciting line of research worthy of further development. In two other studies, EEG-based biomarkers suggest that epileptiform activity (epileptiform discharges, lateralized periodic discharges, generalized periodic discharges, or lateralized rhythmic delta activity) [79] and early seizures [80] are predictive of later development of PTE. These studies underscore the importance of robust, quantitative analysis in defining biomarkers of PTE and in applying statistical modeling to pinpoint the most predictive parameters in the data matrix as biomarkers. Moreover, analyses of the sensitivity, specificity, quantitative cut-off values for PTE prediction are needed to rigorously apply a biomarker in an individual subject [*e.g.,* receiver operating characteristic analysis (ROC)]. While increased abnormal EEG and early post-injury seizures seem like straightforward potential biomarkers, the heterogeneity in the human population, in the injury itself, and in the type of clinical data collected has made it extremely challenging to pinpoint a specific metric useful in predicting PTE. More work is needed to develop these important clinical tools.

Many promising predictive biomarkers of PTE have also been identified in basic science studies and have promise as potential clinical biomarkers. For example, in the

Table 3 Prognostic and diagnostic biomarkers for epileptogenesis, post-traumatic epilepsy, and tissue epileptogenicity after TBI

Modality	Analysis platform	Species	Group comparisons	Tissue	Biomarker	Statistics	Reference
Prognostic & diagnostic biomarker for post-traumatic epileptogenesis							
Molecular	Luminex bead array	Human	Patients with *vs.* without epilepsy after TBI	Serum, CSF	Elevated CSF/serum IL-1β ratio during the 1st post-injury week	Cox multivariate model Hazard ratio 1.34 (CI 1.08–1.67, $p=0.008$)	[73] Diamond et al.
	CLARIOstar multimode plate reader (FD4) ELISA (LPS)	Rat	Non-epileptic *vs.* epileptic rats with lateral FPI	Plasma	Elevated plasma FD4 and LPS levels in rats with PTE	Mann–Whitney	[74] Mazarati et al.
Imaging	T2-w DTI MRI	Rat	Rats with *vs.* without increased seizure susceptibility in the PTZ test after TBI	Amygdala, hippocampus, thalamus	T1σ in S1 cortex T1σ in perirhinal cortex T2 in thalamus T1σ in hippocampus	ROC analysis (AUC) 0.881 0.929 0.893 0.857	[75] Pitkänen and Immonen
	Large-deformation high-dimensional mapping of T2-w-MRI	Rat	Non-epileptic *vs.* epileptic rats with lateral FPI	Hippocampus	Deformation of lateral aspects of the hippocampal surface at 1 wk post-TBI	Multivariate regression model	[43] Shultz et al.
	18F-FDG PET	Rat	Non-epileptic *vs.* epileptic rats with lateral FPI	Hippocampus	Worsened hypometabolism at 1 wk, 1 month, and 3 months post-TBI	Multivariate regression model	[43] Shultz et al.
	T2-w and DTI MRI	Rat	Non-epileptic *vs.* epileptic rats with lateral FPI	Thalamus	T2 and diffusion changes in the ventroposterior nucleus	Logistic regression	[76] Manninen et al.
	MRI T2	Human	Patients with *vs.* without epilepsy after TBI	Cerebral cortex	Hemorrhagic contusion with gliosis wall incompletely surrounding hemosiderin dregs	Cox regression analysis Hazard ratio 6.61 vs. complete gliosis wall	[77] Messori et al.
	Gadolinium-MRI	Human	Patients with *vs.* without epilepsy after TBI	Cerebral cortex	Area of gadolinium leakage around cortical lesion after TBI	ROC analysis (AUC) 0.850	[78] *Data by A Friedman in* Pitkänen et al.
Electrophysiology	10–20 scalp EEG	Human	Patients with *vs.* without epilepsy after TBI	Brain	Epileptiform activities and focal slowing	Multivariate logistic regression Epileptiform abnormalities OR 3.16 (CI 0.99–11.68) EDs OR 4.57 (1.60–21) Focal slowing OR 2.67 (0.97–10.1)	[79] Kim et al.
	Continuous EEG monitoring	Human	Patients with vs. without epilepsy after TBI	Brain	Occurrence of early seizures	Generalized linear model $p=0.026$	[80] Tubi et al.

Table 3 (continued)

Modality	Analysis platform	Species	Group comparisons	Tissue	Biomarker	Statistics	Reference
	Sleep-EEG	Rat	Rats with epilepsy *vs.* no epilepsy after lateral fluid-percussion induced TBI	Brain	Shortening of the duration of sleep spindles occurring at transition from N3 to REM	ROC analysis (AUC) 0.907	[81] Andrade et al.
	EEG	Rat	HFOs differentiate rats which develop epilepsy after lateral fluid-percussion injury from those that will not	Brain	Presence of HFOs during the first 2 post-injury weeks	No data	[82] Bragin et al.
Physiology	-	Rat	Non-epileptic *vs.* epileptic rats with lateral FPI	Body weight	Decrease in body weigh between D0 and D4	ROC analysis (AUC) 0.679	[83] Lapinlampi et al.
Behavioral	-	Mouse	Non-epileptic *vs.* epileptic mice with CCI	Simple assessment of asymmetric behavior test (SNAP test)	Recovery between 1 wk and 2 months	0.870	[84] Di Sapia et al.
Prognostic & diagnostic biomarkers for epileptogenicity							
Electrophysiology	Intracerebral recordings	Rat	Non-epileptic *vs.* epileptic rats with lateral FPI	Brain	Occurrence of HFOs	No data	[85] Bragin et al.
	iEEG or icSEEG	Human	Seizure onset zone *vs.* other brain areas in humans evaluated for epilepsy surgery	Brain	Stereotypical HFOs with waveform similarity Spikes x HFO	No data	[86] Liu et al. [87] Roehri et al.

AUC area under curve; *CI* confidence interval; *CCI* controlled cortical impact; *CSF* cerebrospinal fluid; *D* day; *DTI* diffusion tensor imaging; *EEG* electroencephalogram; *ELISA* enzyme-linked assay; *FD4* fluorescein isothiocyanate–labeled dextran; *FDG* fluorodeoxyglucose; *FPI* fluid-percussion injury; *HFO* high-frequency oscillation; *iEEG* intracranial electroencephalogram; *icSEEG* intracerebral stereoelectroencephalograhy; *iHC* intrahippocampal; *LPS* lipopolysaccharide; *MRI* magnetic resonance imaging; *PET* positron emission tomography; *PTE* post-traumatic epilepsy; *PTZ* pentylenetetrazol; *ROC* receiver operating characteristic

fluid-percussion model of PTE, MRI and FDG-PET imaging at 1 week and 3 months post-TBI time points were able to predict which animals would go onto develop PTE [43]. Multiple EEG biomarkers, which may eventually be useful in treating human PTE, have also been identified as predictive in animal models. These include shortening of sleep spindles [81] and the presence of pathological high frequency oscillations (HFOs) [82]. In these preclinical studies, the predictive power of these metrics was confirmed using robust statistical approaches. In the near future, we hope that these metrics can be investigated in relevant clinical populations to determine if their utility applies to human TBI/PTE.

Identifying and validating biomarkers of PTE is of critical importance for three main reasons. First, aggressive interventions for those at the highest risk of developing PTE could prevent the development of epilepsy. If those interventions have adverse effects, however, clinicians may hesitate to treat unless the risk of developing PTE is known to be high. Validated biomarkers can give clinical confidence, on a case-by-case basis, that using interventions are worthwhile based on patient risk. Second, it is extremely challenging and costly to carry out clinical trials for PTE prevention. Because only a subset of patients with TBI develops PTE, a significant number of patients must be used to conclusively ascertain if a treatment is effective. If a validated biomarker could show which patients were at high-risk, clinical studies could be enriched for patients with the greatest likelihood of developing PTE. This would dramatically reduce the cost and number of patients needed to test new PTE treatments. This is particularly important for mild TBI, where patients often do not seek immediate clinical care after injury, but are still at risk of developing PTE. Perhaps most importantly, biomarkers enable patients and care givers to understand their risk and plan accordingly. Clearly, the development and validation of a clinical biomarker for PTE would greatly impact the field and patients who suffer from TBI.

Genetic Modifiers of PTE

It is not well understood why some people develop PTE after TBI, while others do not. Many factors are likely at play including injury severity, inflammatory response, age at time of injury, time after injury, secondary "hits," including other TBIs, stress, disruption of sleep, and many others. Of course, one must also consider that underlying genetic variations may contribute to the progression of secondary injury and manifestation of PTE. The effect may not be linear but rather depend, for example, on injury severity. A number of human and animal studies suggest that there is reason to believe that genetic variability that is not pathological under normal circumstances predisposes individuals to developing PTE.

Human Studies

While only preliminary analysis of genetic modifiers of PTE have been identified, a number of candidate gene variants have been suggested [89]. *Methylenetetrahydrofolate reductase* (MTHFR) is an enzyme involved in amino acid metabolism. The C677T MTHFR variant has been examined as genetic risk factor for epilepsy, may be over-represented in epilepsy patients, and is suggested to be linked to migraine and alcohol withdrawal seizures. In a study of 800 epileptic patients and 800 controls, the C677T variant was enriched in patients who had documented PTE [90]. While exciting, larger studies need to be done to determine if C677T MTHFR is strongly linked to PTE. *Glutamic acid decarboxylase* (GAD) is an enzyme critical to generating the inhibitory neurotransmitter GABA. Single-nucleotide polymorphisms (SNPs) in GAD1, one of the two GAD isoforms, were shown to be linked to post-traumatic seizures occurring shortly after TBI (< 1 week post-TBI) and PTE (1 week–6 months post-TBI) [91]. Again, these preliminary studies are intriguing but require further investigation to confirm their functional significance and strength of linkage to PTE. Changes in GABAergic inhibition are likely associated with PTE as GABAergic interneurons are lost after TBI [16, 92–94] and restoring GABAergic inhibition after TBI can prevent PTE [72, 95] in animal models. The *adenosine A1 receptor* (A1R) is a G-protein coupled receptor that is powerfully anti-convulsant and neuroprotective due to its ability to activate G-protein coupled inwardly rectifying K (GIRK) channels and inhibit presynaptic Ca^{2+} channels. In a study of over 200 patients with a severe TBI, SNPs in the A1R gene were linked to post-traumatic seizures occurring within one week following injury [96]. Again, A1Rs are closely linked to epilepsy as adenosine acting at A1Rs is thought to play a significant role in terminating seizures [97, 98] and genetic deletion of the A1R gene results in increased mortality in a rodent model of TBI [99]. Perhaps most interestingly, a SNP in the *interleukin-1beta (IL-1b)* gene, an inflammatory cytokine, has been shown to be linked to PTE risk over time [73]. The functional effects of this IL-1b SNP are unknown, but as mentioned above, the CSF/serum IL-1b ratio may also serve as a biomarker of PTE, strongly tying IL-1b to TBI/PTE. Finally, while not linked to PTE, there are several genetic polymorphisms, including APOE4, that are linked to poor outcomes after TBI [100, 101]. By combining genetic modifiers that affect TBI outcomes and early seizures, with those that affect PTE, we can build a more comprehensive understanding of how underlying genetic variation contributes to epileptogenesis. Properly powered clinical studies are critical to this goal.

Animal Studies

Only five studies have used genetically modified mice in PTE studies (Table 2). APP/PS1 mice showed increased prevalence of epilepsy [102]. Pijet et al. [103] showed increased prevalence of epilepsy, increased seizure frequency and susceptibility to PTZ-induced seizures in *Mmp-9* over-expressing mice. Interestingly, deficiency in another extracellular matrix system (urokinase-type plasminogen activator) had minor if any effect on epileptogenesis [59, 60]. Adenosine A1R knockout mice show increased susceptibility to acute post-TBI seizures, but no longer-term risk of epileptogenesis was reported [99].

Overall, understanding the contribution of genetics on the evolution of epileptogenesis is at its infancy. Perhaps the most convincing evidence is the observation of higher incidence of epileptogenesis in CD1 mouse strain as compared to B6 strain [14] (Table 1). Even less is known about the contribution of genetics to therapy response. Further studies to replicate the current observations in larger study populations are warranted. It remains to be studies whether genetic markers can be used in stratification of patient populations in epileptogenesis clinical studies.

In Vitro Approaches to Understand Epileptogenesis and Develop Anti-epileptogenic Treatments

The development of PTE is likely driven by multiple factors which over time transform healthy brain networks in vivo into networks that generate seizures. Because of the in vivo nature of PTE, relatively few purely in vitro approaches exist to model epileptogenesis. One exception to this rule is the organotypic slice culture model of epilepsy developed by the Staley Lab. In this approach, hippocampal brain slices are prepared from neonatal rodents and cultured in vitro for weeks to months. Interestingly, over this time window, organotypic slices undergo dynamic changes in neuronal activities that eventually evolve into in vitro seizure-like events. In the first week of culture, only spike-like activity occurs. By 3 weeks in culture, > 50% of slices display prolonged, ictal-like activity [104, 105]. This evolution of ictal-like activity has been harnessed to investigate candidate mechanisms of epileptogenesis, like PI3K-Akt signaling [106, 107] as well as to perform drug screening aimed at identifying novel anti-convulsant and anti-epileptogenic therapies [108]. When combined with in vivo validation, this approach may hold promise as an alternative to purely in vivo–based drug discovery for anti-convulsant and anti-epileptogenic therapies.

As novel approaches are developed to grow cerebral organoids in vitro from induced pluripotent stem cells (iPSCs), new ways to model TBI and PTE will emerge. Intriguing recent work examines how contusional injury, similar to the controlled cortical impact model, affects neuronal viability, neurotransmission, and cell signaling in cerebral organoids [109]. This study shows that neurons die, that glutamate is released, and that pAKT and GSK3b signaling are reduced after physical injury in cerebral organoids. Whether cerebral organoids go onto develop something like PTE remains to be seen, but this is an exciting step towards developing additional in vitro assays for TBI and later PTE.

In addition to this purely in vitro approach, by coupling in vivo injury with in vitro assays, many studies have identified potential mechanisms of PTE and assayed the effects of various drugs. These include neuronal cell death, excitatory neuron sprouting, neuroinflammation, changes in metabolic activity, glial cell dysfunction, and more.

Conclusions

Recent successes in modeling various epileptogenic human brain injuries in rodents and larger animals [110], in identifying subjects at risk for PTE (high CSF/serum Il-1β, N3-REM spindles), and in pinpointing epileptogenic regions in the injured brain (HFOs) provide promise that novel approaches to identify and treat PTE are closer than ever before. Recent emphasis on clinically relevant study designs and outcome measures, combined with statistically powered preclinical multicenter studies can be expected to advance the field remarkably over the next years [111]. There is hope on the horizon.

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