Seizure 33 (2015) 13–23

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

Traumatic brain injury and epilepsy: Underlying mechanisms leading to seizure

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ARTICLE INFO

Article history:
Received 10 June 2015
Received in revised form 6 October 2015
Accepted 8 October 2015

Keywords:
Post-traumatic epilepsy
Epilepsy models
Traumatic brain injury
Neuroinflammation
Ketogenic therapy

ABSTRACT

Post-traumatic epilepsy continues to be a major concern for those experiencing traumatic brain injury. Post-traumatic epilepsy accounts for 10–20% of epilepsy cases in the general population. While seizure prophylaxis can prevent early onset seizures, no available treatments effectively prevent late-onset seizure. Little is known about the progression of neural injury over time and how this injury progression contributes to late onset seizure development. In this comprehensive review, we discuss the epidemiology and risk factors for post-traumatic epilepsy and the current pharmacologic agents used for treatment. We highlight limitations with the current approach and offer suggestions for remedying the knowledge gap. Critical to this pursuit is the design of pre-clinical models to investigate important mechanistic factors responsible for post-traumatic epilepsy development. We discuss what the current models have provided in terms of understanding acute injury and what is needed to advance understanding regarding late onset seizure. New model designs will be used to investigate novel pathways linking acute injury to chronic changes within the brain. Important components of this transition are likely mediated by toll-like receptors, neuroinflammation, and tauopathy. In the final section, we highlight current experimental therapies that may prove promising in preventing and treating post-traumatic epilepsy. By increasing understanding about post-traumatic epilepsy and injury expansion over time, it will be possible to design better treatments with specific molecular targets to prevent late-onset seizure occurrence following traumatic brain injury.

1. Introduction

Traumatic brain injury (TBI) is a leading cause of acquired epilepsy [1]. In veterans, 57% of seizures can be linked to TBI [2]. Immediately following injury, the brain undergoes distinct electrophysiological changes, which can be detected with electroencephalography [3]. Seizures not only account for heightened morbidity and mortality in the early stages following TBI, but also remain the leading cause of death several years following TBI [4]. Seizure prophylaxis is commonly employed post-injury with variable success [5]. The prophylaxis is primarily used for prevention of single occurrence acute post-traumatic seizure (PTS) but has little efficacy on preventing the recurrent chronic seizures that define post-traumatic epilepsy (PTE). The underlying mechanisms that may contribute to PTE are poorly understood making PTE more likely to be refractory to medical management [6]. Despite prophylaxis treatment, 4–53% of TBI patients still have chronic seizures [7]. Unfortunately, few novel treatments for the prevention of PTE have been discovered over the past century [8].

Abbreviations: AEDs, anti-epileptic drugs; APOE4, apolipoprotein E epsilon 4; BBB, blood brain barrier; BDNF, brain-derived neurotrophic factor; JNK, c-Jun N-terminal kinase; CCI, controlled cortical impact; EEG, electroencephalogram; mTOR, mechanistic target of rapamycin; PTZ, pentylenetetrazol; PTE, post-traumatic epilepsy; PTS, post-traumatic seizure; TBI, traumatic brain injury.

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http://dx.doi.org/10.1016/j.seizure.2015.10.002
1059-1311/

In order to improve treatment options, it is important to elucidate the underlying pathophysiology of PTE. To do so, pre-clinical models should be utilized to understand intrinsic biochemical mechanisms of injury. Animal models can be used to study natural progression toward seizure activity following neural injury [8]. In the past, experimental approaches for studying PTE frequently employed seizure-inducing agents such as kainic acid or pentylenetetrazol (PTZ). While such models have provided compelling evidence that changes in glutamate signaling and GABA-A channels may play a role in acute seizure onset following TBI, they have failed to answer how the natural progression of TBI contributes to late onset seizures [9]. How genetic regulation affects these acute receptor and channel changes is poorly understood and is a topic worthy of investigation [10]. It has been shown that glutamate signaling increases in response to decreased GABAnergic activity [11], and as we discuss later, the phenomenon is likely due to microRNA regulation. The key unanswered question is why some individuals recover from these transient signal changes while others go on to develop PTE [12]. Recent evidence from pre-clinical rodent models suggests that neuroinflammation may play a key physiologic role in shifting the balance toward PTE [13]. We discuss in particular the role of toll-like receptors and how at extended post-injury time points, neuroinflammation may contribute to loss of hippocampal interneurons [9]. Important knowledge has been obtained from both clinical and pre-clinical studies. TBI patients with cerebral contusion and subsequent inflammation are at higher risk for epilepsy than those without contusion [14]. Mechanisms triggered by neuroinflammation such as oxidative stress and mitochondrial dysfunction appear to add to the onset and progression of epilepsy post-TBI and may contribute to the neurodegeneration that has been reported with PTE [15].

In this paper, we will begin with a review of epidemiology and go through treatment options, preclinical models, the biochemical cascade of PTE development, and novel pharmaceutical targets. The epidemiology and symptoms associated with PTE will be discussed with particular emphasis on the patient's gender, injury severity, primary mechanism of injury, and genetic background. We will also highlight current treatment options used for prophylaxis therapy of acute PTS elaborating upon mechanism of action and potential side effects. Potential reasons for treatment ineffectiveness for PTE will be postulated. In order to improve outcomes and reduce late onset seizure occurrence following TBI, biochemical pathways should be investigated using well-designed pre-clinical models. The pros and cons of available models will be outlined with a subsequent overview of what is currently known about the biochemical mechanisms for seizure development post-TBI. Finally, we will address important biochemical pathways warranting further investigation and discuss how these pathways can contribute to the discovery of novel pharmaceutical targets. Because no current treatment option has been shown to completely prevent PTE, the long-term goal is to foster improved treatment approaches by targeting specific and important mechanisms of injury progression. By developing targeted therapy, it is plausible that within the century we can see a drastic reduction in late onset seizure post-TBI.

2. Epidemiology and symptoms

Seizures are a major complication that can occur after TBI, and the development of epilepsy is a serious concern for neurotrauma patients. After TBI, the occurrence of seizures has been categorized as immediate (<24 h), early (1–7 d), or late (>1 wk) [16]. According to the National Institute of Neurological Disorders and Stroke, epilepsy requires the occurrence of two or more spontaneous seizures. The International League Against Epilepsy expanded the definition to include 1 spontaneous seizure with a risk for future seizure [17]. TBI associated with at least two unprovoked, late onset seizures constitutes the diagnosis of PTE; otherwise, the diagnosis is PTS [18]. Additional definitions related to PTE revolve around the degree of head trauma. Many investigators currently use the following: (1) mild TBI (loss of consciousness less than 30 min and no skull fracture); (2) moderate TBI (loss of consciousness more than 30 min and less than 24 h, with or without skull fracture); and (3) severe TBI (loss of consciousness greater than 24 h, with contusion, hematoma, or skull fracture) [19,20].

2.1. Epidemiology

Epidemiological studies have found that PTE accounts for 10–20% of symptomatic epilepsy in the general population, and 5% of all epilepsies [21]. Regarding PTE caused by war, the incidence is much higher in veterans than the incidence in civilian populations. The total incidence of PTE in the civilian population is approximately 2% [21], but in the veteran population it reaches as high as 25% when patients are followed 5 or more years from time of combat [22]. Moreover, the incidence of epilepsy ranges from 22 to 43% (median 34%) five years after TBI in civilians, and the incidence is almost 50% 10 or more years after injury for veterans.

2.2. Clinical presentation

The latency from TBI to the occurrence of the first seizure varies greatly [4]. In general, approximately 80% of individuals who develop PTE, have their first seizure within the first 12 months post-injury, and more than 90% by the end of the second year [23]. After the first late onset seizure (>1 wk from injury), 86% of patients have reported a second seizure within 2 years [24].

Several clinical studies have identified the types of late seizures observed after TBI, which are varied. In a study of 60 patients with moderate to severe TBI, 52% developed generalized seizures, 33% had focal seizures, and 15% had focal seizures with secondary generalization [24]. In another study of 123 patients with PTE, representing 4% of all patients evaluated in the epilepsy monitoring unit, most of them had localization-related epilepsy: 57% had temporal lobe epilepsy, 35% had frontal lobe epilepsy, and 3% each had parietal and occipital lobe epilepsy [6]. Of patients with temporal lobe epilepsy, 44% had mesial temporal sclerosis, 26% had temporal neocortical lesions, and 30% were non-lesional [6].

PTE may present with a myriad of other sequelae. In particular, PTE has been associated with insomnia in veterans where they have an inability to fall or stay asleep [25]. In a large population-based study (N = 1961), persons identified as having depression at discharge have been found to be almost twice as likely to develop PTE [26]. In the same study, participants with three or more chronic comorbid conditions, such as cardiovascular disease or diabetes, at discharge had increased risk of PTE [26]. It has yet to be determined whether the co-morbidities precede development of PTE or are the result of traumatic brain damage.

2.3. Risk factors

A critical determinant for PTE is TBI severity [26]. In a population-based clinical study (N = 4541) of TBI cases occurring between 1935 and 1984 in Olmstead County, Minnesota the investigators found that the five-year cumulative probability of unprovoked seizures was 0.7% in patients with mild TBI, 1.2% for moderate TBI, and 10.0% for severe TBI [19]. For the cohort with 30 years of follow-up, the cumulative incidence was 2.1% for mild TBI, 4.2% for moderate TBI, and 16.7% for severe TBI [19]. In a separate study, Englander and colleagues prospectively followed

647 patients admitted to any of four trauma centers within 24 h of injury. The authors identified a "dose–response" for the number of cerebral contusions and the development of late seizures—the cumulative probability of unprovoked seizures by 2 years was approximately 25% for patients with multiple contusions, compared to 8% for a single contusion and 6% for no contusions. For those with very mild TBI (no acute loss of consciousness, amnesia, confusion, or neurological deficit), only 3 (0.1%) out of 2999 patients developed seizures within 1 year of follow-up compared to 1 (0.1%) out of 994 of the control group with orthopedic injuries, suggesting that the incidence of seizures was not significantly greater than the general population [27].

Other key risk factors for more severe injury include dural penetration, depressed skull fracture, intracranial hematoma, and loss of consciousness or amnesia for more than one day [28]. Hemorrhage and skull fracture are often seen with more severe TBI [29]. Hemorrhage and skull fracture increase inflammation and neuronal excitability, which effectively decreases the threshold for seizures [30]. Neuroinflammation remains elevated well past 8 days in severe TBI, which may account in part for the development of late onset seizures [31].

In addition, the presence of early seizures may predispose individuals to the development of late PTE [22]. Young children are more prone to early seizures, and adolescents and adults to late seizures [22]. Older age may also increase the risk for PTE [28]. Gender overall does not appear to influence risk for PTE, although females may have a higher risk for PTE after milder injuries compared to males [32]. Warfighters are especially susceptible to the development of PTE [2].

Recent evidence from genetic association studies supports the view that certain genetic variants may also increase the risk for PTE (Table 1). Positive findings in these studies are currently preliminary. They have yet to be confirmed in separate studies or in different populations of patients with PTE. For instance, in patients

Table 1
Clinical studies examining potential genetic risk factors for developing seizures after TBI.

Study population	Seizure prevalence	Genes examined	Major findings	Reference
Vietnam War veterans with brain injury *N* = 199	43.7%	• APOE ε4 • GAD • Catechol-O-methyltransferase • GRIN (a glutamate receptor and a subunit of the NMDA) • Brain-derived neurotrophic factor, • Dopamine β-hydroxylase.	• *GRIN*2A rs11074504 and *GAD*2 rs1330582 associated with PTE • No significant difference after multi-comparison	[34]
Patients at level 1 U.S. trauma center with severe TBI *N* = 206	17.2%	• A1 adenosine receptor	• rs3766553 & rs10920573 associated with PTS • Subjects with two variants have a 46.7% chance of late PTS • For rs3766553, AA genotype: increased early PTS • GG genotype: increased late onset PTS • For rs10920573, CT genotype: increased late PTS	[84]
Patients at level 1 U.S. trauma center with severe TBI *N* = 257	19.8%	• GAD1 • GAD2	• No significant associations for GAD2 • For GAD1, rs3828275: increased risk for early PTS • rs769391 and rs3791878: late onset PTS • Both risk variants increased risk of PTS	[85]
Patients at level I trauma center with moderate or severe TBI *N* = 106	20%	• APOE ε4	• APOE ε4 allele relative risk is 2.41 for late onset PTS • APOE ε4 not associated with functional outcome or development of early PTS	[33]
Patients with TBI *N* = 69	16%	• APOE ε4	• No increased risk of PTE in APOE ε4 positive individuals • Odds ratio of a suboptimal outcome was 13.93 with allele • Only 3.7% (1/27) with the allele had good functional outcome vs. 31.0% (13/42) without allelle	[86]
Patients with severe TBI *N* = 322	18.6%	• APOE ε4	• No significant associations • 2 out of 4 with the E4/E4 genotype had late/delayed onset PTS	[87]
Patients with TBI *N* = 56	14.8%	• APOE ε4 genotype • Haptoglobin (Hp) concentration/phenotype • Hp phenotype was determined in previously collected frozen samples for 25 additional PTS and 32 no PTS subjects	• No significant associations for Hp concentration • APOE was not related to neuro-outcome • After adjusting for differences in educational levels, APOE ε4 subjects did worse especially on verbal intellectual and verbal memory skills	[88]
Military personnel *N* = 1600	14–15%	• Methylenetetrahydrofolate reductase (MTHFR) • 1357 (85%) subjects successfully genotyped for MTHFR C677T & 1319 (82%) for MTHFR A1298C	• For C677T, the odds of PTE was 1.81 for the TT vs. CC genotype • Risks stronger in patients with repeated injuries • No relationship between A1298C genotype & PTE	[89]

Note: PTS, post-traumatic seizures; PTE, post-traumatic epilepsy; GCS, Glasgow coma scale; APOE ε4, apolipoprotein E epsilon 4; GAD, glutamic acid decarboxylase; CT, computed tomographic.

with moderate or severe TBI ($N = 106$), the apolipoprotein E epsilon 4 (APOE ε4) allele was associated with a 2.4-fold increased risk of late PTS [33]. However, no significant associations were found in Vietnam War veterans with brain injury ($N = 199$) [34]. Mixed results have been obtained for APOE ε4 and GAD as outlined in Table 1. Additional genetic studies may provide further insights into the pathophysiology of PTE and guide the development of better treatments for PTE. The studies must be sufficiently powered and ideally prospective in nature.

3. Current treatment options

PTE has been shown to cause secondary damage to the brain. The seizure activity can cause hypoxia, increased intracranial pressure, cerebral edema, intracerebral hemorrhage, increased metabolic demand within the brain, and glutamate excitotoxicity [35]. In order to prevent permanent neurological sequela, current treatment of neurotrauma with regards to seizure development falls into one of two categories: prophylaxis for acute seizure or management of PTE, both of which have focused on the use of anti-epileptic drugs (AEDs). To decrease the incidence of seizures post-trauma, the majority of clinicians are prescribing prophylactic medications for patients following head injury [35]. Prophylaxis is currently recommended for severe TBI by leading advisory boards (Brain Trauma Foundation and the American Academy of Neurology) for the first 7 days [4]. While there is evidence that these prophylactic anticonvulsants reduce early seizures, there is no proven benefit for long-term prognosis [36]. Indeed, a meta-analysis of 10 randomized controlled trials showed a pooled relative risk reduction of 0.34 for early seizure prevention indicating that 10 in every 100 patients will be seizure-free from treatment [37]. On the other hand, no beneficial effects on mortality or neurological disability were found regarding the prevention of late-onset seizure. It is also important to note that no randomized controlled trial has shown that one drug is more efficacious than another [38] as outlined for phenytoin, carbamazepine, valproate, and phenobarbital (Table 2). Randomized trials are difficult to perform because all new treatments must be compared to an already available treatment thereby masking potential benefit. Despite their similar uses, the available medications target different pathways. Thus, before prescribing these medications, consideration of injury severity, patient status, and side effect profile must be carefully reviewed [39].

3.1. Phenytoin

Phenytoin increases the refractory period and reversibly inhibits action potentials [40]. In severe TBI, phenytoin has been found to reduce the incidence of early seizures from 14.2% to 3.6% [41]. Also, this drug should only be used within the first 48 h post-trauma because a randomized control trial showed a trend toward higher mortality when used at later time points [35]. In a separate study, the use of this anticonvulsant beyond 1 week was associated with idiosyncratic side effects (Table 2) [37,40]. The onset of rashes is also suggested with a RR of 1.57 from a recent meta-analysis [37]. In addition, long-term prophylaxis has not been shown to improve morbidity, mortality, or PTE development with this drug [35]. The current recommendation is early prophylaxis and acute treatment with each episode of seizure activity.

3.2. Carbamazepine

Another rarely prescribed medication for prophylaxis is carbamazepine [40]. One preliminary study has demonstrated that carbamazepine reduces PTS by 61% [38]. According to a meta-analysis, early preventive treatment with carbamazepine showed a RR of 0.96 for reduction in mortality and disability [37]. This is consistent with other studies demonstrating no association between early prophylaxis and long-term prognosis. It is important to note that this medication is associated with several side effects and is administered intravenously limiting its use (Table 2) [40]. These adverse reactions must be carefully considered before administration and monitored thereafter.

3.3. Valproate

Valproate inhibits GABA transaminase increasing GABA levels in the synaptic cleft [40]. Studies have demonstrated a similar efficacy as compared to phenytoin [38]. However, valproate is also associated with a higher mortality [42]. Potential adverse effects of valproate are outlined in Table 2 [40]. Despite its efficacy, this medication cannot be recommended due to increased mortality in patients with PTS [42].

3.4. Phenobarbital

Phenobarbital is also used for prophylaxis [40]. In decreases excitatory neurotransmitter release at the synaptic terminal [43]. This medication has been studied in a randomized controlled trial to determine its effect on patients with severe head trauma. Phenobarbital was prescribed at a serum drug concentration of 10–25 mg/mL 1-month post-trauma for 3 years, and patients were followed for a 5-year duration [38]. Long-term prophylaxis did not show a statistically significant reduction in seizure occurrence. Phenobarbital is also associated with side effects (Table 2) [40]. In addition, phenobarbital is more likely to be discontinued compared to other drugs (including carbamazepine, phenytoin, and valproate) due to its adverse reactions [44]. Due to overall limited evidence of efficacy in short- and long-term prevention of seizures as well as numerous adverse effects [44], this anticonvulsant should be used only after consideration of other therapeutic options.

Overall, with the current regimen, prophylaxis immediately post-injury is effective for reducing early seizures [37]. However, the use of these medications has not been shown to improve long-term prognosis. Moreover, they have narrow therapeutic safety windows, even in patients without brain injury, which may outweigh the limited beneficial effects.

Table 2
Current prophylactic treatment options.

Anticonvulsant drug	Mechanism	Adverse reactions
Phenytoin	Stabilize inactive form of sodium channel	Fever, nystagmus, leukocytosis, rash, hypersensitivity reactions
Carbamazepine	Stabilize sodium channels in inactive state	Aplastic anemia, agranulocytosis, pancytopenia, Stevens Johnson syndrome, toxic epidermal necrolysis
Phenobarbital	Activate GABA receptors, inhibit calcium channels	Dizziness, fatigue, ataxia, aplastic anemia, panmyelopathy
Valproate	Inhibit sodium channels and GABA transaminase, activate GABA-synthetic enzyme glutamic acid decarboxylase, alter the conductance of calcium and potassium	Thrombocytopenia, hypofibrinogenemia, pancytopenia

4. Pre-clinical models

In order to improve treatment options, pre-clinical models must be designed to understand PTE pathophysiology. Recently, the neurotrauma field has made a push for the development of more predictive pre-clinical models of TBI that are consistent, reproducible, and most importantly, clinically relevant (Table 3). Pre-clinical TBI models should produce similar mechanisms of injury and pathologies as seen in human TBI, including generation of PTE. Over the past decade, the most common pre-clinical model of PTE is the rat fluid percussion model combined with a PTZ challenge [45]. Other models include a weight-drop combined with PTZ [46], controlled cortical impact (CCI) combined with PTZ [47], and CCI combined with electroconvulsive shock as outlined in Table 3 [48]. These models have been used to shed light on novel mechanisms of injury progression leading to seizure. CCI and fluid percussion are typically invasive, in contrast to closed-head injury which is more commonly observed in patients [49]. Blast modeling and weight drop may be more clinically relevant due to simulation of acceleration/deceleration injury and contusion respectively.

Few currently used models can induce the natural progression of PTE without a pharmacologic agent, and require a very severe injury, or require the animals to be very young, or very old and therefore more susceptible to PTE [22]. While a model that induces a natural PTE is ideal, the caveat of increased mortality lies within models of severe TBI. Several reasons account for the limited ability to produce natural progression PTE in rodents. The most prominent reason is lack of detection capabilities. Unlike humans, rodents do not often produce overt signs of seizure-like activity. Therefore brain imaging or electrical scanning becomes imperative to detect activity that may not be represented behaviorally. Additionally, rodents have a shorter lifespan and therefore may not adequately map the time course necessary for PTE development. In order to produce robust effects, an injury model that produces severe brain damage is often utilized.

Thus, while models already exist that exhibit relevant mechanisms of injury and pathologies including PTE, their feasibility for routine experimental studies is limited due to their associated high mortality. As such, an optimized PTE model for the future may be one with a closed-head moderate TBI that could produce a natural seizure over a shorter duration, but continuous seizure activity chronically. At the present time, this type of model has not been established. However, since evidence suggests that blood brain barrier (BBB) disruption contributes to early seizure onset [50], incorporation of robust BBB disruption is suggested for future model development.

Additionally, future assessments of TBI pre-clinical models should include systematic monitoring of several elements to facilitate model development and optimization. These include determining the length of time to seizure onset and continuance of seizures long-term in such models. Also, assessment of pre-clinical models could benefit from more uniformity in seizure detection, with electroencephalogram (EEG) used to determine the number and type of seizures. Moreover, the use of juvenile rodents may not be the most clinically relevant when extrapolating to the human population who typically sustain a TBI. The use of adult rodents would be beneficial in future studies.

Table 3
Preclinical models of PTE.

Study	Species	TBI model	Severity	Interval	Second hit	Outcome measures and key findings
Williams et al., 2006 [90,91]	SD rats	Ballistics	Severe	n/a	*Natural*	Histology; continued EEG recording
Chrzaszcz et al., 2010 [48]	CD1 mice	CCI	Severe	7 d	Electric shock	Histology; cognition; minozac prevents inflammation and seizures in two hit model
Hunt et al., 2010 [92]	CD1 mice	CCI	Severe	n/a	*Natural*	Slice recordings; histology; increased excitatory postsynaptic current in hippocampus
Bolkvadze et al., 2012 [47]	C57 mice	CCI & lateral FPI	Severe	6 mo	PTZ 50 mg/kg	*In vivo* recordings; histology; C57/bl6 mice develop hyperexcitability at different injury thresholds
Nichols et al., 2015 [93]	*Young* SD rats	CCI	Severe	n/a	*Natural*	*In vivo* recordings; slice recordings; enhanced cortical synaptic bursting
Statler et al., 2009 [94]	*Young* SD rats	CCI	Severe	n/a	*Natural*	*In vivo* recordings; histology; EEG spikes common several months post-injury
Hamm et al., 1995 [95]	SD rats	Central FPI	Moderate	24 h	Daily PTZ 25 mg/kg	Cognition; PTZ kindling does not worsen cognitive outcomes post-injury
Mukherjee et al., 2013 [96]	C57 mice	Lateral FPI	Mild	1 mo	PTZ 30 mg/kg	Histology; increased seizure susceptibility
Silva et al., 2013 [15]	Wistar rats	Lateral FPI	Severe	6 wk	PTZ 35 mg/kg	*In vivo* recordings; histology; physical exercise reduces risk of seizures
Echegoyen et al., 2009 [75]	Wistar rats	Lateral FPI	Moderate	6 wk	KA 5 mg/kg	*In vivo* recordings; cannabinoid type-1 receptor antagonist prevents seizures
Bao et al., 2011 [45]	SD rats	Lateral FPI	Moderate	2 wk	PTZ 30 mg/kg	Physiology; histology; seizures worsen structural damage caused by TBI
Kharatishvili et al., 2006 [97]	SD rats	Lateral FPI	Severe	n/a	*Natural*	*In vivo* recordings; histology; 40–50% seizure occurrence following FPI
Zanier et al., 2003 [30]	SD rats	Lateral FPI	Moderate	1 h	KA 9 mg/kg	Glucose metabolism; BBB permeability; histology; hippocampal activation and loss of CA3 and CA4 pyramidal neurons
Kharatishvili et al., 2007 [98]	SD rats	Lateral FPI	Severe	12 mo	PTZ 25 mg/kg	MRI; *in vivo* recordings; histology; EEG correlates with changes seen in hippocampi
Atkins et al., 2010 [66]	SD rats	Parasagittal FPI	Moderate	12 wk	PTZ 30 mg/kg	*In vivo* recordings; physiology; histology; hypothermia prevents hippocampal changes
D'Ambrosio et al., 2005 [99]	SD rats	Parasagittal FPI	Severe	n/a	*Natural*	*In vivo* recordings; morphology; histology; progressive hippocampal and temporal cortex pathology
Golarai et al., 2001 [46]	SD rats	Weight-drop	Mild	15 wk	PTZ 30 mg/kg	Slice recordings; histology; mossy fiber sprouting in dentate gyrus post-injury
Nilsson et al., 1994 [91,99]	SD rats	Weight-drop	Moderate	n/a	*Natural*	*In vivo* recordings; microdialysis; physiology; found increase in aspartate, glutamate, and glycine

Additional research into modeling a more clinically relevant TBI must be undertaken to establish a more natural progression to seizure onset. Recent PTE modeling has decreased the latency of epileptogenesis, but not without a secondary insult using seizure inducing compounds, or electroconvulsive shock [48]. Most PTE models use PTZ as the pharmacological inducer of seizure, with other PTE models using kainic acid following TBI [30]. The choice of which seizure-inducing compound is most relevant depends upon the mechanism under investigation as outlined in Table 3. PTZ induces seizures by inhibiting the inhibitory neurotransmitter GABA (disinhibition), and KA induces seizures by activating the excitatory neurotransmitter glutamate. KA, for instance, would be a good secondary insult to use after TBI when investigating NMDA triggered mechanisms of excitotoxicity. Although these two compounds are validated within the epilepsy field, the idea of pharmacological secondary insult after TBI warrants further investigation. It is currently unknown what triggers late onset seizures in humans and it may be linked to chronic neuroinflammation or another idiopathic insult. The second hit model can be used to establish a mechanistic pathway for seizure progression; but in order to effectively model PTE pre-clinically increased emphasis must be placed on subthreshold doses that lower seizure threshold. Ideally the model will induce full-blown seizure with a subthreshold pharmacologic intervention or a second-hit of lower intensity.

5. Mechanisms of injury

5.1. Glutamate excitotoxicity

The development of adequate models can help increase understanding about generation of an epileptic foci acutely [51]. Animal models have shown that within the first few days post-injury, disruption of microRNAs facilitates the transition toward epileptic activity [52]. The disrupted microRNAs exacerbate glutamate-mediated excitotoxicity post-injury [53]. The induction of the glutamate toxicity may be orchestrated through iron release from damaged blood cells diffusing across a disrupted BBB [50]. The remaining surviving neurons participate in functional or structural adaptations, such as axonal sprouting, to increase the risk for subsequent hyperexcitability [54]. Concurrent with glutamate changes, a substantial reduction in GABA releasing interneurons within the hippocampus leads to enhanced disinhibition at early time points post-injury [9].

5.2. Neuroinflammation

Several days after injury, the damaged brain region can initiate the cell danger response, which consists of a series of injury cascades that halts normal homeostasis [55]. Part of this response is dependent on mechanistic target of rapamycin (mTOR) signaling, which has been suggested to contribute to tissue damage and continued excitotoxicity [56]. mTOR1c, in particular, has been implicated in the pathology of PTE [57]. Acute neuroinflammation activates Akt, which phosphorylates mTOR and contributes to cell-death [56]. Further research is needed to elucidate the long-term effects of mTOR activation.

Another important subacute response is mediated by toll-ligands and toll-like receptors. Toll-like receptors trigger the innate immune system and regulate non-NMDA glutamate channels [58]. Following injury, activation of these toll-like receptors can contribute to continued glutamate excitotoxicity out to several weeks [59]. Wang and colleagues showed that toll-like receptors are upregulated following kainic acid administration [60]. Specifically, toll-like receptor 4 is associated with temporal lobe seizures following trauma [61]. Toll-like receptors on glia trigger a robust gliosis response post-injury [62].

The initial injury cascade is followed by a period of neuroinflammation mediated through activated astrocytes and microglia [63]. Neuroinflammation can last months after injury. Upregulation of phospholipase A2 and lipid metabolism continues to activate this neuroinflammatory cascade several months post-injury [64]. Mutations in the Plaur gene, which traditionally promotes plasmin formation, may make certain individuals more susceptible to sustained neuroinflammation following injury [65]. Reducing this inflammation through selective brain cooling proves promising in preventing late onset seizures in a rodent model [66]. Recent evidence implicates interleukin 1β as a cerebral-spinal fluid marker predictive of persistent neuroinflammation seen with PTE [67].

5.3. Tau pathology

Late onset epilepsy several years post-injury has been associated with tau hyperphosphorylation and neurodegeneration post-injury (Fig. 1) [68]. An imbalance in zinc homeostasis may contribute to tauopathy in PTE patients. An increase in zinc levels has been shown to generate reactive oxygen species in neurons with tau tangles, which may contribute to seizure onset [69]. TBI also causes disruption in A-type potassium channels further leading to release of reactive oxygen species and neuronal damage in the hippocampus [70]. Substantial atrophy of the surrounding entorhinal and perirhinal cortices is commonly seen following initial seizure onset [71]. Furthermore, mTOR complex 1 has been implicated in neurodegeneration leading to sustained seizure activity with increased mossy fiber spreading in the hippocampus [72]. This pre-clinical data is similar to persistent gliosis, cavitation, and hippocampal sclerosis in human TBI patients measured with diffusion tensor tractography [73]. Hippocampal sclerosis is associated with tauopathy in patients with PTE [68].

5.4. Mechanism summary

At acute time points, glutamate excitotoxicity contributes to early onset seizure. Over time secondary injury cascades activate downstream long-term cascades such as mTOR activation and toll-like receptor upregulation. These subacute changes facilitate the transition toward PTE. In conjunction with PTE, tauopathy can develop. Tauopathy can further contribute to seizure generation enhancing chronic neurodegeneration.

6. Novel targets

Selecting therapeutic compounds that have potential efficacy is dependent on two important features. Does the compound target an important pathway linked to seizure progression, and will it produce limited side effects? Once these questions have been successfully answered, it will be important to classify the compound into rescue therapy or preventative treatment. Rescue therapy reduces the number of seizures once they have started. Preventative treatments stop seizures from occurring or starting at extended time points.

While the historical emphasis has been on medical management and/or prophylaxis of seizures acutely in the post-trauma setting, recent studies have shifted focus to the latent period between the traumatic episode and development of late seizures, occurring years post-injury [4]. These studies have explored numerous therapeutic targets ranging from those modulating neurotransmitters both directly and indirectly (i.e. AEDs), intraceullular signal transduction, cannabinoid receptors, inflammation, induction of hypothermia, and utility of a ketogenic diet [4]. The results of these studies have been reviewed extensively

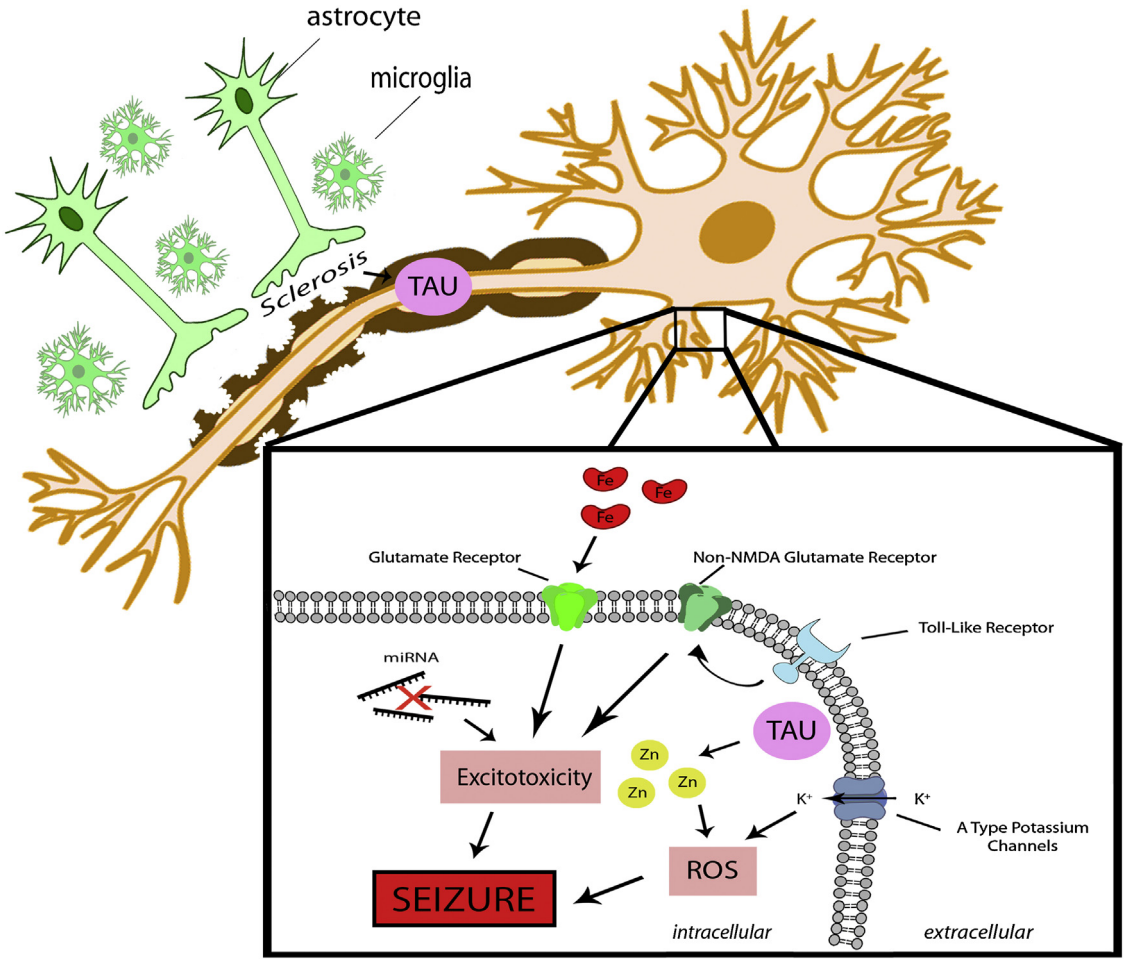

Fig. 1. The initial acute injury (hours–days) following TBI induces glutamate excitability and sclerosis. Reactive oxygen species are generated from the resulting hyperexcitability, which damage the cell. This process is regulated by microRNAs. At subacute time points (days–weeks) inflammation occurs from activated toll-like receptors and non-NMDA glutamate receptors. These further insults exacerbate the damage caused by glutamate toxicity and allow free iron to enter the cell. Over time (months–years) this injury contributes to tau aggregation. Tau interacts with zinc to generate further free radical damage reducing the threshold for late onset seizure.

elsewhere [4] but in the following paragraphs we will briefly summarize the findings of these studies.

6.1. Rescue therapies

SR141716A, also known as Rimonabant® and Acomplia, an inverse agonist of the cannabinoid CB1 receptor previously marketed as an appetite modulator, was tested by Echegoyen and colleagues in pre-clinical studies of seizure threshold post-TBI [75]. Using a lateral fluid-percussion model and kainate to induce seizures at 6 weeks post-TBI, the authors evaluated the ability of SR141716A to modulate the latency to kainate-induced seizures and the total time spent seizing post-TBI [75]. SR141716A administration decreased latency to seizure and decreased total time spent seizing following TBI in comparison to vehicle treatment [75,76]. No protective effects were observed, however, when the compound was administered 20 min post-injury [76]. Despite promising but limited preclinical studies, the compound was pulled from the market due to elevated rates of depression and suicidal thoughts.

Minozac, a promising anti-inflammatory agent being developed for numerous neurological diseases such as Alzheimer's disease and multiple sclerosis, has been evaluated post-TBI in pre-clinical studies and shown to decrease electroconvulsive shock-induced seizure susceptibility at 1 week post-injury [48]. Whether these effects will persist at later time points and if this compound will be evaluated clinically remains to be seen [76]. Regardless, these preliminary studies show some promise regarding inflammation as a therapeutic target for seizure development post-TBI.

6.2. Preventative treatments

Due to the frequently suboptimal results associated with AED use in the management of epilepsy, alternative therapeutic approaches and techniques have been explored at great lengths. One of those most commonly discussed in the clinical literature is the implementation of a ketogenic diet [77]. Ketone bodies have been shown to have anticonvulsant effects with fasting decreasing the amount of seizures in patients with epilepsy (Fig. 2) [77]. This approach was employed by Schwartzkroin and colleagues in a pre-clinical study addressing fluorothyl-induced seizure susceptibility following lateral fluid-percussion injury [78]. However, dietary regimen had no effect on seizure susceptibility in this study when considering seizure threshold and duration [76].

Another non-pharmacological approach to preventing seizures post-TBI previously suggested and evaluated in pre-clinical models is hypothermia. Hypothermia has long been recognized and evaluated as a potential neuroprotective strategy and in some cases has been associated with protective behavioral and biochemical effects, both in pre-clinical and clinical studies of neural injury. Atkins and colleagues evaluated the ability of hypothermia to alter PTZ-induced seizures at chronic time points

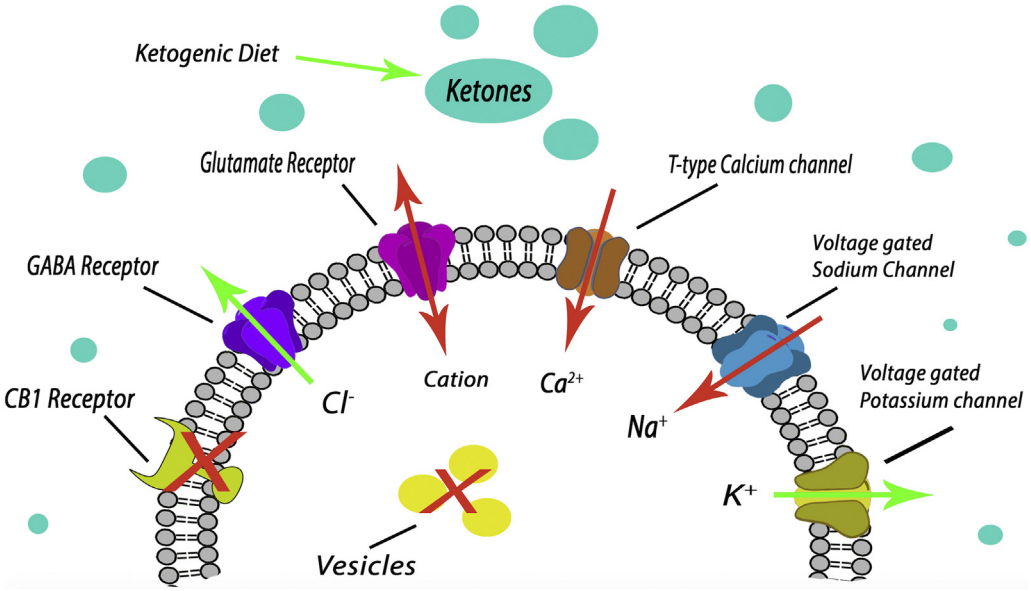

Fig. 2. Novel treatments of epilepsy are often targeted toward the regulation of GABA and glutamate ligand gated channels as well as voltage gated cation channels. Previously explored treatments include: inhibition of cannabinoid receptor CB1, ketogenic diets, and regulation of vesicle activity. These treatments warrant further investigation.

following TBI [66]. The study showed that hypothermia, when administered starting 30 min post-injury for a total of 4 h, reduced the number of seizures induced by PTZ as well as mossy fiber sprouting but had no effect on seizure severity [76].

6.3. Treatment options for drug-resistant PTE

All clinical studies to date have emphasized acute control of seizures post-injury and have failed to identify any agents that successfully modulate seizures chronically (at extended time points post-injury). This is an important consideration because the relative risk of PTE remains heightened even at a decade post-injury, in adults and children [4].

In spite of widespread AED development (over 15 third-generation AEDs since the 1980s), 30–40% of patients experience unsatisfactory control of seizures [38]. Unsatisfactory control or medical intractability, is defined as the failure of two pharmacological agents to control seizures, and is predicted by the presence of neurologic structural anomalies in the temporal cortex, often found in PTE [74]. Further research is being conducted to investigate the protective properties of supplements such as n-acetyl cysteine and progesterone to treat PTE, but the results are so far inconclusive [79,80]. In patients failing medical management, surgical resection may be an option if a seizure focus can be identified on imaging and/or electrophysiological studies [4]. In patients that are not deemed surgical candidates for resection, other management options are available such as placement of a vagal nerve stimulator [4].

6.4. Future investigation

Future work needs to address the mechanisms involved in the development of recurrent excitatory networks that have been documented in pre-clinical and clinical studies alike related to development of PTE, and the approaches to modulate them. Focusing on approaches to alter excessive and recurrent dendrite outgrowth post-trauma may prove advantageous. For this reason, investigation of molecules and pathways implicated in neuronal outgrowth and development may be warranted. Of particular interest is JNK-mediated signaling, which has been implicated previously not only in pre-clinical and clinical studies related to epilepsy development but also in neurodegeneration associated with TBI [81]. Evaluating potential side effects of targeting JNK pathways must be carefully considered.

As mentioned previously, current therapeutics or AEDs largely target voltage-gated cation channels (the α subunit in voltage-gated Na^+ channels or T-type voltage-gated Ca^{2+} channels), or regulate GABA-mediated signaling. Other therapeutic targets related to neurotransmission have been identified with improvement in scientific techniques, namely molecular cloning, and may represent possible targets going forward. This includes numerous Ca^{2+} channel subunits and associated proteins. Likewise, other ion channels (A- and M-type voltage-gated K^+ channels) and ionotropic glutamate receptors may represent other avenues for therapeutic development. New studies from preclinical models of epilepsy have discovered a range of additional targets such as G-protein-coupled receptors ($GABA_B$ and metabotropic glutamate receptors), neurotransmitter transporters (plasma membrane and vesicular transporters), hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channel subunits, and connexins [82]. Importantly, while the aforementioned targets represent direct therapeutic approaches at subacute time points, indirect or upstream signaling pathways may be just as viable. For example, brain-derived neurotrophic factor (BDNF) has long been recognized as playing a role in synaptogenesis and synaptic modification but has also been implicated in epileptogenesis [83]. BDNF exerts an array of effects ranging from gating ion channels to protein phosphorylation to TrkB-mediated activation of intracellular second messenger cascades. All of these changes may successfully modulate functional properties of ion channels [82].

7. Conclusion

PTE continues to remain a serious concern following TBI. Despite widespread use of AEDs in the first 7 days following neurotrauma, the prevalence of late-onset seizure has not decreased in the past century and perhaps most importantly, no treatment options are available or recommended for prevention of these delayed seizures. TBI reduces seizure threshold but overall understanding about progression is not well characterized. In order to improve treatment options that can prevent late-onset seizure, clinically relevant pre-clinical models must be developed

to examine important mechanistic pathways related to seizure onset. One of the most important pathways warranting further investigation is glutamate excitotoxicity and subsequent damage following TBI. Disinhibition of GABA as shown by the PTZ second hit studies is equally important and should be considered. Another area requiring focused investigation is the relationship between seizure activity and neurodegeneration. Despite the complexity of PTE, novel therapeutics currently being investigated in pre-clinical settings appears promising. As novel approaches and therapeutics are carried forward in a transition toward clinical trials, efficacy, safety, and bioavailability must be carefully considered. Increasing the overall understanding of PTE will aid in the development of selective therapeutics for the treatment and prevention of late-onset seizure in the coming decades.

Key point box

1. Post-traumatic epilepsy is a major concern for traumatic brain injury patients with no effective treatments for preventing late onset seizure.
2. Improving pre-clinical models that adequately represent post-traumatic epilepsy is critical for enhancing our understanding of injury progression.
3. Novel therapies will likely target pathways that are implicated in linking acute injury to chronic changes within the brain.

Conflict of interest statement

The authors have no conflicts of interest to report.

Ethical statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Author's contributions

BL – Organization, oversight, writing; LN – wrote section; RT – wrote section; AF – wrote section; YC – wrote section; KS – figure design; JH – critical review; RM – critical review; CR – critical review; ET – critical review; ER – oversight, critical review.

Acknowledgements

The work was supported from a Research Funding and Development Grant from West Virginia University. An American Medical Association Foundation Seed Grant, Neurosurgery Research and Education Foundation Medical Student Summer Research Fellowship, and American Foundation of Pharmaceutical Education Predoctoral Fellowship supported Brandon Lucke-Wold. An American Foundation of Pharmaceutical Education Predoctoral Fellowship supported Aric Logsdon.

References

[1] Campbell JN, Gandhi A, Singh B, Churn SB. Traumatic brain injury causes a tacrolimus-sensitive increase in non-convulsive seizures in a rat model of post-traumatic epilepsy. Int J Neurol Brain Disord 2014;1:1–11.
[2] Salinsky M, Storzbach D, Goy E, Evrard C. Traumatic brain injury and psychogenic seizures in veterans. J Head Trauma Rehabil 2015;30:E65–70.
[3] Schmitt S, Dichter MA. Electrophysiologic recordings in traumatic brain injury. Handb Clin Neurol 2015;127:319–39.
[4] Rao VR, Parko KL. Clinical approach to posttraumatic epilepsy. Semin Neurol 2015;35:57–63.
[5] Gabriel WM, Rowe AS. Long-term comparison of GOS-E scores in patients treated with phenytoin or levetiracetam for posttraumatic seizure prophylaxis after traumatic brain injury. Ann Pharmacother 2014;48:1440–4.
[6] Gupta PK, Sayed N, Ding K, Agostini MA, Van Ness PC, Yablon S, et al. Subtypes of post-traumatic epilepsy: clinical, electrophysiological, and imaging features. J Neurotrauma 2014;31:1439–43.
[7] Caballero GC, Hughes DW, Maxwell PR, Green K, Gamboa CD, Barthol CA. Retrospective analysis of levetiracetam compared to phenytoin for seizure prophylaxis in adults with traumatic brain injury. Hosp Pharm 2013;48:757–61.
[8] Steinmetz S, Tipold A, Loscher W. Epilepsy after head injury in dogs: a natural model of posttraumatic epilepsy. Epilepsia 2013;54:580–8.
[9] Huusko N, Romer C, Ndode-Ekane XE, Lukasiuk K, Pitkanen A. Loss of hippocampal interneurons and epileptogenesis: a comparison of two animal models of acquired epilepsy. Brain Struct Funct 2015;220:153–91.
[10] Wang Y, Hameed MQ, Rakhade SN, Iglesias AH, Muller PA, Mou DL, et al. Hippocampal immediate early gene transcription in the rat fluid percussion traumatic brain injury model. NeuroReport 2014;25:954–9.
[11] Cantu D, Walker K, Andresen L, Taylor-Weiner A, Hampton D, Tesco G, et al. Traumatic brain injury increases cortical glutamate network activity by compromising GABAergic control. Cereb Cortex 2014.
[12] Pitkanen A, Kemppainen S, Ndode-Ekane XE, Huusko N, Huttunen JK, Grohn O, et al. Posttraumatic epilepsy – disease or comorbidity? Epilepsy Behav 2014;38:19–24.
[13] Algattas H, Huang JH. Traumatic brain injury pathophysiology and treatments: early, intermediate, and late phases post-injury. Int J Mol Sci 2014;15:309–41.
[14] Riascos D, Buritica E, Jimenez E, Castro O, Guzman F, Palacios M, et al. Neurodegenerative diversity in human cortical contusion: histological analysis of tissue derived from decompressive craniectomy. Brain Res 2013;1537:86–99.
[15] Silva LF, Hoffmann MS, Gerbatin Rda R, Fiorin Fda S, Dobrachinski F, Mota BC, et al. Treadmill exercise protects against pentylenetetrazol-induced seizures and oxidative stress after traumatic brain injury. J Neurotrauma 2013;30:1278–87.
[16] Qian C, Lopponen P, Tetri S, Huhtakangas J, Juvela S, Turtiainen HM, et al. Immediate, early and late seizures after primary intracerebral hemorrhage. Epilepsy Res 2014;108:732–9.
[17] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55:475–82.
[18] Wang HC, Chang WN, Chang HW, Ho JT, Yang TM, Lin WC, et al. Factors predictive of outcome in posttraumatic seizures. J Trauma 2008;64:883–8.
[19] Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. N Engl J Med 1998;338:20–4.
[20] Christensen J, Pedersen MG, Pedersen CB, Sidenius P, Olsen J, Vestergaard M. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. Lancet 2009;373:1105–10.
[21] Lowenstein DH. Epilepsy after head injury: an overview. Epilepsia 2009;50(Suppl. 2):4–9.
[22] Asikainen I, Kaste M, Sarna S. Early and late posttraumatic seizures in traumatic brain injury rehabilitation patients: brain injury factors causing late seizures and influence of seizures on long-term outcome. Epilepsia 1999;40:584–9.
[23] da Silva AM, Vaz AR, Ribeiro I, Melo AR, Nune B, Correia M. Controversies in posttraumatic epilepsy. Acta Neurochir Suppl (Wien) 1990;50:48–51.
[24] Haltiner AM, Temkin NR, Dikmen SS. Risk of seizure recurrence after the first late posttraumatic seizure. Arch Phys Med Rehabil 1997;78:835–40.
[25] Lopez MR, Cheng JY, Kanner AM, Carvalho DZ, Diamond JA, Wallace DM. Insomnia symptoms in South Florida military veterans with epilepsy. Epilepsy Behav 2013;27:159–64.
[26] Ferguson PL, Smith GM, Wannamaker BB, Thurman DJ, Pickelsimer EE, Selassie AW. A population-based study of risk of epilepsy after hospitalization for traumatic brain injury. Epilepsia 2010;51:891–8.
[27] Gilad R, Boaz M, Sadeh M, Eilam A, Dabby R, Lampl Y. Seizures after very mild head or spine trauma. J Neurotrauma 2013;30:469–72.
[28] Annegers JF, Coan SP. The risks of epilepsy after traumatic brain injury. Seizure 2000;9:453–7.
[29] Liesemer K, Bratton SL, Zebrack CM, Brockmeyer D, Statler KD. Early post-traumatic seizures in moderate to severe pediatric traumatic brain injury: rates, risk factors, and clinical features. J Neurotrauma 2011;28:755–62.
[30] Zanier ER, Lee SM, Vespa PM, Giza CC, Hovda DA. Increased hippocampal CA3 vulnerability to low-level kainic acid following lateral fluid percussion injury. J Neurotrauma 2003;20:409–20.
[31] Kovesdi E, Kamnaksh A, Wingo D, Ahmed F, Grunberg NE, Long JB, et al. Acute minocycline treatment mitigates the symptoms of mild blast-induced traumatic brain injury. Front Neurol 2012;3:111.
[32] Cancelliere C, Donovan J, Cassidy JD. Is sex an indicator of prognosis after mild traumatic brain injury: A systematic analysis of the findings of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury and the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 2015.
[33] Diaz-Arrastia R, Gong Y, Fair S, Scott KD, Garcia MC, Carlile MC, et al. Increased risk of late posttraumatic seizures associated with inheritance of APOE epsilon4 allele. Arch Neurol 2003;60:818–22.
[34] Raymont V, Salazar AM, Lipsky R, Goldman D, Tasick G, Grafman J. Correlates of posttraumatic epilepsy 35 years following combat brain injury. Neurology 2010;75:224–9.
[35] Agrawal A, Timothy J, Pandit L, Manju M. Post-traumatic epilepsy: an overview. Clin Neurol Neurosurg 2006;108:433–9.

[36] Young KD, Okada PJ, Sokolove PE, Palchak MJ, Panacek EA, Baren JM, et al. A randomized, double-blinded, placebo-controlled trial of phenytoin for the prevention of early posttraumatic seizures in children with moderate to severe blunt head injury. Ann Emerg Med 2004;43:435–46.
[37] Schierhout G, Roberts I. Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. Cochrane Database Syst Rev 2001; CD000173.
[38] Torbic H, Forni AA, Anger KE, Degrado JR, Greenwood BC. Use of antiepileptics for seizure prophylaxis after traumatic brain injury. Am J Health Syst Pharm 2013;70:759–66.
[39] Salazar AM, Jabbari B, Vance SC, Grafman J, Amin D, Dillon JD. Epilepsy after penetrating head injury. I. Clinical correlates: a report of the Vietnam Head Injury Study. Neurology 1985;35:1406–14.
[40] Verrotti A, Scaparrotta A, Grosso S, Chiarelli F, Coppola G. Anticonvulsant drugs and hematological disease. Neurol Sci 2014;35:983–93.
[41] Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med 1990;323:497–502.
[42] Temkin NR, Dikmen SS, Anderson GD, Wilensky AJ, Holmes MD, Cohen W, et al. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. J Neurosurg 1999;91:593–600.
[43] Sohn RS, Ferrendelli JA. Anticonvulsant drug mechanisms. Phenytoin, phenobarbital, and ethosuximide and calcium flux in isolated presynaptic endings. Arch Neurol 1976;33:626–9.
[44] Elafros MA, Bui E, Birbeck GL. Medication side effects among people with epilepsy taking phenobarbital in Zambia. Epilepsy Res 2014;108:1680–4.
[45] Bao YH, Bramlett HM, Atkins CM, Truettner JS, Lotocki G, Alonso OF, et al. Posttraumatic seizures exacerbate histopathological damage after fluid-percussion brain injury. J Neurotrauma 2011;28:35–42.
[46] Golarai G, Greenwood AC, Feeney DM, Connor JA. Physiological and structural evidence for hippocampal involvement in persistent seizure susceptibility after traumatic brain injury. J Neurosci 2001;21:8523–37.
[47] Bolkvadze T, Pitkanen A. Development of post-traumatic epilepsy after controlled cortical impact and lateral fluid-percussion-induced brain injury in the mouse. J Neurotrauma 2012;29:789–812.
[48] Chrzaszcz M, Venkatesan C, Dragisic T, Watterson DM, Wainwright MS. Minozac treatment prevents increased seizure susceptibility in a mouse two-hit model of closed skull traumatic brain injury and electroconvulsive shock-induced seizures. J Neurotrauma 2010;27:1283–95.
[49] Guilliams K, Wainwright MS. Pathophysiology and management of moderate and severe traumatic brain injury in children. J Child Neurol 2014.
[50] Mishra M, Singh R, Mukherjee S, Sharma D. Dehydroepiandrosterone's antiepileptic action in $FeCl_3$-induced epileptogenesis involves upregulation of glutamate transporters. Epilepsy Res 2013;106:83–91.
[51] Irimia A, Van Horn JD. Epileptogenic focus localization in treatment-resistant post-traumatic epilepsy. J Clin Neurosci 2014.
[52] Wang C, Ji B, Cheng B, Chen J, Bai B. Neuroprotection of microRNA in neurological disorders (Review). Biomed Rep 2014;2:611–9.
[53] Hameed MQ, Goodrich GS, Dhamne SC, Amandusson A, Hsieh TH, Mou D, et al. A rapid lateral fluid percussion injury rodent model of traumatic brain injury and post-traumatic epilepsy. NeuroReport 2014;25:532–6.
[54] Gill R, Chang PK, Prenosil GA, Deane EC, McKinney RA. Blocking brain-derived neurotrophic factor inhibits injury-induced hyperexcitability of hippocampal CA3 neurons. Eur J Neurosci 2013;38:3554–66.
[55] Naviaux RK. Metabolic features of the cell danger response. Mitochondrion 2014;16:7–17.
[56] Berdichevsky Y, Dryer AM, Saponjian Y, Mahoney MM, Pimentel CA, Lucini CA, et al. PI3K-Akt signaling activates mTOR-mediated epileptogenesis in organotypic hippocampal culture model of post-traumatic epilepsy. J Neurosci 2013;33:9056–67.
[57] Bockaert J, Marin P. mTOR in brain physiology and pathologies. Physiol Rev 2015;95:1157–87.
[58] Maroso M, Balosso S, Ravizza T, Liu J, Aronica E, Iyer AM, et al. Toll-like receptor 4 and high-mobility group box-1 are involved in ictogenesis and can be targeted to reduce seizures. Nat Med 2010;16:413–9.
[59] Li Y, Korgaonkar AA, Swietek B, Wang J, Elgammal FS, Elkabes S, et al. Toll-like receptor 4 enhancement of non-NMDA synaptic currents increases dentate excitability after brain injury. Neurobiol Dis 2015;74:240–53.
[60] Wang FX, Liu SY, Zheng X, Chen X, Lu LX, Chen B, et al. TLR1 expression in mouse brain was increased in a KA-induced seizure model. Inflamm Res 2015;64:487–95.
[61] Liang Y, Lei Z, Zhang H, Xu Z, Cui Q, Xu ZC. Toll-like receptor 4 is associated with seizures following ischemia with hyperglycemia. Brain Res 2014;1590:75–84.
[62] Atmaca HT, Kul O, Karakus E, Terzi OS, Canpolat S, Anteplioglu T. Astrocytes, microglia/macrophages, and neurons expressing Toll-like receptor 11 contribute to innate immunity against encephalitic *Toxoplasma gondii* infection. Neuroscience 2014;269:184–91.
[63] Karve IP, Taylor JM, Crack PJ. The contribution of astrocytes and microglia to traumatic brain injury. Br J Pharmacol 2015.
[64] Ueda Y, Kitamoto A, Willmore LJ, Kojima T. Hippocampal gene expression profiling in a rat model of posttraumatic epilepsy reveals temporal upregulation of lipid metabolism-related genes. Neurochem Res 2013;38:1399–406.
[65] Ndode-Ekane XE, Pitkanen A. Urokinase-type plasminogen activator receptor modulates epileptogenesis in mouse model of temporal lobe epilepsy. Mol Neurobiol 2013;47:914–37.
[66] Atkins CM, Truettner JS, Lotocki G, Sanchez-Molano J, Kang Y, Alonso OF, et al. Post-traumatic seizure susceptibility is attenuated by hypothermia therapy. Eur J Neurosci 2010;32:1912–20.
[67] Diamond ML, Ritter AC, Failla MD, Boles JA, Conley YP, Kochanek PM, et al. IL-1beta associations with posttraumatic epilepsy development: a genetics and biomarker cohort study. Epilepsia 2014;55:1109–19.
[68] Zheng P, Shultz SR, Hovens CM, Velakoulis D, Jones NC, O'Brien TJ. Hyperphosphorylated tau is implicated in acquired epilepsy and neuropsychiatric comorbidities. Mol Neurobiol 2014;49:1532–9.
[69] Szewczyk B. Zinc homeostasis and neurodegenerative disorders. Front Aging Neurosci 2013;5:33.
[70] Lei Z, Deng P, Li J, Xu ZC. Alterations of A-type potassium channels in hippocampal neurons after traumatic brain injury. J Neurotrauma 2012;29:235–45.
[71] Kharatishvili I, Pitkanen A. Association of the severity of cortical damage with the occurrence of spontaneous seizures and hyperexcitability in an animal model of posttraumatic epilepsy. Epilepsy Res 2010;90:47–59.
[72] Guo D, Zeng L, Brody DL, Wong M. Rapamycin attenuates the development of posttraumatic epilepsy in a mouse model of traumatic brain injury. PLoS ONE 2013;8:e64078.
[73] Kori P, Garg RK, Malhotra HS, Gupta RK, Verma R, Singh MK, et al. Evaluation of cerebral white-matter micro-structural alterations in patients with medically refractory epilepsy using diffusion tensor tractography. Epilepsy Res 2013;107:82–90.
[74] Kwan P, Sander JW. The natural history of epilepsy: an epidemiological view. J Neurol Neurosurg Psychiatry 2004;75:1376–81.
[75] Echegoyen J, Armstrong C, Morgan RJ, Soltesz I. Single application of a CB1 receptor antagonist rapidly following head injury prevents long-term hyperexcitability in a rat model. Epilepsy Res 2009;85:123–7.
[76] Pitkanen A, Bolkvadze T. Head trauma and epilepsy. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, editors. Jasper's basic mechanisms of the epilepsies. Bethesda, MD. 2012.
[77] Masino SA, Kawamura M, Wasser CD, Pomeroy LT, Ruskin DN. Adenosine, ketogenic diet and epilepsy: the emerging therapeutic relationship between metabolism and brain activity. Curr Neuropharmacol 2009;7:257–68.
[78] Schwartzkroin PA, Wenzel HJ, Lyeth BG, Poon CC, Delance A, Van KC, et al. Does ketogenic diet alter seizure sensitivity and cell loss following fluid percussion injury? Epilepsy Res 2010;92:74–84.
[79] Gunther M, Davidsson J, Plantman S, Norgren S, Mathiesen T, Risling M. Neuroprotective effects of N-acetylcysteine amide on experimental focal penetrating brain injury in rats. J Clin Neurosci 2015;22:1477–83.
[80] Howard RB, Sayeed I, Stein D. Suboptimal dosing parameters as possible factors in the negative Phase III clinical trials of progesterone in TBI. J Neurotrauma 2015.
[81] Cole-Edwards KK, Musto AE, Bazan NG. c-Jun N-terminal kinase activation responses induced by hippocampal kindling are mediated by reactive astrocytes. J Neurosci 2006;26:8295–304.
[82] Meldrum BS, Rogawski MA. Molecular targets for antiepileptic drug development. Neurotherapeutics 2007;4:18–61.
[83] Scharfman HE. Brain-derived neurotrophic factor and epilepsy – a missing link? Epilepsy Curr 2005;5:83–8.
[84] Wagner AK, Miller MA, Scanlon J, Ren D, Kochanek PM, Conley YP. Adenosine A1 receptor gene variants associated with post-traumatic seizures after severe TBI. Epilepsy Res 2010;90:259–72.
[85] Darrah SD, Miller MA, Ren D, Hoh NZ, Scanlon JM, Conley YP, et al. Genetic variability in glutamic acid decarboxylase genes: associations with post-traumatic seizures after severe TBI. Epilepsy Res 2013;103:180–94.
[86] Friedman G, Froom P, Sazbon L, Grinblatt I, Shochina M, Tsenter J, et al. Apolipoprotein E-epsilon4 genotype predicts a poor outcome in survivors of traumatic brain injury. Neurology 1999;52:244–8.
[87] Miller MA, Conley Y, Scanlon JM, Ren D, Ilyas Kamboh M, Niyonkuru C, et al. APOE genetic associations with seizure development after severe traumatic brain injury. Brain Inj 2010;24:1468–77.
[88] Anderson GD, Temkin NR, Dikmen SS, Diaz-Arrastia R, Machamer JE, Farhrenbruch C, et al. Haptoglobin phenotype and apolipoprotein E polymorphism: relationship to posttraumatic seizures and neuropsychological functioning after traumatic brain injury. Epilepsy Behav 2009;16:501–6.
[89] Scher AI, Wu H, Tsao JW, Blom HJ, Feit P, Nevin RL, et al. MTHFR C677T genotype as a risk factor for epilepsy including post-traumatic epilepsy in a representative military cohort. J Neurotrauma 2011;28:1739–45.
[90] Williams P, White A, Ferraro D, Clark S, Staley K, Dudek FE. The use of radiotelemetry to evaluate electrographic seizures in rats with kainate-induced epilepsy. J Neurosci Methods 2006;155:39–48.
[91] Nilsson P, Ronne-Engstrom E, Flink R, Ungerstedt U, Carlson H, Hillered L. Epileptic seizure activity in the acute phase following cortical impact trauma in rat. Brain Res 1994;637:227–32.
[92] Hunt RF, Scheff SW, Smith BN. Regionally localized recurrent excitation in the dentate gyrus of a cortical contusion model of posttraumatic epilepsy. J Neurophysiol 2010;103:1490–500.
[93] Nichols J, Perez R, Wu C, Adelson PD, Anderson T. Traumatic brain injury induces rapid enhancement of cortical excitability in juvenile rats. CNS Neurosci Ther 2015;21:193–203.
[94] Statler KD, Scheerlinck P, Pouliot W, Hamilton M, White HS, Dudek FE. A potential model of pediatric posttraumatic epilepsy. Epilepsy Res 2009;86:221–3.

[95] Hamm RJ, Pike BR, Temple MD, O'Dell DM, Lyeth BG. The effect of postinjury kindled seizures on cognitive performance of traumatically brain-injured rats. Exp Neurol 1995;136:143–8.
[96] Mukherjee S, Zeitouni S, Cavarsan CF, Shapiro LA. Increased seizure susceptibility in mice 30 days after fluid percussion injury. Front Neurol 2013;4:28.
[97] Kharatishvili I, Nissinen JP, McIntosh TK, Pitkanen A. A model of posttraumatic epilepsy induced by lateral fluid-percussion brain injury in rats. Neuroscience 2006;140:685–97.
[98] Kharatishvili I, Immonen R, Grohn O, Pitkanen A. Quantitative diffusion MRI of hippocampus as a surrogate marker for post-traumatic epileptogenesis. Brain 2007;130:3155–68.
[99] D'Ambrosio R, Fender JS, Fairbanks JP, Simon EA, Born DE, Doyle DL, et al. Progression from frontal-parietal to mesial-temporal epilepsy after fluid percussion injury in the rat. Brain 2005;128:174–88.