Published in final edited form as:

Neurobiol Dis. 2019 March ; 123: 100–109. doi:10.1016/j.nbd.2018.08.006.

Targeting neurodegeneration to prevent post-traumatic epilepsy

Idrish Ali[a,b], **Juliana C. Silva**[a,b], **Shijie Liu**[a,b], **Sandy R. Shultz**[a,b], **Patrick Kwan**[a,b], **Nigel C. Jones**[a,b], and **Terence J. O'Brien**[a,b,*]

[a]Department of Neuroscience, Central Clinical School, Monash University, The Alfred Hospital Melbourne, Australia

[b]Department of Medicine (Royal Melbourne Hospital), The University of Melbourne, Melbourne, Australia

Abstract

In the quest for developing new therapeutic targets for post-traumatic epilepsies (PTE), identifying mechanisms relevant to development and progression of disease is critical. A growing body of literature suggests involvement of neurodegenerative mechanisms in the pathophysiology of acquired epilepsies, including following traumatic brain injury (TBI). In this review, we discuss the potential of some of these mechanisms to be targets for the development of a therapy against PTE.

Keywords

Neurodegeneration; Tauopathies; β amyloid; Neuroinflammation; Traumatic brain injury; Post-traumatic epilepsy

1. Introduction

Epilepsy is a common chronic group of neurological disorders that is characterized by the occurrence of recurrent unprovoked seizures. Post-traumatic epilepsy (PTE) accounts for up to 20% of epilepsies due to an identifiable acquired cause, i.e. "acquired epilepsies", and follows a traumatic brain injury that initiates a process of epileptogenesis, often lasting months to years, before the first epileptic seizures are observed. The mechanisms underlying epileptogenesis are not clearly understood, but probably involve many structural and molecular alterations that alter neuronal excitation-inhibition balance and render the brain prone to generate recurrent spontaneous seizures (Avoli et al., 2016). The long duration of the pathogenesis of PTE makes it challenging to separate causal mechanisms contributing to epilepsy development from other pathological events associated with the neurotrauma which are unrelated to epileptogenesis.

Neurodegeneration is one of the characteristic brain pathologies associated with acquired epilepsies such as PTE, although the direct relationship with the development of

*Corresponding author at: Department of Neuroscience, Central Clinical School, Monash University, The Alfred Hospital, Melbourne, Australia. te.obrien@alfred.org.au (T.J. O'Brien).

spontaneous recurrent seizures is ambiguous (eg: (Brandt et al., 2006; Pitkanen et al., 2005). Nevertheless, neurodegeneration within epileptogenic regions may trigger neuroinflammation (or vice versa), network re-organization and/or cascades of molecular changes, some or all of which may contribute to the transformation from a normal to an epileptic brain network (Acharya et al., 2008). The purpose of this review is to summarise and critically analyse neurodegenerative processes as potential casual mediators of acquired epilepsy following a traumatic brain injury.

In the quest to develop antiepileptic treatments that are disease-modifying - as opposed to those providing only symptomatic relief - it is necessary to identify new biological targets that are critical to the development and maintenance of the epileptic state. In this regard, new insights can be obtained from the overlapping mechanisms of neurodegeneration that may be involved in epilepsy and neurodegenerative diseases such as Alzheimer's (AD). Patients with neurodegenerative conditions such as AD have a significantly increased risk to develop epilepsy compared to age matched controls (Abou-Khalil, 2010; Friedman et al., 2012; Nicastro et al., 2016). The accuracy of prevalence rates of epilepsy in AD are limited due to methodological difficulties of performing such studies (Friedman et al., 2012; Giorgi et al., 2017). Studies have reported that up to 64% of AD patients will undergo at least one unprovoked seizures with prevalence of epilepsy in AD patients to be up to 10 fold higher than in age matched controls (Forsgren et al., 1996; Hauser et al., 1986; Risse et al., 1990). The pathological mechanisms frequently described in neurodegenerative conditions such as hyperphosphorylated tau, ß-amyloid pathology, chronic neuroinflammation are all associated with epileptic disorders. This evidence comes from studies of specimens from resected epileptogenic brain tissue from epilepsy patients who have undergone surgery for drug resistant temporal lobe epilepsy, as well as consistent robust evidences from the animal models of acquired epilepsy (Liu et al., 2016; Thom et al., 2011) The possibility of involvement of common underlying neurodegenerative mechanisms is further supported by the alteration of epilepsy outcomes on modification of these pathways (discussed in next section). However, it remains to be seen whether such alterations in epilepsy outcomes may be directly relevant to neurodegeneration mechanisms or secondary effects of modifying them. In this review, we will discuss some of the neurodegenerative mechanisms including tauopathies, amyloid pathology and neuroinflammation pathways that are relevant to PTE, mechanisms by which they may contribute to epileptogenesis or seizure susceptibility and whether modifying such mechanisms can be a target for anti-epilepto-genesis or disease-modifying treatments (Table 1). These pathways may not be the only neurodegenerative mechanisms initiated after TBI, however the ones discussed in this review have the most evidence for their relevance to epileptogenesis.

2. Tauopathies

2.1. Evidences of involvement in epilepsy

Tau is a microtubule-associated protein (MAPT) that is involved in maintaining neuronal health by affecting physiological functions including axonal transport and microtubule stabilization. For normal functioning of these processes a balance between the binding and nonbinding states of tau to the microtubules is critical. This balance is in turn regulated by

partially phosphorylated tau and controlled by kinases and phosphatase enzymes (Lee and Leugers, 2012; Morris et al., 2011). However, in a pathological environment, the balance between the non-phosphorylated and phosphorylated tau is disturbed. This leads to deposits of hyper phosphorylated tau and unbinding of tau to microtubules inducing cytoskeletal destabilization and axonal as well as synaptic dysfunctions (Lee and Leugers, 2012). These events likely contribute to the cessation of cell viability and progressing to apoptosis (Kondo et al., 2015). Apart from being associated with neurodegenerative conditions such as Alzheimer's disease and frontotemporal dementias (Rostgaard et al., 2015), an increase in hyperphosphorylated tau has also been reported following TBI (Blennow et al., 2012; Kulbe and Hall, 2017; Shultz et al., 2015). As for the evidence of involvement in the pathogenesis of epilepsy, hyperphosphorylated tau has been widely reported in clinical brain samples following surgical resection in temporal lobe epilepsy patients (Liu et al., 2017b; Puvenna et al., 2016; Sen et al., 2007; Thom et al., 2011). Similarly, pathological evaluations of brain samples from experimental models of acquired epilepsies have reported tauopathies associated with neurodegeneration and axonal dysfunction. Such evidences have been consistent across models including administration of excitotoxicants that experimentally induce status epilepticus in animals, which then leads to development of epileptic seizures or in kindling-induced seizure models (Liang et al., 2009; Liu et al., 2016; Tian et al., 2010). Likewise, alterations in tau proteins in the cerebrospinal fluid have also been reported in patients with epilepsy. Shahim et al. (2014) reported a reduction in total and phosphorylated tau within the cerebrospinal fluid in epilepsy patients following seizures. On the contrary, another study that included only patients with tonic clonic/secondary generalized seizures reported an increase in phospho and total tau in cerebrospinal fluid of the patients 48 h after seizures (Palmio et al., 2009). The discrepancy in fidings could be related to the fact that the study by Shahim et al. (2014) pooled data from patients with different seizure severities including convulsive and non-convulsive seizures to non-convulsive status epilepticus. Similarly, increased phospho and total tau levels were reported following status epilepticus and was indicative of poor prognosis and a higher risk of developing epilepsy (Monti et al., 2015). Overall, these findings clearly suggest that tauopathies are related to epileptic seizures and can be observed not only in pathological evaluation of brains but could also be seen in cerebrospinal fluid.

Direct evidences come from genetic modifications in mice models that displayed alterations in the susceptibility to epilepsy development or acute seizures. Triple transgenic mouse model of AD with mutations in human amyloid precursor (hAPP), presenilin-1 and with hyperphosphorylated tau displays increased susceptibility to pilocarpine-induced acute seizures (Yan et al., 2012a). Similarly, Tg4510 tau transgenic mouse shows increased afterdischarge durations and accelerated kindling during amygdala kindling epileptogenesis (Liu et al., 2017a).

Likewise, reduction of total endogenous tau in a model of AD that expressed hAPP, reduced behavioural deficits in learning and memory as well as protected them against excitotoxicity (Roberson et al., 2007). hAPP mice with tau knockout underwent a reduced mortality, displayed less severe seizures and a longer latency to seizures following a pentylenetetrazole (PTZ) challenge in young (Roberson et al., 2007) as well as old mice (Li et al., 2014). Similar effects of reducing tau were reported in mice after kainic acid induced seizures

(Devos et al., 2013). The seizure protective effects of tau inhibition were independent of amyloid pathology and were not only relevant to chemoconvulsant-induced seizures. Protective effects of genetically inhibiting tau were also observed in genetic models of epilepsy. Genetic inhibition of Tau in Kcnal$^{(-/-)}$ mice that displays spontaneous seizures due to lack of Kv1.1 delayed rectifier currents showed protective effects against seizure frequency and related comorbidities (Holth et al., 2013). Reduction in seizure sensitivity was also reported in the same study using two bang sensitive drosophila mutants following genetic tau inhibition (Holth et al., 2013). Moreover, tau inhibition in genetic mouse model of Dravet syndrome with mutation in voltage gated sodium channel gene prevented high mortality, and reduced the frequency of spontaneous and febrile seizures (Gheyara et al., 2014).

Some of the effects on seizure susceptibility could be the result of phenotypic changes from genetic manipulations and developmental compensatory mechanisms as a result of tau knockout. More direct evidences come from pharmacological manipulations to inhibit hyperphosphorylated tau that has shown protective effects against seizure induction as well as shown anti-epileptogenesis effects (Jones et al., 2012; Liu et al., 2016). These evidences point to clear involvement of hyperphosphorylated tau to pathophysiological mechanisms that are relevant to pathology of both genetic and acquired forms of epilepsy.

2.2. Mechanisms relevant to epileptogenesis and possible targeting for prevention of PTE

Hyperphosphorylated tau could contribute to a cascade of events such as neuronal network re-organization including mossy fiber sprouting (Decker et al., 2016; Ghosal and Pimplikar, 2011; Huang et al., 2013; Tian et al., 2010), aberrant neuronal cell migration with hippocampal granule cell layer dispersion (Kandratavicius et al., 2013), NR2B receptor mediated glutamate release (Decker et al., 2016) and neuroplasticity changes (Sotiropoulos et al., 2017) that are highly relevant to epilepsy development. However, studies showing a causal relation of hyperphosphorylated tau to above mentioned mechanisms are lacking and some or most of these effects can be considered to be associative at best. Furthermore, such neurodegenerative mechanisms could induce an inflammatory reaction that may in turn lead to enhanced excitation (see next section for details) and lead to a vicious cycle of even more cell death. An unstable/unbound microtubule assembly at the axon initial segment as an outcome of hyperphosphorylated tau is suggested to enhance excitability (Carletti et al., 2016; Matsumoto and Sakai, 1979). Though a large proportion of literature has suggested an enhanced excitability in genetic mouse models of hyperphosphorylated tau, a recent studies using either P301L tau transgenic mouse model or a triple-transgenic mouse found that there is impaired excitability in CA1 hippocampal neurons. Specifically higher threshold for action potential initiation and firing frequency as well as reduced seizure-like activity after 4-aminopyridine challenge respectively (Hatch et al., 2017; Mondragon Rodriguez et al., 2018). Such a reduced excitability in these mouse models may contribute to hippocampal and cognitive dysfunction, specifically in the case of study by Mondragon Rodriguez et al. (2018), the authors used young (1-month-old) mice and suggest that increased phosphorylation of tau in early AD disease onset may be a compensatory mechanism for increased network excitability. Overall pro-epileptogenic effects of hyperphosphorylated tau may not be only mediated by alterations in neuronal excitability but may be driven by

complex interaction of alterations in network excitability with other mechanisms relevant to epileptogenesis as described earlier.

Contribution of tauopathies to pro-epileptogenic mechanisms has provided an attractive mechanism to target anti-epileptogenesis. Tau inhibition by genetic mechanisms as discussed earlier has shown protective effects against seizures following administration of chemoconvulsants as well as in genetic epilepsy models (Gheyara et al., 2014; Holth et al., 2013; Roberson et al., 2007). However, some of the differences in findings regarding bidirectional changes in excitability in genetic tau knock out mice could be an outcome of developmental compensation or phenotypic changes in mouse model. Nevertheless, studies aiming for pharmacological targeting of tauopathies have shown clear results in terms of protecting against seizures and epileptogenesis.

Pharmacological interventions have focused both on inhibiting the phosphorylation and enhancing the de-phosphorylation pathways of tau. For a detailed discussion of pathways relevant to tau phosphorylation and dephosphorylation, the readers are suggested to refer to the book chapter by Zheng et al. (2017). Tau phosphorylation is mainly governed by the protein kinases such as glycogen synthase kinase 3 (GSK3) and cyclin dependent kinase 5 (CDK5) that induce phosphorylation in serine and threonine residues of the tau protein. Studies have suggested pharmacological inhibition of GSK3 using lithium can lead to reduced tau phosphorylation and formation of neurofibrillary tangles in mouse models with GSK3 and tau overexpression (Engel et al., 2006). Another study using old Tgtau30 mice showed reduced neurofibrillary tangles after chronic administration of lithium, though, without affecting the motor and working memory deficits (Leroy et al., 2010). Importantly, such inhibition of GSK3 pathway not only rescued tau hyperphorphorylation and neurofibrillary tangles but also inhibited neurodegeneration in AD models (Noble et al., 2005). Direct evidence of inhibiting GSK3 pathway to inhibit axonal damage from epilepsy models also exists. Liu et al. (2017b) reported a reduction in the axonal damage following inhibition of GSK3 or CDK5 by lithium and roscovitine in PTZ kindled rats (Liu et al., 2017b). Similarly, inhibition of GSK3p by 4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione (TDZD-8) showed reduced neurodegeneration induced by kainic acid administration without affecting the severity of acute seizures (Bhowmik et al., 2015). Effects of targeting GSK3 pathway have only been described in AD models or post-acute seizures, though consistent findings of neuroprotection in seizure models supports potential for future studies for anti-epileptogenesis trials.

The other pathway targeted against tauopathies is dephosphorylating mechanisms of tau. In physiological conditions the phosphorylating effects of GSK3 and CDK5 are countered by tau phosphatases. Protein phosphatase 2A (PP2A) is a major tau phosphatase and its reduction in epilepsy models has been shown to be associated with hyperphosphorylated tau (Liu et al., 2016).

Sodium selenate, a potent PR55 activator (heterotrimer of PP2A), to reduce phosphorylated tau showed reduced network hyperexcitability and susceptibility to seizure induction in three different seizure models, namely— 6-Hz corneal electrical stimulation, PTZ and amygdala kindling (Jones et al., 2012). Similar seizure suppressant effects of sodium selenate were

also observed in a genetic model of Lafora disease in addition to improving the motor and memory deficits in this model (Sanchez-Elexpuru et al., 2017). While considering effects on epileptogenesis in epilepsy models, we have recently shown that inhibition of tau phosphorylation by sodium selenate inhibits epileptogenesis in three different models of acquired epilepsies (Liu et al., 2016). In this study, sodium selenate significantly delayed the progression of amygdala kindling epileptogenesis as well as reduced the number of spontaneous seizures per day and average duration of each seizure in the chronic epileptic period following kainic acid-induced status epilepticus, an effect that even persisted beyond treatment period. Similar disease-modifying effects were also observed in a PTE model following severe traumatic brain injury in rats (Liu et al., 2016). In this study, the treatment group displayed significantly fewer seizures per day, as well as a reduced average duration of each seizures. Similar to the kainic acid model, the effects on seizure frequency were sustained even after the drug treatment had ceased, suggestive of a disease modifying effect of sodium selenate treatment (Liu et al., 2016). Furthermore, targeting phosphorylated tau using sodium selenate also protects neuronal damage, brain atrophy as well as behavioural outcomes in this model that are often associated with epileptogenesis (Jones and O'Brien, 2013). Similar to genetic knock down of tau, pharmacological inhibition of tau has also been reported to improve disease pathology. Using antisense oligonucleotides to selectively decrease endogenous tau expression, DeVos et al. (2013) showed reduced seizure susceptibility in two acute seizure models with high correlation between seizure severities to tau expression. This finding supports for potentially investigating strategies to decrease endogenous tau in anti-epileptogenesis mechanisms.

Hyperphosphorylation of tau has been widely reported in experimental TBI models (Hawkins et al., 2013; Shultz et al., 2015), and also in brain tissues from human patients acutely after TBI (Albayram et al., 2017; Seo et al., 2017; Shultz et al., 2015; Thom et al., 2011). The peripheral total tau in blood of military personnel who have suffered a TBI was significantly higher than no-TBI controls, and this elevation was associated with chronic neurological symptoms (Olivera et al., 2015). Tau hyperphosphorylation has been considered a component of secondary injury following traumatic brain injury (Blennow et al., 2012; McKee et al., 2013) and is associated with decreased PP2A levels (Chen et al., 2010), the main dephosphorylating mechanism of tau. In this regard, we have previously reported a strong increase in the levels of phosphorylated tau with a concomitant reduction of PP2A activity, using a fluid percussion injury rat model of TBI (Shultz et al., 2015). Furthermore, administering the PP2A activator sodium selenate led to reduced phosphorylated tau levels, reduced brain damage including progressive atrophy of brain structures and white matter damage as well as inhibited behavioural abnormalities relevant to TBI including memory impairments, anxiety-like behavior and neuromotor performance. Reduced motor and cognitive behavioural abnormalities have also been reported after genetic inhibition of tau (Cheng et al., 2014). Importantly, inhibition of hyperphophorylated tau following TBI has been shown to inhibit development of PTE and related brain injury (Liu et al., 2016). Despite minimal direct evidences in models of PTE, findings in models of TBI suggest involvement of tauopathies in pathological outcomes and disease progression following TBI that could be highly relevant to PTE development and potential targeting thereof.

Findings described above warrants for future studies targeting taupathies in models of PTE. Similarly, a complete biological/biochemical mechanism for anti-epileptogenesis or neuroprotection observed by inhibiting tau-phosphorylation using sodium selenate is not established and off target effects are not clarified. In this regard, studies have delineated roles of cis versus trans isomers of phosphorylated Thr231-Pro motif in tau, suggesting that the trans form is physiological and the *cis* form contributes to the pathological events of hyperphosphorylated tau (Liou et al., 2003; Nakamura et al., 2012). Furthermore, a recent study from the same group targeted *cis* isoform of phophorylated-tau in TBI mice by an antibody and reversed ultrastructural pathologies of axonal microtubules, defective cortical axonal long-term potentiation, and inhibited neurodegeneration (Kondo et al., 2015). Such strong findings establish a new strategy that can be utilized to target neurodegenerative conditions as wells as PTE. At the same time, it also provides a platform for future investigations in understanding the molecular pathways relevant to other pharmacological modulators of tauopathies including sodium selenate, which has been shown to be effective against development of PTE.

3. APP and Beta-amyloid

3.1. Relevance to TBI and epilepsy

The amyloid precursor protein (APP) and its well-known proteolytic product, the amyloid-β peptide (Aβ), are recognized for playing a central role on the pathophysiology of Alzheimer's disease (AD), and the deleterious effects of its overexpression and clearance failure are well described in the literature (Masters and Selkoe, 2012; Mucke and Selkoe, 2012). However, the fact that APP is one of the first proteins to be overexpressed after a brain injury is a less known fact, and even though the consequences for this are still controversial, it might have an impact in the development of PTE (Blennow et al., 2012, Nature review, 2016, 2, 1–19).

Evidences for this overexpression come both from different animal models of TBI and human studies. An increase in APP immunoreactivity was observed in neurons and in astrocytes after a focal cerebral injury in rats by needle stabbing or weight drop (Lewen et al., 1995; Lewen et al., 1996; Otsuka et al., 1991). Within hours of a diffuse brain injury using the midline fluid percussion model in adult rats, APP expression was globally elevated in cortex and hippocampus; and also, as early as 1 h after an insult using the lateral fluid percussion model (Murakami et al., 1998; Pierce et al., 1996). Likewise, in a weight fall model of brainstem injury in adult rats, Yang et al. (2014) found an increase in APP mRNA levels 1 h post-impact, that peaked 3 h after injury and declined to baseline within 24 h. Similarly, as soon as 30 min post-impact in an ovine TBI model, APP mRNA was up-regulated (Van den Heuvel et al., 1999).

In humans, the findings are not different from the experimental studies and a fact worth noting is that APP immunohistochemistry is a well-validated and effective tool for diagnosing diffuse traumatic brain injury in the forensic practice and has been in use for more than 10 years (Hayashi et al., 2015). Because APP anterograde transport along axons to the synapse is disrupted in brain insult, it accumulates in the form of axonal bulbs and can be detected within hours after TBI, with some cases being detected as early as 35 min

(Hortobagyi et al., 2007; Ikonomovic et al., 2004). A post-mortem study analyzed 152 patients after severe head injury with survival times ranging from four hours to 2.5 years, and found amyloid-β deposits in one or more cortical areas in 30% of the cases, and also increased APP immunoreactivity in neurons in the vicinity of amyloid-β deposits (Roberts et al., 1994). Interestingly, the amyloid-β levels in cerebrospinal and interstitial cerebral fluid (ISF) in patients after TBI correlates with the overall neurological status of the patient, in the sense that the levels increased as status improved, remained stable in stable patients and decreased when status worsened (Magnoni and Brody, 2010). This reduction in the amyloid-β ISF levels may be a consequence of the reduction of brain neuronal and synaptic activity due to injury, but it may also reflect an increased deposition of amyloid-β into insoluble aggregates; consequently, an increase in the ISF amyloid-β levels, correlating with patient recovery, might be an indication of the peptide clearance from the extracellular space although this has not been demonstrated yet (Magnoni and Brody, 2010).

Although APP upregulation after injury has been demonstrated in a number of human and animal studies, the interpretation of this fact is still under debate. Primarily, findings can be divided in two main bodies of evidence and interpreted in two different perspectives. First, that neuronal cells upregulate APP as an attempt to repair the damage caused by injury; and second, that this is a deleterious consequence of the injury itself and that APP worsens outcomes post-injury. Both perspectives will be discussed here.

The protective aspect of APP upregulation finds support in the non-amyloidogenic processing of APP. In this physiologically competing pathway, APP is cleaved within the amyloid-ß region by α- and γ-secretases releasing the secreted fragment APP α (sAPPα) and an acidic intracellular domain (AICD) (for review see Muller et al., 2017). While the products of the amyloidogenic pathway, amyloid-ß peptide and the secreted fragment APP ß (sAPPß) may favour amyloid aggregation, sAPPα has been suggested to be neuroprotective and have a number of physiological properties that highlights its importance as a potential therapeutic target (for review see Mockett et al. (2017). Studies with transgenic models of AD have pointed towards the theory that APP processing is driven through the non-amyloidogenic pathway as an attempt to protect the brain against injury-induced cell death (Thornton et al., 2006; Van den Heuvel et al., 1999). In fact, in the APP/PS1 mouse an up-regulation in the expression of genes encoding proteins involved in Aß clearance, and a reduction in Aß plaques was observed after severe TBI was induced by controlled cortical impact (CCI) (Miszczuk et al., 2016). Similar results were found in a different transgenic model, the PDAPP mice, in which a reduction in Aß deposit was reported even 8 months after injury while sham animals displayed increasing amyloid burden (Nakagawa et al., 1999). Likewise, aged PDAPP mice (22–24 months) with abundant Aβ plaques, when subjected to TBI exhibited a reduction in Aβ burden in the ipsilateral hippocampus compared to the contralateral site, 16 weeks post-injury (Nakagawa et al., 2000). Interestingly, mice lacking APP (APP-KO) are more vulnerable to TBI, exhibiting worst outcomes compared to the wild-type controls (WT) after a mild CCI, i.e. increased hippocampal cell loss and greater lesion volume, therefore supporting a potential protective role of APP in brain injury (Corrigan et al., 2012a). Moreover, an intracerebroventricular administration of recombinant sAPPα 15 min after a moderate injury could rescue the

damage and the functional deficits to the point that the APP-KO were no longer significantly different to the WT mice (Corrigan et al., 2012b).

Nevertheless, besides the increased risk of developing Alzheimer's by almost 2-fold after a brain injury, increasing evidence supports the fact that amyloid upregulation and deposition may also contribute to the establishment of PTE (Kenney et al., 2018). It is known that unprovoked seizures occur at rates at least 8–10-fold higher in AD patients than in the general population, and at even higher rates in autosomal-dominant and early onset cases (Amatniek et al., 2006; Mendez and Lim, 2003; Scarmeas et al., 2009). Even though AD is a complex disorder and amyloid accumulation is only one of its pathological hallmarks, recent findings have strongly suggested that soluble Aβ oligomers when start to deposit, increase neuronal excitability and induce network reorganization that leads to hippocampal hyperactivation (Huijbers et al., 2015; Vossel et al., 2017). While hippocampal hyperactivation only occurs in the stage of mild cognitive impairment (the initial stage of AD), epileptiform activity and seizures can occur throughout the whole course of disease, and seizures that precede the onset of cognitive decline might reflect the epileptogenic potential of Aβ, which begins to accumulate more than 10 years before clinical signs of dementia (Bakker et al., 2015; Villemagne et al., 2013; Vossel et al., 2013).

The amyloid-ß peptide may be found in different forms in the brain, as soluble monomers, oligomers, or protofibrils before aggregating into insoluble fibrils (Walsh et al., 1999; Walsh and Selkoe, 2007). The plaques are then formed outside the cell in a more advanced stage of accumulation and exert its neurodegenerative influence by a number of pathological mechanisms (Masters and Selkoe, 2012). However, it is becoming increasingly clear that the stages prior to the formation of the plaques are critical and that high levels of the soluble forms of amyloid-β disrupts synaptic transmission and impairs the excitation/inhibition balance leading to network hyperactivity (Busche et al., 2012; Mucke and Selkoe, 2012; Palop and Mucke, 2016). Indeed, a study with the APdE9 mouse model of AD reported high prevalence of seizures and increased neuronal excitability in brain slices of these mice that was attributable to the proto-fibrillar form of Aß (Minkeviciene et al., 2009). The sustained resting membrane potential depolarization found in the transgenic brain slices could be mimicked by pre-incubating wild-type slices with proto-fibrillar but still soluble amyloid peptides, strongly supporting Aβ as a trigger for the overexcitability (Minkeviciene et al., 2009). Another study that analyzed 4 lines of transgenic mice expressing familial mutant or wild-type hAPP also found spontaneous seizure activity in cortical and hippocampal networks, although nonconvulsive (Palop et al., 2007). This aberrant excitatory neuronal activity induced by hAPP/Aß triggers compensatory inhibitory mechanisms that leads to a remodeling of hippocampal circuits, consequently constraining the capacity for synaptic plasticity and contributing to network dysfunction (Palop et al., 2007).

3.2. Mechanisms of APP metabolites relevant to epileptogenesis and possible targeting for prevention of PTE

The exact mechanism of how Aß induces neuronal hyperexcitability is still an open question. However, Ren et al. (2018) have proposed a mechanism based on the excessive dopamine release in the frontal cortex promoted by Aß in AD and in the fact that dopamine

1 (Dl) receptor is involved in Aß-induced epileptic activity (Costa et al., 2016; Wu et al., 2007). By using whole-cell recordings in acute mouse brain slices they found that Aβ promotes dopamine release in the anterior cingulate cortex, excessively activating Dl receptors on fast-spiking interneurons and dramatically inhibiting GABA release from these interneurons (Ren et al., 2018). Therefore, by disrupting GABAergic inhibitory input, this sequence of events then leads to an excitatory/inhibitory imbalance and consequently hyperexcitability of excitatory pyramidal cells. Whether this model is also useful to explain the development of PTE after injury is something that still needs to be further investigated. Furthermore, what aggravates the impact of this amyloid cascade of events in brain injury is the fact that increased synaptic activity also seems to increase Aß levels in brain interstitial fluid through synaptic exocytosis, then creating a self-sustained cycle in which amyloid is in the center (Born et al., 2014; Cirrito et al., 2005; Noebels, 2011).

Another important component that reinforces this feedback loop is inflammation and its role in the development of PTE is discussed in another section of this review. In regard to amyloid-ß, its accumulation has been shown to induce microglia activation and release of pro-inflammatory mediators, which are also a big part of the neurodegeneration observed in AD (Aboud et al., 2013; Heneka et al., 2015). On the other hand, as reviewed by Webster et al. (2017) neuroinflammation per se is both a seizure trigger post-TBI and a common consequence of epileptic seizure activity. Therefore, if APP processing is driven through the amyloidogenic pathway after injury, Aβ toxic species could also promote epileptogenesis through inflammatory mechanisms.

Though not only Aβ contributes to epileptogenesis in this scenario, and it is important to consider that patients with APP duplications are also at greater risk for seizure development, as are Down syndrome patients with dementia (Cabrejo et al., 2006; Menendez, 2005). Consistently, AD mice models that overexpress APP also show hyper-excitation in individual neurons; careful monitoring of EEG often reveal epileptiform activity and spontaneous seizures in cortical and hippocampal networks (Busche et al., 2012; Busche et al., 2008; Minkeviciene et al., 2009; Palop et al., 2007). However, the problem with these AD transgenic models is that because the animals overexpress APP from birth and throughout cortical development, it is hard to delineate if the amyloid-β fragments alone, the APP and its metabolites or even both are responsible for the epileptiform activity. In this context, a recent study by Born et al. (2014) used a controllable APP-transgenic model to separate these factors and evaluate how each one contributes to network hyperactivity. It was found that genetically suppressing APP overexpression from birth until 6 weeks of age delayed the appearance of epileptiform activity, but they also found that regardless of age as long as the transgene was suppressed abnormal EEG discharges were also absent. In contrast, a reduction of Aß using a γ-secretase inhibitor failed to reduce the frequency of spike-wave discharges, suggesting that APP and not Aß is responsible for epileptiform activity in these particular mice.

The modulation of APP secretases as a therapeutic approach is still subject to further research. Even though Born et al. (2014) showed that pharmacological inhibition of γ-secretase failed to prevent EEG abnormalities, in the study of Loane et al. (2009) it decreased Aß levels by 25%, reduced neurodegeneration and improved motor and cognitive

recovery after CCI induced TBI. This study also demonstrated that targeting β-secretase may also be useful, as mice lacking this APP processing enzyme displayed reduced cell loss and behavioural deficits after injury compared to the WT (Loane et al., 2009). Nevertheless, the non-amyloidogenic pathway, in particular the fragment sAPPα, might be worth exploiting and a better alternative as a therapeutical target in the brain injury scenario. sAPPα has been shown to have a number of physiological effects including neurotrophic, neuroprotective, neurogenic, gene expression and protein synthesis stimulation, long-term potentiation (LTP) and memory enhancement (reviewed by Mockett et al. (2017)). In regards to its neuroprotective properties, the regions of interest within sAPPα sequence were narrowed down to two domains (D1 and D6) related to their heparin binding sites and the ability of binding heparin sulphate proteoglycans (HSPGs) (Corrigan et al., 2011). As the D1 heparin binding site (APP96–110) has already proven to promote neurite outgrowth, Corrigan and colleagues administered the APP96–110 peptide intracerebroventricularly following CCI in the same APP-KO mice and could reproduce the results obtained with the sAPPα treatment (Corrigan et al., 2014; Small et al., 1994). Furthermore, improved cognitive outcomes and reduced axonal injury were also observed following APP96–110 administration in Sprague-Dawley rats after a diffuse TBI, suggesting that this peptide within sAPPα might be responsible for its neuroprotective properties (Corrigan et al., 2014).

Another potential disease-modifying therapeutical target for TBI that could impact the development of PTE is through inhibition of the c-Jun N-terminal kinase (JNK). Rehman et al. (2017) treated 2 different models of TBI mice with SP600125, a specific JNK inhibitor, and observed remarkable reductions in APP expression levels and amyloid-β production, inhibition of inflammatory responses, apoptotic neurodegeneration among other pathological features of TBI and AD-related pathology. Remarkably, treatment with SP600125 also seems to redirect APP processing from the amyloidogenic to the non-amyloidogenic pathway, without affecting Aß clearance but suppressing its production (Rehman et al., 2017). Aberrant activation of JNK intracellular signaling cascade has been reported in AD patients and in AD mouse models suggesting that it might be involved in a number of neurodegenerative mechanisms associated to the disease, but this study was the first to report the benefits of targeting JNK to improve AD-related TBI outcomes (Mehan et al., 2011; Rehman et al., 2017; Shoji et al., 2000).

Lastly, targeting amyloid as a therapeutic approach in TBI involves investigating 3 main strategies: inhibition of amyloid production, prevention of its aggregation or promotion of its clearance (Schenk et al., 2012). These attempts to mitigate Aß impact in the brain have been pursued through inhibition or modulation of ß- and γ-secretases, blocking of Aß aggregation and neutralization of oligomer toxicity, or Aß immunization to promote plaque clearance. However even with a number of anti-Aß treatments under clinical investigation at the moment, there has been no real progress towards plaque reduction or improvements in neurodegeneration processes (Hung and Fu, 2017). Although these approaches have been explored in the AD research field, the findings can promote insights and bolster the rationale for developing an amyloid therapy for TBI. More importantly, these treatments have not yet been explored in animal models of epilepsy, thus the relevance of whether preventing the generation of toxic amyloid species and amyloid aggregation is beneficial in terms of seizure development is still an open question. Besides, the studies herein mentioned targeting anti-

amyloid therapies in TBI models have not investigated seizure outcomes, only neurodegeneration features and cognitive improvements, highlighting the need for continued efforts in this area.

4. Neuroinflammation

Neuroinflammation is perhaps one of the most common pathological processes investigated and known to contribute to neurodegeneration following a brain trauma, as well as for its contribution to the development of epilepsies of both genetic and acquired forms (Amhaoul et al., 2016; Okuneva et al., 2015; Sun et al., 2017; Webster et al., 2017). Neuroinflammation following a traumatic injury includes many characteristic events such as activation of brain resident glial cells including microglia and astrocytes, transmigration of peripheral immune cells as well as upregulation and release of inflammatory chemokines and cytokines within local brain area as well as in distant regions including peripheral circulation (Aronica et al., 2017; Jassam et al., 2017; Webster et al., 2017). It is considered to be a major factor leading to secondary injury and neurodegeneration processes following the initial primary injury. These processes can contribute to neurodegeneration, enhancement of excitability, pruning of synapses, neuronal plasticity, neurogenesis, survival and expression of synaptic proteins on to newly formed neurons (Ali et al., 2018; Chugh et al., 2015; Iori et al., 2016; Le Feuvre et al., 2002). A more detailed evaluation of downstream pathways of how neuroinflammation can contribute to epileptogenesis has been reviewed previously (Webster et al., 2017). Of note is a recent study by Semple et al. (2017) that reported protective effect of an interleukin 1ß receptor antagonist with a reduced seizure susceptibility to evoked seizures in a mouse model of pediatric TBI along with a non-significant trend to reduced frequency of spontaneous seizures in this model. A detailed description of possibilities of targeting these in PTE has been discussed in detail in other section of this NBD supplement (Saleti et al., 2018).

Since inflammation is also one of the main repair mechanisms, here we discuss specifically whether modulating rather than complete suppression can be neuroprotective. Adverse outcomes relevant to chronic inflammation following a TBI include progression of pathological condition to neurodegenerative disorders such as AD and Parkinson’s disease (PD) (Lozano et al., 2015; Utagawa et al., 2008). Chronic neuroinflammation with microglia activation and macrophage infiltration underlying pathology of these disorders involves clearing up of accumulation of ß-amyloid plaques or neurofibrillary tangles. This process is compromised by an imbalance in the pro- and anti-inflammatory cytokine release with the presence of predominantly pro-inflammatory cytokines contributing to neurodegeneration (Condello et al., 2018; Laatsch et al., 2004; Laurent et al., 2018). This highlights the fact that neuroinflammation is a very heterogeneous process and the activation of immune cells in terms of their expression and release of pro- or anti-inflammatory cytokines, which has been termed to be representing a Th-1/ classical Ml or Th-2/ alternate M2 immune activation needs consideration. If unchecked, a dysregulated Ml immune response within the brain can become neurotoxic due to release of pro-inflammatory cytokines that are intended to clear up the damaged tissue. Such an immune activation in brain can be identified by the presence of markers such as pro-inflammatory cytokines including IL-1ß or TNF-α. On the other hand, an M2 response leads to the release of anti-inflammatory cytokines and growth factors

intended to promote growth and repair mechanisms, and can be identified by expression of markers such as arginasel, Ym1 and Fizz1 and release of anti-inflammatory cytokines including IL-10. These activation states of immune cells with their respective release of pro- or anti-inflammatory cytokines may also be relevant in neurodegeneration and repair after a TBI and progression to PTE.

Polarization in the microglia activation has also been reported (reviewed in (Xu et al., 2017a)) following traumatic brain injury and promoting M2/M1 ratio has shown neuroprotective effects and reduced axonal injury (Gao et al., 2016; Xu et al., 2017b). It is not known whether modification in this balance could be beneficial in protecting against PTE after a TBI. An interesting study using a genetic mouse model of progressive myoclonus epilepsy showed altered M1/M2 microglia activation balance towards an Ml phenotype before the initiation of epileptic seizures in these mice at one month age (Okuneva et al., 2015). Another recent study displayed a simultaneous expression of Ml and M2 markers during chronic epilepsy in post status epilepticus models of acquired epilepsies, though a predominantly Ml phenotype was clearly observable during the early periods after the induction of status epilepticus (Benson et al., 2015). This suggests a potential role of an M1/M2 microglia activation imbalance in pathogenesis of epileptic seizures which may be also relevant following TBI and related development of PTE. With regards to the possibility of therapeutic targeting such immune alterations, a recent study using mesenchymal stem cells to deliver interleukin-13 within the hippocampus in experimental model of epileptogenesis failed to induce a widespread induction of M2 response, and therefore a reduction in epileptogenesis (Ali et al., 2017a). Whereas, others using strategies of implanting mesenchymal stem cells have shown positive outcomes in epilepsy in association with stimulation of an anti-inflammatory immune response (reviewed in (Agadi and Shetty, 2015)). M2 promoting strategies as treatment target against PTE has not been evaluated yet, but is merits future investigations.

5. Discussion and clinical relevance

Neurodegenerative mechanisms have been widely associated with the pathophysiology of acquired epilepsies as well as following a traumatic brain injury, and represent promising targets for the development of anti-epileptogenic therapies to prevent PTE. Though, it has to be considered that neurodegeneration, at least in animal models, has not been consistently reported to be related to the development of epilepsy (Bertoglio et al., 2017; Pitkanen et al., 2005). Therefore, it must be considered how the neurodegeneration pathways discussed in this review may lead to the development of acquired epilepsies including PTE. For instance, phosphorylation of tau has been associated with a number of other molecular and pathological characteristics of acquired epilepsies such as mossy fiber sprouting, NMDA receptor subunit function, granule cell layer dispersion and alterations in neuronal plasticity (Decker et al., 2016; Kandratavicius et al., 2013; Sotiropoulos et al., 2017). Since these findings are at best associative in nature it is not possible to pinpoint to a particular mechanism linking neurodegeneration to epilepsy development. Furthermore, tau is a Microtubule Associated Protein (MAP) and it is interesting to consider whether tau is only such protein that could be targeted against PTE, or whether other relevant MAPs could be of therapeutic value. In this regard, MAP2 levels in cerebrospinal fluid have been recently

reported as a biomarker for diffuse brain injury severity and a pointer to early mortality in TBI patients (Papa et al., 2018). MAP2 is also a MAP component, localized on neuronal cell bodies and dendrites regulating spine morphology and neuronal plasticity, is known to be dysregulated both following TBI as well as in epilepsy models (Folkerts et al., 1998; Kandratavicius et al., 2013; Posmantur et al., 1996; Savina and Shchipakina, 2011; Zeng et al., 2017). Since it shares some of the dephosphorylating mechanisms with tau proteins including PP2A (Sanchez et al., 2000), a sodium selenate-mediated increase in MAP2 dephosphorization and subsequent increase in neuronal survival cannot be ruled out. Accordingly, involvement of other MAPs such as MAPI and Echinoderm microtubule-associated protein-like protein 5 (EML5) in epilepsy pathogenesis has been suggested (An et al., 2003; Sun et al., 2015), however, a detailed discussion of these is not in the scope of this review. Similar to tauopathies, Aβ accumulation in the brain is known to be associated with epileptogenesis by altering dopaminergic neurons and in turn release of GABA from interneurons (Ren et al., 2018), neuronal circuit reorganization and axonal sprouting (Yan et al., 2012b) as well as neuroinflammation (Aboud et al., 2013). These suggest that the outcomes on the excitatory/inhibitory balance that leads to seizure generation is a complex interplay of several mechanistic pathways including contribution from neurodegeneration.

Genetic and pharmacological manipulations of neurodegenerative mechanisms in animal models have been suggested for possible targeting of anti-epileptogenesis trials in post-traumatic epileptogenesis. Though, in general there is scarcity of evidences in animal models of post-traumatic epileptogenesis due to a very long follow up required in post-TBI models for development of epilepsy and a relatively low incidence (20–30%) in adult TBI rodent models. This renders undertaking adequate, statistically powered, studies challenging in terms of expenses as well as the logistics of performing such studies. However, the role of neurodegenerative mechanisms in other acquired epilepsy models and TBI outcomes strongly suggest it is important to invest in this line of research.

In this regard, two of the pathways are particularly promising – inhibition of tau phorphorylation by sodium selenate and inhibition of pro-inflammatory interleukin 1ß. Targeting tauopathies with the use of sodium selenate has shown effectiveness in inhibiting epileptogenesis in three different models of acquired epilepsy, including the one initiated following TBI (Liu et al., 2016). Sodium selenate has already been reported to be safe during phase I and phase II trials for non-epilepsy conditions (Corcoran et al., 2010; Malpas et al., 2016), and so could rapidly be translated into human anti-epileptogenesis studies post-TBI. Similarly, effectiveness of modifying interleukin 1ß signaling has shown promising effects in models of acquired epilepsies (Fukuda et al., 2009; Noe et al., 2013) including in a model of TBI (Semple et al., 2017). Interleukin 1ß antagonist Kineret is already commercially available for treatment of rheumatoid arthritis. In addition, clinical case reports have also suggested promise of improving outcomes in epilepsy patients (Desena et al., 2018; Kenney-Jung et al., 2016). Further validation of these in animal models of PTE is being undertaken in the EpiBioS4Rx (Epilepsy bioinformatics study for antiepileptogenic therapy) Center Without Walls funded by NIH, which will test new therapies to prevent PTE, in a multi centered preclinical trial scenario (discussed in detail in another work in this special issue: Saletti et al 2018). Overall, we provided several neurodegenerative mechanisms that may be relevant to development of PTE. Some of those may still be at the

stage of proof of concept evidence whereas some others have already shown clear potential for progressing into clinical trials targeting the development of PTE.

References

Aboud O, et al., 2013 Epilepsy: neuroinflammation, neurodegeneration, and APOE genotype. Acta Neuropathol. Commun 1, 41. [PubMed: 24252240]

Abou-Khalil BW, 2010 How important is Alzheimer's disease as a risk factor for unprovoked seizures and epilepsy in the elderly? Epilepsy Curr 10 (2), 36–37. [PubMed: 20231919]

Acharya MM, et al., 2008 Progress in neuroprotective strategies for preventing epilepsy. Prog. Neurobiol 84, 363–404. [PubMed: 18207302]

Agadi S, Shetty AK, 2015 Concise Review: Prospects of Bone Marrow Mononuclear Cells and Mesenchymal Stem Cells for Treating Status Epilepticus and Chronic Epilepsy. Stem Cells 33, 2093–2103. [PubMed: 25851047]

Albayram O, et al., 2017 Cis P-tau is induced in clinical and preclinical brain injury and contributes to post-injury sequelae. Nat. Commun 8.

Ali I, et al., 2017a Intracerebral delivery of the M2 polarizing cytokine interleukin 13 using mesenchymal stem cell implants in a model of temporal lobe epilepsy in mice. Epilepsia 58, 1063–1072. [PubMed: 28374921]

Ali I, et al., 2018 Decreased post-synaptic density-95 protein expression on dendrites of newborn neurons following CX3CR1 modulation in the epileptogenic adult rodent brain. Cell Mol. Immunol 15 (4), 414–417. [PubMed: 29082919]

Amatniek JC, et al., 2006 Incidence and predictors of seizures in patients with Alzheimer's disease. Epilepsia 47, 867–872. [PubMed: 16686651]

Amhaoul H, et al., 2016 P2X7 receptor antagonism inhibits seizure severity in a chronic model of temporal lobe epilepsy. Neuropharmacology 105, 175–185. [PubMed: 26775823]

An SJ, et al., 2003 Accumulation of microtubule-associated proteins in the hippocampal neurons of seizure-sensitive gerbils. Mol. Cells 15, 200–207. [PubMed: 12803483]

Aronica E, et al., 2017 Neuroinflammatory targets and treatments for epilepsy validated in experimental models. Epilepsia 58 (Suppl. 3), 27–38.

Avoli M, et al., 2016 Specific imbalance of excitatory/inhibitory signaling establishes seizure onset pattern in temporal lobe epilepsy. J. Neurophysiol 115, 3229–3237. [PubMed: 27075542]

Bakker A, et al., 2015 Response of the medial temporal lobe network in amnestic mild cognitive impairment to therapeutic intervention assessed by fMRI and memory task performance. Neuroimage Clin 7, 688–698. [PubMed: 25844322]

Benson MJ, et al., 2015 Complex alterations in microglial M1/M2 markers during the development of epilepsy in two mouse models. Epilepsia 56, 895–905. [PubMed: 25847097]

Bertoglio D, et al., 2017 Kainic acid-induced post-status epilepticus models of temporal lobe epilepsy with diverging seizure phenotype and neuropathology. Front. Neurol 8, 588. [PubMed: 29163349]

Bhowmik M, et al., 2015 Activation of AKT/GSK3beta pathway by TDZD-8 attenuates kainic acid induced neurodegeneration but not seizures in mice. Neurotoxicology 46, 44–52. [PubMed: 25453207]

Blennow K, et al., 2012 The neuropathology and neurobiology of traumatic brain injury. Neuron 76, 886–899. [PubMed: 23217738]

Born HA, et al., 2014 Genetic suppression of transgenic APP rescues Hypersynchronous network activity in a mouse model of Alzeimer's disease. J. Neurosci 34, 3826–3840. [PubMed: 24623762]

Brandt C, et al., 2006 Treatment with valproate after status epilepticus: effect on neuronal damage, epileptogenesis, and behavioral alterations in rats. Neuropharmacology 51, 789–804. [PubMed: 16806297]

Busche MA, et al., 2008 Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. Science 321, 1686–1689. [PubMed: 18802001]

Busche MA, et al., 2012 Critical role of soluble amyloid-beta for early hippocampal hyperactivity in a mouse model of Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A 109, 8740–8745. [PubMed: 22592800]

Cabrejo L, et al., 2006 Phenotype associated with APP duplication in five families. Brain 129, 2966–2976. [PubMed: 16959815]

Carletti F, et al., 2016 Hippocampal hyperexcitability is modulated by microtubule-active agent: evidence from in vivo and in vitro epilepsy models in the rat. Front. Cell. Neurosci 10, 29. [PubMed: 26903814]

Chen LJ, et al., 2010 Compression alters kinase and phosphatase activity and tau and MAP2 phosphorylation transiently while inducing the fast adaptive dendritic remodeling of underlying cortical neurons. J. Neurotrauma 27, 1657–1669. [PubMed: 20568963]

Cheng JS, et al., 2014 Tau reduction diminishes spatial learning and memory deficits after mild repetitive traumatic brain injury in mice. PLoS One 9, e115765. [PubMed: 25551452]

Chugh D, et al., 2015 Alterations in brain inflammation, synaptic proteins, and adult hippocampal neurogenesis during epileptogenesis in mice lacking synapsin2. PLoS One 10, e0132366. [PubMed: 26177381]

Cirrito JR, et al., 2005 Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. Neuron 48, 913–922. [PubMed: 16364896]

Condello C, et al., 2018 Microglia-mediated neuroprotection, TREM2, and Alzheimer's disease: evidence from optical imaging. Biol. Psychiatry 83, 377–387. [PubMed: 29169609]

Corcoran NM, et al., 2010 Open-label, phase I dose-escalation study of sodium selenate, a novel activator of PP2A, in patients with castration-resistant prostate cancer. Br. J. Cancer 103, 462–468. [PubMed: 20648008]

Corrigan F, et al., 2011 The neuroprotective domains of the amyloid precursor protein, in traumatic brain injury, are located in the two growth factor domains. Brain Res 1378, 137–143. [PubMed: 21215734]

Corrigan F, et al., 2012a Characterisation of the effect of knockout of the amyloid precursor protein on outcome following mild traumatic brain injury. Brain Res 1451, 87–99. [PubMed: 22424792]

Corrigan F, et al., 2012b sAPPalpha rescues deficits in amyloid precursor protein knockout mice following focal traumatic brain injury. J. Neurochem 122, 208–220. [PubMed: 22519988]

Corrigan F, et al., 2014 The neuroprotective activity of the amyloid precursor protein against traumatic brain injury is mediated via the heparin binding site in residues 96–110. J. Neurochem 128, 196–204. [PubMed: 23919582]

Costa C, et al., 2016 Epilepsy, amyloid-beta, and D1 dopamine receptors: a possible pathogenetic link? Neurobiol. Aging 48, 161–171. [PubMed: 27701029]

Decker JM, et al., 2016 The Tau/A152T mutation, a risk factor for frontotemporal-spectrum disorders, leads to NR2B receptor-mediated excitotoxicity. EMBO Rep 17, 552–569. [PubMed: 26931569]

Desena AD, et al., 2018 Systemic autoinflammation with intractable epilepsy managed with interleukin-1 blockade. J. Neuroinflammation 15, 38. [PubMed: 29426321]

Devos SL, et al., 2013 Antisense reduction of tau in adult mice protects against seizures. J. Neurosci 33, 12887–12897. [PubMed: 23904623]

Engel T, et al., 2006 Chronic lithium administration to FTDP-17 tau and GSK-3beta overexpressing mice prevents tau hyperphosphorylation and neurofibrillary tangle formation, but pre-formed neurofibrillary tangles do not revert. J. Neurochem 99, 1445–1455. [PubMed: 17059563]

Folkerts MM, et al., 1998 Disruption of MAP-2 immunostaining in rat hippocampus after traumatic brain injury. J. Neurotrauma 15, 349–363. [PubMed: 9605349]

Forsgren L, et al., 1996 Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. Epilepsia 37, 224–229. [PubMed: 8598179]

Friedman D, et al., 2012 Seizures and epilepsy in Alzheimer's disease. CNS Neurosci. Ther 18, 285–294. [PubMed: 22070283]

Fukuda M, et al., 2009 Interleukin-1beta enhances susceptibility to hyperthermia-induced seizures in developing rats. Seizure 18, 211–214. [PubMed: 19004647]

Gao J, et al., 2016 Human Neural Stem Cell Transplantation-Mediated Alteration of Microglial/Macrophage Phenotypes after Traumatic Brain Injury. Cell Transplant 25, 1863–1877. [PubMed: 26980267]

Gheyara AL, et al., 2014 Tau reduction prevents disease in a mouse model of Dravet syndrome. Ann. Neurol 76, 443–456. [PubMed: 25042160]

Ghosal K, Pimplikar SW, 2011 Aging and excitotoxic stress exacerbate neural circuit reorganization in amyloid precursor protein intracellular domain transgenic mice. Neurobiol. Aging 32, 2320 (e1–9).

Giorgi FS, et al., 2017 Treatment of epilepsy in patients with Alzheimer's disease. Expert. Rev. Neurother 17, 309–318. [PubMed: 27687685]

Hatch RJ, et al., 2017 Hyperphosphorylated tau causes reduced hippocampal CA1 excitability by relocating the axon initial segment. Acta Neuropathol 133, 717–730. [PubMed: 28091722]

Hauser WA, et al., 1986 Seizures and myoclonus in patients with Alzheimer's disease. Neurology 36, 1226–1230. [PubMed: 3092131]

Hawkins BE, et al., 2013 Rapid accumulation of endogenous tau oligomers in a rat model of traumatic brain injury. J. Biol. Chem 288, 17042–17050. [PubMed: 23632019]

Hayashi T, et al., 2015 Two different immunostaining patterns of beta-amyloid precursor protein (APP) may distinguish traumatic from nontraumatic axonal injury. Int. J. Legal Med 129, 1085–1090. [PubMed: 26249371]

Heneka MT, et al., 2015 Neuroinflammation in Alzheimer's disease. Lancet Neurol 14, 388–405. [PubMed: 25792098]

Holth JK, et al., 2013 Tau loss attenuates neuronal network hyperexcitability in mouse and Drosophila genetic models of epilepsy. J. Neurosci 33, 1651–1659. [PubMed: 23345237]

Hortobagyi T, et al., 2007 Traumatic axonal damage in the brain can be detected using beta-APP immunohistochemistry within 35 min after head injury to human adults. Neuropathol. Appl. Neurobiol 33, 226–237. [PubMed: 17359363]

Huang WJ, et al., 2013 GSK-3beta may be involved in hippocampal mossy fiber sprouting in the pentylenetetrazole-kindling model. Mol. Med. Rep 8, 1337–1342. [PubMed: 24002180]

Huijbers W, et al., 2015 Amyloid-beta deposition in mild cognitive impairment is associated with increased hippocampal activity, atrophy and clinical progression. Brain 138, 1023–1035. [PubMed: 25678559]

Hung SY, Fu WM, 2017 Drug candidates in clinical trials for Alzheimer's disease. J. Biomed. Sci 24, 47. [PubMed: 28720101]

Ikonomovic MD, et al., 2004 Alzheimer's pathology in human temporal cortex surgically excised after severe brain injury. Exp. Neurol 190, 192–203. [PubMed: 15473992]

Iori V, et al., 2016 Modulation of neuronal excitability by immune mediators in epilepsy. Curr. Opin. Pharmacol 26, 118–123. [PubMed: 26629681]

Jassam YN, et al., 2017 Neuroimmunology of traumatic brain injury: time for a paradigm shift. Neuron 95, 1246–1265. [PubMed: 28910616]

Jones NC, O'Brien TJ, 2013 Stress, epilepsy, and psychiatric comorbidity: how can animal models inform the clinic? Epilepsy Behav 26, 363–369. [PubMed: 23099287]

Jones NC, et al., 2012 Targeting hyperphosphorylated tau with sodium selenate suppresses seizures in rodent models. Neurobiol. Dis 45, 897–901. [PubMed: 22182692]

Kandratavicius L, et al., 2013 Microtubule-associated proteins in mesial temporal lobe epilepsy with and without psychiatric comorbidities and their relation with granular cell layer dispersion. Biomed. Res. Int 2013, 960126. [PubMed: 24069608]

Kenney K, et al., 2018 Dementia after moderate-severe traumatic brain injury: coexistence of multiple proteinopathies. J. Neuropathol. Exp. Neurol 77, 50–63. [PubMed: 29155947]

Kenney-Jung DL, et al., 2016 Febrile infection-related epilepsy syndrome treated with anakinra. Ann. Neurol 80, 939–945. [PubMed: 27770579]

Kondo A, et al., 2015 Antibody against early driver of neurodegeneration cis P-tau blocks brain injury and tauopathy. Nature 523, 431–436. [PubMed: 26176913]

Kulbe JR, Hall ED, 2017 Chronic traumatic encephalopathy-integration of canonical traumatic brain injury secondary injury mechanisms with tau pathology. Prog. Neurobiol 158, 15–44. [PubMed: 28851546]

Laatsch LK, et al., 2004 Investigating the neurobiological basis of cognitive rehabilitation therapy with fMRI. Brain Inj 18, 957–974. [PubMed: 15370896]

Laurent C, et al., 2018 Tau and neuroinflammation: what impact for Alzheimer's disease and tauopathies? Biom. J 41, 21–33.

Le Feuvre R, et al., 2002 Extracellular ATP and P2X7 receptors in neurodegeneration. Eur. J. Pharmacol 447, 261–269. [PubMed: 12151017]

Lee G, Leugers CJ, 2012 Tau and tauopathies. Prog. Mol. Biol. Transl. Sci 107, 263–293. [PubMed: 22482453]

Leroy K, et al., 2010 Lithium treatment arrests the development of neurofibrillary tangles in mutant tau transgenic mice with advanced neurofibrillary pathology. J. Alzheimers Dis 19, 705–719. [PubMed: 20110614]

Lewen A, et al., 1995 Traumatic brain injury in rat produces changes of beta-amyloid precursor protein immunoreactivity. Neuroreport 6, 357–360. [PubMed: 7756628]

Lewen A, et al., 1996 Changes in microtubule-associated protein 2 and amyloid precursor protein immunoreactivity following traumatic brain injury in rat: influence of MK-801 treatment. Brain Res 719, 161–171. [PubMed: 8782876]

Li Z, et al., 2014 Seizure resistance without parkinsonism in aged mice after tau reduction. Neurobiol. Aging 35, 2617–2624. [PubMed: 24908165]

Liang Z, et al., 2009 Dysregulation of tau phosphorylation in mouse brain during excitotoxic damage. J. Alzheimers Dis 17, 531–539. [PubMed: 19363259]

Liou YC, et al., 2003 Role of the prolyl isomerase Pin1 in protecting against age-dependent neurodegeneration. Nature 424, 556–561. [PubMed: 12891359]

Liu SJ, et al., 2016 Sodium selenate retards epileptogenesis in acquired epilepsy models reversing changes in protein phosphatase 2A and hyperphosphorylated tau. Brain 139, 1919–1938. [PubMed: 27289302]

Liu SJ, et al., 2017a Accelerated kindling epileptogenesis in Tg4510 tau transgenic mice, but not in tau knockout mice. Epilepsia 58, E136–E141. [PubMed: 28710841]

Liu X, et al., 2017b N-methyl-D-aspartate receptors mediate epilepsy-induced axonal impairment and tau phosphorylation via activating glycogen synthase kinase-3beta and cyclin-dependent kinase 5. Discov. Med 23, 221–234. [PubMed: 28595035]

Loane DJ, et al., 2009 Amyloid precursor protein secretases as therapeutic targets for traumatic brain injury. Nat. Med 15, 377–379. [PubMed: 19287391]

Lozano D, et al., 2015 Neuroinflammatory responses to traumatic brain injury: etiology, clinical consequences, and therapeutic opportunities. Neuropsychiatr. Dis. Treat 11, 97–106.

Magnoni S, Brody DL, 2010 New perspectives on amyloid-beta dynamics after acute brain injury: moving between experimental approaches and studies in the human brain. Arch. Neurol 67, 1068–1073. [PubMed: 20837849]

Malpas CB, et al., 2016 A Phase IIa randomized control trial of VEL015 (sodium selenate) in mild-moderate Alzheimer's disease. J. Alzheimers Dis 54, 223–232. [PubMed: 27447428]

Masters CL, Selkoe DJ, 2012 Biochemistry of amyloid beta-protein and amyloid deposits in Alzheimer disease. Cold Spring Harb. Perspect. Med 2, a006262. [PubMed: 22675658]

Matsumoto G, Sakai H, 1979 Microtubules inside the plasma membrane of squid giant axons and their possible physiological function. J. Membr. Biol 50, 1–14. [PubMed: 501731]

McKee AC, et al., 2013 The spectrum of disease in chronic traumatic encephalopathy. Brain 136, 43–64. [PubMed: 23208308]

Mehan S, et al., 2011 JNK: a stress-activated protein kinase therapeutic strategies and involvement in Alzheimer's and various neurodegenerative abnormalities. J. Mol. Neurosci 43, 376–390. [PubMed: 20878262]

Mendez M, Lim G, 2003 Seizures in elderly patients with dementia: epidemiology and management. Drugs Aging 20, 791–803. [PubMed: 12964886]

Menendez M, 2005 Down syndrome, Alzheimer's disease and seizures. Brain Dev 27, 246–252. [PubMed: 15862185]

Minkeviciene R, et al., 2009 Amyloid beta-induced neuronal hyperexcitability triggers progressive epilepsy. J. Neurosci 29, 3453–3462. [PubMed: 19295151]

Miszczuk D, et al., 2016 Traumatic Brain Injury Increases the Expression of Nos1, Abeta Clearance, and Epileptogenesis in APP/PS1 Mouse Model of Alzheimer's Disease. Mol. Neurobiol 53, 7010–7027. [PubMed: 26671618]

Mockett BG, et al., 2017 Therapeutic potential of secreted amyloid precursor protein APPsalpha. Front. Mol. Neurosci 10, 30. [PubMed: 28223920]

Mondragon Rodriguez S, et al., 2018 Phosphorylation of tau protein correlates with changes in hippocampal theta oscillations and reduces hippocampal excitability in Alzheimer's model. J. Biol. Chem 293 (22), 8462–8472. [PubMed: 29632073]

Monti G, et al., 2015 Cerebrospinal fluid tau proteins in status epilepticus. Epilepsy Behav 49, 150–154. [PubMed: 25958230]

Morris M, et al., 2011 The many faces of tau. Neuron 70, 410–426. [PubMed: 21555069]

Mucke L, Selkoe DJ, 2012 Neurotoxicity of amyloid beta-protein: synaptic and network dysfunction. Cold Spring Harb. Perspect. Med 2, a006338. [PubMed: 22762015]

Muller UC, et al., 2017 Not just amyloid: physiological functions of the amyloid precursor protein family. Nat. Rev. Neurosci 18, 281–298. [PubMed: 28360418]

Murakami N, et al., 1998 Experimental brain injury induces expression of amyloid precursor protein, which may be related to neuronal loss in the hippocampus. J. Neurotrauma 15, 993–1003. [PubMed: 9840772]

Nakagawa Y, et al., 1999 Traumatic brain injury in young, amyloid-beta peptide overexpressing transgenic mice induces marked ipsilateral hippocampal atrophy and diminished Abeta deposition during aging. J. Comp. Neurol 411, 390–398. [PubMed: 10413774]

Nakagawa Y, et al., 2000 Brain trauma in aged transgenic mice induces regression of established abeta deposits. Exp. Neurol 163, 244–252. [PubMed: 10785464]

Nakamura K, et al., 2012 Proline isomer-specific antibodies reveal the early pathogenic tau conformation in Alzheimer's disease. Cell 149, 232–244. [PubMed: 22464332]

Nicastro N, Assal F, Seeck M, 2016 From here to epilepsy: the risk of seizure in patients with Alzheimer's disease. Epileptic Disord 18 (1), 1–12.

Noble W, et al., 2005 Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopathy and degeneration in vivo. Proc. Natl. Acad. Sci. U. S. A 102, 6990–6995. [PubMed: 15867159]

Noe FM, et al., 2013 Pharmacological blockade of IL-1beta/IL-1 receptor type 1 axis during epileptogenesis provides neuroprotection in two rat models of temporal lobe epilepsy. Neurobiol. Dis 59, 183–193. [PubMed: 23938763]

Noebels J, 2011 A perfect storm: Converging paths of epilepsy and Alzheimer's dementia intersect in the hippocampal formation. Epilepsia 52 (Suppl. 1), 39–46.

Okuneva O, et al., 2015 Abnormal microglial activation in the Cstb(−/−) mouse, a model for progressive myoclonus epilepsy, EPM1. Glia 63, 400–411. [PubMed: 25327891]

Olivera A, et al., 2015 Peripheral total tau in military personnel who sustain traumatic brain injuries during deployment. JAMA Neurol 72, 1109–1116. [PubMed: 26237304]

Otsuka N, et al., 1991 Rapid appearance of beta-amyloid precursor protein immunoreactivity in damaged axons and reactive glial cells in rat brain following needle stab injury. Brain Res 568, 335–338. [PubMed: 1814579]

Palmio J, et al., 2009 Cerebrospinal fluid tau as a marker of neuronal damage after epileptic seizure. Seizure 18, 474–477. [PubMed: 19428269]

Palop JJ, Mucke L, 2016 Network abnormalities and interneuron dysfunction in Alzheimer disease. Nat. Rev. Neurosci 17, 777–792. [PubMed: 27829687]

Palop JJ, et al., 2007 Aberrant excitatory neuronal activity and compensatory remodelin of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. Neuron 55, 697–711. [PubMed: 17785178]

Papa L, et al., 2018 Temporal profile of microtubule-associated protein 2: a novel indicator of diffuse brain injury severity and early mortality after brain trauma. J. Neurotrauma 35, 32–40. [PubMed: 28895474]

Pierce JE, et al., 1996 Immunohistochemical characterization of alterations in the distribution of amyloid precursor proteins and beta-amyloid peptide after experimental brain injury in the rat. J. Neurosci 16, 1083–1090. [PubMed: 8558237]

Pitkanen A, et al., 2005 Administration of diazepam during status epilepticus reduces development and severity of epilepsy in rat. Epilepsy Res 63, 27–42. [PubMed: 15716080]

Posmantur RM, et al., 1996 Diminished microtubule-associated protein 2 (MAP2) immunoreactivity following cortical impact brain injury. J. Neurotrauma 13, 125–137. [PubMed: 8965322]

Puvenna V, et al., 2016 Is phosphorylated tau unique to chronic traumatic encephalopathy? Phosphorylated tau in epileptic brain and chronic traumatic encephalopathy. Brain Research 1630, 225–240. [PubMed: 26556772]

Rehman SU, et al., 2017 Inhibition of c-Jun N-terminal kinase protects against brain damage and improves learning and memory after traumatic brain injury in adult mice. Cereb. Cortex 1–19. [PubMed: 28365777]

Ren SQ, et al., 2018 Amyloid beta causes excitation/inhibition imbalance through dopamine receptor 1-dependent disruption of fast-spiking GABAergic input in anterior cingulate cortex. Sci. Rep 8, 302. [PubMed: 29321592]

Risse SC, et al., 1990 Myoclonus, seizures, and paratonia in Alzheimer disease. Alzheimer Dis. Assoc. Disord 4, 217–225. [PubMed: 2264979]

Roberson ED, et al., 2007 Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. Science 316, 750–754. [PubMed: 17478722]

Roberts GW, et al., 1994 Beta amyloid protein deposition in the brain after severe head injury: implications for the pathogenesis of Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 57, 419–425. [PubMed: 8163989]

Rostgaard N, et al., 2015 Cerebrospinal fluid biomarkers in familial forms of Alzheimer's disease and frontotemporal dementia. Dement. Geriatr. Cogn. Disord 40, 54–62. [PubMed: 25998699]

Saletti PG, Ali I, Casillas-Espinosa PM, Semple BD, Lisgaras C, Moshe SL, Galanopoulou AS, 2018 In search of antiepileptogenic treatments for post-traumatic epilepsy. Neurobiol Dis

Sanchez C, et al., 2000 Phosphorylation of microtubule-associated protein 2 (MAP2) and its relevance for the regulation of the neuronal cytoskeleton function. Prog. Neurobiol 61, 133–168. [PubMed: 10704996]

Sanchez-Elexpuru G, et al., 2017 Sodium selenate treatment improves symptoms and seizure susceptibility in a malin-deficient mouse model of Lafora disease. Epilepsia 58, 467–475. [PubMed: 28098937]

Savina TA, Shchipakina TG, 2011 cAMP-dependent phosphorylation of microtubuleassociated protein-2 during treatment of sodium valproate and audiogenic kindling. Bull. Exp. Biol. Med 152, 53–57. [PubMed: 22803039]

Scarmeas N, et al., 2009 Seizures in Alzheimer disease: who, when, and how common? Arch. Neurol 66, 992–997. [PubMed: 19667221]

Schenk D, et al., 2012 Treatment strategies targeting amyloid beta-protein. Cold Spring Harb. Perspect. Med 2, a006387. [PubMed: 22951439]

Semple BD, et al., 2017 Interleukin-1 receptor in seizure susceptibility after traumatic injury to the pediatric brain. J. Neurosci 37, 7864–7877. [PubMed: 28724747]

Sen A, et al., 2007 Pathological tau tangles localize to focal cortical dysplasia in older patients. Epilepsia 48, 1447–1454. [PubMed: 17441989]

Seo JS, et al., 2017 Transcriptome analyses of chronic traumatic encephalopathy show alterations in protein phosphatase expression associated with tauopathy. Exp. Mol. Med 49.

Shahim P, et al., 2014 Cerebrospinal fluid biomarkers of beta-amyloid metabolism and neuronal damage in epileptic seizures. Eur. J. Neurol 21, 486–491. [PubMed: 24372994]

Shoji M, et al., 2000 JNK activation is associated with intracellular beta-amyloid accumulation. Brain Res. Mol. Brain Res 85, 221–233. [PubMed: 11146125]

Shultz SR, et al., 2015 Sodium selenate reduces hyperphosphorylated tau and improves outcomes after traumatic brain injury. Brain 138, 1297–1313. [PubMed: 25771151]

Small DH, et al., 1994 A heparin-binding domain in the amyloid protein precursor of Alzheimer's disease is involved in the regulation of neurite outgrowth. J. Neurosci 14, 2117–2127. [PubMed: 8158260]

Sotiropoulos I, et al., 2017 Atypical, non-standard functions of the microtubule associated Tau protein. Acta Neuropathol. Commun 5, 91. [PubMed: 29187252]

Sun JJ, et al., 2015 Echinoderm microtubule-associated protein -like protein 5 in anterior temporal neocortex of patients with intractable epilepsy. Iran J. Basic Med. Sci 18, 1008–1013. [PubMed: 26730336]

Sun M, et al., 2017 Treatment with an interleukin-1 receptor antagonist mitigates neuroinflammation and brain damage after polytrauma. Brain Behav. Immun 66, 359–371. [PubMed: 28782716]

Thom M, et al., 2011 Neurofibrillary tangle pathology and Braak staging in chronic epilepsy in relation to traumatic brain injury and hippocampal sclerosis: a postmortem study. Brain 134, 2969–2981. [PubMed: 21903728]

Thornton E, et al., 2006 Soluble amyloid precursor protein alpha reduces neuronal injury and improves functional outcome following diffuse traumatic brain injury in rats. Brain Res 1094, 38–46. [PubMed: 16697978]

Tian FF, et al., 2010 Potential roles of Cdk5/p35 and tau protein in hippocampal mossy fiber sprouting in the PTZ kindling model. Clin. Lab 56, 127–136. [PubMed: 20476644]

Utagawa A, et al., 2008 Systemic inflammation exacerbates behavioral and histopathological consequences of isolated traumatic brain injury in rats. Exp. Neurol 211, 283–291. [PubMed: 18355811]

Van den Heuvel C, et al., 1999 Upregulation of amyloid precursor protein messenger RNA in response to traumatic brain injury: an ovine head impact model. Exp. Neurol 159, 441–450. [PubMed: 10506515]

Villemagne VL, et al., 2013 Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol 12, 357–367. [PubMed: 23477989]

Vossel KA, et al., 2013 Seizures and epileptiform activity in the early stages of Alzheimer disease. JAMA Neurol 70, 1158–1166. [PubMed: 23835471]

Vossel KA, et al., 2017 Epileptic activity in Alzheimer's disease: causes and clinical relevance. Lancet Neurol 16, 311–322. [PubMed: 28327340]

Walsh DM, Selkoe DJ, 2007 A beta oligomers - a decade of discovery. J. Neurochem 101, 1172–1184. [PubMed: 17286590]

Walsh DM, et al., 1999 Amyloid beta-protein fibrillogenesis. Structure and biological activity of protofibrillar intermediates. J Biol Chem 274, 25945–25952. [PubMed: 10464339]

Webster KM, et al., 2017 Inflammation in epileptogenesis after traumatic brain injury. J. Neuroinflammation 14, 10. [PubMed: 28086980]

Wu J, et al., 2007 Dopamine release in prefrontal cortex in response to beta-amyloid activation of alpha7 * nicotinic receptors. Brain Res 1182, 82–89. [PubMed: 17935702]

Xu H, et al., 2017a The polarization states of microglia in TBI: a new paradigm for pharmacological intervention. Neural. Plast 2017, 5405104. [PubMed: 28255460]

Xu X, et al., 2017b Anti-inflammatory and immunomodulatory mechanisms of atorvastatin in a murine model of traumatic brain injury. J. Neuroinflammation 14, 167. [PubMed: 28835272]

Yan XX, et al., 2012a Chronic temporal lobe epilepsy is associated with enhanced Alzheimer-like neuropathology in 36 x Tg-AD mice. Plos One 7

Yan XX, et al., 2012b BACE1 elevation is associated with aberrant limbic axonal sprouting in epileptic CD1 mice. Exp. Neurol 235, 228–237. [PubMed: 22265658]

Yang S, et al., 2014 Expression of amyloid-beta protein and amyloid-beta precursor protein after primary brain-stem injury in rats. Am J Forensic Med Pathol 35, 201–205. [PubMed: 24949598]

Zeng X, et al., 2017 The expression of G protein-coupled receptor kinase 5 and its interaction with dendritic marker microtubule-associated protein-2 after status epilepticus. Epilepsy Res 138, 62–70. [PubMed: 29080472]

Zheng P, et al., 2017 Animal Models of Acquired Epilepsy and Tauopathies Academic Press.

Table 1

Summarizing the neurodegenerative mechanisms including Tauopathies, amyloid pathology and neuroinflammation in patients and animal models with TBI.

Model	Mechanism/s investigated	Intervention/s	Outcomes	Reference
TBI patients	Hyper-phosphorylated-Tau	Not evaluated	Increased Hyperphophorylated-Tau	(Shultz et al., 2015)
Repeatative TBI in patients	Hyper-phosphorylated-Tau	Not evaluated	Increased phosphorylated tau in rTBI patients that were similar to observation in temporal lobe epilepsy patients	(Puvenna et al., 2016)
TBI patients	Hyper-phosphorylated-Tau	Not evaluated	Phopho-Tau associated with TBI history but not seizures	(Thom et al., 2011)
Traumatic encephalopathy patients	PP2A activity	Not evaluated	Decreased PP2A activity and associated genes in patients	(Seo et al., 2017)
Military personnel with TBI	Total Tau	Not evaluated	Increased total tau in blood that related to increased post concussive neurological symptoms	(Olivera et al., 2015)
TBI patients	Cis-Tau	Not evaluated	Cis-Phospho-Tau increased in cortical axons and CSF and correlated with axonal injury and clinical outcomes	(Albayram et al., 2017)
rTBI in mice		Specific neutralizing antibody against cis phosho-Tau	Attenuates neuropathology and brain dysfunction.	
Lateral fluid percussion injury model in Long-Evans rat	PR55 and PP2A levels regulating Hyper-phosphorylated-Tau	Tau phosphatase activator-sodium selenate	TBI reduced PR55 and PP2A activity and increased phosphor-Tau expression that was reversed by sodium selenate. Reduced brain damage and improved behavioural outcomes.	(Shultz et al., 2015)
Lateral fluid percussion injury model in Long-Evans rat	Hyper-phosphorylated-Tau	Tau phosphatase activator-sodium selenate	Reduced epileptic seizure frequency and duration in treated rats with effects observable even following washout period	(Liu et al., 2016)
Parasagittal FPI model in rats	Hyper-phosphorylated-Tau	Not evaluated	Increased oligomeric and Phospho-Tau	(Hawkins et al., 2013)
Mechanical compression in rats	Hyper-phosphorylated-Tau and microtubule associated protein-2	Not evaluated	Increased phosphorylation of Tau and MAP2 with decrease PP2A activity within minutes	(Chen et al., 2010)
Mild rTBI in mice	Total Tau	Complete ablation/partial reduction of Tau	Reduced spatial learning and memory deficits along with reduced level of axonopathy	(Cheng et al., 2014)
Surgical excision of human temporal cortex after TBI	APP overexpression	Not evaluated	Increase in APP levels after TBI in patients.	(Ikonomovic et al., 2004) (Roberts et al., 1994)
Post-mortem study with 152 patients that had severe TBI				
Needle stabbing or weight drop in rats	APP overexpression	Not evaluated	Increase in APP levels after TBI in different animal models.	(Lewen et al., 1995)/ (Otsuka et al., 1991) (Murakami et al., 1998) (Yang et al., 2014)
Midline fluid percussion model in rats				

Model	Mechanism/s investigated	Intervention/s	Outcomes	Reference
–Weight fall model of brainstem injury in rats				(Van den Heuvel et al., 1999)
Ovine TBI model				
Severe controlled cortical impact in APP/PS1 mice	APP processing after injury	Not evaluated	Up-regulation in the expression of genes encoding proteins related to Aß clearance.	(Miszczuk et al., 2016)
Controlled cortical impact in young PDAPP mice	APP processing after injury	Not evaluated	Reduction in Aβ deposit after injury while sham animals displayed increasing amyloid burden.	(Nakagawa et al., 1999) (Nakagawa et al., 2000)
Controlled cortical impact in aged PDAPP mice			Reduction in Aß burden in the ipsilateral hippocampus after injury in mice with abundant plaques.	
Mild controlled cortical impact in APP-KO mice	APP role after injury	Not evaluated	APP-KO mice exhibit worst outcomes after injury compared to wild-type controls.	(Corrigan et al., 2012a)
Moderate controlled cortical impact in APP-KO mice	APP role after injury	Intracerebroventricular injection of sAPPα 15 min after injury	sAPPα treatment rescued damage and functional deficits in APP-KO mice.	(Corrigan et al., 2012b)
Controlled cortical impact in mice	APP metabolites	γ-secretase inhibitor	Reduced Aß levels by 25%, reduced neurodegeneration and improved motor and cognitive recovery after TBI.	(Loane et al., 2009)
Controlled cortical impact in APP-KO mice	APP metabolites	Intracerebroventricular injection of APP 96–110 peptide	Improvement of outcomes post-injury similar to the treatment with sAPPα.	(Corrigan et al., 2011)
Diffuse TBI in Sprague-Dawley rats	APP metabolites	Intracerebroventricular injection of APP 96–110 peptide	Reduced axonal injury and improved cognitive outcomes.	(Corrigan et al., 2014)
Feeney's weight drop model and repetitive mild TBI in mice	APP metabolites	SP600125 (JNK inhibitor)	Reduction in APP expression levels and Aß production, inhibition of inflammatory responses and apoptotic neurodegeneration.	(Rehman et al., 2017)
Pediatric TBI model in mice	Interleukin-1β	Kineret (Interleukin-1 receptor antagonist)	IL-1Ra treated mice displayed improved spatial learning behavior, less cortical damage and showed fewer evoked seizures compared to controls	(Semple et al., 2017)
Severe controlled cortical impact in mice	M1/M2 polarization Neuroinflammation	Intracerebral injection of human neural stem cells	No change in lesion size but reduced accumulation of amyloid precursor protein, transition of microglia towards M2 phenotype	(Gao et al., 2016)
Controlled cortical impact in mice				(Xu et al., 2017b)
	M1/M2 polarization Neuroinflammation		Improved M2/M1 ratio with increased anti-inflammatory cytokine expression, reduced total microglia/macrophage expression, reduced peripheral invasion of immune cells, reduced apoptosis and improved behavioural deficits	