Open Access

The role of protein phosphatase 2A tau axis in traumatic brain injury therapy

Maibouge Tanko Mahamane Salissou[1*], Mahaman Yacoubou Abdoul Razak[2,3], Xiaochuan Wang[2] and Rabiu AbduSSALAM Magaji[4]

Abstract

Background: Traumatic brain injury (TBI) is a debilitating disorder due to trauma caused by an external mechanical force eventually leading to disruption in the normal function of the brain, with possible outcomes including permanent or temporary dysfunction of cognitive, physical, and psychosocial abilities. There have been several studies focusing on the search and innovation of neuroprotective agents that could have therapeutic relevance in TBI management. Due to its complexity, TBI is divided into two major components. The first initial event is known as the primary injury; it is a result of the mechanical insult itself and is known to be irreversible and resistant to a vast variety of therapeutics. The secondary event or secondary brain injury is viewed as a cellular injury that does not manifest immediately after the trauma but evolved after a delay period of hours or several days. This category of injury is known to respond favorably to different pharmacological treatment approaches.

Main body: Due to the complexity in the pathophysiology of the secondary injury, the therapeutic strategy needs to be in a multi-facets model and to have the ability to simultaneously regulate different cellular changes. Several studies have investigated in deep the possible approaches relying on natural compounds as an alternative therapeutic strategy for the management of TBI. In addition, many natural compounds have the potential to target numerous different components of the secondary injury including neuroinflammation, apoptosis, PP2A, tau, and Aβ among others. Here, we review past and current strategies in the therapeutic management of TBI, focusing on the PP2A-tau axis both in animal and human subjects. This review uncovers, in addition, a variety of compounds used in TBI therapy.

Conclusion: Despite beneficial therapeutic effects observed in animals for many compounds, studies are still needed to be conducted on human subjects to validate their therapeutic virtues. Furthermore, potential therapeutic virtues observed among studies might likely be dependent on the TBI animal model used and the type of induced injury. In addition, specificity and side effects are challenges in TBI therapy specifically which site of PP2A dysfunction to be targeted.

Keywords: TBI, PP2A, Tau

1 Background

Traumatic brain injury (TBI) is usually observed in the elderly population with its prognosis influenced by an increase in age, cumulating to global burdens including deaths and permanent disabilities. TBI disrupts normal brain homeostatic state and is ranked as a major health problem covering around 10 million people worldwide [1]. When a brain injury is derived from head trauma, it is usually categorized into acute brain injury consisting of mild TBI also referred to as concussion with its associated short-term sequelae and catastrophic brain injury which can be fatal, due to hematoma. The latter known as chronic traumatic encephalopathy (CTE) is usually initiated by repeated head trauma which begins several years after the sports career ends, and it is known to share

*Correspondence: salissoum@africau.edu; smaibouge@yahoo.com
[1] College of Health, Natural and Agriculture Sciences, Africa University, P.O. Box 1320, Mutare, Zimbabwe
Full list of author information is available at the end of the article

Mahamane Salissou *et al. Beni-Suef Univ J Basic Appl Sci*   (2022) 11:41

Page 2 of 12

many characteristics with neurodegenerative disorders [2–7].

The most common causes of TBI are contact sports, vehicle crashes in addition to physical violence and war injuries. Central nervous system injury triggers both molecular as well as cellular cascades that will eventually lead to neurological diseases including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [1], stipulating an urge to continuously search for better management strategies. Several studies implicated TBI as one of the most important risk factors in the etiology and pathogenesis of AD and other neurodegenerative disorders. Accumulating evidence from several studies showed that TBI triggers tau hyperphosphorylation by downregulating PP2A activity whereby in some studies plaques are found diffusely in both axons and extracellular in 30% of human subjects after severe TBI [8–16]. Tau accumulation in axons without tangle-like pathologies in addition are pathological characteristics of these patients. Reports from animal studies implicated TBI in initiating a hippocampus-dependent cognitive decline and synaptic dysfunction which correlates with asparaginyl endopeptidase (AEP) activation. In addition, I_2^{PP2A} (inhibitor 2 of PP2A, also called SET) underwent mis-translocation from nucleus of neurons to cytoplasm, in favor of AEP interaction with SET, and tau hyperphosphorylation in the hippocampus of TBI rats, therefore, indirectly involving PP2A and tau pathology in the pathogenesis of TBI [17, 18]. This opens an avenue for the search of strategies that could modulate the PP2A/tau axis as an alternative means or therapeutics in TBI management.

2 Main text

2.1 Pathophysiology of TBI

Among all types of TBI, repetitive mild brain traumas, typically found in professional athletes engaged in contact sports and military veterans deployed in wars, usually lead to CTE known as a unique pattern of neurodegeneration [10, 11]. Brain injury following TBI takes place in two main steps, eventually leading to alteration of behavioral, physical, and cognitive functions [19]. These two steps include primary damage which is the result of mechanical injury and coincides with perturbation in cerebral blood flow, as well as metabolism [20, 21]. The acidosis occurring in the brain tissue due to injury will ultimately lead to tau hyperphosphorylation by enhancing AEP auto-activation [22]. In addition, focal injuries, which are consequences of direct impact on the brain, cause tissue compression at the site of impact and are often worse in cases of severe TBI [23]. The primary injury secondary to the mechanical trauma itself followed by several additional secondary injury

cascades (SIC), collectively will give rise to additional TBI-associated pathology cumulating in numerous neurological disabilities. Clinically TBI manifestations are directly linked with the intensity of primary injury and the longevity of the secondary cascades. In Secondary Injury Cascades/Mechanisms, TBI correlates with a massive release of amino acids, notably glutamic acid, which is known to have adverse effects on neurons and astrocytes, by causing overstimulation of ionotropic as well as metabotropic glutamate receptors [24, 25]. This condition induced excitotoxic events, catabolic effects, and an acellular attempt for compensation of changes in ionic gradients and metabolic needs that increase free radical production. The high expression level of free radicals which included reactive oxygen species (ROS) and reactive nitrogen species (RNS) leads to oxidative stress [26]. These phenomena altered the brain vasculature and trigger necrotic and apoptotic cell death [27]. In view of these aforementioned events, several approaches having multifaceted pharmacological effects that may provide neuroprotection following TBI including targeting PP2A and tau have been adopted [28]. The normal status of tau phosphorylation is balanced between protein kinases' and phosphatases' activities. Of key interest, the phosphatase activity is largely led by a distinct pool of PP2A enzymes and is known to be implicated in the majority of neuronal tau dephosphorylation [27]. PP2A is known to negatively regulate inflammation, apoptosis as well as protect against neurodegeneration [29]. Due to the critical importance of PP2A in tau regulation, and its known alteration in neurodegenerative disorders including TBI, we will subsequently discuss the relevance of the PP2A/tau axis in therapeutic strategies for TBI (Table 1).

2.2 Tau pathology in TBI

TBI is a well-known risk factor for the development of neurodegeneration and dementia late in life. Repetitive mild TBI (rmTBI) correlated directly with CTE characterized by focal perivascular to widespread Alzheimer-type neurofibrillary pathology of hyperphosphorylated tau. Studies in animal models revealed hyperphosphorylation of tau after TBI. [10, 11]. Hyperphosphorylation of tau is associated with the pathogenesis of several neurodegenerative disorders [30–32] and has been characterized as a component of secondary injury in TBI [3, 28, 33]. In 1970, Corsellis et al. revealed neurofibrillary tangles found in neocortical areas of boxers diagnosed with CTE [34]. Based on these findings, several studies have demonstrated in deep hyperphosphorylation of tau take place in TBI precisely CTE which is a tau pathology having morphological features including accumulation of hyperphosphorylated tau (p-tau) protein as neurofibrillary tangles (NFTs), astrocytic tangles (ATs), and neurites

Table 1 PP2A Tau cascade modulators and their mechanism of action

PP2A and tau modulators	Compounds	Mechanisms	Experimental model
Direct PP2A activator	Sodium selenite	Activate PR55 reduce phosphorylated tau increased protein phosphatase 2A activity and PR55 expression	Rats by fluid percussion injury in rats [78]
Indirect PP2A modulator	AEP inhibitor/AENK	Decreased the AEP interaction with SET and the cytosolic SET retention, reduce tau phosphorylation	Controlled cortical impact TBI rats [17, 18]
Direct PP2A modulator of B-subunit	Ferulic acid	Prevented the injury-induced reduction in PP2A subunit B levels	MCAO-induced animals [59]
PP2A agonist	FTY720	FTY720 induced PP2A activation dephosphorylation and activation of TTP	Early brain injury (EBI) rat model [83]
Modulators of serine/threonine PP PPP3CA PPP3CB		Prevent deregulation of PPP3CA PPP3CB hyperphosphorylation of tau in (CTE)	Cell lines, animal models, and post-mortem brain tissue of patients with CTE [85, 86]
Tau target compounds	AAVrh.10anti-p-Tau	suppress p-Tau accumulation	Murine CTE model induced by TBI [93]
Ac-tau target compounds	Cis-p-tau antibody	Blocks early cistauosis spreading of tau-mediated neurodegeneration	TBI mice with cis-p-tau [95]
Tau target by AAV9-mediated gene delivery	Chimeric protein	(N-terminal RNA recognition domain of TDP-43, RAVER1) decrease Ac Tau	Animal models of TBI and mouse embryonic stem cells [97]
ac-tau target	p300/CBP inhibitors	Blocking GAPDH S-nitrosylation, inhibiting p300/CBP by salsalate or diflunisal,	TBI Human and animal model [67]
PP2A activator	Zinc chelating Agents	Upregulate PP2A chemically or genetically and alleviates zinc-induced tau hyperphosphorylation	Human-tau transgenic mice [106]

striking clusters which appear in the vicinity of small blood vessels of the cortex, where typical clusters are observed in sulcal depths [35, 36]. In addition to those findings, studies using brains of long-term survivors of TBI comprising adult athletes and war veterans revealed deposition of p-tau protein as neurofibrillary tangles [28, 37]. Moreover, p-tau and NFTs pathology have been found in the brains of adolescents one hour after occurrence of TBI [38, 39]. Besides, pre-clinical TBI studies in human subjects revealed TBI as a risk factor for tauopathies through the induction of tau hyperphosphorylation and aggregation [40]. Similarly, studies by repetitive mild TBI in adolescent tauopathy mice indicated an increase in tau in the visual system [41]. Furthermore, both human TBI studies and experimental studies in animals indicated the persistence in microglial activation and tau pathology under repetitive concussive head injury (rCHI). The key links in tau pathology in correlation to TBI regarding vascular abnormalities is well known for its involvement in neurofibrillary tangle formation in AD [42]. Neuropathological data demonstrated that CTE is a tauopathy closely associated with CVD with characteristics including over-accumulation of hyperphosphorylated tau protein as NFTs and pre-tangles in a form of a cluster [9]. In acceleration/deceleration injury study in animals, tau was able to undergo phosphorylation, aggregation then it becomes misfolded, and lastly cleaved to yield neurotoxic tau peptide fragments [36, 43]. Furthermore, an increase

in CSF tau level after TBI could be a result of axonal injury. In TBI settings, trauma-induced CVD in addition leads to the release of tau, its hyperphosphorylation, and early deposition after TBI. In fact, recent studies directly associate the endothelium and vascular factors in tau pathology, given evidence that the endothelial isoform of nitric oxide synthase (eNOS) rescues neurons from tau phosphorylation [44, 45]. In brief, hyperphosphorylation of tau has been demonstrated in a variety of TBI models, including repetitive mild TBI (rmTBI), controlled cortical impact (CCI), and fluid percussion injury [16, 46–48], and is known to play a key role in the etiopathogenesis of CTE. Taking all these aforementioned studies together, it is clear that tau pathology is strongly associated with TBI.

2.2.1 PP2A: the main phosphatase regulating tau in TBI

Studies indicated that both repeated mTBI and single msTBI increased levels of p-tau due to a decrease in the main phosphatase, PP2A, as the levels of PP2Ac were discovered to be significantly lower in TBI [9]. Of note, PP2A is a mammalian heterotrimeric holoenzyme whose 'A' and a catalytic 'C' subunit, interact with one among the abundant family of regulatory 'B' subunits. Among its subfamily, 23 isoforms have been well characterized [49]. PP2A activity is controlled by many mechanisms, including post-translational modifications [38]. The most largely expressed neuronal PP2A holoenzyme comprises the Bα (or PPP2R2A or PR55) regulatory subunit

Mahamane Salissou *et al. Beni-Suef Univ J Basic Appl Sci*   (2022) 11:41

Page 4 of 12

(PP2A/Bα) having the strongest affinity for tau, therefore, indicating the highest tau phosphatase property [39, 50]. It is established that tau undergoes direct site-specific dephosphorylation by PP2A and PP2A accounts for ~71% of total tau phosphatase activity in the human brain, whereby it modulates tau phosphorylation at multiple Ser/Thr phospho-sites in vitro and in vivo [51–53]. Besides PP2A/Bα, other additional PP2A isoforms are well known to control phospho-tau levels through indirect mechanisms, by regulating upstream tau protein kinases [54, 55]. Furthermore, another subunit referred to as B56δ subunit-containing PP2A isoforms indirectly influenced tau phosphorylation through dephosphorylation and subsequent activation of Glycogen Synthase Kinase 3 beta (GSK3β) [56] as evidenced by the fact that knockout of B56δ trigger progressive tau phosphorylation at pathological sites implicated in tauopathies [57]. Moreover, downregulating PP2A/PR55 levels and/or a drop in level of PP2A activity has been demonstrated following experimental brain injury [58, 59] and this event facilitates tau hyperphosphorylation [60].
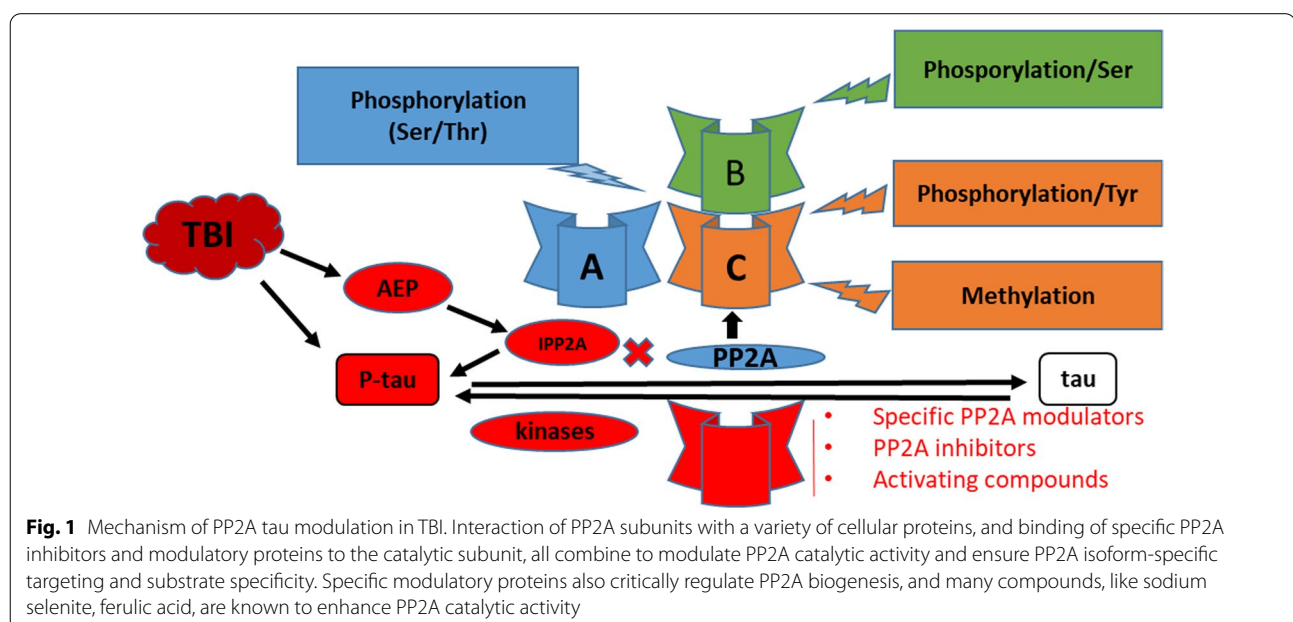
Protein phosphatase 2A is targeted by several endogenous regulators including SET (or I_2^{PP2A}), which is known as a powerful inhibitor that binds to the PP2A C subunit giving rise to blockage of its tau phosphatase properties [61, 62]. The primary location of SET is in the nucleus; however, under acidic conditions, it underwent cytoplasmic translocation. The cytoplasmic sequestration of SET is associated with a reduction in PP2A activity and its methylation and favors tau phosphorylation status at Ser202 [42]. Trans located SET at cytoplasmic

compartment has been detected in susceptible AD neurons, in TBI [63] and Down syndrome [64], and contribute to one among the several mechanisms for the abnormally elevated levels of phosphorylated tau associated with these disorders. Collectively these studies strongly indicated PP2A is implicated in TBI in association with tau pathology.

2.3 Modulating of PP2A-tau cascades in TBI therapy
2.3.1 *Targeting direct and indirectly PP2A-tau in TBI therapy*
The time-course of tau phosphorylation and imbalance in kinases (GSK-3β, CDK5 and Akt) and phosphatase (PP2A) levels under conditions such as single moderate-severe TBI (msTBI) or repeated mild TBI (rmTBI) lead to a decrease in PP2Ac level, stipulating a potential loss of phosphatase activity. Concomitantly in these conditions, there are increased levels of p-tau, up to 3 months post-injury because of the decrease in the main phosphatase, PP2A, with levels of PP2Ac found to be significantly lower [9]. In this perspective, several studies have revealed that targeting PP2A either directly or indirectly could provide a potential beneficial effect by alleviating tau hyperphosphorylation in the case of TBI (Table 1, Fig. 1). In a TBI study using the rat model of fluid percussion injury, traumatic brain injury gave rise to a decline in PR55 expression level and protein phosphatase 2A activity, with a concomitant rise in the expression level of phosphorylated tau as well as the ratio of phosphorylated tau to total tau. Similarities in findings were also documented in post-mortem brain from patients diagnosed with acute human traumatic brain injury [13–15].

Fig. 1 Mechanism of PP2A tau modulation in TBI. Interaction of PP2A subunits with a variety of cellular proteins, and binding of specific PP2A inhibitors and modulatory proteins to the catalytic subunit, all combine to modulate PP2A catalytic activity and ensure PP2A isoform-specific targeting and substrate specificity. Specific modulatory proteins also critically regulate PP2A biogenesis, and many compounds, like sodium selenite, ferulic acid, are known to enhance PP2A catalytic activity

Furthermore in animal studies using rat model of percussion fluid injury treatment with compound, sodium selenate known as a potent PR55 activator, causes a reduction in phosphorylated tau and improves traumatic brain injury outcome. The potential mechanism is by enhancing protein phosphatase 2A activity as well as PR55 expression level that will ultimately result in a decreased proportion of phosphorylated tau to total tau, thus alleviating brain injury, and enhancing behavioral outcomes in rats that underwent a fluid percussion injury [13–15]. Additionally, a study conducted by Yi [17, 18] revealed that indirectly targeting PP2A, by AEP inhibitor/AENK decreased the AEP interaction with SET and the cytosolic SET retention, thereby reducing tau phosphorylation, alleviating synaptic damage, and finally recovering learning and memory potential in TBI rats. In this perspective, compounds' including apolipoprotein E-derived therapeutic peptide have shown a similar beneficial effect in TBI; however, the mechanism remained unclear in the case of tau pathology in association with PP2A [65] regarding compounds including COG133, an ApoE mimetic peptide [66, 67]. Furthermore, among other, strategies of modulating PP2A tau cascades in TBI setting one study revealed that zinc chelation could upregulate PP2A either chemically or genetically and alleviate zinc-induced hyperphosphorylation of tau whereas a mutation of Y307 to phenylalanine prevented zinc-dependent tyrosine phosphorylation as well as inactivation of PP2A. Furthermore, the aforementioned study indicated that Zinc activate Src, while PP2, a specific Src family kinases (SFKs) inhibitor, alleviated zinc-dependent phosphorylation of PP2A. In another parallel study in human-tau transgenic mice, zinc chelator recovered PP2A activity, prevented Src activation, and alleviated phosphorylation of tau. Taken together, these studies indicated that zinc triggers protein phosphatase 2A inactivation and tau hyperphosphorylation mediated via Src-dependent pathway, suggesting that modulation of zinc homeostasis may be a valuable strategy in therapy for AD and the related TBI tauopathies [68].

2.3.2 SET-PP2A target for TBI therapy

The phosphorylation status of tau is maintained within the normal physiological range by activities of protein kinases and protein phosphatases [69] which, after TBI, underwent alteration precisely during the secondary damage initiated by direct mechanical tissue deformation [70]. The SET protein, also referred to as inhibitor 2 of protein phosphatase 2A (I_2^{PP2A}), potently causes inhibition of PP2A activity by interacting with its catalytic subunit PP2Ac and thus is termed as I_2^{PP2A} [71]. Despite its dominant location in the nucleus, I_2^{PP2A}/SET translocates to the cell cytoplasmic compartment after its

cleavage at N175 into N- and C-terminal fragments; both fragments cause inhibition of PP2A and thereby enhance hyperphosphorylation of tau [61, 62]. Acidic conditions in the brain tissue, as in TBI, could give rise to hyperphosphorylation of tau by causing induction of AEP. TBI can cause an increase in the serum level of lactate in the brain tissue [70], which may facilitate the activation of AEP. Thus, AEP plays a key role in the hyperphosphorylation of tau following TBI. Similar effects, such as hyperphosphorylation of tau and activation of AEP through cleavage of I_2^{PP2A} and its translocation from the nucleus to the cytoplasm of neurons, were reported in rmTBI in 3xTg-AD mice. Overload of calcium and the release of excitatory amino acids, two major initiating events in secondary damage after TBI, can initiate ischemia, hypoxia, and increase in lactic acid [70], and thereby acidosis of the brain tissue [72] and lysosomal pathological changes [73]. These are all situations in which AEP can be activated and enhance the cleavage of I_2^{PP2A} [74] that is associated with a significant cytoplasmic translocation of I_2^{PP2A}, where it co-localizes with hyperphosphorylated tau, thus stipulating a potential increase in blockage of PP2A activity which enhances hyperphosphorylation of tau in the cytoplasm of neurons [75]. In brief, studies from different human TBI patients as well as TBI animal models demonstrated the role of the AEP-I_2^{PP2A}-PP2A pathway in hyperphosphorylation of tau in acidic conditions such as in TBI [10, 11], and targeting this pathway could be very valuable in managing TBI and related disorders.

2.3.3 PP2A modulators

Tau hyperphosphorylation is well characterized as a key event of secondary injury in TBI conditions [76]. Of particular interest to the dephosphorylation of tau, PP2A heterotrimers made up of the PR55 regulatory B-subunit (PP2A/PR55) account as the most abundant tau phosphatase in the brain [54]. The downregulation of PP2A/PR55 serum level and/or a decrease in PP2A activity was documented after experimental brain insults. Mechanical compression gives rise to decreased PP2A activity in cortical neurons in vivo, while inhibition of PP2A induces the phosphorylation of Microtubules Associated Protein2 (MAP2). Therefore, PP2A appears to be one of the most important enzymes regulating the phosphorylation of MAP2 and tau following brain compression. The transient activation of kinases observed following compression may thus assist the phosphorylation of MAP2, as they have in common a similar time course. The ferulic acid compound may play a role in the modulation of PP2A subunit B expression level in ischemic brain injury conditions and neuronal cells injury induced by glutamate [58, 59]. It was shown that ferulic acid

drastically causes a reduction of infarct volume in the cerebral cortex of the middle cerebral artery occlusion (MCAO) animals. Moreover, investigations using proteomics approaches clearly revealed a reduction in PP2A subunit B in MCAO animals while treatment with ferulic acid prevented the injury-induced decrease in PP2A subunit B levels. Furthermore, this study uncovered a reduction in the number of PP2A subunit B-positive cells in this setting, while ferulic acid was able to rescue the fall in PP2A level [59, 60]. Taken together, these studies showed that pharmacologically using a compound that increases PP2A/PR55 may alleviate hyperphosphorylation of tau and could be of beneficial therapeutic virtue to TBI outcome.

2.3.4 PP2A specific activators

The PR55 is known as a core B-subunit of main tau phosphatase PP2A. Several PR55 activators have been investigated and are known to reduce phosphorylated tau and improve traumatic brain injury and other neurodegenerative disorders in animal studies [13–15, 58]. In a study using fluid percussion injury (FPI) model, FPI downregulated PP2A/PR55 protein expression as well as PP2A activity leading to tau hyperphosphorylation. Similar effects were also observed in post-mortem brains from human TBI patients [58, 77]. Accordingly, sodium selenite compound, a specific activator of PP2A that has provided some beneficial effect in neurodegenerative disorders, significantly raise the PP2A/PR55 level, decreased hyperphosphorylated tau and recovered brain damage and behavioral impairments in post-FPI. Therefore, making sodium selenate is an alternative therapeutic compound in the management of TBI [13–15, 77]. Besides, studies using FPI similar therapeutic virtue of sodium selenate were also reported in mild traumatic brain injuries by up-regulating PP2A/PR55 and dephosphorylating tau. Another parallel study using repeated mild traumatic brain injuries which were also associated with phosphorylation of tau and downregulation of PP2A/PR55, and brain atrophy sodium selenate treatment was able to increased PP2A/PR55, and decreased tau phosphorylation, prevented brain damage, and cognitive dysfunction in rats. Collectively, these studies implicated PP2A/PR55 and tau as key mechanistic proteins in the pathophysiological process of TBI and certified the uses of Specific PP2A Activators such as sodium selenate as a novel and translatable treatment for these common injuries [13–15, 78].

2.3.5 PP2A agonists

Previous studies indicate that PP2A could cause activation of protein tristetraprolin (TTP) through dephosphorylation at both S52 and S178, leading to destabilization of target mRNAs [79]. In this perspective pharmacological treatment using both PP2A and its agonist, FTY720, has shown neuroprotective potential against neuronal apoptosis in traumatic brain injury, acute ischemia, and neurodegenerative disorders [80, 81]. Early brain injury (EBI) as a consequence of subarachnoid hemorrhage (SAH) can give rise to inflammatory cascades and neuronal abnormalities. The potential mechanism of how PP2A acts upstream of TTP signaling both in vitro and in vivo [82] is by the mRNA-destabilizing TTP which might play a role as an anti-inflammatory factor that triggers the decay of cytokine transcripts leading to a variety of neurological disorders including glioma [83]. A recent study demonstrated the effects of TTP regulation via dephosphorylation, in a rat model of SAH, by PP2A. In this setting, the PP2A agonist FTY720, short interfering (si)RNAs that target TTP and PP2A were injected into rats by intra-cerebroventricular route 24 h before SAH [83], an effect that led to increased endogenous PP2A and TTP levels following SAH. In addition this study suggested that the PP2A agonist FTY720 induced PP2A activation leading to dephosphorylation and activation of TTP and decreased production of tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8. Furthermore, siRNA-mediated TTP knockdown recovered the anti-inflammatory potential of FTY720 treatment, stipulating that PP2A correlated with TTP activation in vivo. Collectively, those studies clearly revealed that PP2A activation by PP2A agonists could facilitate the anti-inflammatory as well as the anti-apoptotic potential of TTP and therefore uncover an effective therapeutic approach against EBI following SAH.

2.3.6 Targeting PP2A in CTE therapy

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disorder that is associated with repetitive head injuries wherein diseased neurons, tau aggregates in different patterns as a diagnostic neuropathological key morphological event of the disease. Studies suggested that early initiation of neuroprotective therapy by inhibiting the acute, subacute, and early chronic secondary injury phases will decrease the occurrence of the tauopathy that is the key neuropathology seen in CTE [84]. The single neuroprotective approach as therapeutic alternative is known to rescue the progressive brain damage in CTE however it shown some limitations. Since a variety of cellular dysfunctions can give rise to tau dysfunction, which can, in turn, lead to many cellular abnormalities, a multi-mechanistic neuroprotective combinational approach to CTE prevention and interruption will likely be needed. In that perspective, a study by sequencing total RNA and analysis of post-mortem brain tissue collected from diagnosed patients

with CTE led to the discovery of transcriptome signature changes associated with CTE [85, 86]. This study leads to the characterization of genes associated with the MAP kinase and calcium-signaling pathways which were found to be drastically downregulated in the CTE setting. The perturbation in the expression of PP2A and the related tauopathy associated with CTE in this setting involved common pathological mechanisms closer to that of Alzheimer's disease. These studies, both *in vivo* and *in vitro* furthermore indicated a drastic reduction in PPP3CA/PP2B phosphatase activity which is directly linked with increases in phosphorylated tau proteins. Taken together, these findings revealed PP2A-dependent neurodegeneration and could serve as novel therapeutic strategies to alleviate the tauopathy initiated by CTE. Dysregulation of PPP3CA correlated with hyperphosphorylation of tau in CTE, as evidenced by a study showing a reduction in PPP3CA and PPP3CB mRNA levels in CTE. The perturbation in PP2A expression might likely play a role in contributing to tauopathy in CTE, which implies that regulating serine/threonine PP2A level of expression and activity could serve as an alternative therapeutic strategy for the prevention of tauopathy in CTE and other neurodegenerative disorders [85, 86].

2.3.7 Indirect modulator of PP2A: role of AEP inhibitors
AEP is the key cysteine proteinase implicated in the cleavage of I_2^{PP2A} and is contributing to tau hyperphosphorylation in the AD brain [87]. Activation of AEP due to primary/secondary brain damage is known as a mechanism by which TBI leads to tau hyperphosphorylation that would eventually contribute to CTE pathology [10, 11]. TBI triggers hippocampal-dependent cognitive impairments and synaptic dysfunction associated with AEP activation leading to miss-translocation of I_2^{PP2A}, the inhibitor 2 of PP2A, from the neuronal nucleus to the cytoplasm, causing an increase in AEP interaction with SET, and tau hyperphosphorylation in the hippocampus of rats [17, 18]. This phenomenon can serve in the drug discovery of compounds that can causes blockage of I_2^{PP2A} cytoplasmic translocation as an alternative therapeutic strategy in TBI. In this perceptive, a compound known as AENK also known as an inhibitor of SET has shown some beneficial neuroprotective effects against TBI, wherein a study conducted by Yi [17, 18], AENK treatment was able to cause restoration of SET back to its original location in the nucleus, from the cytoplasm, and thus rescued tau pathologies, recovering TBI-induced cognitive impairment in rats. These findings have further highlighted a novel etiopathogenic mechanism of TBI-related AD, which is triggered by activation of AEP, accumulation of SET in the cytoplasm, enhanced tau pathology, and cognitive impairments. This stipulates that decreasing AEP activity by AEP inhibitor could provide beneficial effects to AD patients having TBI. Furthermore, in that study, hippocampal PP2A activity was found to be decreased in parallel with the increased cytoplasmic SET in TBI rats. Collectively, results from these studies suggest that TBI induces AEP activation, and the activated AEP (aAEP) then trapped SET in the cytoplasm, which in turn by inhibiting PP2A may legitimate the rise in tau hyperphosphorylation. Interestingly, the pathway through which TBI leads to tau pathology is dependent on I_2^{PP2A} cytoplasmic retention and the activation of AEP [88]. Additionally, evidence from another study, where oxygen–glucose deprivation (OGD) was induced in rat primary hippocampal neurons to mimic brain acidification environment like in TBI, revealed that OGD causes AEP activation, then SET translocate from neuronal nucleus to cytoplasmic compartment leading to PP2A inhibition, hyperphosphorylation of tau and a decrease in synaptic proteins in neurons [17, 18]. Furthermore prevention of AEP activation with AEP inhibitor drastically decreased OGD-induced cytoplasmic SET retention, subsequently reducing tau hyperphosphorylation and recovered synaptic function in primary neurons [17, 18].

2.3.8 Tau a direct target in TBI therapy
Several lines of evidence revealed that traumatic brain injury contributes to the development of tauopathy-related dementia [89–91]. Previous studies revealed that there is a rapid formation of oligomeric and phosphorylated tau proteins after TBI in animal studies. Based on these observations, strategies have been implemented using antibodies to detect oligomeric and phosphorylated tau proteins in a non-transgenic rodent model of parasagittal fluid percussion injury, and these revealed oligomeric and phosphorylated tau proteins up to 2 weeks post-TBI. Furthermore, these findings revealed that diagnostic tools and therapeutic approaches that focus only on toxic forms of tau may yield earlier detection with safety and effectiveness for tauopathies caused by repetitive neurotrauma. In addition, it was indicated that TBI triggers the formation of tau oligomers, which may represent a potential link between TBI and sporadic tauopathies and could be of significant importance, whereby targeting tau oligomers may be useful for the prevention of dementia following TBI [92]. In another study conducted by Sacremento et al., direct injection in the CNS of adeno-associated virus (AAV) vector encoding an anti-p-tau antibody generates sufficient levels of anti-p-tau in the CNS and prevent p-tau to accumulate, thus rescuing the pathogenic event in a murine CTE model in which p-tau accumulation was induced by repeated TBI with

the closed cortical impact method. Using safety doses applicable to human subjects, the study revealed that CNS administration of AAVrh.10 anti-p-tau possesses therapeutic virtue and thus a novel strategy to prevent the CTE consequences of TBI [93]. Recent studies used acetylated tau (ac-tau) as a therapeutic target, whereby TBI triggers acetylation of tau at sites acetylated in the human AD brain which is orchestrated by S-nitrosylated-GAPDH, simultaneously leading to inactivation of Sirtuin1 deacetylase and activation of p300/CBP acetyltransferase, giving rise to an increase in the level of neuronal ac-tau [67, 94]. Furthermore, in this setting, subsequent tau mis-localization initiated the neurodegenerative process. Therefore, therapeutic strategies either by blockage of GAPDH S-nitrosylation, inhibiting p300/CBP, or stimulation of Sirtuin1, all protected mice against the neurodegenerative process, neurobehavioral abnormalities, blood and brain accumulation of ac-tau following TBI [67]. Overproduction of ac-tau in the human AD brain is further increased in AD patients with a documented history of TBI, and patients who had received the p300/CBP inhibitors, salsalate, or diflunisal, displayed decreased incidence of AD and clinically diagnosed TBI [67]. Also, following TBI in mice, neurons prominently produce cis-p-tau, which causes and spreads cis-p-tau pathologic changes. This ultimately gives rise to widespread tau-dependent neurodegeneration and brain atrophy, while supplementation of TBI mice with a cis-p-tau antibody not only causes blockage of early cistauosis but also rescued the progression and spreading of tau-mediated neurodegeneration and brain atrophy, and restored to normal brain histopathologic features and improved functional outcomes in alleviating TBI [95].

2.3.8.1 Targeting tau by TDP-43 in TBI   A conducted transcriptome analysis of CTE brains revealed a reduced expression of *PPP3CA*, a subunit of calcineurin that dephosphorylates tau [85, 86]. Furthermore, cleavage of TDP-43 by activated calpain and caspase-3 in TBI setting could cause a decreased TDP-43 level [96]. Collectively, those events are risk determinants in CTE and are insufficient to cause tau tangle formation but might facilitate the pathological conversion of the wild-type tau that will eventually lead to neuronal loss and cognitive dysfunction. Notably, pathological TDP-43 inclusions are also characterized in most CTE brains, indicating a convergent mechanism of neurodegeneration. As a therapeutic approach, an AAV9-mediated gene delivery was employed in animal models and clinical trials to deliver a chimeric protein comprised of the N-terminal RNA recognition domain of TDP-43 fused to an unrelated splicing repressor (RAVER1). This approach was approved through

mouse embryonic stem cells [97]. In brief, this strategy is of key-value in preventing the pathological conversion of tau and would greatly slow disease progression by delaying the occurrence of tau pathology.

2.4 Remarks and future directions
From a perspective point of view, there are obstacles with specificity and 'off-target' effects of some of PP2A regulatory compounds in TBI and other neurodegenerative diseases. Typically, pharmacological targeting of SET to 'disinhibit' PP2A catalytic subunit could also pose significant side effects. For example, a study revealed that FTY720, a PP2A modulator, was found to dramatically increase the risk for malignancies in recipients [98]. Apolipoprotein E-mimetic peptides, in addition to their PP2A modulation, also downregulate p38 activity [99]. Still, a challenging condition is the toxicity of long-term use of PP2A/tau-targeting compounds which require prior evaluation since phosphorylated tau, like PP2A, is also found in other cell types, which causes huge challenges for systemic PP2A/tau-directed strategies [100]. Further challenges in CTE therapy are animal models utilized to further characterize CTE and repetitive TBI. Many have failed to recapitulate the tau pathology seen in CTE or required the use of transgenic mice already predisposed to develop tau pathology [101]. Therefore, there is still much to be elucidated regarding the progression of CTE following brain injury. Despite the fact that some apolipoprotein E-derived therapeutic peptides like COG133 have shown beneficial effects in TBI, still, their mechanism of action remained to be elucidated in detail [65]. Another molecule is memantine, a drug that has provided beneficial effects in AD by targeting I_2^{PP2A} [63]. Despite the fact that treatment with memantine after rmTBI mitigates the accumulation of phosphorylated tau, its potential mechanism of action needs to be assessed in deep [102, 103] Another drug, metformin, acts by interfering with PP2A degradation and has provided beneficial effects in AD [104]. However, even though metformin also provided a neuroprotective effect in TBI [105], its role in modulating the PP2A-tau cascade remains to be elucidated in the TBI setting. Furthermore, a PP2A agonist TTP has shown therapeutic virtue in EBI [83], and many studies have proposed mechanisms to explain the anti-inflammatory effects of PP2A/TTP, including p38 MAPK phosphorylation [83]. It, therefore, cannot be excluded in EBI setting the possibility that this pathway plays a role in the neuroprotective effects of PP2A and TTP.

Challenges in PP2A tau cascade based therapeutic strategies are due to the follwing reasons: Most studies having promising beneficial theupeutic effect are based on animals studies. To draw a final conclusion on their

therapeutic effect further studies need also to be conduct or translated in human subjects. Addtional arising matters in PP2A tau based therapy are mainly due to the complex pathophysiolgical process of TBI. Therefore to identifie the stage during the course of the disease to iniate the theapy will still causes challenges. Still challenges are to identify strategies that could target the multiple facets of the disease process. Furthermore, some animal models of TBI are challenging since they could not reproduce the same pathological processes as it occurs in human subjects. Therefore, they could not efficiently predict the pictorial events occurring in humans.

3 Conclusions

The present review demonstrated that the PP2A-tau cascade could play a key role and can be exploited pharmacologically in the management of TBI. However, for "PP2A activators" and drugs targeting tau to be validated as therapeutics for tauopathies including TBI, there are still many barriers to be overcome in developing valid PP2A-based therapies or direct tau target-based therapy. Despite their beneficial therapeutic virtue, for many compounds, their mechanisms of action still need to be assessed in deep in TBI therapy. The bellow matters raised a question as to which of the primary mechanism of PP2A dysfunction must be prioritized for targeting. It is unclear how pharmacological "PP2A (re)activation" will recover the collective function of specific PP2A holoenzymes and PP2A modulators that become downregulated at the protein level in TBI. Specificity and side effects are obstacles because of the broad spectrum of PP2A enzymes, their large abundance, and their key roles in many physiological processes. Finally, remarks that PP2A-tau targeting compounds can enhance TBI-like pathology originate from investigations in animal models that do not reproduce the complexity of the pathology encountered in humans, as evidenced by the fact that the use of animal models to further characterize CTE and repetitive TBI leads to failures whereby many of those models have failed to recapitulate the tau pathology seen in CTE.

Abbreviations

TBI: Traumatic brain injury; Aβ: Amyloid beta; PP2A: Protein phosphatase A 2; CTE: Chronic traumatic encephalopathy; AD: Alzheimer's disease; PD: Parkinson's disease; ALS: Amyotrophic lateral sclerosis; AEP: Asparaginyl endopeptidase; SET: I_2^{PP2A} inhibitor 2 of PP2A; SIC: Secondary injury cascades; ROS: Reactive OXYGEN SPECIES; NFTs: Neurofibrillary tangles; ATs: Astrocytic tangles; rCHI: Repetitive concussive head injury; GSK3β: Glycogen synthase kinase beta; CDK5: Cyclin-dependent kinase five; msTBI: Moderate-severe TBI; rmTBI: Repeated mild TBI; MAP2: Microtubules associated protein2; MCAO: Middle cerebral artery occlusion; FPI: Fluid percussion injury; TTP: Protein tristetraprolin; SAH: Subarachnoid hemorrhage; OGD: Oxygen–glucose deprivation; AAV: Adeno-associated virus.

Declarations

Ethical approval and consent to participate
Not applicable.

Consent to publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]College of Health, Natural and Agriculture Sciences, Africa University, P.O. Box 1320, Mutare, Zimbabwe. [2]Department of Pathophysiology, School of Basic Medicine, Key Laboratory of Education Ministry of China for Neurological Disorders, Tongji Medical College, Huazhong University of Science and Technology, Hang Kong 13 Road, P.O. Box 430030, Wuhan, Hubei, China. [3]Cognitive Impairment Ward of Neurology Department, The Third Affiliated Hospital, Shenzhen University, Shenzhen, China. [4]Department of Human Physiology, Faculty of Medicine Ahmadu, Bello University, P.O. Box 2555, Samaru, Zaria, Kaduna, Nigeria.

References
1. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC (2007) The impact of traumatic brain injuries: a global perspective. NeuroRehabilitation 22(5):341–353
2. Bieniek KF, Ross OA, Cormier KA, Walton RL, Soto-Ortolaza A, Johnston AE, DeSaro P, Boylan KB, Graff-Radford NR, Wszolek ZK, Rademakers R, Boeve BF, McKee AC, Dickson DW (2015) Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank. Acta Neuropathol 130(6):877–889
3. Blennow K, Hardy J, Zetterberg H (2012) The neuropathology and neurobiology of traumatic brain injury. Neuron 76(5):886–899
4. Cho H, Hyeon SJ, Shin J-Y, Alvarez VE, Stein TD, Lee J, Kowall NW, McKee AC, Ryu H, Seo J-S (2020) Alterations of transcriptome signatures in head trauma-related neurodegenerative disorders. Sci Rep 10(1):8811
5. Cruz-Haces M, Tang J, Acosta G, Fernandez J, Shi R (2017) Pathological correlations between traumatic brain injury and chronic neurodegenerative diseases. Transl Neurodegener 6(1):20
6. Montenigro PH, Corp DT, Stein TD, Cantu RC, Stern RA (2015) Chronic traumatic encephalopathy: historical origins and current perspective. Annu Rev Clin Psychol 11:309–330
7. Woerman AL, Aoyagi A, Patel S, Kazmi SA, Lobach I, Grinberg LT, McKee AC, Seeley WW, Olson SH, Prusiner SB (2016) Tau prions from Alzheimer's disease and chronic traumatic encephalopathy patients propagate in cultured cells. Proc Natl Acad Sci 113(50):E8187–E8196
8. Chen XH, Johnson VE, Uryu K, Trojanowski JQ, Smith DH (2009) A lack of amyloid β plaques despite persistent accumulation of amyloid β

in axons of long-term survivors of traumatic brain injury. Brain Pathol 19(2):214–223

9. Collins-Praino L, Gutschmidt D, Sharkey J, Arulsamy A, Corrigan F (2018) Temporal changes in tau phosphorylation and related kinase and phosphatases following two models of traumatic brain injury.

10. Hu W, Tung YC, Zhang Y, Liu F, Iqbal K (2018) Involvement of activation of asparaginyl endopeptidase in tau hyperphosphorylation in repetitive mild traumatic brain injury. J Alzheimers Dis 64(3):709–722

11. Hu W, Tung YC, Zhang Y, Liu F, Iqbal K (2018) Involvement of activation of asparaginyl endopeptidase in tau hyperphosphorylation in repetitive mild traumatic brain injury. J Alzheimers Dis 64:709–722

12. Johnson VE, Stewart W, Smith DH (2010) Traumatic brain injury and amyloid-β pathology: a link to Alzheimer's disease? Nat Rev Neurosci 11(5):361–370

13. Shultz SR, Wright DK, Zheng P, Stuchbery R, Liu S-J, Sashindranath M, Medcalf RL, Johnston LA, Hovens CM, Jones NC (2015) Sodium selenate reduces hyperphosphorylated tau and improves outcomes after traumatic brain injury. Brain 138(5):1297–1313

14. Shultz SR, Wright DK, Zheng P, Stuchbery R, Liu S-J, Sashindranath M, Medcalf RL, Johnston LA, Hovens CM, Jones NC, O'Brien TJ (2015) Sodium selenate reduces hyperphosphorylated tau and improves outcomes after traumatic brain injury. Brain J Neurol 138(Pt 5):1297–1313

15. Shultz SR, Wright DK, Zheng P, Stuchbery R, Liu S-J, Sashindranath M, Medcalf RL, Johnston LA, Hovens CM, Jones NC, O'Brien TJ (2015) Sodium selenate reduces hyperphosphorylated tau and improves outcomes after traumatic brain injury. Brain 138(5):1297–1313

16. Tran HT, LaFerla FM, Holtzman DM, Brody DL (2011) Controlled cortical impact traumatic brain injury in 3xTg-AD mice causes acute intra-axonal amyloid-β accumulation and independently accelerates the development of tau abnormalities. J Neurosci 31(26):9513–9525

17. Liu Y, Guo C, Ding Y, Long X, Li W, Ke D, Wang Q, Liu R, Wang J-Z, Zhang H (2020) Blockage of AEP attenuates TBI-induced tau hyperphosphorylation and cognitive impairments in rats. Aging 12(19):19421

18. Liu Y, Guo C, Ding Y, Long X, Li W, Ke D, Wang Q, Liu R, Wang J-Z, Zhang H, Wang X (2020) Blockage of AEP attenuates TBI-induced tau hyperphosphorylation and cognitive impairments in rats. Aging 12(19):19421–19439

19. Hellewell SC, Yan EB, Agyapomaa DA, Bye N, Morganti-Kossmann MC (2010) Post-traumatic hypoxia exacerbates brain tissue damage: analysis of axonal injury and glial responses. J Neurotrauma 27(11):1997–2010

20. Stiefel MF, Spiotta A, Gracias VH, Garuffe AM, Guillamondegui O, Maloney-Wilensky E, Bloom S, Grady MS, LeRoux PD (2005) Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. J Neurosurg 103(5):805–811

21. Werner C, Engelhard K (2007) Pathophysiology of traumatic brain injury. Br J Anaesth 99(1):4–9

22. Basurto-Islas G, Gu J-H, Tung YC, Liu F, Iqbal K (2018) Mechanism of tau hyperphosphorylation involving lysosomal enzyme asparagine endopeptidase in a mouse model of brain ischemia. J Alzheimers Dis 63(2):821–833

23. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J-D, Coopersmith CM (2016) The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315(8):801–810

24. Floyd CL, Gorin FA, Lyeth BG (2005) Mechanical strain injury increases intracellular sodium and reverses Na+/Ca2+ exchange in cortical astrocytes. Glia 51(1):35–46

25. Yi J-H, Hazell AS (2006) Excitotoxic mechanisms and the role of astrocytic glutamate transporters in traumatic brain injury. Neurochem Int 48(5):394–403

26. Metodiewa D, Kośka C (1999) Reactive oxygen species and reactive nitrogen species: relevance to cyto (neuro) toxic events and neurologic disorders. An overview. Neurotox Res 1(3):197–233

27. Sontag E, Nunbhakdi-Craig V, Lee G, Bloom GS, Mumby MC (1996) Regulation of the phosphorylation state and microtubule-binding activity of Tau by protein phosphatase 2A. Neuron 17(6):1201–1207

28. Johnson VE, Stewart W, Smith DH (2012) Widespread tau and amyloid-beta pathology many years after a single traumatic brain injury in humans. Brain Pathol 22(2):142–149

29. Nematullah M, Hoda M, Khan F (2018) Protein phosphatase 2A: a double-faced phosphatase of cellular system and its role in neurodegenerative disorders. Mol Neurobiol 55(2):1750–1761

30. Ballatore C, Lee VM-Y, Trojanowski JQ (2007) Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. Nat Rev Neurosci 8(9):663–672

31. Grundke-Iqbal I, Iqbal K, Tung Y-C, Quinlan M, Wisniewski HM, Binder LI (1986) Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci 83(13):4913–4917

32. Morris M, Maeda S, Vossel K, Mucke L (2011) The many faces of tau. Neuron 70(3):410–426

33. Thom M, Liu JY, Thompson P, Phadke R, Narkiewicz M, Martinian L, Marsdon D, Koepp M, Caboclo L, Catarino CB (2011) Neurofibrillary tangle pathology and Braak staging in chronic epilepsy in relation to traumatic brain injury and hippocampal sclerosis: a post-mortem study. Brain 134(10):2969–2981

34. Bruton C, Freeman-Browne D (1973) The aftermath of boxing. Psychol Med 3:270–303

35. Baugh CM, Stamm JM, Riley DO, Gavett BE, Shenton ME, Lin A, Nowinski CJ, Cantu RC, McKee AC, Stern RA (2012) Chronic traumatic encephalopathy: neurodegeneration following repetitive concussive and subconcussive brain trauma. Brain Imaging Behav 6(2):244–254

36. McKee AC, Stein TD, Kiernan PT, Alvarez VE (2015) The neuropathology of chronic traumatic encephalopathy. Brain Pathol 25(3):350–364

37. Johnson VE, Stewart W, Trojanowski JQ, Smith DH (2011) Acute and chronically increased immunoreactivity to phosphorylation-independent but not pathological TDP-43 after a single traumatic brain injury in humans. Acta Neuropathol 122(6):715–726

38. Sents W, Ivanova E, Lambrecht C, Haesen D, Janssens V (2013) The biogenesis of active protein phosphatase 2A holoenzymes: a tightly regulated process creating phosphatase specificity. FEBS J 280(2):644–661

39. Xu Y, Chen Y, Zhang P, Jeffrey PD, Shi Y (2008) Structure of a protein phosphatase 2A holoenzyme: insights into B55-mediated Tau dephosphorylation. Mol Cell 31(6):873–885

40. Edwards G III, Zhao J, Dash PK, Soto C, Moreno-Gonzalez I (2020) Traumatic brain injury induces tau aggregation and spreading. J Neurotrauma 37(1):80–92

41. Xu L, Ryu J, Nguyen JV, Arena J, Rha E, Vranis P, Hitt D, Marsh-Armstrong N, Koliatsos VE (2015) Evidence for accelerated tauopathy in the retina of transgenic P301S tau mice exposed to repetitive mild traumatic brain injury. Exp Neurol 273:168–176

42. Chasseigneaux S, Clamagirand C, Huguet L, Gorisse-Hussonnois L, Rose C, Allinquant B (2014) Cytoplasmic SET induces tau hyperphosphorylation through a decrease of methylated phosphatase 2A. BMC Neurosci 15(1):1–14

43. Huber BR, Meabon JS, Martin TJ, Mourad PD, Bennett R, Kraemer BC, Cernak I, Petrie EC, Emery MJ, Swenson ER (2013) Blast exposure causes early and persistent aberrant phospho-and cleaved-tau expression in a murine model of mild blast-induced traumatic brain injury. J Alzheimers Dis 37(2):309–323

44. Austin SA, Katusic ZS (2016) Loss of endothelial nitric oxide synthase promotes p25 generation and tau phosphorylation in a murine model of Alzheimer's disease. Circ Res 119(10):1128–1134

45. Ramos-Cejudo J, Wisniewski T, Marmar C, Zetterberg H, Blennow K, de Leon MJ, Fossati S (2018) Traumatic brain injury and Alzheimer's disease: the cerebrovascular link. EBioMedicine 28:21–30

46. Cheng JS, Craft R, Yu G-Q, Ho K, Wang X, Mohan G, Mangnitsky S, Ponnusamy R, Mucke L (2014) Tau reduction diminishes spatial learning and memory deficits after mild repetitive traumatic brain injury in mice. PLoS ONE 9(12):e115765

47. Kane MJ, Angoa-Pérez M, Briggs DI, Viano DC, Kreipke CW, Kuhn DM (2012) A mouse model of human repetitive mild traumatic brain injury. J Neurosci Methods 203(1):41–49

48. Mouzon BC, Bachmeier C, Ferro A, Ojo JO, Crynen G, Acker CM, Davies P, Mullan M, Stewart W, Crawford F (2014) Chronic neuropathological and neurobehavioral changes in a repetitive mild traumatic brain injury model. Ann Neurol 75(2):241–254

49. Hoffman A, Taleski G, Sontag E (2017) The protein serine/threonine phosphatases PP2A, PP1 and calcineurin: a triple threat in the regulation of the neuronal cytoskeleton. Mol Cell Neurosci 84:119–131

50. Sontag E, Nunbhakdi-Craig V, Lee G, Brandt R, Kamibayashi C, Kuret J, White CL, Mumby MC, Bloom GS (1999) Molecular interactions among protein phosphatase 2A, tau, and microtubules: implications for the regulation of tau phosphorylation and the development of tauopathies. J Biol Chem 274(36):25490–25498

51. Goedert M, Cohen ES, Jakes R, Cohen P (1992) p42 MAP kinase phosphorylation sites in microtubule-associated protein tau are dephosphorylated by protein phosphatase 2A1. Implications for Alzheimer's disease [corrected]. FEBS Lett 312(1):95–99

52. Liu F, Grundke-Iqbal I, Iqbal K, Gong CX (2005) Contributions of protein phosphatases PP1, PP2A, PP2B and PP5 to the regulation of tau phosphorylation. Eur J Neurosci 22(8):1942–1950

53. Qian W, Shi J, Yin X, Iqbal K, Grundke-Iqbal I, Gong CX, Liu F (2010) PP2A regulates tau phosphorylation directly and also indirectly via activating GSK-3beta. J Alzheimers Dis 19(4):1221–1229

54. Shi Y (2009) Serine/threonine phosphatases: mechanism through structure. Cell 139(3):468–484

55. Sontag E, Fedorov S, Kamibayashi C, Robbins D, Cobb M, Mumby M (1993) The interaction of SV40 small tumor antigen with protein phosphatase 2A stimulates the map kinase pathway and induces cell proliferation. Cell 75(5):887–897

56. Yu UY, Yoo BC, Ahn J-H (2014) Regulatory B subunits of protein phosphatase 2A are involved in site-specific regulation of tau protein phosphorylation. Korean J Physiol Pharmacol 18(2):155–161

57. Louis JV, Martens E, Borghgraef P, Lambrecht C, Sents W, Longin S, Zwaenepoel K, Pijnenborg R, Landrieu I, Lippens G (2011) Mice lacking phosphatase PP2A subunit PR61/B'δ (Ppp2r5d) develop spatially restricted tauopathy by deregulation of CDK5 and GSK3β. Proc Natl Acad Sci 108(17):6957–6962

58. Chen L-J, Wang Y-J, Tseng G-F (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(9):1657–1669

59. Koh P-O (2013) Ferulic acid attenuates the injury-induced decrease of protein phosphatase 2A subunit B in ischemic brain injury. PLoS ONE 8(1):e54217

60. Bolognin S, Blanchard J, Wang X, Basurto-Islas G, Tung YC, Kohlbrenner E, Grundke-Iqbal I, Iqbal K (2012) An experimental rat model of sporadic Alzheimer's disease and rescue of cognitive impairment with a neurotrophic peptide. Acta Neuropathol 123(1):133–151

61. Arnaud L, Chen S, Liu F, Li B, Khatoon S, Grundke-Iqbal I, Iqbal K (2011) Mechanism of inhibition of PP2A activity and abnormal hyperphosphorylation of tau by I2PP2A/SET. FEBS Lett 585(17):2653–2659

62. Arnaud L, Chen S, Liu F, Li B, Khatoon S, Grundke-Iqbal I, Iqbal K (2011) Mechanism of inhibition of PP2A activity and abnormal hyperphosphorylation of tau by I2PP2A/SET. FEBS Lett 585:2653–2659

63. Chohan MO, Khatoon S, Iqbal I-G, Iqbal K (2006) Involvement of I2PP2A in the abnormal hyperphosphorylation of tau and its reversal by Memantine. FEBS Lett 580(16):3973–3979

64. Facchinetti P, Dorard E, Contremoulins V, Gaillard M-C, Déglon N, Sazdovitch V, Guihenneuc-Jouyaux C, Brouillet E, Duyckaerts C, Allinquant B (2014) SET translocation is associated with increase in caspase cleaved amyloid precursor protein in CA1 of Alzheimer and Down syndrome patients. Neurobiol Aging 35(5):958–968

65. Zhao Y, Li J, Tang Q, Gao J, Chen C, Jing L, Zhang P, Li S (2014) Apolipoprotein E mimetic peptide protects against diffuse brain injury. Neural Regen Res 9(5):463

66. Laskowitz DT, McKenna SE, Song P, Wang H, Durham L, Yeung N, Christensen D, Vitek MP (2007) COG1410, a novel apolipoprotein E-based peptide, improves functional recovery in a murine model of traumatic brain injury. J Neurotrauma 24(7):1093–1107

67. Shin M-K, Vázquez-Rosa E, Koh Y, Dhar M, Chaubey K, Cintrón-Pérez CJ, Barker S, Miller E, Franke K, Noterman MF (2021) Reducing acetylated tau is neuroprotective in brain injury. Cell 184(10):2715-2732.e2723

68. Pasinetti GM (2012) Role of olfactory receptors in traumatic brain injury-associated tauopathy. Biological psychiatry. Elsevier

69. Wang Y, Mandelkow E (2016) Tau in physiology and pathology. Nat Rev Neurosci 17(1):22–35

70. Xiong Y, Mahmood A, Chopp M (2013) Animal models of traumatic brain injury. Nat Rev Neurosci 14(2):128–142

71. Li M, Makkinje A, Damuni Z (1996) The myeloid leukemia-associated protein SET is a potent inhibitor of protein phosphatase 2A (∗). J Biol Chem 271(19):11059–11062

72. Enevoldsen EM, Cold G, Jensen FT, Malmros R (1976) Dynamic changes in regional CBF, intraventricular pressure, CSF pH and lactate levels during the acute phase of head injury. J Neurosurg 44(2):191–214

73. Castejón O (2004) Lysosome abnormalities and lipofucsin content of nerve cells of oedematous human cerebral cortex. J Submicrosc Cytol Pathol 36(3–4):265–271

74. Ishizaki T, Erickson A, Kuric E, Shamloo M, Hara-Nishimura I, Inácio ARL, Wieloch T, Ruscher K (2010) The asparaginyl endopeptidase legumain after experimental stroke. J Cereb Blood Flow Metab 30(10):1756–1766

75. Arif M, Wei J, Zhang Q, Liu F, Basurto-Islas G, Grundke-Iqbal I, Iqbal K (2014) Cytoplasmic retention of protein phosphatase 2A inhibitor 2 (I2PP2A) induces Alzheimer-like abnormal hyperphosphorylation of Tau. J Biol Chem 289(40):27677–27691

76. Stern RA, Daneshvar DH, Baugh CM, Seichepine DR, Montenigro PH, Riley DO, Fritts NG, Stamm JM, Robbins CA, McHale L (2013) Clinical presentation of chronic traumatic encephalopathy. Neurology 81(13):1122–1129

77. Sontag J-M, Nunbhakdi-Craig V, Montgomery L, Arning E, Bottiglieri T, Sontag E (2008) Folate deficiency induces in vitro and mouse brain region-specific downregulation of leucine carboxyl methyltransferase-1 and protein phosphatase 2A Bα subunit expression that correlate with enhanced tau phosphorylation. J Neurosci 28(45):11477–11487

78. Tan XL, Wright DK, Liu S, Hovens C, O'Brien TJ, Shultz SR (2016) Sodium selenate, a protein phosphatase 2A activator, mitigates hyperphosphorylated tau and improves repeated mild traumatic brain injury outcomes. Neuropharmacology 108:382–393

79. Marchese FP, Aubareda A, Tudor C, Saklatvala J, Clark AR, Dean JL (2010) MAPKAP kinase 2 blocks tristetraprolin-directed mRNA decay by inhibiting CAF1 deadenylase recruitment. J Biol Chem 285(36):27590–27600

80. Cipriani R, Chara JC, Rodríguez-Antigüedad A, Matute C (2015) FTY720 attenuates excitotoxicity and neuroinflammation. J Neuroinflamm 12(1):1–14

81. Sangodkar J, Farrington CC, McClinch K, Galsky MD, Kastrinsky DB, Narla G (2016) All roads lead to PP 2A: exploiting the therapeutic potential of this phosphatase. FEBS J 283(6):1004–1024

82. Ross E, Naylor A, O'neil J, Crowley T, Ridley M, Crowe J, Smallie T, Tang T, Turner J, Norling L (2017) Treatment of inflammatory arthritis via targeting of tristetraprolin, a master regulator of pro-inflammatory gene expression. Ann Rheum Dis 76(3):612–619

83. Yin J, Li R, Liu W, Chen Y, Zhang X, Li X, He X, Duan C (2018) Neuroprotective effect of protein phosphatase 2A/tristetraprolin following subarachnoid hemorrhage in rats. Front Neurosci 12:96

84. Kondo A, Shahpasand K, Mannix R, Qiu J, Moncaster J, Chen C-H, Yao Y, Lin Y-M, Driver JA, Sun Y (2015) Antibody against early driver of neurodegeneration cis P-tau blocks brain injury and tauopathy. Nature 523(7561):431–436

85. Seo J-S, Lee S, Shin J-Y, Hwang YJ, Cho H, Yoo S-K, Kim Y, Lim S, Kim YK, Hwang EM (2017) Transcriptome analyses of chronic traumatic encephalopathy show alterations in protein phosphatase expression associated with tauopathy. Exp Mol Med 49(5):e333–e333

86. Seo J-S, Lee S, Shin J-Y, Hwang YJ, Cho H, Yoo S-K, Kim Y, Lim S, Kim YK, Hwang EM, Kim SH, Kim C-H, Hyeon SJ, Yun J-Y, Kim J, Kim Y, Alvarez VE, Stein TD, Lee J, Kim DJ, Kim J-I, Kowall NW, Ryu H, McKee AC (2017) Transcriptome analyses of chronic traumatic encephalopathy show alterations in protein phosphatase expression associated with tauopathy. Exp Mol Med 49(5):e333–e333

87. Basurto-Islas G, Grundke-Iqbal I, Tung YC, Liu F, Iqbal K (2013) Activation of asparaginyl endopeptidase leads to Tau hyperphosphorylation in Alzheimer disease. J Biol Chem 288(24):17495–17507

88. Iqbal K, Bolognin S, Wang X, Basurto-Islas G, Blanchard J, Tung YC (2013) Animal models of the sporadic form of Alzheimer's disease: focus on the disease and not just the lesions. J Alzheimers Dis 37(3):469–474

89. Castellani RJ, Perry G (2017) Dementia pugilistica revisited. J Alzheimers Dis 60(4):1209–1221

90. Corsellis J, Bruton C, Freeman-Browne D (1973) The aftermath of boxing1. Psychol Med 3(3):270–303

91. Katsumoto A, Takeuchi H, Tanaka F (2019) Tau pathology in chronic traumatic encephalopathy and Alzheimer's disease: similarities and differences. Front Neurol 10:980

92. Hawkins BE, Krishnamurthy S, Castillo-Carranza DL, Sengupta U, Prough DS, Jackson GR, DeWitt DS, Kayed R (2013) Rapid accumulation of endogenous tau oligomers in a rat model of traumatic brain injury: possible link between traumatic brain injury and sporadic tauopathies. J Biol Chem 288(23):17042–17050

93. Sacramento CB, Sondhi D, Rosenberg JB, Chen A, Giordano S, Pey E, Lee V, Stiles KM, Havlicek DF, Leopold PL (2020) Anti-phospho-tau gene therapy for chronic traumatic encephalopathy. Hum Gene Ther 31(1–2):57–69

94. Min S-W, Cho S-H, Zhou Y, Schroeder S, Haroutunian V, Seeley WW, Huang EJ, Shen Y, Masliah E, Mukherjee C (2010) Acetylation of tau inhibits its degradation and contributes to tauopathy. Neuron 67(6):953–966

95. Lu KP, Kondo A, Albayram O, Herbert MK, Liu H, Zhou XZ (2016) Potential of the antibody against cis-phosphorylated tau in the early diagnosis, treatment, and prevention of Alzheimer disease and brain injury. JAMA Neurol 73(11):1356–1362

96. Yang Z, Lin F, Robertson CS, Wang KK (2014) Dual vulnerability of TDP-43 to calpain and caspase-3 proteolysis after neurotoxic conditions and traumatic brain injury. J Cereb Blood Flow Metab 34(9):1444–1452

97. Ling JP, Pletnikova O, Troncoso JC, Wong PC (2015) TDP-43 repression of nonconserved cryptic exons is compromised in ALS-FTD. Science 349(6248):650–655

98. Li Y, Zhou T, Wang Y, Ning C, Lv Z, Han G, Morris J, Taylor E, Wang R, Xiao H (2017) The protumorigenic potential of FTY720 by promoting extramedullary hematopoiesis and MDSC accumulation. Oncogene 36(26):3760–3771

99. Christensen DJ, Ohkubo N, Oddo J, Van Kanegan MJ, Neil J, Li F, Colton CA, Vitek MP (2011) Apolipoprotein E and peptide mimetics modulate inflammation by binding the SET protein and activating protein phosphatase 2A. J Immunol 186(4):2535–2542

100. Taleski G, Sontag E (2018) Protein phosphatase 2A and tau: an orchestrated 'Pas de Deux. FEBS Lett 592:1079–1095

101. Ojo JO, Mouzon BC, Crawford F (2016) Repetitive head trauma, chronic traumatic encephalopathy and tau: challenges in translating from mice to men. Exp Neurol 275:389–404

102. Khan S, Ali A, Kadir B, Ahmed Z, Di Pietro V (2021) Effects of memantine in patients with traumatic brain injury. ReCALL 9:13

103. Mei Z, Qiu J, Alcon S, Hashim J, Rotenberg A, Sun Y, Meehan WP III, Mannix R (2018) Memantine improves outcomes after repetitive traumatic brain injury. Behav Brain Res 340:195–204

104. Kickstein E, Krauss S, Thornhill P, Rutschow D, Zeller R, Sharkey J, Williamson R, Fuchs M, Köhler A, Glossmann H (2010) Biguanide metformin acts on tau phosphorylation via mTOR/protein phosphatase 2A (PP2A) signaling. Proc Natl Acad Sci 107(50):21830–21835

105. Rahimi S, Ferdowsi A, Siahposht-Khachaki A (2020) Neuroprotective effects of metformin on traumatic brain injury in rats is associated with the AMP-activated protein kinase signaling pathway. Metab Brain Dis 35(7):1135–1144

106. Zhao W, Varghese M, Ho L, Dams-O'Connor K, Gordon W, Pasinetti G (2012) P3-029: Role of olfactory receptors in traumatic brain injury-associated tauopathy. Alzheimer's Dement 8(4S_Part_13):P464–P464

Publisher's Note