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EXPERT REVIEW

Neurotransmitter changes after traumatic brain injury: an update for new treatment strategies

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Abstract

Traumatic brain injury (TBI) is a pervasive problem in the United States and worldwide, as the number of diagnosed individuals is increasing yearly and there are no efficacious therapeutic interventions. A large number of patients suffer with cognitive disabilities and psychiatric conditions after TBI, especially anxiety and depression. The constellation of post-injury cognitive and behavioral symptoms suggest permanent effects of injury on neurotransmission. Guided in part by preclinical studies, clinical trials have focused on high-yield pathophysiologic mechanisms, including protein aggregation, inflammation, metabolic disruption, cell generation, physiology, and alterations in neurotransmitter signaling. Despite successful treatment of experimental TBI in animal models, clinical studies based on these findings have failed to translate to humans. The current international effort to reshape TBI research is focusing on redefining the taxonomy and characterization of TBI. In addition, as the next round of clinical trials is pending, there is a pressing need to consider what the field has learned over the past two decades of research, and how we can best capitalize on this knowledge to inform the hypotheses for future innovations. Thus, it is critically important to extend our understanding of the pathophysiology of TBI, particularly to mechanisms that are associated with recovery versus development of chronic symptoms. In this review, we focus on the pathology of neurotransmission after TBI, reflecting on what has been learned from both the preclinical and clinical studies, and we discuss new directions and opportunities for future work.

Introduction

Traumatic brain injury (TBI) affects 2.8 million people annually in the U.S. [1], and over 10 million people worldwide [2]. The economic burden of TBI, both in direct healthcare costs and lost revenue, is enormous, as injured persons often fail to return to work and incur significant morbidity and mortality [3]. The past two decades have produced over 200 Phase II or higher interventional trials for TBI. The pathological mechanisms targeted in TBI clinical trials parallels trends in preclinical research, falling into several general categories, including mitigating damage-related tauopathy [4], acute intervention for physiologic stabilization [5], cell replacement strategies to re-establish plasticity [6, 7], attenuating acute (minutes to days), subacute (days to weeks) and chronic (months to years) inflammation [8, 9], restoring cell and tissue metabolism [10], and modulating neurotransmission [11, 12] (Fig. 1).

A common theme among TBI clinical trials is their failure. While some failed due to low enrollment or change in sponsor priorities, many were terminated for futility. Twenty-four percent of the interventional clinical trials in the last decade address neurotransmitter systems (Fig. 2); the small successes in TBI clinical research thus far originate from trials that fix on neurotransmitter dysfunction, restore electrical activity, or treat post-traumatic depression [12–16]. There are over 40 ongoing or completed registered clinical trials targeting major neurotransmitter systems,

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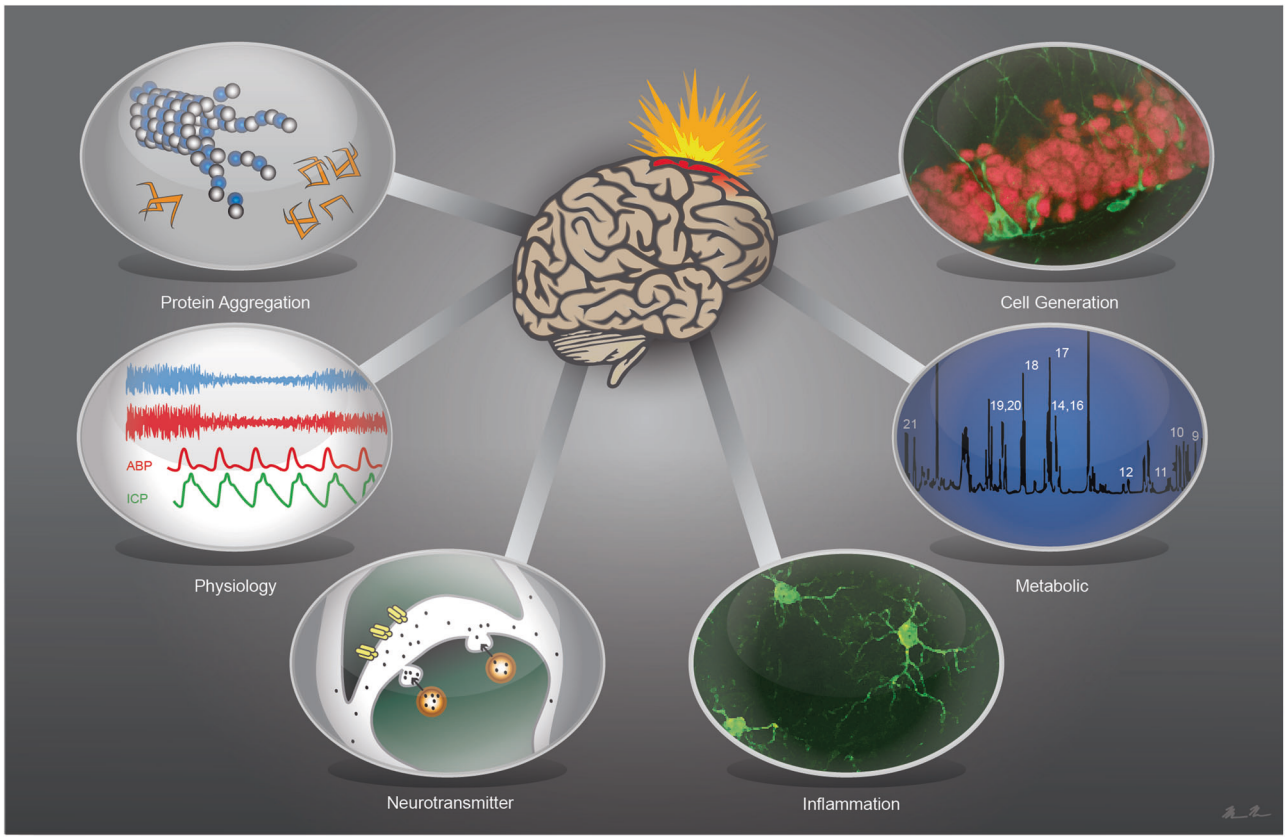

Fig. 1 Strategies to treat acute and chronic TBI currently under investigation (counterclockwise from top left). Molecular targeting of damage-related tauopathy to delay or prevent chronic cognitive effects of TBI. Improving treatments for elevated intracranial pressure and new diagnostics to guide measured improvements in acute patient management. Pharmacological manipulation of transmitter systems to alleviate cognitive and behavioral symptoms. Molecular targeting of acute and chronic inflammatory responses, to mitigate secondary damage. Pharmacological and dietary interventions to support cell and tissue metabolism and alleviate endocrine dysfunction. Manipulating endogenous repair mechanisms to boost neurogenesis or otherwise replace or repopulate damaged tissue and re-establish plasticity. In this review, we focus on the pathophysiological changes on neurotransmitter systems and the studies targeting neurotransmission

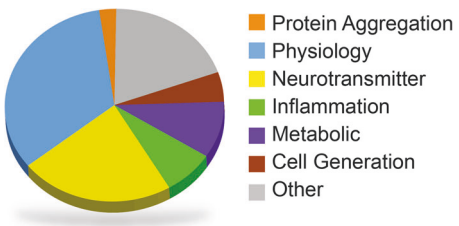

Fig. 2 Completed and ongoing clinical trials for traumatic brain injury. Of 203 interventional clinical trials, 3% are targeting Tau aggregation or other tauopathy, 34% acute physiological disruption or intracranial pressure, 23.6% neurotransmitter systems, 9.9% metabolic interventions, 7.4% inflammation or immune function, 4.9% neurogenesis or stem cell therapy, and 17.2% employ a variety of other strategies including behavioral interventions, transcranial stimulation, and/or neuromodulation

encompassing more than 4000 patients; the published, completed trials are summarized below and in Table 1. Inspired by this theme, this review focuses on preclinical and clinical studies of neurotransmitter systems after TBI, the lessons learned from this work, and consideration of new leads for the field.

Pathophysiology of TBI: state of the field

TBI severity is graded by a clinical assessment of the extent of coma, the Glasgow Coma Scale (GCS), which classifies patients using a minimum score of 3 to a maximum score of 15 [17, 18]. This score was designed as a clinical assessment tool, but is routinely used to categorize patients for inclusion in clinical trials. Using this nomenclature, the majority of TBIs are categorized as mild (GCS 13−15), and may include a brief loss of consciousness, confusion, disorientation, and memory dysfunction, frequently with no abnormalities on conventional diagnostic imaging [17]. Mild TBI typically results from mechanical or rotational force to the head resulting in a period of altered sensorium, including sports-related concussions. In contrast, moderate (GCS 9−12) and severe (GCS ≤ 8) TBIs are more often associated with high-velocity impacts (motor vehicle accidents) or significant acceleration−deceleration injury. This nomenclature for categorizing TBI, although universally used,

Table 1 Recently completed controlled (placebo controlled unless otherwise stated) clinical trials of neurotransmitter systems in traumatic brain injury

Study title	Drug	Neurotransmitter system	*N*	Severity	Timing[a]	Type of study	Summary of study results	Reference
Magnesium sulfate for brain injury	Magnesium sulfate	Glutamate	499	Moderate-severe	Acute	Single-center double-blind placebo-controlled RCT	No improvement in mortality or functional outcome	Temkin et al. [78]
Effectiveness of amantadine hydrochloride for treatment of severe traumatic brain injury	Amantadine	Glutamate and acetylcholine	184	Severe	Subacute	Multicenter double-blind placebo-controlled RCT	Improvement in functional recovery in patients with disorders of consciousness	Giacino et al. [12]
Utility of amantadine hydrochloride in the treatment of post-traumatic irritability	Amantadine	Glutamate and dopamine	76	All	Chronic	Single-center double-blind placebo-controlled RCT	Improvement in irritability and aggression	Hammond et al. [110]
Amantadine for the treatment of brain injury irritability and aggression: a multi-site study	Amantadine	Glutamate and dopamine	168	All	Chronic	Multicenter double-blind placebo-controlled RCT	Improved irritability by patient perspective (but not observers)	Hammond et al. [111]
Assess safety and efficacy of levetiracetam for seizure prevention	Levetiracetam and phenytoin	General	52	Severe	Acute	Single-center, single-blind RCT	Better long-term outcomes in patients treated with levetiracetam versus phenytoin	Szaflarski et al. [14]
Levetiracetam to prevent post-traumatic epilepsy	Levetiracetam	General	126	Moderate-severe	Acute	Multicenter open label nonrandomized trial	Leviteracetam is safe in TBI patients at high risk for post-traumatic epilepsy	Klein et al. [13]
Cholinergic augmentation with donepezil after traumatic brain injury	Donepezil	Acetylcholine	20	All	Chronic	Single-center double-blind placebo-controlled randomized crossover trial	Improvement in cognitive testing	Zhang et al. [127]
Effects of rivastigmine on cognitive function in patients with traumatic brain injury	Rivastigmine	Acetylcholine	157	All	Chronic	Multicenter double-blind placebo-controlled RCT	No improvement in cognitive performance after 12 weeks of treatment	Silver et al. [129]
Atomoxetine for attention deficits following traumatic brain injury	Atomoxetine	Norepinephrine	55	Moderate-severe	Chronic	Single-center double-blind placebo-controlled RCT with placebo run-in	No improvement in attention	Ripley et al. [138]
Effect of bromocriptine on attentional deficits after traumatic brain injury	Bromocriptine	Dopamine	12	Moderate-severe	Subacute and chronic	Single-center double-blind placebo-controlled crossover study	No enhanced attention	Whyte et al. [147]
Study to evaluate the efficacy and safety of armodafinil as treatment for patients With excessive sleepiness associated With mild or moderate closed traumatic brain injury	Armodafinil	Dopamine	117	Mild -moderate	Chronic	Multicenter double-blind placebo-controlled RCT with 12-month open-label extension	Improvement in mean sleep latency	Menn et al. [15]
Sertraline for major depression during year following traumatic brain injury	Sertraline	Serotonin and dopamine	62	Moderate-Severe	Subacute and chronic	Single-center double-blind placebo-controlled RCT	No difference in depression, but improvement in processing speed	Fann et al. [158]
Treatment of post-traumatic brain injury depression	Sertraline	Serotonin	52	All	Chronic	Single-center double-blind placebo-controlled RCT		Ashman et al. [155]

Table 1 (continued)

Study title	Drug	Neurotransmitter system	*N*	Severity	Timing[a]	Type of study	Summary of study results	Reference
							No difference in depression, quality of life, or outcome measures	
Early administration of sertraline on depressive syndromes	Sertraline	Serotonin	99	Moderate-Severe	Subacute	Single-center double-blind placebo-controlled RCT	No change in depressive symptoms	Novack et al. [154]
Impact of early administration of sertraline on cognitive symptoms	Sertraline	Serotonin	99	Moderate-Severe	Subacute	Single-center double-blind placebo-controlled RCT	No improvement in cognitive symptoms	Banos et al. [157]
A randomized controlled trial of antidepressant continuation for major depression following traumatic brain injury	Citalopram	Serotonin	21	All	Chronic	Single-center double-blind placebo-controlled randomized continuation trial	No difference in relapse rates of depression	Rapoport et al. [156]
Treatment strategy to prevent mood disorders following traumatic brain injury	Sertraline	Serotonin	94	All	Subacute	Single-center double-blind, placebo-controlled, parallel-group RCT	Prevention of depression onset without change in neuropsychological outcomes	Jorge et al. [16]

[a]Time after injury: acute = within first hours to days; subacute = weeks to months; chronic = 6 months or greater

lacks an appreciation of the pathophysiology behind injury [19].

Despite the static TBI taxonomy, much has been learned about the pathophysiology of TBI. TBI involves both the primary physical injury to brain tissues and molecular cascades that propagate injury into surrounding tissue, a phenomenon known as secondary injury (reviewed in refs. [20, 21]). These cascades include unregulated neurotransmitter and ion release, cell swelling, diffuse axonal injury, free radical production, mitochondrial dysfunction, inflammatory cytokines, and altered gene transcription [20]. Secondary events further exacerbate the direct consequences of primary injury [20, 22]. As a result, TBI pathophysiology evolves over weeks to months, making behavioral outcomes, particularly in mild injuries without focal lesions, difficult to predict [23, 24]. Despite the large gains in our understanding of the molecular events occurring in the brain following injury, efforts to translate these findings to clinical practice have almost universally failed. The reasons for this are numerous, not the least of which is crossing the wide gap from relatively homogeneous research population to a highly diverse clinical population [25].

Methodologies for studying TBI in humans include behavioral and cognitive evaluations, ante-mortem imaging, accessible tissue samples (including cerebrospinal fluid in severe TBI), or postmortem analysis of structural and molecular changes. However, research in humans is challenging due to heterogeneity in injury severity and physiology, covarying factors such as time from injury, age, sex, lifestyle factors, comorbid illness, patient availability for follow-up, and technical limitations [26–28]. Animal models overcome some of these obstacles, but have limitations as well. Preclinical TBI is performed under anesthesia and some models require directly accessing the brain [29]. Behavioral evaluations of many aspects of executive function including attention, processing speed, motivation, and response inhibition in rodents require labor-intensive training of the rodents prior to testing [30]. While there are inherent challenges in interpreting behavioral changes in animal models, fundamental brain structures and cellular organization are similar between rodent and human and many behavioral endophenotypes are well validated [30, 31].

There are four primary in vivo injury models in rodents: fluid percussion injury, controlled cortical impact, weight-drop acceleration impact, and blast injury [29]. These models vary in the biomechanics of damage and progression of pathology, but produce similar cognitive and behavioral deficits and changes in brain biochemistry [29]. Ultimately, different mechanisms of injury, i.e. direct cortical impact versus blast, may converge on defects of neurotransmission resulting in a similar spectrum of

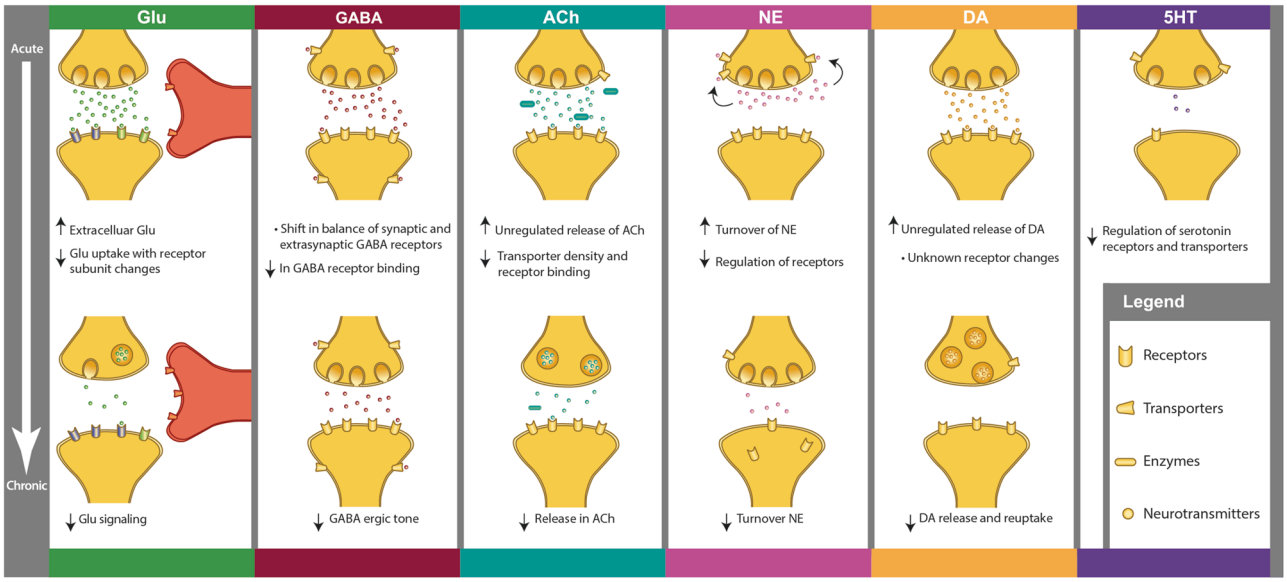

Fig. 3 Summary of temporal changes in neurotransmitter systems after experimental TBI. In acute TBI, there are increases in extracellular glutamate (green panel) and decreases in glutamate uptake due to changes in excitatory amino acid transporter (EAAT) isoform expression. Within hours after experimental TBI, there are decreases in NMDA receptor subunits, and changes in AMPA receptor subunit composition. Chronically, there is sustained depression of glutamate signaling including changes in postsynaptic receptor composition, decreased astroglial (red process) EAAT expression, and a shift in the relative expression of neuronal and glial transporters. Changes in GABA signaling (red panel) include an acute shift in the balance of synaptic and extrasynaptic receptors acutely after injury. There is chronic dysregulation of GABAergic tone with mechanisms that vary by brain region, illustrated here as decreases in GABA receptor binding. In cortex, excessive inhibitory control results from structural change in pyramidal neurons. In subcortical regions, there is a change in the composition and localization of GABA receptors that may contribute to epileptogenic potential. For acetylcholine (Ach) (blue panel), there is an initial unregulated release of ACh and decreases in transporter density and receptor binding beginning as early as 1 h after TBI. However there is chronic cholinergic hypofunction associated with decreased evoked release of Ach and changes in acetylcholinesterase activity. With norepinephrine (NE) (pink panel) there is an immediate accelerated turnover of NE and concurrent down-regulation of receptors. The accelerated turnover is quickly reversed and remains suppressed weeks after injury, leaving chronic down-regulation of NE receptors and associated decreased signaling. TBI initiates changes in both receptor and transporter expression that regulate dopamine (DA) (orange panel) function. Acutely, elevated tissue dopamine levels can remain elevated for weeks. However, there is chronic dopaminergic hypofunction illustrated by changes in presynaptic terminal dopamine recycling and decreases in DA tonic and evoked release. Serotonin (purple panel) changes are characterized by sustained decreases in both transporters and receptors after TBI

cognitive and behavioral changes [32]. There is no single in vivo model of TBI that is objectively superior to other models at producing robust behavioral and cognitive effects, and decisions regarding the selection of a preclinical model may depend on injury mechanisms and study objectives. In vitro models of TBI, including slice culture, primary cell culture, and immortalized cell lines, permit a more precise focus on specific aspects of injury mechanics and cellular mechanisms [33]. In combination, these models provide powerful tools for mechanistic studies of initial damage responses, restoration of homeostasis, and long-term neurochemical plasticity after TBI that are impossible in human subjects.

Neurotransmission shapes behavior and cognition after TBI

The strength and timing of excitatory and inhibitory transmission (E/I balance) within neural circuits shapes activity-dependent plasticity required for behavioral adaptation to environmental stimuli [34]. Repetitive activation at excitatory synapses increases synaptic strength through long-term potentiation (LTP). The balance of LTP and the related phenomenon long-term depression (LTD) coordinate changes in synaptic strength linked to learning and memory. Neuroplastic function requires coordination of pre- and postsynaptic neurons in cohesive circuits, as well as diffusional signals from surrounding glia [11]. Driven by preclinical findings, a fundamental theme in TBI research is modulating neurotransmission to support and restore adaptive plasticity, E/I balance, and the overall capacity of the injured brain to respond appropriately to incoming stimuli [35, 36].

Even TBIs categorized as mild may profoundly affect learning and memory, concentration, and processing speed [37, 38]. TBI may subtly impact multiple domains of executive functioning, including goal identification, planning, behavioral flexibility, problem solving, self-awareness, and insight [39]. These changes frequently result in

impaired decision making, low frustration tolerance, and difficulty returning to premorbid levels of function [39]. The effects of TBI on cognition and executive function can be immediate and permanent [40].

Additionally, anxiety and depression frequently develop after TBI [41, 42], sometimes months or years after injury [41]. Post-TBI depression and anxiety are associated with poor treatment response [43, 44], and frequently coincide with cognitive symptoms [45]. The mechanisms underlying post-TBI depression are unknown, but are not tied to injury severity [46]. However, secondary processes after TBI are independently implicated in depression, including impaired neurogenesis [47], inflammation and microglial activation [48], and glutamate system dysfunction [49]. As with many chronic neurodegenerative conditions, post-TBI neuropsychiatric and cognitive symptoms likely involve damage to homeostatic mechanisms, ultimately resulting in deterioration of the molecular machinery underlying effective neurotransmission in response to environmental demands.

As damage and recovery process are ongoing, the landscape of neurotransmission continues to evolve well into chronic stages, months to years after injury (Fig. 3). Understanding how regulation of transmitter systems is altered after TBI, the progression of these changes over time, and the cumulative impact of damage to transmitter systems that work together to coordinate behavioral responses will be instrumental in developing effective treatment strategies. Here, we describe the current understanding of how TBI impacts major transmitter systems, strategies implemented to mitigate the effects of TBI, and lingering knowledge gaps within the field.

Glutamatergic neurotransmission in TBI

Glutamate, the predominant excitatory neurotransmitter in the brain, signals through metabotropic and ionotropic receptors localized to synaptic and extrasynaptic membranes on neurons and glial. Extracellular glutamate levels are regulated by a family of membrane-bound excitatory amino acid transporters (EAATs) found on postsynaptic neurons and astrocytes [50]. Glutamate release and reuptake is tightly regulated to optimize synaptic transmission and prevent excitotoxicity from excessive extracellular glutamate [51]. Alterations in glutamate buffering and reuptake modulate synaptic function, leading to neuroplastic changes in learning and memory [52]. Thus, if acute deficits in glutamate regulation become persistent, they may contribute to the long-term cognitive and emotional deficits common after TBI.

Data from both humans and animal models indicate that in the initial minutes and hours, post-TBI, release of glutamate and ions plays an important role in initiating secondary injury cascades [53–56]. Elevated extracellular potassium impairs astrocytic potassium conductance essential for glutamate uptake and transporter-mediated buffering [57, 58]. In severe injuries, high levels of extracellular glutamate and impaired glial uptake contribute to propagating waves of regional electrophysiological hyperactivity followed by depolarization (cortical spreading depolarizations, CSDs), that temporarily silences synaptic activity [5, 59–61]. CSDs are often repetitive and associate with increases in extracellular glutamate and lactate [59]. In severe injuries, high or intermittently high levels of extracellular glutamate may continue for a week or longer [54, 55], with the initial unregulated release of glutamate followed by sustained depression of glutamate signaling [62, 63] (Fig. 3).

Preclinical findings

In preclinical models of moderate-severe TBI, *N*-methyl-D-aspartic acid (NMDA) glutamate receptor subunit expression is decreased within hours as NMDAR hyperactivity is followed by receptor hypofunction [64, 65]. However, a study of severe injury using a PET ligand selective for open NMDA channels, ^{18}F-GE-179, found an increase in open NMDA channels within 5−6 days and an even more widespread increase in NMDA channel activation 6 weeks after injury [66]. After severe injury there is an initial increase in expression of calcium-permeable AMPA receptors, which may reverse later [67, 68]. Activity and expression of glutamate transporters is also disrupted in acute, mild-moderate injury, impairing uptake capacity [58, 69, 70] and glutamate cycling between astrocytes and neurons. It is unknown whether changes in the cellular patterns of EAAT expression, such as increased expression of typically astroglial EAAT isoforms on neurons and microglia, are pathological, compensatory, or both [71–73]. In human cortex, expression of EAAT2 on glial cells was decreased within a day after TBI, while reduced expression of EAAT2 was still evident in postmortem samples with post-injury survival times of months or years [74].

Clinical findings

Clinical attempts to prevent acute neurotoxicity in moderate-severe TBI by blocking NMDAR signaling failed to improve outcomes [75, 76]. Although there are a number of technical and methodological challenges associated with these trials, they did not account for two key biological factors. First, the rapid reversal from glutamatergic hyperexcitability to hypoexcitability possibly resulted in drug treatments further exacerbating glutamatergic hypofunction [62, 77, 78]. Second, is a failure to appreciate the biology of

synaptic versus extrasynaptic NMDA receptors [76, 79]. Blocking extrasynaptic NMDA signaling may initiate neuronal apoptosis [76, 80], amplifying secondary damage after injury. Ultimately, exclusive targeting of NMDA-mediated glutamate signaling failed to re-establish an appropriate excitatory (glutamate) and inhibitory (GABA) environment that could positively impact recovery trajectory.

GABAergic neurotransmission in TBI

Inhibitory Gamma aminobutyric acid (GABA) transmission balances excitatory glutamatergic signaling. E/I balance integrates inhibitory and excitatory signaling through feedback (direct response to excitatory activity) and feedforward (stimulation of other GABAergic neurons) mechanisms [34]. E/I balance represents a fundamental biological process found in circuits throughout the CNS, and perturbations of this factor typically yield dysfunction of synapses and circuits, leading to alterations in behavior and function [81].

Preclinical findings

GABA signals through ionotropic $GABA_A$ or $GABA_C$ receptors or metabotropic $GABA_B$ receptors. $GABA_A$ receptors are the most well studied of the GABA receptors and are heteromeric pentamers derived from at least 19 separate proteins classified by sequence homology into six classes [82]. $GABA_A$ receptors are targeted to synaptic or extrasynaptic membranes by their subunit composition, and synaptic or extrasynaptic localization of $GABA_A$ receptors determines tonic and phasic inhibitory tone, respectively [83, 84]. Increased expression of extrasynaptic $GABA_A$ receptors increases GABAergic tone, but concurrently reduces the phasic response [83]. Within a week after TBI, there is a shift in the balance of synaptic $GABA_A$ versus extrasynaptic GABA receptors [85, 86], summarized in Fig. 3. This suggests a change in E/I balance or synaptic scaling due to the differences in downstream signaling following activation of these differentially localized receptors. Twelve hours after moderate-severe TBI, GABAR binding was decreased [87], while another group found increased GABA receptor binding near the lesion center several days after severe injury [66].

Taken together, these findings indicate a role for alterations of GABA receptor expression and function in TBI. Acute changes in the expression of genes regulating GABA, glutamate, and E/I balance as part of the initial response to TBI may stabilize through epigenetic mechanisms, leading to long-lasting changes in homeostatic control [88]. Damage to mechanisms governing E/I balance and an inability to either repair or compensate may ultimately lead to inappropriate neural response and maladaptive plasticity [11, 89].

E/I balance: a moving target

Preclinical findings

Changes in the cellular machinery regulating glutamatergic and GABAergic signaling only provide indirect evidence of altered E/I balance after TBI, while preclinical models afford access to direct measurements of excitation and inhibition in neural circuits after experimental injury. Within hours of mild injury, hippocampal LTP is suppressed, consistent with overall glutamatergic hypofunction reported early in TBI [90–93]. Notably, changes in the brain following injury are not limited to the lesion center, or even adjacent areas, but may include widely distributed brain circuits. For example, in disparate cortical regions, decreased firing frequency, increased latency of evoked response, and elevated action potential thresholds persist at least several days after mild or moderate injury to the sensory cortex [94–96]. Concurrently, there are differential shifts in E/I balance within the hippocampal circuit and impairment of LTP and NMDA-evoked currents in CA1 [97, 98]. Also within this timeframe, inhibitory signaling in the amygdala is decreased, suggesting hyperexcitability in subcortical structures regulating emotion [99].

Disruption of E/I balance continues to change over weeks, months, and years, as TBI progresses through subacute and chronic phases, although mechanisms underlying these changes are not uniform across or within brain regions. Two weeks after moderate-severe experimental injury, exaggerated GABAergic inhibition in frontal cortex is reversible by GABA inhibitors, but over time GABAergic tone is restored and cortical hypo-excitation reflects hypotrophy in deep-layer cortical pyramidal neurons [100, 101]. In the dentate gyrus there is a gradual loss of phasic GABAergic inhibition over 6 months ipsilateral to severe injury, becoming bilateral over time [102]. Evoked responses to extrasynaptic GABAR agonist are diminished both early after moderate-severe TBI and chronically [103]. Also in severe injury, tonic GABAergic inhibition in the dentate gyrus may increase over time [104]. Remodeling of hippocampal circuits in severe TBI increases excitatory inputs from CA3 and granule cells into hilar interneurons 10 weeks after injury. In contrast, inhibitory inputs to the dentate gyrus are decreased, leaving the overall balance of signaling excitatory [105]. After severe injury, spontaneous epileptiform electrical activity increases in hippocampus within weeks of injury, along with the stimulus threshold to initiate LTP [106], while after mild injury LTP can be initiated, but not sustained [107]. These changes highlight

the complexity of the post-injury milieu, where individual circuits, cells and/or synapses may differentially respond to pharmacological interventions.

Clinical findings

Thought to reflect changes in E/I balance, post-traumatic seizures have a cumulative incidence of up to 20% by 5 years [108]. The latency period associated with the development of post-traumatic epilepsy further supports progressive pathological changes in E/I balance after injury. Clinical trials to prevent post-traumatic seizures after moderate to severe TBI effectively prevented early (within 7 days) but not later seizures [13, 14, 109]. Phenytoin and leviteracetam are anti-epileptic medications whose mechanisms of action are thought to involve diffuse blockage of voltage-gated channels. The clinical effectiveness of these drugs for subacute but not chronic seizure is additional evidence that E/I balance evolves over the course of injury.

Emerging shifts in E/I balance suggest that modulating glutamate and/or GABA neurotransmission could restore neuroplastic function and improve cognitive symptoms in chronic TBI. The NMDAR antagonist/dopamine agonist, amantadine, 100 mg twice daily, alleviated aggressive behavior after TBI [110], but the evidence for efficacy in other behavioral domains was equivocal [111–113]. In a multicenter study of 184 patients, amantadine (maximum dose 200 mg twice daily) administered subacutely (initiated 4−16 weeks after injury) improved functional recovery in patients with disorders of consciousness [12]. A similar drug, the uncompetitive NMDA receptor antagonist memantine [114, 115], was approved for clinical trials but small sample size ($n = 11$) and early termination due to lack of enrollment provided uninterpretable results (NCT00462228).

Taken together, these data suggest a central role for abnormalities of glutamate and GABA neurotransmission in acute and chronic TBIs of varying severity. Changes encompassing receptors, transporters, release mechanisms, and signaling cascades clearly establish that defects of neuroplasticity emerge following brain injury. However, the glutamate and GABA neurotransmitter systems do not operate in isolation. Excitatory and inhibitory tone is modulated by inputs from local and widely distributed diverse subtypes of neurons.

Acetylcholine neurotransmission in TBI

Cholinergic inputs into frontal cortex and hippocampus regulate attention and memory consolidation. Acetylcholine signals through two classes of receptor expressed on both neurons and glia, G-protein-coupled muscarinic receptors which can be excitatory or inhibitory, and ionotropic (nicotinic) receptors which are excitatory [116]. Acetylcholine synthesis, release, and degradation are regulated by presynaptic choline acetyltransferase (ChAT), the vesicular transporter vAChT, and postsynaptic acetylcholinesterase (AChE), respectively [116]. Acetylcholine release can increase spontaneous activity, facilitate evoked responses, or inhibit evoked responses [117]; however, the overall effect of acetylcholine signaling in cortex is to enhance NMDA-mediated currents [116, 117]. Acetylcholine release exhibits both cue-evoked spikes in acetylcholine receptor activity, as well as slower increases in activity corresponding to attentional processes [118].

Preclinical findings

After TBI, there is acute release of acetylcholine that increases extracellular acetylcholine concentration followed by long-term suppression of acetylcholine signaling [119, 120], illustrated in Fig. 3. Receptor binding and vChAT transporter density decrease in preclinical models of moderate injury as early as 1 h after TBI, and may persist for at least 3 days [87, 119, 121]. Two weeks after injury, evoked release of acetylcholine is impaired in moderate TBI animals [122]. In mild TBI patients, acetylcholine hypofunction and decreased AChE activity can be evident more than a year after injury [120].

Preclinical and postmortem evidence indicate cholinergic projections from basal forebrain are susceptible to damage after TBI [119, 123]. Cortical projections from the basal forebrain may be particularly vulnerable to accumulation of neurofibrillary tangles and tau protein aggregation, potentially contributing to chronic, cholinergic hypofunction after TBI [123].

Clinical findings

A variety of pro-cholinergic agents, including receptor agonists [124], cholinesterase inhibitors [125], and mechanisms activating acetylcholine release [126], showed promise in preclinical TBI models. Acetycholinesterase inhibitors, notably donepezil and rivastigmine, went to randomized controlled trials (RCTs) [127–129]. Both drugs showed mildly beneficial effects in specific cognitive domains of attention and short-term memory [127–129]. In chronic (>1 year) mild TBI subjects recruited from a previous rivastigmine trial, patients who responded to a minimum daily dose of 3 mg daily of rivastigmine had significantly lower initial acetylcholinesterase activity than nonresponders [130]. Although hampered by the small sample sizes common to most human imaging studies, additional studies of this kind, specifically identifying

biologically distinct subpopulations of TBI subjects, may provide important insight into tailoring treatment strategies.

Catecholamines in TBI

The principal source of forebrain the catecholamines dopamine (DA) and norepinephrine (NE) is dorsal midbrain (DA) and brainstem (NE) [131]. Changes in DA and NE after TBI are summarized in Fig. 3. Catecholaminergic nuclei are vulnerable to direct brainstem damage and shearing of projections to forebrain, and are particularly susceptible to metabolic stress due to intrinsically high energy requirements [131]. Catecholaminergic nuclei receive reciprocal projections from cortex, and damage to these inputs from forebrain after TBI will affect catecholaminergic regulation. Tonic NE signaling mediates arousal and wakefulness, while phasic firing is associated with attentional focus and vigilance [131, 132].

Preclinical findings

The most consistent preclinical finding for noradrenergic signaling is turnover of norepinephrine [131]. The initial accelerated turnover of cortical NE reverses by 6 h, and suppression of NE turnover is still evident 8 weeks after moderate-severe injury [133–135]. Concurrent downregulation of α_1 adrenoreceptors is evident within 30 min after TBI [136, 137]. Atomoxetine (80 mg/day for 14 days), an NE uptake inhibitor, provided no significant improvement in attention or in self-reported post-injury depressive symptoms [138].

Dopamine signals through G-protein-coupled receptors [131] and is removed from the synapse by the neuronal dopamine transporter DAT or enzymatic degradation [139]. In preclinical models of moderate TBI, there is a progressive loss of dopaminergic neurons in the substantia nigra [140, 141], evident from 2 weeks and continuing for months post injury. Similar to other neurotransmitters, there is an acute rise in extracellular dopamine evident 1 h after moderate-severe injury, which is sustained in some regions for a day or more [131, 142]. Regional increases in tissue dopamine levels potentially last considerably longer, up to several weeks in severe injury [143]. However, other studies support an initial increase in tissue dopamine followed closely by prolonged dopaminergic hypofunction in severe injury [144, 145]. Preclinical studies suggest dopaminergic dysfunction after TBI is driven by defects in tonic and evoked dopamine release, as well as impaired dopamine reuptake into neurons, rather than through alterations in dopamine receptor expression [144, 145]. PET imaging indicates regional changes in both DAT activity and D2 receptor binding in human TBI [131, 146].

Clinical findings

Dopamine has potent modulatory effects on glutamate transmission suggesting that dopaminergic drugs have potential to improve cognitive domain symptoms after TBI. The D2-dopamine receptor agonist bromocriptine, titrated to a dose of 5 mg twice daily for 6 weeks, performed no better than placebo in resolving cognitive symptoms [147]. Methylphenidate and amphetamines, typically used to treat disorders of attention, produced equivocal effects on cognition, although interpretation of study results is limited by small sample sizes [148, 149]. Armodafinil (50−150 mg/12 weeks), an indirect dopamine agonist approved for treating narcolepsy, was effective in increasing wakefulness and sleep latency in TBI patients with excessive sleepiness in a dose-dependent manner [15]. Similar to the amantadine trial [12], dopamine modulation demonstrates efficacy for improving wakefulness, but long-term positive effects on cognition are unproven.

Serotonin neurotransmission in TBI

Serotonin originates in the raphe nucleus and is distributed throughout the forebrain. There are at least 16 serotonin receptors expressed on both excitatory and inhibitory neurons [81] and once released, serotonin is taken up by presynaptic serotonin transporters [150].

Preclinical findings

After moderate-severe TBI, serotonin transporters are downregulated within a day and remain downregulated for at least 2 weeks [151] (Fig. 3). In preclinical models of moderate-severe injury, the tricyclic antidepressant imipramine (20 mg/kg for 2 or 4 weeks) and the selective serotonin reuptake inhibitor (SSRI), fluoxetine (10 mg/kg for 4 weeks), increased neurogenesis measured 4 weeks after TBI; only the tricyclic improved recognition memory [6, 152]. Neither of these medications have gone into clinical trials for reversal of cognitive defects in TBI.

Clinical findings

As depression and anxiety develops in many patients after injury, and post-TBI depression has clinical features that mirror noninjury depression, it has been presumed that SSRIs could be useful for prevention and treatment of post-TBI depression. Over 25 RCTs, open label, or case studies have tested SSRIs as treatment for post-TBI depression and cognitive dysfunction, with varying results [153]. Disruption of the serotonergic system likely begins soon after injury. Subacute (initiated on average

at 3 weeks post-TBI) administration of the SSRI sertraline for 12 weeks, at a dose of up to 100 mg/day mitigated depressive symptoms during the course of treatment, but did not provide lasting protection against development of post-TBI depression [154–156]. Sertraline did not prevent or improve deficits in attention, memory, or executive function [16, 157]. A recent trial, however, showed improvement in information processing in doses up to 200 mg/day, but suggested the dopaminergic activity of sertraline as the mechanism [158]. In summary, the SSRIs are promising interventions for improving post-TBI depression in chronic TBI, but improvement in cognitive symptoms after TBI needs further study.

Adenosine neurotransmission in TBI

Adenosine signals through G-protein-coupled A1,A2A, A2B and A3 receptors or through a myriad of metabotropic P2X and P2Y receptors, expressed throughout the brain [159, 160]. Adenosine accumulates rapidly after injury due to breakdown of adenosine triphosphate [159]. Adenosine levels are regulated by 5′-nucleotidases, which generate adenosine from adenosine phosphates, adenosine deaminase, which converts adenosine to inosine, adenosine kinase which phosphorylates adenosine to become adenosine monophosphate, and nucleoside transporters, none of which are well studied after TBI [159].

Adenosine acts presynaptically to suppress excitatory transmitter release and postsynaptically to maintain hyperpolarization [159, 161]. Adenosine triphosphate released from astrocytes stimulates hippocampal interneurons as part of homeostatic regulation of E/I balance [162, 163]. However, adenosine itself can suppress tonic GABAergic signaling and astroglial glutamate uptake [164, 165]. Signaling through A1 and A2A receptors has opposing effects on excitation; A1R is primarily inhibitory, while A2AR facilitates synaptic signaling [161]. Local glutamate levels regulate adenosine A2AR signaling [166], while imbalance in adenosine signaling affects working and short-term memory, and goal directed or effortful behavior [161].

Preclinical findings

While the adenosine neurotransmitter machinery is only recently gaining attention in experimental TBI, extracellular concentrations of adenosine, and its metabolites inosine and hypoxanthine are known to increase within minutes after injury [167]. Extracellular adenosine returns to basal levels within an hour, but inosine and hypoxanthine remain elevated [167]. Genetic knockout of the A1 receptor results in lethal status epilepticus after experimental TBI [168]. Conversely, attenuation of A2A receptor signaling improves aspects of TBI symptomology [169, 170]. The modulatory roles of the adenosine neurotransmitter system suggests this system as a high-yield substrate for pharmacological intervention. Supporting this hypothesis, polymorphisms of adenosine regulatory genes are associated with an increased risk for developing post-traumatic epilepsy [171–173].

In summary, a single neurotransmitter-focused approach has not (so far) delivered targets yielding efficacious therapies for the cognitive effects of TBI. A more integrated approach accounting for diverse neurotransmitter systems is needed to develop novel therapeutics to modulate and/or restore function to premorbid states.

Integration of diverse neurotransmitter systems: modulation of E/I balance

Effective neurotransmission requires constant rebalancing of excitatory and inhibitory signaling. Collectively and with varying impact, diverse neurotransmitter systems work cooperatively in healthy brain to fine-tune E/I balance [174]. Hypofunctional D1-dopamine receptor signaling impairs LTP in hippocampus [175], and interactions between dopamine and acetylcholine facilitate LTP in frontal cortex [176]. The D2-dopamine receptor directly interacts with both adenosine and metabotropic glutamate receptors to modulate excitatory transmission [175]. Cholinergic and dopaminergic neurons contact both glutamatergic neurons and GABAergic interneurons, tuning the response of the neuronal ensemble [176]. Comodulation of synaptic plasticity by dopamine and serotonin also cooperatively shifts E/I balance towards either LTP or LTD [81]. NE sensitizes cortical circuits reflecting its role in vigilance and risk assessment [174], while decreasing serotonin signaling through 5-HT1A receptors potentiates circuit inhibition [177].

Concerted actions of multiple transmitter systems coordinate neurotransmission at individual synapses and within neural circuits across multiple temporal scales. The effects of injury on the coordination between neurotransmitter systems to regulate cognitive and emotional processing, at any stage of injury, is poorly understood. The complex nature of neurotransmission, including the intricate interactions between neurotransmitter systems, suggests that less-specific drugs may be more efficacious than highly selective compounds. This notion is supported by the relatively promiscuous receptor binding profiles of the TCAs and amantadine, drugs that appear to provide improvement in a few symptom domains of TBI [178–180].

Opportunities for future work

Despite intense interest in identifying the underpinnings of cognitive and behavioral symptoms after TBI, there are still significant gaps in our understanding of how injury impacts neurotransmission. For example, very little is known about extrasynaptic signaling mechanisms after TBI. In contrast to synaptic NMDAR signaling that promotes cell survival, extrasynaptic NMDAR signaling activates cell death pathways and likely contributes to early cell loss and excitotoxicity after TBI [79]. Extrasynaptic NMDAR signaling also antagonizes coupling of glutamate signaling to protein transcription, blocking processes required for memory consolidation and potentially contributing to cognitive dysfunction well after acute stages of injury [181].

Extrasynaptic glutamate comes from several sources, including astrocytic release and spillover from neuronal synapses. The cystine-glutamate antiporter, xCT, is a significant source of extrasynaptic glutamate [182]. Glutamate released by astrocytes into the extrasynaptic space via system x_C^- can stimulate metabotropic glutamate receptors peripheral to the synapse as well as extrasynaptic ionotropic receptors [182]. System x_c^- also contributes to the physiologic roles of extrasynaptic glutamate in synaptic scaling [183]. Expression and activity of xCT and system x_c^- is regulated by cytokine signaling (notably IL-1β and TNFα), NO^- and other reactive species, growth factors, and neuronal activity, linking inflammation and metabolic stress to regulation of synaptic strength and excitatory transmission [182]. Pharmacologically blocking system x_c^- produces defects in working memory and long-term memory; however hyperactivity of system x_c^- is potentially even more damaging due to excitotoxic activation of extrasynaptic NMDARs [182]. Despite the recognized role of system x_c^- in tuning excitatory transmission, it has not been studied in TBI.

Recent studies indicate that lactate can function as a neurotransmitter [184, 185], through a G-protein-coupled receptor, hydrocarboxylic receptor 1 HCA1 (GPR81). HCA1 is expressed on pyramidal neurons in cerebellum, hippocampus, and cortex, and to a lesser extent astrocytes [184, 186]. HCA1 activation suppresses neuronal activity [187] and HCA1 signaling requires high extracellular lactate concentrations. These findings suggest HCA1 is activated in response to injury or intense neural activity [184]. Interestingly, an acute (minutes to hours) increase in brain lactate after severe TBI [10, 188] is associated with poor outcomes [189]. Paradoxically, sodium lactate infusion shows some beneficial effect and is being trialed to prevent acute increases in intracranial pressure in severe injury [190]. Whether HCA1 activation contributes to either the beneficial or negative effects of acutely elevated lactate levels after TBI is unknown. It is also unknown whether the metabolic switch to aerobic glycolysis and subsequent increase in lactate production in activated glia influences HCA1 signaling in TBI or other inflammatory neurodegenerative disorders.

Metabolic imaging approaches such as magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) have great potential to provide insight into the regulation and function of brain activity and amino acid neurotransmitter systems after TBI, particularly when combined with other imaging modalities. However, these technologies are not yet being used to maximal effect in TBI research. MRS studies report both increased [191, 192] and decreased [193, 194] tissue concentrations of glx, the combined glutamate/glutamine signal. Inconsistencies may have to do with timing, ROI, subject populations, or methodological differences. In general, interpretation of imaging studies in TBI is hindered by small sample size. Despite available PET ligands for all of the major transmitter systems, it has been only minimally utilized [130, 146, 195, 196].

Conclusion

Pathological processes after brain injury continuously evolve (Fig. 4) [197], and we are only now beginning to understand compensatory and recovery mechanisms that could be enhanced [198–200]. There are abundant opportunities for improvement in study design and outcomes reporting in TBI clinical drug trials [112, 201]. Most previous clinical trials included patients with similar injury severities graded by GCS, but overlooked key clinical features and commonalities in the pathophysiology of injury [19, 202]. The next big clinical trials will involve identifying the appropriate patient populations for targeted therapeutic interventions. Currently an international effort is underway to advance innovation in TBI therapeutics via comparative effectiveness research and open source data sharing. The international initiative for TBI research (InTBIR), a collaborative between the European Commission, the National Institutes of Health, and the Canadian Institute of Health Research, is tasked with changing the face of TBI research by 2020 [203, 204]. A crucial part of the new infrastructure for TBI research includes creation and utilization of Common Data Elements for TBI [205]. The Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) [205] and the Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI) [206] prospective longitudinal observational studies are critical to this effort. Data collected will be publically available for research through the Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system [207, 208]. These data will allow more nuanced

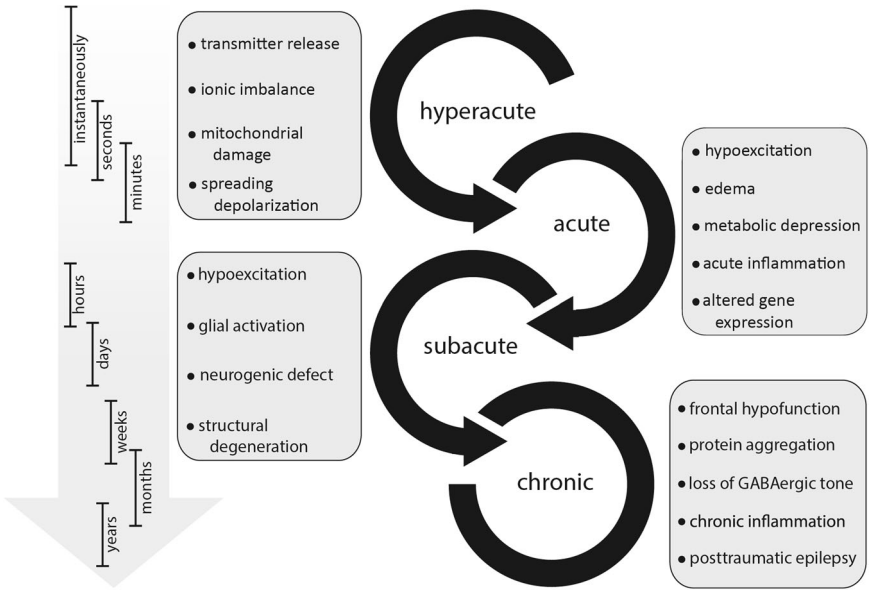

Fig. 4 Temporal evolution of TBI pathophysiology. In response to mechanical damage, there is a rapid unregulated release of ions and transmitters and mitochondrial damage that can result in edema, and transient cell membrane depolarizations. Unregulated transmission quickly leads to metabolic depression and hypofunction. Mechanisms of damage and repair, including changes in gene expression, induction of inflammatory glial responses, structural remodeling of proteins, cells, and circuits, and proliferation of neurons and glia are ongoing from acute, through subacute and into chronic stages of injury. In response to these secondary damage signals, regional differences in E/I balance can develop leading to regional hypofunction or hyperexcitability and chronic neurological, cognitive, and behavioral symptoms

approaches in selecting study populations and stratifying treatment responses. Identifying commonalities in study subpopulations is a promising focus for future tailoring of TBI treatment. Finally, focusing treatment strategies on individual neurotransmitters has not been successful. Identifying pathophysiological measures that reflect circuit level changes in plasticity, such as CSDs, may present an opportunity to integrate findings from diverse neurotransmitter systems and provide new targeting strategies for this difficult to treat condition.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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