Emerging Therapies in Traumatic Brain Injury

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Despite decades of basic and clinical research, treatments to improve outcomes after traumatic brain injury (TBI) are limited. In severe TBI, with few exceptions, supportive measures such as controlling brain swelling using osmolar therapy or barbiturates, and/or surgical interventions remain the standard of care. In severe TBI, development of novel therapies targeting secondary injury has been the topic of considerable research, but failures in translation continue to mount with the recently published clinical trial on erythropoietin1 and recent halting of the PROTECT trial of progesterone therapy (personal communication, David Wright, MD). Only treatment with amantadine in the subacute phase has translated—from the controlled cortical impact (CCI) model of TBI in rats to moderate–severe TBI in humans.2 In mild TBI
(mTBI), empiric therapies targeting sequelae such as cognitive impairment and posttraumatic stress disorder are often used. However, there has been little research on therapies in mTBI, secondary injury pathways, or the link between mTBI and neurodegenerative disease. Given the increased recognition of the scope of the problem, the growth in funding for TBI research, and the expanding discussion of therapies, an acceleration of research into the treatment of TBI across the injury spectrum is emerging and there is cause for optimism. Using a mechanism-based approach we will define the targets and emerging therapies for TBI. We will address emerging therapies for TBI across the spectrum of severity and the continuum of care, from the field to rehabilitation. We will discuss TBI therapy using 11 categories, namely, (1) excitotoxicity and neuronal death, (2) brain edema, (3) mitochondrial and oxidative stress, (4) axonal injury, (5) inflammation, (6) ischemia and cerebral blood flow (CBF) dysregulation, (7) cognitive enhancement, (8) augmentation of endogenous neuroprotection, (9) cellular therapies, (10) combination therapy, and (11) TBI resuscitation.

**Therapies Targeting Excitotoxicity and Neuronal Death**

Excitotoxicity and its link to neuronal death pathways in TBI has been richly explored, and yet after 45 years of research most antie excitotoxic therapies have failed to translate. New understanding of glutamatergic neurotransmission inspires optimism that future drugs will be more effective.

**Excitotoxicity after Traumatic Brain Injury**

Presynaptic glutamate release depolarizes post-synaptic neurons by opening ion channels such as N-methyl-D-aspartate receptors (NMDARs) that permit Na\(^+\) and Ca\(^{2+}\) to surge into cells. Excitotoxic events occur early after TBI and trigger apoptosis, necrosis, necroptosis, autophagy, or pyroptosis (none of which are mutually exclusive). Ca\(^{2+}\) overload is a key feature that is upstream to cell-death signaling. Na\(^+\) overload is less significant, but may contribute to neuronal swelling. After TBI, there is a surge in extracellular glutamate followed by persistent elevations. Extracellular glutamate increases intracellular Ca\(^{2+}\) (iCa\(^{2+}\)) by activating neuronal glutamate receptors (GluRs) like NMDARs and \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPArs). Release of Ca\(^{2+}\) from intracellular stores in organelles also contributes to excitotoxicity.

**Necrosis and Apoptosis**

Nuclear Ca\(^{2+}\) promotes neuronal survival by inducing protective genes like brain-derived neurotrophic factor (BDNF). In contrast, cytoplasmic Ca\(^{2+}\) is toxic. Necrotic death is triggered in part by calpains—Ca\(^{2+}\) activated cysteine proteases that destroy survival substrates. Traumatic brain injury induces rapid and sustained iCa\(^{2+}\) elevations and calpain activation. Blocking calpain activity in TBI models reduces tissue loss. Increased iCa\(^{2+}\) also overwhelms mitochondria resulting in oxidative stress, mitochondrial permeability transition pore (MPTP) opening and cytochrome c release. This activates the intrinsic pathway (capase-9 dependent). Apoptotic cell death has been characterized after TBI. Therapies that block executioner caspses reduce tissue loss and improve outcome.

**Additional Excitotoxic Death Pathways**

Necroptosis (programmed necrosis) is regulated by receptor-interacting serine/threonine-protein kinase (RIPK1/3) and mixed lineage kinase domain-like. Necroptosis is induced by co-incubation of tumor necrosis factor \(\alpha\) (TNF\(\alpha\)) with Z-VAD-FMK (a pan caspase inhibitor). Alone, TNF\(\alpha\) stimulates the extrinsic cell death receptor-mediated apoptotic pathway (capsase-8 dependent). Caspase-8 cleaves and destroys RIPK preventing its activation. The addition of Z-VAD during TNF\(\alpha\) – induced apoptosis in neurons stabilizes RIPK1/3 activating necroptosis. The necrotic inhibitor necrostatin-1 inhibits neuronal death after TBI. However, excitotoxicity induces necroptosis in cultured neurons, but accounts for a fraction of the cell death. Autophagy is a homeostatic mechanism that regulates catabolism of damaged organelles (macroautophagy). Loss of autophagy may contribute to neurodegenerative disease, whereas overactivation may promote cell death. There is marked upregulation of autophagy after TBI. Mice treated with the autophagy inhibitor 3-methyladenine show reduced neuronal death after TBI. However, autophagy may also be beneficial late after TBI by helping to “clean-up” injured brain. Microglia can also release glutamate, enhance excitotoxicity, and promote inflammasome-mediated cell death (pyroptosis) linked to caspase-1. All of these cell death pathways are targets for TBI therapy.

**Antie excitotoxic Therapy**

Excitotoxicity plays a key role in tissue damage after TBI. Vespa et al reported early posttraumatic subclinical seizure activity and its deleterious effects after severe TBI. Most strategies to reduce excitotoxicity include averting Ca\(^{2+}\) accumulation, or inhibiting downstream death signaling (caspases/apoptosis or calpains/necrosis). Historically NMDARs have been key targets. Nonselective NMDAR antagonists like MK801 are neuroprotective in TBI models. However, they failed in clinical TBI due to psychosomatic side effects, inadvertent death of select brain regions (cingulate and retrosplenial cortex), and limited therapeutic window. Progress in NMDAR-mediated neurotransmission has revealed greater complexity than previously appreciated—and may better inform therapy. N-Methyl-D-aspartate receptors consist of heterodimeric glutamate receptor (GluR) subunits including NR1, NR2A, and NR2B. NR2A containing NMDARs are enriched in the synapse (synaptic NMDARs). NR2B containing NMDARs are enriched at extrasynaptic sites (extrasynaptic NMDARs). Spatial distribution of NMDARs greatly affects excitotoxic signaling. Activation of synaptic NMDARs is neuroprotective. They increase nuclear Ca\(^{2+}\), activate CREB, BDNF, protein kinase B (AKT), phosphorylated-JACOB (pJACOB), and upregulate antioxidants. In contrast, activation of extrasynaptic NMDARs by glutamate spillover after TBI has the opposite effect. Extrasynaptic...
NMDARs increase cytoplasmic Ca$^{2+}$, inhibit CREB, AKT, p-JACOB, BDNF, active calpain, stimulate death-associated protein kinase (DAPK), and activate autophagy. Extra-synaptic NMDARs play a role in cell death in TBI. The selective NR2B antagonist Ro 25–6981 inhibits induction of autophagy after TBI. Stretch injury increases NR2B/NMDAR currents, which open AMPARs. That deleterious cascade is prevented by the NR2B antagonists Ro 25–6981 and memantine (a lipophilic form of amantadine). Memantine (Namenda) was tested in rodent TBI many years ago. Recently it was discovered to block extrasynaptic NMDARs while sparing synaptic NMDAR function. It is approved by the U.S. Food and Drug Administration (FDA) to treat dementia and has proved a more tolerable NMDAR antagonist than MK801. Memantine and other next-generation NR2B-selective antagonists deserve additional study.

**Considerations for Chronic Recovery after Traumatic Brain Injury**

Long-term blockade of NMDARs may limit recovery of brain function. Even mTBI disturbs synaptic processes resulting in impaired network connectivity. Abnormal synaptic connectivity may reflect aberrant decreases in glutamatergic neurotransmission or overactivation of GABAergic inhibitory input. Levetiracetam (Keppra; UCB, Brussels, Belgium) is often used to control seizures in severe TBI patients. Although the mechanisms of action are not fully understood they involve GABAergic activation and inhibition of presynaptic glutamate release. Cognition remains largely intact in patients on levetiracetam. It is curious to speculate if levetiracetam may help balance long-term excitatory/inhibitory disturbances in neurotransmission after TBI. Zou et al recently reported benefit from chronic treatment with levetiracetam after CCI in rats. Thus, one approach might be to use a potent NMDAR antagonist like memantine early after TBI, to block excitotoxicity and then transition to therapies that fine-tune glutamatergic activity during recovery such as levetiracetam. - Fig. 1 provides an overview of excitotoxicity and its link to the neuronal death pathways along with emerging therapies.

**Therapies Targeting Brain Edema**

Brain edema has been a TBI target for decades. It is identified and continuously monitored in patients with severe TBI by imaging, clinical examination, and intracranial pressure (ICP) monitoring. Cerebral edema is caused by two main mechanisms—cellular (traditionally called cytotoxic) and vasogenic—resulting from a disturbance in the blood–brain barrier (BBB). There are no therapies in clinical practice designed to prevent edema, rather than simply to treat it once it has occurred. Treatments for brain edema are limited to the use of osmolar agents (mannitol, hypertonic saline), which aid in water removal, sedatives like barbiturates, which can lower the cerebral metabolic rate and reduce brain swelling (via a coupled reduction in cerebral blood volume), cerebrospinal fluid (CSF) drainage via a ventriculostomy, and craniectomy. These guidelines-based therapies are routinely used in severe TBI. However, they have toxicities. For example, increasing serum sodium to > 170 mEq/L to manage refractory brain swelling after severe TBI caused an increased rate of acute renal failure, thrombocytopenia, and acute respiratory distress syndrome. Also, the decompressive craniectomy (DECRA) trial failed to show improved outcome in adults with severe TBI (although it decreased ICP). Some have thus even begun to question the use of ICP monitoring in patients with severe TBI; this remains controversial. A recent randomized controlled trial (RCT) by Chesnut et al showed that outcomes after severe TBI did not differ between patients managed with ICP monitoring versus clinical exam/imaging—although the use of therapies for brain swelling was similar or greater in the patients treated based on the clinical exam/imaging. In contrast, other recent clinical studies have shown that even short periods of increased ICP unfavorably affect outcome, and new preclinical work suggests that very modest levels of raised ICP (< 20 mm Hg) may be deleterious. Brain edema might even contribute to secondary damage in mTBI if astroocyte swelling at the cellular level compromises astrocyte function.

**Novel Pathways of Edema Formation**

New understandings of the molecular underpinnings of brain edema are revealing new targets and therapies. Laird et al outlined molecular events that could contribute to the development of brain edema after TBI (Fig. 2). After TBI, neuronal necrosis can induce release of the danger signal high-mobility protein box 1 (HMGB-1). HMGB-1 binds to toll-like receptor-4 (TLR-4) on microglia and triggers interleukin-6– (IL-6–) mediated aquaporin-4 (AQP4) channel upregulation in astrocytes, mediating edema formation. AQP4 is a membrane channel that regulates water transport. Consistent with this hypothesis, IL-6 and HMGB-1 are increased in human CSF after severe TBI. HMGB-1 is also linked to brain edema in TBI models. In addition to binding to TLR4, HMGB-1 interacts with the receptor for advanced glycation end product (RAGE); the RAGE pathway may play a role in vasogenic edema/breakdown of BBB, while TLR4 may mediate cellular edema. Cerebrospinal fluid levels of HMGB-1 correlate with unfavorable outcome after TBI. More discussion of this pathway is provided later in this review. Finally, Simard et al reported that sulfonfonylurea receptor 1 (SUR1) contributes to the development of brain edema. SUR1 channels conduct monovalent cations, are upregulated after TBI, and function independent of Na$^+$–K$^+$ ATPase activity.

**Emerging Therapies to Prevent Brain Edema**

Effort has been directed at developing new therapies for brain edema in TBI. The anti-inflammatory drug glycyrrhizin inhibits HMGB-1 from binding to RAGE and prevents BBB breakdown and vasogenic edema. Similarly, Okuma et al reported a reduction of edema in a rodent model using an anti-HMGB1 monoclonal antibody. Edema could also be reduced by inhibiting TLR4 with VGX-1027, which is in clinical trials for inflammatory diseases. Other therapies targeting HMGB-1/TLR4 are discussed later. AQP4 is another edema target in TBI. Injection of small-interfering RNA targeting AQP4 reduced brain edema in rats and selective AQP4
antagonists are in development (personal communication, Marc Pelletier). The SUR1 receptor blocker glibenclamide (Glyburide) is another promising therapy that reduces edema in TBI models. It is in a phase II clinical trial (NCT-01132703) in TBI. These new agents give hope for improved management of brain edema. Studies in preclinical models are also needed to determine if reducing edema blunts secondary injury independent of ICP or reduced CBF, including studies in mTBI.

**Mitochondrial Targeting Therapies and Oxidative Stress**

Mitochondria have important functions ranging from generation of ATP to production of reactive oxygen species (ROS), which are important in the regulation of life and death decisions in cells. Dysfunctional mitochondria can also generate inflammatory and vasoactive mediators. Timely elimination of dysfunctional mitochondria via macroautophagy is essential particularly in postmitotic cells such as neurons. Mitochondrial dysfunction has been reported in experimental models and humans after TBI, and is a robust target because alterations in mitochondrial function persist days after injury.

**Role of Oxidative Stress in Traumatic Brain Injury**

Oxidative stress plays a key role after TBI. It is classically described as a misbalance between the generation of free radicals and the body’s ability to detoxify them. However, this definition fails to describe the essential roles free radicals

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**Fig. 1** Strategies to modulate traumatic brain injury- (TBI-) induced excitotoxicity while maintaining beneficial glutamatergic activation. Glutamate is an essential neurotransmitter in brain function. Normal release of glutamate from presynaptic neurons activates synaptic NMDARs (NR2A enriched) on postsynaptic neurons. Synaptic NMDAR activation promotes nuclear CA2⁺ influx. Synaptic-to-nuclear CA2⁺ communication transmits prosurvival signals (CaMKIV and CREB). The transcription factor CREB induces neuroprotective BNDF. Also, synaptic NMDAR activity stimulates expression of other protective AIDs. Traumatic brain injury alters CA2⁺/calmodulin biochemistry to favor toxic cytoplasmic signaling. Extracellular glutamate activates distal extrasynaptic NMDARs (NR2B enriched). Extrasynaptic NMDARs promote cell death (top-left). They oppose synaptic NMDAR/CaMKIV prosurvival responses and activate calpains and DAPK, and inhibit AKT survival signaling. Drugs approved by the U.S. Food and Drug Administration targeting excitotoxicity include (identified by Ø): (1) Memantine — blocks extrasynaptic NMDAR, (2) ceftriaxone and raloxifene — increases expression of glutamate uptake transporters in astrocytes, and (3) levetiracetam — may inhibit high presynaptic glutamate release by modulating inhibitory GABAergic input to excitatory neurons. ALS, amyotrophic lateral sclerosis; CBF, cerebral blood flow; CTE, chronic traumatic encephalopathy; NMDAR, N-methyl-D-aspartate receptor; GluN2A/NR2A, glutamate N2A subunit; GluN2B/NR2B, glutamate N2B subunit; CREB, cAMP response element binding protein; GLT-1, glial glutamate transporter 1; GLAST, glutamate/aspartate transporter; AKT, protein kinase B; DAPK, death-associated protein kinase; BDNF, brain-derived neurotrophic factor; AID, activity-regulated inhibitor of death; CaMK, CA2⁺/calmodulin dependent protein kinase.
play in normal neuronal function, such as long-term potentiation. A more contemporary definition, “disruption of redox signaling and control,” recognizes the compartmentalized nature of these events.

For a thorough evaluation of oxidative stress, a battery of studies, including (1) assessment of generation of free radicals; (2) quantification of oxidation products of lipids, proteins, and DNA; and (3) evaluation of radical scavenging capacity, should be performed. All of these components of oxidative stress occur after experimental and clinical TBI.

Several sacrificial antioxidants and free radical scavengers have been explored in TBI, such as PEG-SOD, tirilazad, and edaravone. Although they have shown efficacy in TBI models, clinical trials failed to confirm efficacy. The limitations of general antioxidant strategies include narrow therapeutic window, inability to cross the BBB, and lack of targeting of the specific causes of oxidative stress. Without a targeted approach, the use of sacrificial antioxidants and free radical scavengers will fail.

Mitochondrial Failure after Traumatic Brain Injury

Mitochondria are a major intracellular source of ROS with production of superoxide and its dismutation product hydrogen peroxide. Other sources of oxidative stress after TBI include NADPH oxidase, nitric oxide (NO) synthases, xanthine oxidase, and transition metals, which can be released by hemorrhage. Underlying mechanisms of increased production of ROS by mitochondria include dysfunction of electron transport and impairment in Ca²⁺ buffering. Mitochondria are also targets of ROS, which can promote MPTP opening, leading to apoptosis. Mitochondrial DNA, which encodes elements for electron transport, is also a target for free radical damage. Thus, oxidative stress can impair mitochondrial function, which in turn generates more oxidative stress in a vicious cycle.

Targeting Mitochondrial after Traumatic Brain Injury

Several strategies have been designed to combat mitochondrial dysfunction, including alternative fuels and MPTP inhibitors. Preliminary studies in adults describe the safety of cyclosporine, a MPTP inhibitor, when given after severe TBI. These strategies target different components of mitochondrial dysfunction, but fail to localize into mitochondria. Recently small molecules have been discovered that can selectively accumulate in mitochondria and bind targets in the organelle to exert their effects. Several strategies have been used, including (1) conjugation to lipophilic cations such as triphenylphosphonium that take advantage of negative membrane potential of mitochondria, and (2) binding to a specific mitochondrial target such as cardiolipin (CL), a phospholipid exclusively found in the inner mitochondrial membrane.
membrane. Both strategies are effective at delivering therapies into mitochondria. Compounds in the first category have not been tested in TBI. One of them, Mito-Q (a ubiquinone moiety linked to triphenyl-phosphonium), was used in recent human trials in Parkinson disease and hepatitis C. Compounds in the second category include Szeto-Schiller (SS) peptides. Their uptake into mitochondria is thought to be independent of membrane potential, with a high affinity binding to inner membrane. They contain four alternating aromatic amino acids and some have antioxidant activity. One of these peptides, SS-31, protects mitochondria, accelerates ATP recovery, and reduces infarct size in the heart.

Another class of compounds in the second category promising for TBI are the hemagamicdin-nitroxides (GS-nitroxide), inspired by the shared ancestry between mitochondria and bacteria, taking advantage of chemical moieties used in antibacterial agents (the antibiotic gramicidin S) with high affinity for the inner membrane. One GS-nitroxide, XJB-5-131, was shown to partition almost exclusively into neuronal mitochondria in vitro, penetrate the BBB, prevent TBI-induced CL oxidation and caspase activation, and improve lesion volume and neurocognitive outcome after TBI. This is an exciting targeted strategy for TBI.

In summary, there is promising experimental success in application of mitochondria-targeted redox regulators in treatment of TBI, and these approaches deserve significant future efforts.

**Therapies Targeting Neuroinflammation**

Evidence suggests the inflammatory response, including cytokines, chemokines, microglial activation, and recruitment of circulating leukocytes, mediates secondary injury and/or repair after TBI. Traumatic brain injury causes the release of endogenous danger signals (i.e., extracellular ATP and HMGB-1), which bind to pattern recognition receptors such as TLR4 on neurons and glia to activate the immune response. Activated microglia undergo a phenotypic shift from an anti-inflammatory (M2) state to a proinflammatory and procytotoxic (M1) state. M1 microglia proliferate and migrate to the injury site and (1) form a barrier between damaged and healthy tissue, (2) increase expression of proinflammatory cytokines such as TNFα and IL-1β, and (3) release ROS and reactive nitrogen species. Chronic microglial activation develops and may mediate chronic traumatic encephalopathy (CTE) and neurodegenerative diseases.

**Dual Role of Inflammation in TBI**

Studies of the role of TNFα after TBI reveal the dual effects of inflammation in secondary injury and repair. Scherbel et al using a TNF KO mouse reported evidence of early neuroprotection in the KO at 48 hour; however, TNF KO mice had persistent motor deficits and more tissue loss at 4 weeks compared with wild-type. Balancing neurotoxicity with repair must be considered for therapies that modulate inflammation. Preclinical work with thalidomide analogs (TNFα synthesis inhibitor) and etanercept (fusion protein that binds to and inhibits TNFα) have shown benefit early after TBI.

**HMGB-1/TLR4 Pathway Inhibition**

HMGB1/TLR4 pathway inhibitors were previously discussed. They also block secondary injury due to immune activation. Ethyl pyruvate, an inhibitor of HMGB1 secretion, and resatorvid, a small molecule inhibitor of TLR4, improved outcome and reduced levels of TNFα and IL-1β in rodent TBI models. These drugs have not yet been evaluated in clinical trials for TBI.

**Other Anti-Inflammatory Agents**

Minocycline, a lipophilic tetracycline antibiotic with several proposed mechanisms of action, including inhibition of microglial activation, reduces IL-1β production, lesion volume, and functional deficits in TBI models. A phase 1 clinical trial of minocycline in TBI is recruiting patients. IL-1β antagonism via intraventricular injection of anti-IL-1β antibody and transgenic overexpression of IL-1 receptor antagonist (IL-1ra) reduced lesion volume and improved outcomes in TBI models. A recent phase 2 trial in adults with severe TBI randomized 20 patients to receive 100-mg recombinant human IL-1ra (Anakinra) for 5 days, an FDA-approved dose for rheumatoid arthritis. Adverse events did not differ in treatment and control groups. Cerebral microdialysis showed increased levels of IL-1ra with treatment and a shift in the cytokine/chemokine profile. HMG-CoA reductase inhibitors (statins) have several proposed mechanisms of action after TBI (antia apoptotic, antioxidant, increase CBF, and neurogenesis); however, the primary mechanism is likely anti-inflammatory. Two clinical studies of statins have been conducted—a RCT of rosuvastatin in 20 adults with TBI that showed improved memory with treatment, and a retrospective study showing a 76% relative risk reduction for mortality in patients treated with statins before injury. Larger RCTs are needed.

**Promoting Inflammation-Mediated Regeneration**

Another approach is to promote shifting microglia from the M1 to the M2 phenotype. Currently under investigation for treating multiple sclerosis, therapies such as glatiramer acetate, interferon-β, or dimethyl fumarate may promote the beneficial aspects of neuroinflammation—neurogenesis and repair—while reducing cytotoxic mediators. A similar approach is being adapted from spinal cord injury research with the use of “pro-inflammatory” therapy: G-CSF alone or in combination with mesenchymal stem cells. These therapies may also be useful late in the course of the disease to mitigate CTE.

**Therapies Targeting Traumatic Axonal Injury**

Therapies targeting traumatic axonal injury (TAI) is a prominent feature of TBI and represents a vital target across the spectrum of injury severity. In classic studies, Pavlishock showed that TAI is a fundamental component of secondary injury after TBI and thus a key therapeutic target. Progression of TAI involves TBI-induced dysregulation of Na channels, in turn causing increased Ca influx into axons,
calpain activation with loss of microtubules, neurofilament im­paction with impaired axoplasmic transport, and mitochondrial failure with permeability transition pore opening and oxidative stress. The aforementioned novel strategies targeting mitochondrial failure may be particularly efficacious in TAI. Smith et al recently identified categories of therapies for TAI based on work in TBI models: (1) cytoskeleton stabilization, (2) ion homeostasis, (3) protease inhibition, (4) mitochondrial protection, (5) mild hypothermia, and (6) other therapies. We will review and update those categories (Fig. 3).

**Cytoskeleton Stabilization**

Loss of microtubule function devastates axonal transport. Unfortunately, data are limited on approaches to block this mechanism. The chemotherapeutic drug Taxol can inhibit chemical depolymerization of microtubules during stretch. Taxol has not been tested in TBI in vivo, but recently produced axonal preservation after spinal cord injury in rats.

**Ion Homeostasis**

There has also been limited work targeting \( \text{Ca}^{2+} \) accumulation linked to TAI. Rather, focus has been on downstream signaling cascades such as calpain activation. Therapies targeting major breaches in membrane disruption such as Kollidon VA64 show promise in TBI models.

**Protease Inhibition**

Beneficial effects of calpain inhibition on TAI have been shown in rodent TBI models for over a decade, including use of MDL28170, AK295, and SJA-6017. However, lack of brain bioavailability and target specificity have limited the development of calpain inhibitors. Recent studies have suggested that citicoline suppresses calpain activation after TBI. However, the failed COBRIT clinical trial with citicoline argues against this agent. Given the evidence supporting a role for calpain in TAI, it is disappointing that additional calpain inhibitors are not available.

**Mitochondrial Protection**

Mitochondrial failure may worsen \( \text{Ca}^{2+} \) overload and exacerbate TAI. Preclinical work has shown benefit from cyclosporine A (CsA) on TAI. Inhibition of MPTP opening is suggested as the mechanism for this effect. However, clinical studies with CsA have been equivocal. The aforementioned GS-nitroxides or N-acetyl cysteine (NAC) amide are logical candidates to study.

**Hypothermia**

Preclinical work shows that mild hypothermia can attenuate TAI. Sadly clinical trials in TBI have failed. Surprisingly, hypothermia failed to attenuate the increase in CSF levels of myelin basic protein after severe TBI in children. Mild hypothermia was recently shown to markedly attenuate TAI.

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![Fig. 3](https://via.placeholder.com/150)

**Fig. 3** Emerging therapies to limit traumatic axonal injury (TAI) after traumatic brain injury (TBI). Cellular and molecular events in the TAI cascade include \( \text{Ca}^{2+} \) accumulation with calpain activation and resultant microtubule proteolysis, MPTP opening, and oxidative stress. Direct membrane poration can also mediate injury. Emerging therapies (identified by \( \bigcirc \)) include calpain antagonists (MDL28170, AK295, SJA-6017), and taxol, which may prevent microtubule polymerization. Therapies targeting mitochondria include CsA that blocks MPTP, FK506 that may target calcineurin induced translocation of BAD, and XJB-5–131 and NACA that target oxidative stress in mitochondria. Kollidon VA64 may directly reseal membranes. Mild hypothermia may reduce TAI by multiple mechanisms. CsA, Cyclosporin A; NACA, N-acetyl cysteine amide.
after repetitive mTBI in rats. Mild hypothermia deserves exploration in mTBI.

Other
In addition to CsA, the calcineurin inhibitor FK506 has been shown to reduce TAI, particularly in unmyelinated axons. It is unclear whether this is independent of effects on mitochondria. Therapies targeting oxidative damage have also been suggested to reduce TAI—these were discussed previously.

Therapies Targeting Cerebral Blood Flow Dysregulation and Ischemia
After TBI, CBF dysregulation develops and may contribute to secondary damage. In mTBI, vascular dysregulation could mediate vulnerability to a second hit. Cerebral blood flow is often reduced early after severe TBI. This may result from a coupled reduction in brain activity, but can be pathologic during excitation. Cerebrovascular resistance (CVR) is controlled at the macro- and microvascular level. At the microvascular level, it is coupled to brain metabolic activity. Recently, Hall et al showed that pericytes positioned around brain capillaries mediate dilation that produces a much greater change in CBF (19% vs. 3%) than dilation of arteries alone—implicating pericyte-mediated dilation as the major contributor to changes in CBF. Key metabolites identified included the vasodilators nitric oxide (NO) and prostaglandin-E2 (PGE2) and the vasoconstrictor 20-hydroxyeicosatetraenoic acid (20-HETE). They implicated the relative production of these metabolites in regulating pericyte dilatation and thus CBF. The potent vasoconstrictor endothelin-1 (ET-1) may also contribute to CBF dysregulation after TBI.

Modulating Nitric Oxide
Nitric oxide is a potent vasodilator and may be useful to treat ischemia after TBI. Conversely, NO at high levels can be converted to peroxynitrite, which can worsen damage. This paradox has yielded interventions that augment NO delivery or block NO production after TBI. The primary clinical strategy to increase NO delivery is with inhaled NO. Inhaled NO is FDA-approved for neonatal respiratory failure. Studies suggest that inhaled NO improves collateral circulation and outcomes in TBI models. However, in newborn piglets, the NO donor sodium nitroprusside did not prevent impaired autoregulation during hypotension after TBI, implying that NO augmentation may only be beneficial in normotensive states. This is important, given that NO augmentation can produce hypotension that may mitigate benefit. Whether inhaled NO is a viable approach remains to be determined. Nitric oxide synthase inhibitors are also being explored in TBI. A phase II placebo controlled trial with the NO synthase inhibitor VAS 203 was just completed in 32 adults with TBI (NOSTRA; NCT 02012582). It suggested improved outcomes, but renal injury was a concern. It is unknown if NO augmentation or inhibition is preferred. A targeted approach to NO delivery to maximize microvascular affects coupled with selective inhibition of inducible NOS (iNOS) to prevent nitrosative stress might be considered. However, sustained inhibition of iNOS may be deleterious given that iNOS KO mice exhibit marked impairments in cognitive outcome.

Modulating ET-1
In TBI, ET-1 levels in CSF are increased and linked to unfavorable outcomes. However, in a phase 2b trial, the ET receptor A antagonist clazosentan failed to improve outcomes after subarachnoid hemorrhage (SAH). New ET-1 antagonists remain to be tested in TBI.

Statins
HMG-CoA reductase inhibitors (statins) are used for cholesterol reduction. As discussed, they have anti-inflammatory effects, but also upregulate eNOS and increase NO production, leading to improved capillary patency. Clinical trials with statins suggest a potential benefit on outcome in TBI, although the role of effects on CBF is unclear. In stroke, an RCT of lovastatin is in phase 2 trials (NeuSTART, NCT01976936). The optimal choice of statin and dosing for BBB penetration also remain unclear. Results from larger RCTs in TBI are needed to define the utility of these agents in TBI.

Cytochrome P450 Metabolites
Cytochrome P450 produces two classes of arachidonic acid metabolites with opposing microvascular effects. Hydroxylation produces 20-HETE, a potent vasoconstrictor, while epoxidation produces epoxyeicosatrienoic acids (EETs), which are vasodilatory. Both 20-HETE and EETs are autoregulatory mediators. Inhibition of 20-HETE formation by NO is an essential pathway of PGE2-mediated pericyte dilatation. Inhibition of 20-HETE formation or prevention of EET metabolism can reduce lesion volume in stroke and SAH models. 20-HETE is involved in reduced CBF in cortical spreading depression—a secondary injury mechanism implicated in TBI. Thus, cytochrome P450 arachidonic acid metabolites affect CBF after TBI. It remains to be determined whether targeting these pathways can improve outcome after TBI.

Enhancing Oxygen Delivery
Another approach to reduce ischemic damage is to improve oxygen delivery despite CBF reductions—such as with perfluorocarbon-enhanced oxygen delivery. A safety/efficacy RCT is evaluating the perfluorocarbon Oxycyte (STOP-TBI; NCT00908063). Mild hypothermia has also been shown to reduce CBF dysregulation after TBI. This includes benefit injury in repetitive mTBI.

In summary, an emerging area TBI is mitigating microvascular dysregulation. These approaches and others deserve further investigation in TBI, including testing in mTBI.

Cognitive Enhancement
Many rehabilitation strategies have been used to enhance cognitive function after TBI. Some of the most effective preclinical rehabilitative strategies in TBI have been neurostimulant pharmacotherapies, and as discussed below,
successful clinical translation of this approach in an RCT was recently achieved. Thus, we will focus on these agents as emerging TBI therapies.

**Catecholamine Agonists**
Catecholamine agonists promote functional recovery after TBI. This was confirmed in weight drop cortical contusion or ablation models in rats and/or cats. Because norepinephrine antagonists block or reestablish deficits, the noradrenergic system has been implicated. However, clinical and experimental research shows that the dopamine (DA) system is also involved in both injury and rehabilitative processes. Methylphenidate, a psychostimulant and DA transporter inhibitor, exhibits pharmacological properties similar to amphetamine, but without undesirable sympathomimetic effects. In a study assessing motor function after sensorimotor cortex injury in rats, a single dose of methylphenidate followed by symptom relevant experience (rehabilitation) in promoting functional recovery after TBI. Moreover, daily treatment with methylphenidate beginning as late as 24 hours after CCI in rats revealed less spatial memory de

ment effects and dosing for male versus female rats. Amantadine accelerates the rate of functional recovery after TBI. Moreover, treatment with methylphenidate beginning as late as 24 hours after injury. In a study assessing motor function after sensorimotor cortex injury in rats, a single dose of methylphenidate followed by symptom relevant experience (rehabilitation) in promoting functional recovery after TBI. Moreover, daily treatment with methylphenidate beginning as late as 24 hours after CCI in rats revealed less spatial memory deficits versus controls. Wagner et al has shown that methylphenidate exhibits some restorative capacity for striatal DA neurotransmission after experimental TBI; their additional work suggests potential sex differences in methylphenidate treatment effects and dosing for male versus female rats.

**Amantadine—A Translational Success**
With success in preclinical studies as well as phase 2 and phase 3 clinical trials, amantadine (Symmetry; Endo Pharmaceuticals, Malvern, PA) is a promising drug for TBI rehabilitation. Daily treatment with amantadine (for 20 d) after CCI in rats revealed improvements in spatial memory performance deficits versus saline-treated counterparts. Higher doses also benefit cognition after fluid percussion. Clinically, amantadine accelerates the rate of functional recovery in vegetative or minimally conscious patients during the subacute phase after TBI. It exerts its effects by increasing extracellular DA by blocking reuptake and by facilitating synthesis. In addition to its presynaptic actions, amantadine increases the density of postsynaptic DA receptors or alters their conformation, which may be clinically important. Because the mechanism of action of amantadine differs from other DA-releasing drugs, it is likely that the dopaminergic effects of amantadine are a combination of presynaptic and postsynaptic effects. It also blunts NMDAR activation.

**Bromocriptine**
Delayed or chronic treatment with the D2 receptor agonist bromocriptine also improves the acquisition of spatial and working memory in rats after CCI. Bromocriptine (5 mg/kg) has been shown to increase extracellular DA levels in rats, suggesting that enhanced presynaptic DA neurotransmission may have mediated the benefit at this dose. Bromocriptine also attenuated lipid peroxidation, suggesting antioxidant effects. Further support for dopaminergic activity in restoring functional recovery after TBI comes from a preclinical study showing that selegiline (L-deprenyl), which enhances the action of DA by inhibiting its main catalytic enzyme in brain, monoamine oxidase-B, improved cognitive outcome when given daily for 7 days after fluid percussion injury. Clinical studies showing benefits of DA augmentation after TBI also exist.

Thus enhancing catecholamine neurotransmission during the chronic postinjury phase may be a useful adjunct in ameliorating the neurobehavioral sequelae of TBI in humans. Additional studies are warranted.

**Augmenting Endogenous Neuroprotectants**
Evolution has provided several naturally occurring neuroprotective mechanisms. Perhaps the “low-hanging fruit” for increasing therapeutic options for TBI patients resides in augmenting the mechanisms that allowed the brain to evolve in the first place.

**Adenosine as an Archetype for Endogenous Neuroprotection**
Adenosine is released by tissue injury via several pathways. Breakdown of ATP is one source of adenosine in the injured brain (the traditional route). Recently, an alternative 2,3′ cAMP pathway was discovered, and involves production of adenosine from mRNA breakdown via 2,3′cAMP. This latter pathway appears to play a major role after TBI. Adenosine acts on cell surface receptors (A1, A2A, A2B, and A3) and engages signal transduction that is neuroprotective in TBI. Activation of A1 receptors attenuates post-TBI excitotoxicity. Mice null for A1 receptors suffer lethal status epilepticus after TBI and variants in the A1 receptor genes associate with postranstraumatic seizures in TBI patients. Moreover, A1 receptor KO mice exhibit enhanced microglial proliferation after TBI. However, systemic effects of A1 agonists (bradycardia, hypotension) limit their use in TBI. A more effective strategy might be to enhance adenosine levels in the brain or increase A1 receptor numbers and/or signaling. One approach would be to upregulate enzymes that produce adenosine. For example, isoflurane increases activity of the adenosine-forming enzyme ecto-5′-nucleotidase (CD73) by stimulating release of microparticles, which may contribute to its neuroprotection. Another approach would be to administer chronically and prophylactically an A1 receptor blocker with a short half-life. This would upregulate A1 receptor numbers and signaling in the brain, yet post-TBI the antagonist would dissipate rapidly, leaving enhanced adenosine signaling at the time of greatest need. Improved outcomes are seen in TBI patients with caffeine (a short half-life adenosine receptor antagonist) in their CSF at the time of injury. Finally, adenosine kinase (ADK) is a key enzyme in the breakdown of adenosine. Adenosine kinase increases markedly in the astrocyte scar and limits adenosine availability chronically after TBI. Given the anticonvulsant effects of A1 receptors, blocking ADK or using other strategies to
overexpress adenosine may represent a therapy for postrau-
matic seizures. Huber et al.\textsuperscript{183} used grafts of adenosine-
releasing fibroblasts to suppress seizures in rats. A1 receptor gene
polymorphisms are strongly associated with postrau-
matic seizures.\textsuperscript{177} Thus, it may be possible to use a personal-
ized medicine approach to define patients who might benefit
from adenosine augmentation therapy.

Other Endogenous Neuroprotectants

There are many other endogenous neuroprotectants emerg-
ing as therapies for TBI. Augmentation of trophic factors such
as BDNF, or immediate early gene products such as HSP, could
improve outcome after TBI.\textsuperscript{184} It was recently shown that
remote preconditioning using tourniquet inflation/deflation
may mediate benefit in ischemia/reperfusion via local elabo-
ration of nitrite—which is converted to NO in regions of tissue
hypoxia.\textsuperscript{185} Systemic nitrite therapy might yield similar
effects.\textsuperscript{186} An endogenous neuroprotectant receiving atten-
tion in Parkinson disease is uric acid, which has antioxidant
effects.\textsuperscript{187} Finally, regulators of cold stress such as RNA-
binding motif 3 (RBM3) stabilize mRNAs and may underlie
benefit in hypothermia.\textsuperscript{188} New drugs are targeting RBMs.\textsuperscript{189}

Cellular Therapies

Therapies designed to replenish cells lost after TBI may help
improve outcome. Methodologies include supplementation of
exogenous stem cells or therapies that enhance endoge-
nous neurogenesis in the adult brain. Both approaches have
promise based on studies in TBI models. New approaches are
being used to enhance the regenerative capacities of these
cellular therapies in hopes of developing interventions that
can ultimately promote recovery in patients.

Administration of Exogenous Cells

Traumatic brain injury can be associated with loss of neurons
and other cells in multiple brain regions. Administration of
exogenous bone marrow stromal cells in rats, via intracra-
al,\textsuperscript{190} intra-arterial,\textsuperscript{191} or intravenous delivery,\textsuperscript{192} results in a
portion of transplanted cells migrating into the brain paren-
chyma, and is associated with improved motor function after
TBI.\textsuperscript{190,193} Survival of stromal cells is associated with in-
creased production of BDNF and nerve growth factor.\textsuperscript{192} In
other studies, transplantation of neural stem cells\textsuperscript{194,195} and
the coadministration of neural stem cells and olfactory
ensheathing cells similarly improve motor performance after
TBI.\textsuperscript{196} However, it is unclear whether the regenerative
capacity of transplantation is dependent upon the incorpo-
ration of the exogenous cells, the production of soluble
growth permissive factors, or their combination. Two studies
provide evidence for complex dynamics between the contribu-
tions of exogenous cell survival and the release of soluble
factors that promote regeneration after TBI. Intracranial
administration of human bone marrow stromal cells in a
collagen scaffold matrix enhances the survival of the stromal
cells in the cortex and improves motor function compared
with administration of stromal cells alone.\textsuperscript{52} Coadminis-
tration of the collagen scaffold also enhanced corticospinal tract
sprouting in the denervated spinal cord,\textsuperscript{197} suggesting con-
tributions from both the surviving stromal cells and soluble
factors that promote regeneration after TBI. Tajiri et al.\textsuperscript{198}
studied soluble factors released from transplanted human
adipose-derived stem cells that may play a role in recovery
after TBI. Delivery of either the adipose-derived stem cells or
conditioned media improved outcome in rats after TBI.
However, knockdown of two long noncoding RNAs, impor-
tant for cellular differentiation, blunted the recovery. These
data indicate that regeneration can be enhanced with soluble
factors in the absence of transplanted cells. They reveal the
potential of transplantation approaches and highlight the
complex dynamics between stem cells and growth permissive
factors in promoting recovery.

Enhancing the Generation and Survival of
Newborn Cells

Therapies that enhance the generation of newborn neurons
are also attractive after TBI. Enhancement of neurogenesis
after TBI with growth factors, neuroprotective agents, and
hypothermia promotes cellular proliferation and increases
the generation of newborn neurons in neurogenic regions of
the injured brain.\textsuperscript{199–202} These studies have also shown that
an enhancement of postransplantation neurogenesis in the weeks
after TBI is associated with improved neurobehavioral per-
formance. Hippocampal immature neurons are particularly
sensitive to brain injury in the days postinjury.\textsuperscript{202} Promoting
survival of neural stem cells and immature neurons is a
promising target to improve outcome.\textsuperscript{203} Blaya et al\textsuperscript{204}
evaluated the efficacy of the neuroprotective agent P730-A20 to
promote the survival of immature neurons, as this drug
blocks apoptosis in immature neurons. Treatment with
P730-A20 improved immature neuron density, increased
the number of newly generated neurons, and improved
cognitive performance. This highlights the promise of ther-
apies promoting newborn neuron survival and incorporation
into the injured brain.

Clinical Trials of Cellular Therapy

There are several clinical trials exploring cellular therapy in
TBI. Recently a study addressing “Safety of Autologous Stem
Cell Treatment for TBI in Children” (NCT00254722) was
completed. The objective of that phase 1 study was to
determine if bone marrow precursor cell harvest and autolo-
gous transplantation (within 36 h of injury and by intrave-
nous route) is safe in children after TBI. The study was
completed; a phase II trial is recruiting (NCT01851083). There
is also an open label study of “Autologous Bone Marrow
Mononuclear Cells in TBI” (NCT0202810), in which bone
marrow-derived mononuclear cells are given intrathecally.
That study is also recruiting.

Combination Therapy

Combination therapy is attractive to overcome translational
challenges. Incomplete understanding of dose–response rela-
tionships and poor central nervous system (CNS) penetration
of therapies are factors widely acknowledged to contribute to
failed clinical trials.\textsuperscript{205–207} The heterogeneity of TBI and its complex pathophysiology suggest that it is unlikely that any single agent can address all of the secondary injury mechanisms.\textsuperscript{205} The success of combination therapies that enhance drug exposure or have complementary mechanisms of action in cancer and human immunodeficiency virus has further increased enthusiasm for this approach in TBI research.

**Emerging Combination Therapies**

In 2008, the NIH convened a workshop on multidrug combinations for TBI. The recommendation was to combine therapies with complementary targets and effects rather than focus on a single target with multiple therapies.\textsuperscript{207} Several combination therapies meeting this definition are being investigated. One of the most promising combines the anti-inflammatory agent minocycline and the glutathione precursor NAC. Effects of minocycline were discussed previously. N-acetyl cysteine is a precursor for synthesis of the antioxidant glutathione, impacts glutamatergic transmission, and despite poor CNS penetration improved outcomes in some TBI models and in blast-induced mTBI in humans.\textsuperscript{208–210} When given together, benefits of the combination exceed that of the single agents studied in CCI and mTBI models.\textsuperscript{211,212} N-acetyl cysteine is used in another combination therapy designed to improve drug exposure. Our group is testing coadministration of the FDA-approved organic acid transporter and multidrug resistance-associated protein inhibitor, probenecid, with NAC in preclinical and phase I pediatric studies (NCT01322009). The aim is to overcome membrane barriers, such as the BBB, to synergistically improve NAC bioavailability and antioxidant reserves after TBI. Preclinical pharmacokinetic (PK) data show that probenecid increases NAC brain penetration in juvenile rats two- to threefold as early as 1 hour after injury.\textsuperscript{213} Outcome studies are underway. Other combinations such as progesterone plus vitamin D are in early stages of preclinical investigation.\textsuperscript{214}

**Addressing Unique Challenges of Combination Therapy**

Interactions between therapies may alter PK (dose-concentration relationships) or pharmacodynamic (concentration-effect relationships) properties of either therapy. They may be additive, synergistic, or antagonistic. Thus, studies using full-factorial designs at multiple dosing levels are ideal.\textsuperscript{207} These data are used to identify combinations and sequences of therapies that achieve greater efficacy and lower toxicity than either therapy alone. Specific statistical approaches to identify synergism are advocated.\textsuperscript{215} Coadministered therapies should also be evaluated for physicochemical incompatibilities to ensure systemic bioavailability. As with single drugs, it is imperative to measure brain concentrations of therapies used in combination to optimize their potential for success.

**Therapies Targeting TBI Resuscitation in Polytrauma**

Traumatic brain injury is often accompanied by secondary insults (hypotension, hemorrhage, hypoxemia) that worsen outcome.\textsuperscript{216} However, given their complexity, clinical studies commonly exclude these patients, and few animal models have been developed to investigate therapies. Optimal resuscitation of the TBI patient with polytrauma continues to present unique challenges and remains understudied.

**Resuscitation Fluids**

The mainstay of resuscitation involves fluids: crystalloids, colloids, and/or blood products. Crystalloids are the initial therapy; however, large volumes are often needed, which can exacerbate brain edema.\textsuperscript{217} Colloids, given their improved ability at maintaining intravascular volumes, are attractive; however, in the SAFE study, TBI patients resuscitated with albumin had raised ICPs and greater mortality compared with saline-treated patients.\textsuperscript{218} Traumatic brain injury-induced BBB permeability may have allowed extravasation of albumin into brain—potentially rebound brain edema.\textsuperscript{219} Thus, small molecule colloids may be problematic early after TBI. Blood products are not available for prehospital use.

**Emerging Resuscitation Agents**

Given the risk of exacerbation of brain edema with current resuscitation fluids, new therapies are being investigated, including novel, ultra-small-volume resuscitation agents. Polynitroxylated pegylated hemoglobin (PNPH) is one agent that may represent an out-of-hospital bridge to transfusion. Polynitroxylated pegylated hemoglobin is a bovine-based hemoglobin that, in an effort to eliminate toxicity of cell-free hemoglobin, is covalently bonded with antioxidant nitroxide moieties and polyethylene glycol side chains. Polynitroxylated pegylated hemoglobin is being developed as a small-volume resuscitation solution. In a model of TBI plus hemorrhage, it dramatically reduced resuscitation fluid requirements compared with crystalloid.\textsuperscript{220,221} It also reduced ICP, brain edema, and neuronal death.\textsuperscript{220,221} Unlike conventional free hemoglobins, it has surprising in vitro neuroprotective effects.\textsuperscript{221} It is in preclinical development. Traditional resuscitation approaches focus on improving tissue perfusion by increasing circulating blood volume. An alternative might entail modification of microcirculatory blood flow. Drag-reducing polymers (DRPs) at nM levels markedly reduce the resistance of microvascular flow, improving tissue perfusion.\textsuperscript{222,223} Drag-reducing polymers, such as long-chain polyethylene glycol (kDa > 10⁶), improve perfusion and reduce mortality in models of hemorrhagic shock.\textsuperscript{224} Drag-reducing polymers thus could maintain brain perfusion despite using a volume-limited resuscitation.

**Conventional Resuscitation Plus Antiedema Therapies**

Although volume-limiting resuscitation strategies hold promise in TBI, treatment with the aforementioned novel drugs targeting brain edema (Kollidon VA64, glibenclamide, AQP4 antagonists) could reduce the deleterious effects of resuscitation fluids on edema after TBI. Preclinical studies of these drugs are needed in models of TBI plus hemorrhage/polytrauma.
Other Therapies

Many more emerging therapies are on the horizon, including the use of transcranial low level laser,\textsuperscript{225} nutraceuti-
cals,\textsuperscript{226,227} lithium,\textsuperscript{228} modulating cell cycle\textsuperscript{229} and targeting microhemorrhage,\textsuperscript{230} among many others. This brief list illustrates the level of creativity in our dynamic research field.

Conclusion

This review is far from comprehensive. However, given our goal to address mechanism-based emerging therapies across the injury-severity spectrum, and from the field to rehabilitation, we chose to provide a “survey” across key mechanisms. There are many other promising agents worthy of investigation. We also believe that the recent surge in interest in mTBI may identify new targets in severe TBI—particularly given the fact that in patients with severe TBI, brain regions outside of areas of major disruptions are likely to be plagued by the pathomechanisms seen in mTBI. Thus, new investigations into therapies for mTBI may provide new opportunities for treatment of severe TBI. For example, emerging mechanisms in mTBI, such as disturbances in the balance between excitatory and inhibitory pathways or disturbances in synchronization,\textsuperscript{42,231} could be important in severe TBI—layered upon the classical injury paradigms (\textsuperscript{\textbullet Fig. 4}). Finally, to complement rehabilitation and cognitive enhancing therapies currently used chronically after TBI, new approaches to break the link between TBI and chronic neurodegenerative diseases including CTE are needed (\textsuperscript{\textbullet Fig. 4}). The current golden age of TBI research thus represents a special opportunity for the development of breakthroughs in the field.

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ary Clinical Research Scholars Program (PE).

References


\textbullet Fig. 4 A contemporary view of therapeutic targets across the spectrum of traumatic brain injury (TBI) from mild to severe includes classical secondary injury pathways along with novel mechanisms such as excitation inhibition imbalance and functional asynchrony that have come to the forefront in mild TBI. Therapies to embellish rehabilitation-based strategies to break the link between TBI and chronic neurodegenerative diseases such as chronic traumatic encephalopathy (CTE) are also needed. Therapies are identified by Ø. ALS, amyotrophic lateral sclerosis.


Rao VLR, Dogan A, Todd KG, Bowen KK, Dempsey RJ. Neuroprotection by memantine, a non-competitive NMDA receptor antagonist after traumatic brain injury in rats. Brain Res 2001;911:96–100

Xia P, Chen HSV, Zhang D, Lipton SA. Memantine preferentially blocks extrasynaptic over synaptic NMDA receptor currents in hippocampal autopsies. J Neurosci 2010;30(33):11246–11250


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46 Lee CY, Chen CC, Liou HH. Leviracetam inhibits glutamate transmission through presynaptic P/Q-type calcium channels on the granule cells of the dentate gyrus. Br J Pharmacol 2009;158(7):1753–1762

47 Wakita M, Kotani N, Kogure K, Akaite N. Inhibition of excitatory synaptic transmission in hippocampal neurons by leviracetam involves Zn²⁺-dependent GABA type A receptor-mediated presynaptic modulation. J Pharmacol Exp Ther 2014;348(2):246–259


73 Robertson CL. Mitochondrial dysfunction contributes to cell death following traumatic brain injury in adult and immature animals. J Bioenerg Biomembr 2004;36(4):363–368


78 Jones DP. Redefining oxidative stress. Antioxid Redox Signal 2006;8(9–10):1865–1879


83 Bayr H, Kagan VE, Tyurina YY, et al. Assessment of antioxidant reserves and oxidative stress in cerebrospinal fluid after severe
89 Zorov DB, Juhaszova M, Sollott S. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiol Rev 2014; 94(3):909–950
95 Van Houten B, Woshner Y, Santos JH. Role of mitochondrial DNA in toxic responses to oxidative stress. DNA Repair (Amst) 2006; 5(2):145–152
100 Smith RA, Murphy MP. Animal and human studies with the mitochondria-targeted antioxidant MitoQ. Ann N Y Acad Sci 2010;1201:96–103
106 Aguzzi A, Barres BA, Bennett ML. Microglia: scapegoat, saboteur, or something else? Science 2013;339(616):156–161

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170 Brannan T, Martínez-Tica J, Di Rocco A, Yahr MD. Low and high dose bromocriptine have different effects on striatal dopamine release: an in vivo study. J Neural Transm Park Dis Dement Sect 1993;6(2):81–87


176 Kochanek PM, Vagni VA, Janesko KL, et al. Adenosine A1 receptor knockout mice develop lethal status epilepticus after experimen-


212 Shear DA, Tortella FC. A military-centered approach to neuroprotection for traumatic brain injury. Front Neurol 2013;4:73


218 Macias CA, Kameneva MV, Tenhunen JJ, Puyana JC, Fink MP. Survival in a rat model of lethal hemorrhagic shock is prolonged following resuscitation with a small volume of a solution containing a drag-reducing polymer derived from aloe vera. Shock 2004;22(2):151–156


