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Decoding Hippocampal Signaling Deficits after Traumatic Brain Injury

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Abstract

There are more than 3.17 million people coping with long-term disabilities due to traumatic brain injury (TBI) in the United States. The majority of TBI research is focused on developing acute neuroprotective treatments to prevent or minimize these long-term disabilities. Therefore, chronic TBI survivors represent a large, underserved population that could significantly benefit from a therapy that capitalizes on the endogenous recovery mechanisms occurring during the weeks to months following brain trauma. Previous studies have found that the hippocampus is highly vulnerable to brain injury, in both experimental models of TBI and during human TBI. Although often not directly mechanically injured by the head injury, in the weeks to months following TBI, the hippocampus undergoes atrophy and exhibits deficits in long-term potentiation (LTP), a persistent increase in synaptic strength that is considered to be a model of learning and memory. Decoding the chronic hippocampal LTP and cell signaling deficits after brain trauma will provide new insights into the molecular mechanisms of hippocampal-dependent learning impairments caused by TBI and facilitate the development of effective therapeutic strategies to improve hippocampal-dependent learning for chronic survivors of TBI.

Keywords

Learning; Long-term potentiation; Memory; Protein kinase; Synapse; Traumatic brain injury

Introduction

Over 1.7 million people sustain a traumatic brain injury (TBI) every year in the United States and 124,000 remain permanently disabled [1]. The resulting economic burden is approximately \$56.3 billion per year [2]. An incident that takes only a second to occur can result in lifelong devastating consequences. People who have had a TBI are 1.8 times likely to report subsequent binge drinking, 1.5 times likely to be depressed, 2.3–4.5 times likely to develop Alzheimer's, 7.5 times likely to die, and 29 times more likely to develop epilepsy [3–7]. Not only are there great personal costs, but there are also profound negative societal consequences; for example, an estimated 87% of prison inmates have incurred a head injury in their lifetime [8].

The neurological and behavioral sequelae of TBI develop over the course of days to months after the initial trauma. Most behavioral recovery is observed during the first 6 months after injury [9]. However, this recovery often plateaus or declines between 6–12 months after the

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TBI [10]. Although there are endogenous reparative mechanisms, these are simply not sufficient to achieve full recovery for most people with moderate to severe TBI. The majority of TBI research is focused on preventing or reducing the early devastating consequences of TBI by developing acute neuroprotective strategies. However, there are an estimated 3.17 million people in the US who are coping with long-term disabilities from a TBI [11]. This underserved population would benefit greatly from rehabilitative therapies that capitalize upon ongoing endogenous plasticity mechanisms.

Structural and Functional Changes in the Hippocampus

Memory problems are particularly common in human TBI patients, either as a consequence of direct effects on memory encoding or via secondary effects on concentration and attention [12–15]. Several memory modalities are affected by TBI; for the purposes of this review, we will limit our focus to declarative memory which is affected in a significant percentage of TBI patients [12, 13]. The commonality of declarative memory deficits is due, in part, to the unique vulnerability of the hippocampus to TBI. The hippocampus is critical for the formation of declarative memories and *in vivo* magnetic resonance imaging has revealed a high prevalence of hippocampal atrophy among both moderate and severe TBI patients [12, 16–19]. This has been thought to contribute to the significant percentage of TBI patients reporting long-term hippocampal-dependent memory impairments, significantly interfering with patient recovery and quality of life [12, 13]. Using experimental models of brain injury, many studies have reported hippocampal-dependent learning deficits lasting for weeks to months [20–26].

One of the first mechanisms hypothesized to cause hippocampal-dependent learning deficits after TBI was hippocampal atrophy due to cellular and synaptic loss. Hippocampal atrophy is a common finding among chronic TBI survivors and is replicated in various experimental models of TBI [27, 28]. The atrophy of the hippocampus is not limited to the ipsilateral side, and is often bilateral and encompassing the fornix, resulting in deafferentation [12, 16–18, 29]. The cellular and synaptic loss is progressive, although there is some recovery of synaptic loss [30–34]. Particular areas of the hippocampus are more vulnerable than others; dentate hilar neurons, CA3 pyramidal cells, and newborn neurons in the inner granule layer of the dentate gyrus are selectively lost after TBI [32, 33, 35–39]. These lost cells are not likely replaced. TBI induces neurogenesis within the dentate gyrus which peaks within 1–2 weeks after TBI [40, 41]. It is uncertain whether this increase is sustained since the numbers of doublecortin-positive cells, a marker of immature neurons, are decreased from 14 days to 12 weeks post-injury [37, 39]. Axonal sprouting in both the dentate gyrus and stratum radiatum of area CA1 has also been observed and may be a potential regenerative response of the hippocampus [31, 34, 35, 42, 43]. The cellular and synaptic loss, although significant, is not profound. Atrophy of the hippocampus averages approximately only 10–15% in chronic TBI survivors [12, 17, 19]. However, lesion studies have found that a loss of at least 20–30% of the dorsal hippocampus and at least 39–52% of the ventral hippocampus is required to begin to observe impairments in hippocampal-dependent learning tasks [44].

There is a correlation between the amount of hippocampal atrophy due to cellular loss and the degree of hippocampal-dependent learning impairment during CNS injury [16, 44, 45]. There are exceptions though; during aging there are significant memory impairments resulting from altered synaptic function and loss of select neuronal populations [46–50]. Conversely, during epilepsy, significant hippocampal cell loss does not always result in measurable, significant hippocampal-dependent learning impairments [51]. In fact, lesion studies have found that just 26% of the hippocampus is capable of supporting hippocampal-dependent water maze spatial learning [44]. Together, these studies suggest that other mechanisms may also contribute to the deficits in hippocampal learning after TBI.

Synaptic Plasticity Changes after TBI

To identify other functional changes in the hippocampus that may contribute to memory loss, studies began to investigate if neurotransmission and synaptic plasticity mechanisms such as long-term potentiation (LTP), a persistent increase in synaptic strength and considered to be a model for learning and memory, are altered after TBI. In particular, laboratories have consistently found that there are significant TBI-induced electrophysiological changes that vary across different regions of the hippocampus. In area CA1 of the hippocampus, most studies have reported that basal excitatory synaptic transmission, as assessed by measuring the excitatory postsynaptic potential (EPSP) in response to varying stimulus intensities, is depressed from hours to days after TBI [33, 36, 52–56]. An increase in the population spike amplitude and a decrease in the population spike threshold have also been reported, suggesting that the balance of inhibition and excitation is altered [33, 52, 57–59]. The depression in basal EPSPs in area CA1 resolves within 1–2 weeks after TBI [53, 56] and future studies remain to determine if either inhibitory or excitatory basal synaptic transmission is altered in the months to years after TBI [60]. Conversely, in the perforant path pathway to the dentate gyrus, an enhancement of basal EPSPs [33, 36, 42, 54, 61] and a depression of basal inhibitory postsynaptic currents have typically been observed [33, 35, 38, 60, 62–64].

These regional-specific changes in basal synaptic transmission correspond to alterations in LTP. In area CA1 of the hippocampus, both post-tetanic potentiation, the initial potentiation observed within seconds after the tetanus, and the expression of LTP are impaired from hours to 8 weeks post-injury [25, 52, 53, 55, 57, 65–68]. In contrast, in the dentate gyrus, the expression of LTP lasting for 60 min is impaired for at least 7 days after TBI [36, 54].

The decrease in basal EPSPs in area CA1 of the hippocampus has confounded the interpretation of the impairments in LTP. Since most studies tetanized the hippocampal slices at currents that elicited an EPSP that was 40–50% of the maximum elicited EPSP, fewer afferent fibers were stimulated in hippocampal slices from TBI animals since the maximum elicited EPSP is lower in TBI hippocampal slices [33, 36, 52–56]. To compensate for this, Norris and colleagues adjusted the stimulus strength to give comparable EPSPs from sham and TBI hippocampal slices prior to the tetanus. They found that there were still deficits in hippocampal LTP at the Schaffer collater-CA1 pathway at 2 days, but not at 7 and 14 days post-injury [53]. The authors interpreted this result to indicate that there is recovery of afferentation of the CA1 region of the hippocampus in the days following injury, which corresponds to the partial recovery in synaptic density observed using anatomical techniques [24, 34]. These results suggest that the molecular mechanisms that contribute to basal synaptic transmission and LTP are impaired after TBI and that endogenous reparative or compensatory mechanisms, while certainly active in the hippocampus after mild to moderate trauma, are not sufficient to fully reverse the TBI-induced deficits in synaptic transmission and plasticity.

While LTP has been extensively investigated after TBI, long-term depression (LTD), a candidate mechanism of forgetting, has been studied by only a few groups with differing results. In area CA1 of the hippocampus, it has been reported that LTD is unaffected [55, 68] or enhanced by TBI [65]. These results may be due to the injury models used, fluid-percussion versus controlled cortical impact, which yield some differences in the patterns of hippocampal pathology [32, 33, 69]. Further studies are needed to investigate if LTD is altered in other regions of the hippocampus.

Biochemistry of Synaptic Plasticity and Learning

The molecular basis for the chronic deficits in hippocampal LTP remains unclear, and understanding how these biochemical mechanisms are affected by TBI will foster the development of pharmacological therapies to improve learning and memory after TBI. The molecular mechanisms that underlie LTP are well known and parallel to some extent the molecular mechanisms that underlie memory formation in the hippocampus. They consist of a series of interacting, overlapping biochemical events. Induction of LTP, as well as the initial formation of hippocampal memories, requires the activation of L- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and *N*-methyl-D-aspartate (NMDA) type glutamate receptors as well as voltage-dependent calcium channels (VDCCs), which influx calcium into the postsynaptic neuron. Intracellular calcium activates multiple protein kinases that subserve memory formation (Fig. 1). Some of these include extracellular signal-regulated kinase (ERK) 1/2, calcium/calmodulin-dependent protein kinase (CaMK) II, CaMKI, CaMKIV, protein kinase (PK) C and PKA [70–74]. Administration of ERK1/2, PKC, PKA, or general CaMK inhibitors impairs performance on several hippocampal-dependent learning tasks [70, 71, 75–77]. Consistent with this, genetic studies have confirmed the necessity of these protein kinases for hippocampal learning. Knockout mice for ERK2, CaMKII, CaMKIV, PKC, or PKA exhibit deficits in water maze learning and contextual fear conditioning – hippocampal-dependent learning tasks [72, 74, 78–81]. Thus, calcium influx initiates a cascade of biochemical events to increase synaptic strength via activation of ERK1/2, CaMKs, PKC, and PKA.

These studies have revealed differential requirements for protein kinases during short-term versus long-term memory formation, depending upon the learning task. Inhibition of ERK1/2 or PKA selectively interferes with long-term, but not short-term memory formation [77, 78, 81]. This is similar to the temporal requirements for hippocampal LTP, where inhibition of ERK1/2 activation blocks the maintenance phase, but not the induction phase of LTP [71]. ERK1/2 is required for long-term memory formation and maintenance of LTP by stimulating gene transcription through the transcription factor cAMP response-element binding protein (CREB) [82]. A comparison of the impairments in LTP with an ERK1/2 inhibitor versus the impairments in LTP after TBI reveals some similarities; for both maintenance is impaired (Fig. 2).

Biochemical Changes within the Hippocampus after TBI

The studies above suggest that activation of protein kinases required for the maintenance of LTP and their downstream effectors may be altered chronically after TBI. While many studies have contributed to our understanding of TBI-induced biochemical changes in the hippocampus in the acute stages after injury, few have been completed for the chronic stages of TBI.

Acutely after TBI, and in particular for the fluid-percussion brain injury model, there is a large increase in intracellular calcium in the cortex and hippocampus that lasts for up to 4 days [83]. These global changes in calcium signaling through glutamate excitotoxicity and potassium depolarization waves stimulate several calcium-dependent cell signaling pathways that are also activated during hippocampal-dependent memory formation. We and others have found that the protein kinases CaMKI, II and IV, as well as ERK1/2 and PKC are activated within hours after TBI, and then return to basal levels by 24 hr (Fig. 3) [23, 84–90]. In contrast, cAMP levels and PKA activation are decreased from 4–24 hr after TBI and then return to basal levels by 3 days [91]. These changes are rapid and transient, and return to noninjured levels over the course of hours to days.

Similarly, expression of the neurotrophins brain-derived neurotrophic factor and nerve-growth factor are rapidly and markedly increased after TBI [92, 93]. In addition, the trkB receptor phosphorylation and mRNA levels increase from 3–6 hr post-injury [84, 92]. However, this stimulation of neurotrophin signaling is not sustained beyond 2 weeks after injury.

Correspondingly, the downstream effectors of these biochemical signaling pathways are typically transiently activated as well (Fig. 4). Several groups have reported that downstream of ERK1/2 and CAMKIV, the transcription factor CREB is activated within 30 min of TBI in the CA3 region of the hippocampus [22, 84, 88, 94]. There are intriguing suggestions that dendritic protein translation is misregulated since cytoplasmic element binding protein, a dendritic translation factor, is transiently activated within hours after trauma, yet activity-regulated cytoskeleton-associated protein, whose mRNA is dendritically localized, is down-regulated at 2 weeks post-injury [87, 95]. In addition, trauma induces a rapid activation of mammalian target of rapamycin and subsequent phosphorylation of the mRNA transcription regulators: eukaryotic initiation factor 4E (eIF4E), eukaryotic initiation factor 4E binding protein-1 (4E-BP-1), p70 ribosomal S6 kinase (p70S6K), and ribosomal S6 protein (rpS6) [96]. Non-specific activation of these protein kinases and their downstream effectors throughout the dendritic tree may disrupt the machinery in place for synapse-specific potentiation of individual synapses during learning and memory formation. Thus, activation of the protein kinases that underlie memory formation during TBI throughout the neuron may be a potential mechanism underlying retrograde amnesia after head injury [26, 33, 89].

Upstream of these protein kinase signaling pathways are changes in several neurotransmitter receptor systems. The AMPA-type glutamate receptor subunit 1 (GluR-A) is phosphorylated at the CaMKII site (Ser831) and dephosphorylated at the PKA site (Ser845) at 1 hr after TBI [87]. There is a small, but significant increase in GluR-A levels in crude synaptosome fractions at 48 hr after TBI [87, 97]. NMDA receptor levels and phosphorylation change in a biphasic manner, with a transient increase in the minutes to hours following trauma, and then decreasing below sham levels at 4–7 days, with a restoration to basal, non-injured levels by 2 weeks following injury [97–100]. Trafficking and tethering of these receptors at the synapse may also be altered since there are significant decreases in postsynaptic density protein-95 and synapse-associated protein 97 between 1–7 days post-injury [101–103]. These biochemical findings are consistent with electrophysiological findings demonstrating that NMDA and AMPA currents are decreased at 7 days post-injury [68]. Similarly, metabotropic glutamate receptors decrease at 7 days post-injury and then recover back to non-injured levels by 15 days [104]. Further studies are needed to assess changes in these receptors in specific subregions of the hippocampus given the opposing shifts in excitation/inhibition observed in area CA1 versus the dentate gyrus region [33, 36, 38, 42, 52–55, 58, 61, 62, 68].

Besides glutamate receptors, significant depression in modulatory neurotransmitter systems has been reported; these changes are typically more persistent than the alterations observed with glutamate receptors. Binding to the $\alpha 7$ nicotinic acetylcholine receptor and levels of muscarinic acetylcholine receptors are persistently depressed for at least 3 weeks after trauma [105, 106]. Both evoked release of acetylcholine and dopamine are depressed for at least 2 weeks after trauma [107, 108]. β -adrenergic receptors are also depressed, but more transiently with a recovery to baseline by 24 hr post-injury [109]. Modulatory neurotransmitters are very important for attention and concentration during learning, and depression in the dopaminergic and cholinergic systems may underlie this commonly reported neurological sequelae after TBI [14, 15]. Thus, nearly all of these synaptic

plasticity molecules are transiently altered in the hippocampus after TBI, but how they are regulated during the rehabilitative stages in a person coping with a TBI is unknown.

Experimentally, there are intriguing indications that cellular signaling pathways after TBI may be chronically misregulated. At 30 days after FPI, studies have found that calcium homeostasis in cultured hippocampal neurons from the CA3 region is misregulated [110, 111]. Although basal calcium levels and peak calcium entry during glutamate stimulation are similar between non-injured and injured CA3 hippocampal neurons, restoration of basal calcium levels is impaired. These findings indicate that activation of calcium-dependent signaling pathways is likely to be misregulated [83, 98]. Indeed, there is support for an increase in calcium-dependent phosphatase activity. Protein phosphatase 2b (i.e. calcineurin) activity is increased for up to 2–3 weeks after TBI, but both activity and protein levels return to non-injured levels after 3 weeks [102, 112].

Rehabilitation Strategies for Restoring Hippocampal Function

Rehabilitative strategies for restoring hippocampal memory functioning have had some success in the clinic [113]. There are significant changes in basal levels of neurotransmitters after TBI, and evoked release of dopamine and acetylcholine are depressed after TBI [107, 108]. This has provided experimental support for the use of a dopamine agonists and acetylcholinesterase inhibitors. Dopaminergic augmentation using bromocriptine and amantidine improve working memory and likely act on the prefrontal cortex [114, 115]. Methylphenidate and dextroamphetamine, which increase both dopamine and norepinephrine release, improve arousal, speed of processing and attention, but do not directly improve hippocampal cognitive impairments [116, 117]. Cholinesterase inhibitors, such as donepezil, rivastigmine, and less commonly prescribed physostigmine, have been tested as cognitive enhancers. These have had mixed success, with studies demonstrating only a modest improvement in cognitive impairments [113, 118–120]. Although NMDA receptor antagonists have been tested extensively to reduce glutamate excitotoxicity acutely after TBI, NMDA receptor agonists demonstrate efficacy at improving hippocampal synaptic plasticity and learning deficits after experimental TBI [67, 121]. This alternative pharmacotherapy has yet to be translated to the clinic.

Due to a lack of FDA-approved standard of care for pharmacological therapies available to chronic TBI patients, focus has been on physical and cognitive therapy [113]. There is substantial clinical evidence demonstrating the benefits of physical and cognitive therapy after TBI [122, 123]. Similarly, environmental enrichment and physical exercise improve outcome in experimental TBI by stimulating expression of synaptic plasticity molecules [23, 124].

Although these studies indicate that there is promise in developing a pharmacological treatment to improve learning deficits after TBI, the lack of an understanding of the underlying biochemical mechanisms that cause impairments in hippocampal synaptic plasticity and learning after TBI impedes substantial progress in the field. To identify the relevant therapeutic targets to restore hippocampal synaptic plasticity and learning, we determined if the molecular mechanisms of synaptic plasticity are misregulated in the hippocampus at chronic time points after brain trauma.

To investigate chronic impairments in protein kinase signaling after TBI, adult Sprague Dawley rats received sham surgery or parasagittal FPI. At 2, 8, or 12 weeks after sham surgery or FPI, we dissected the ipsilateral, injured hippocampus and generated acute hippocampal slices to study neuronal responses to stimulation. The hippocampal slices were stimulated with a potassium pulse or glutamate to trigger a transient depolarization and brief calcium influx into neurons. We found that there was a significant increase in ERK1/2 and

CREB activation in hippocampal slices from sham surgery animals, but not from TBI animals [125]. Total and basal phosphorylation levels of ERK1/2 and CREB were not significantly altered from sham, non-injured levels at 2 and 8 weeks post-injury, suggesting that this was a deficit in activation of these signaling molecules, not a persistent decrease in basal levels. These data demonstrate that the remaining hippocampal neurons have impairments in the ability to activate cell signaling pathways critical for hippocampal synaptic plasticity and memory formation, and in particular, the ERK1/2 and CREB signaling pathways are vulnerable to disruption from brain trauma. Further work remains to determine if activation of other critical protein kinase pathways such as the CaMKs, PKA, or PKC are similarly affected by TBI.

Concluding Remarks

The majority of research in TBI is geared toward preventing disabilities from ever occurring, by intervening within the first hours to days after injury. Even though we will likely achieve successful acute neuroprotective strategies that will pass Phase III clinical trials and become standard of care, we still have a very large, underserved population of patients who are coping with chronic disabilities from TBI [11]. There are profound effects of the chronic disabilities from a TBI, not only for the patient, but also for their family and community. The deficits in learning and memory, communication skills, walking ability, self-care, and ability to return to the community as functional members are devastating, resulting in substantial numbers of TBI patients exhibiting depression and substance abuse [4, 7]. With the development of cognitive enhancers, this underserved population could regain significant functioning, by enhancing endogenous synaptic plasticity mechanisms. By decoding the molecular basis for chronic deficits in hippocampal synaptic transmission and plasticity after TBI, we will be able to use this knowledge to develop rationally-derived therapeutic strategies that will improve learning and memory in chronic TBI survivors.

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Fig. 1.

The biochemical mechanisms required for hippocampal LTP and memory formation share many similar pathways. During induction of LTP, i.e. the first initial minutes after tetanization (arrow), there is a supralinear entry of calcium via VDCCs and NMDA receptors. This calcium influx activates several protein kinases including the CaMKs, PKA, and PKC. They either directly phosphorylate glutamate receptors to increase conductance through the receptors or phosphorylate proteins involved in the insertion of the receptors in the postsynaptic membrane. This leads to the potentiation of synaptic transmission. During the maintenance of LTP and long-term memory formation, several protein kinases including CaMKIV, ERK1/2, and PKA regulate transcription factors which increase gene transcription to enact structural changes at the synapse to maintain this potentiation.

Fig. 2.

A comparison of the deficits in hippocampal LTP elicited by an ERK1/2 inhibitor versus induced by experimental TBI. A MAP kinase kinase (MEK) inhibitor to selectively inhibit ERK1/2 has no effect on the initial potentiation after tetanic stimulation to induce LTP, but blocks maintenance of LTP (a). Adapted from [71]. Moderate TBI results in similar deficits in hippocampal LTP (b). At 2 weeks after TBI, LTP was induced by tetanization of the Schaffer collateral pathway. Although the synaptic response is potentiated in the first few minutes after tetanization, the degree of potentiation in TBI hippocampal slices is not maintained as compared to sham hippocampal slices (C.M.A. and J.D.A. unpublished observations) [25, 52, 53, 55, 57, 65–68].

Fig. 3.

Many cellular signaling pathways are acutely activated after TBI, but rapidly return to non-injured levels. CaMKI, CaMKII, CaMKIV, and ERK1/2 are activated after TBI, whereas PKA activation is reduced. Nearly all of these biochemical changes return to sham, non-injured levels within 3–7 days after brain trauma. Adapted from [87, 88, 91].

Fig. 4.

Schematic of how the biochemical signaling pathways that underlie hippocampal LTP are altered after TBI. Pathways that are stimulated are illustrated in black, and pathways that are decreased are denoted in red. TBI induces depolarization of neurons and postsynaptic calcium entry which subsequently activates CaMKK and its downstream substrates CaMKI and CaMKIV. PKC and CaMKII are also activated by the increase in postsynaptic calcium. Downstream of CaMKII is the dendritic mRNA translation factor, CPEB, which is transiently phosphorylated. Whether this leads to an increase in dendritic mRNA translation after TBI is still unknown. In contrast to most pathways, cAMP levels and PKA activation are decreased immediately after TBI. This results in differential effects on the AMPA-type glutamate receptor subunit 1: increased phosphorylation at the CaMKII site (Ser831) and decreased phosphorylation at the PKA site (Ser845). TBI also induces an increase in the neurotrophins BDNF and NGF, which activate ERK1/2 and mTOR. Downstream of ERK1/2 and mTOR are multiple translation and transcription factor signaling pathways, including mitogen-activated protein kinase-interacting kinase 1 (Mnk1), eIF4E, 4E-BP1, p70S6K, and rpS6. CREB phosphorylation increases after TBI, although the exact protein kinase that regulates CREB during TBI is still unknown and likely candidates include p90 ribosomal S6 kinase (p90RSK) and CaMKIV. Modulatory neurotransmitter release and their receptors are depressed after TBI; these include a transient decrease in β-adrenergic receptor levels (β-AR) and acetylcholine receptor binding and levels. Although all of these molecules change rapidly after TBI, most return to basal levels within 2–4 weeks after brain trauma.