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Biologic and plastic effects of experimental traumatic brain injury treatment paradigms and their relevance to clinical rehabilitation

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Abstract

Neuroplastic changes, whether induced by traumatic brain injury (TBI) or therapeutic interventions, alter neurobehavioral outcome. Here we present several treatment strategies that have been evaluated using experimental TBI models and discuss potential mechanisms of action (i.e., plasticity) and how such changes affect function.

Introduction

Traumatic brain injury (TBI) as a significant health care issue

TBI affects 1.4 to 2 million individuals in the United States annually [1–3]. Approximately 300,000 of the cases are severe enough to warrant hospitalization, where 50,000 die. Of the survivors, 100,000 endure long-term behavioral disturbances that adversely affect quality of life [4,5] and require rigorous and costly rehabilitative therapy [6]. While the emotional toll of TBI cannot be calculated, the economic cost accounts for billions of dollars each year [2,6]. Hence, TBI is a serious and survivable medical problem with limited treatment options. This review will focus on therapeutic paradigms after experimental TBI and how such information may benefit clinical practice.

Diaschisis as a framework to characterize experience and treatment dependent plasticity

Although acute mechanisms of secondary injury influence the degree and type of deficits that those with TBI experience, the chronic period after injury is characterized by multiple neurotransmitter alterations and cellular dysfunction that also contribute to behavioral impairment. During this chronic period the brain is amenable to neuroplasticity, repair, and recovery, and the potential for these processes can be augmented using relevant rehabilitation strategies. One conceptual framework by which TBI recovery occurs is

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through the attenuation of post-traumatic neural depression [7] or *diaschisis*, as first described by von Monakow [8–10], and later as *remote functional depression* by Feeney and colleagues [11]. Diaschisis refers to functional depression of neurons remote from, but anatomically connected to, the site of focal injury. The theory of diaschisis posits that the functional effects can be either reversible or permanent. The mechanisms by which diaschisis resolves, include the resolution of decreased cerebral glucose metabolism [12,13], changes in synaptic plasticity [14–16], and cortical reorganization [14], each of which can contribute to early recovery [7,17].

Diaschisis, and the plastic changes that occur with it after TBI, can be manipulated by multiple types of behavioral experience (i.e., rehabilitation). The role of exercise in plasticity and TBI recovery is reviewed in detail elsewhere in this supplement. In the subsequent section we describe environmental enrichment (EE), which is another form of behavioral experience, and its important role in neuroplasticity and recovery.

Environmental enrichment as a rehabilitation-relevant therapy for TBI

EE consists of an enlarged living environment with increased social interaction and novel stimuli that together promote physical and cognitive stimulation [18]. EE induces a plethora of neuroplastic changes after brain injury, such as, but not limited to, increased neuron size and density, dendritic branching and spine density, number of neuronal synapses and synaptic size, and tissue volume in rodent cortex [19–23]. EE also promotes neurogenesis, angiogenesis, and survival of hippocampal neurons [23]. Several studies in experimental models of TBI suggest that relatively brief exposure (e.g., 3 weeks) of EE can confer behavioral benefits. Specifically, EE facilitates learning and memory after both controlled cortical impact [18,24,25] and fluid percussion brain injury [26–28] and also improves motor performance [18,24,25]. Thus, EE has been established as a reasonable rodent correlate of clinical rehabilitation. However, the effect of brief EE in female rats does not appear to be as consistent as it is in male rats [29].

The majority of research assessing the potential of EE to mimic rehabilitation after TBI consists of continuous exposure to the living milieu. However, clinical rehabilitation after brain injury consists of a limited amount of physical and occupational therapy. In practice, the length of time (i.e., intensity) in therapy after TBI varies from a minimum of 1 hr up to a maximum of 8 hrs per day depending on the rehabilitation setting [30–33]. Thus, while the range of clinical rehabilitation may be varied, it is certainly shorter than the continuous nature of EE in the laboratory. The difference between the relatively short duration of daily clinical rehabilitation after TBI and the continuous nature of experimental EE emphasizes a disparity between the experimental model and the clinical environment it attempts to model.

In an attempt to address this discrepancy, our laboratory has been working on a series of studies determining the therapeutic window of EE efficacy to further understand its potential contribution to clinical rehabilitation. Specifically, we recently evaluated the effects of an abbreviated enrichment paradigm consisting of 2, 4, or 6 hrs of EE per day, vs. continuous exposure, which may be viewed as more akin to clinical rehabilitation. We hypothesized that the abbreviated EE groups would exhibit greater motor recovery and cognitive performance versus the standard housed group and would also perform comparably to the continuous EE group. Consistent with our hypothesis, the group receiving 6-hr of daily EE performed comparably to the continuous EE group [34], but surprisingly, the groups receiving 2-hr and 4-hr of daily EE did not benefit from the limited exposure and were not different from non-enriched controls [34]. Although the translational potential to human beings is not fully elucidated, this finding suggests that there may be a certain threshold of enrichment that is necessary to elicit neurobehavioral recovery within this model of TBI that may have clinical implications for rehabilitation [34]. Moreover, other factors of inpatient rehabilitation such

as social living increase stimulation over what the patient may receive in therapy alone. Results of clinical studies have shown that increasing the intensity of rehabilitation in patients with TBI resulted in significantly shorter hospital admission and greater functional improvements [31], and that 4-hour per day rehabilitation program resulted in a quicker return to independent functional status than 2 hours per day [33]. These clinical reports are consistent with our experimental results in that varied exposure to rehabilitation in the clinical setting or enrichment in the experimental setting can be linked to improved outcomes or behavioral performance.

Another disparity between the clinic and the laboratory involves the time of initiation and duration of EE on neurobehavioral recovery after TBI. In the laboratory, EE is typically introduced immediately after TBI and is continued until all behavioral manipulations have been completed. While this paradigm has consistently shown improvement on motor and cognitive performance after brain trauma [18,24–29], the continuous-exposure nature is inconsistent with what happens in the real world where patients typically do not begin rehabilitation immediately after injury and also do not receive similar lengths of rehabilitation.

Thus, to address this important issue, we introduced adult male rats to the EE either immediately after TBI, or one week later and then compared their performance to standard housed rats using our established motor (assessment during the first week after injury) and cognitive behavioral assessment (during the second week after injury) tasks. Motor function was facilitated in the TBI groups that received either early or continuous EE vs. those receiving delayed or no EE. In contrast, cognitive performance was enhanced in the TBI groups that received continuous or delayed EE vs. the early EE or standard groups. Taken together, we believe that EE-mediated functional improvement after TBI is contingent on task-specific neurobehavioral experience [24,35].

Potential mechanisms of EE-mediated behavioral improvement after TBI

Although behavioral improvements and structural alterations in the brain have been traditionally characterized with EE, the molecular events that mediate these environmentally induced improvements in function after injury are gaining interest [36]. Neurotrophins have been hypothesized to be an important neural substrate in EE and TBI because of their role in cell survival and neural plasticity [37]. Exposure to complex environments in normal animals can increase neurotrophin protein expression in multiple brain regions [38].

Brain-derived neurotrophic factor (BDNF) is the most abundant and widely distributed neurotrophin in the central nervous system. BDNF is a polypeptide that plays an important role in the survival, differentiation, and outgrowth of neurons both during and after development [39]. Regional increases in BDNF expression have been noted in normal animals after long term EE [40] and with running [41]. Although increases in hippocampal BDNF gene expression have been noted during the first 2–3 days after experimental TBI [42], both TBI and post-injury EE have been associated with altered hippocampal BDNF mRNA levels in male rats chronically (14 days) after injury [27]. In fact, some reports actually suggest decreased BDNF gene expression for animals housed in EE following focal ischemic injury [43]. However, recent studies, including those cited in this supplement (pS64), suggest hippocampal increases in BDNF protein expression after a delayed course of voluntary exercise [44] after experimental TBI. Our work, also, suggests that despite a lack of behavioral effects with EE, robust increases in hippocampal BDNF levels can be elicited with a short course of EE for female rats after experimental TBI [45]. These results are supported by other literature demonstrating links between exercise, estrogen and hippocampal BDNF expression [46] and suggest, at least in part, that the capacity for neurotrophin mediated plasticity in the injured brain may be gender specific. In the absence

of EE or other types of behavioral experience, additional studies support a role for neurotrophin administration in promoting long-term recovery. Chronic pericontusional administration of BDNF does not improve behavioral outcome or hippocampal cell survival [47]. However, intraparenchymal administration of both basic fibroblast growth factor and nerve growth factor reduces cognitive deficits in experimental TBI [48,49]. These positive studies suggest that improved recovery might be secondary to stimulation of brain repair and neuroplasticity.

Neurotransmitters and plasticity

Dopamine (DA)—Several lines of evidence suggest that CNS plasticity and neurorecovery can be manipulated pharmacologically, particularly by targeting dopamine (DA) systems with neurostimulants. Results of research to date suggests that DA systems are key pathways involved in attention, task salience, and cognition, and that these pathways are chronically impaired after TBI [50]. Alterations in both pre- and postsynaptic dopaminergic proteins in the striatum and frontal cortex have been documented, including important proteins involved in DA synthesis and uptake [50–54]. Decreases in striatal dopamine transporter (DAT) expression, a key protein in regulating the extracellular half-life of DA, have been documented in humans [55]. Further, research demonstrates that striatal neurotransmission is impaired, and this finding appears to be the result of TBI-induced changes in DA protein functionality [51,53]. Importantly, results of follow-up studies suggest that TBI mediated impairments involving in vivo DA striatal neurotransmission can be restored with daily methylphenidate treatment at doses previously shown to provide beneficial effects on spatial learning in experimental TBI [51,53]. Gender may influence optimal dosing strategies for MPH based on the fact that doses of MPH that result in behavioral improvements in TBI males increase motor activity, but not spatial learning, in female rats after TBI [56].

Bromocriptine (BRO), a D₂ receptor agonist, reduces lipid peroxidation, improves spatial learning, and attenuates hippocampal cell loss when administered acutely after CCI injury in male rats [57]. Furthermore, a chronic and delayed administration paradigm of BRO enhances both working and reference memory [58]. Clinically, anecdotal reports have described functional improvement after TBI following BRO treatment, with or without occupational and physical therapy [59–63]. In a small double-blind, placebo-controlled crossover study, BRO treatment was reported to improve performance on clinical measures of executive function [64]. However, BRO appeared to be ineffective in attenuating attention deficits in moderate to severe TBI patients [65].

In addition to BRO, amantadine hydrochloride (AMH) has also been reported to improve performance in the clinical rehabilitative period after TBI. Specifically, Zafonte et al [66] and Wu and Garmel [67] reported improved scores on the activities of daily living scales in case reports of TBI patients treated with AMH. General improvements in global functioning have also been reported in brief case reports [68,69]. In patients demonstrating indications of diffuse axonal injury after TBI, AMH appeared to be effective in improving cognition independent of the timing of administration [70]. Potential mechanisms associated with AMH treatment may include not only an augmentation of DA neurotransmission, but also increases in glucose metabolism [71]. However, as reported with other pharmacotherapies (e.g., BRO) AMH did not provide benefits in all studies [72,73]. A review on AMH use after TBI concluded that it appears to safely improve both arousal and cognition [74]. An experimental study using a daily treatment regimen of AMH after cortical impact injury in rats revealed a significant improvement in learning and memory performance relative to the untreated controls [75]. Thus, further studies using AMH appear warranted in both the laboratory and rehabilitation setting after TBI.

Acetylcholine (ACh)—Cholinergic systems are important for memory and cognition, and evidence suggests chronic impairments can occur after TBI. Specifically, TBI produces hippocampal and medial septal cell loss, as well as disturbances in cholinergic neurotransmission [76,77]. A time-dependent loss of choline acetyltransferase (ChAT) enzymatic activity and ChAT positive cells has also been reported after TBI [78–82]. Similar to findings associated with experimental TBI, patients also show damage in cholinergic regions [83], including widespread cholinergic deafferentation [84,85], and dysfunction in acetylcholine dependent regions located in the hippocampus, thalamus, and frontal cortex [86,87].

Moreover, cholinergic projections to the hippocampus and cerebral cortex play an important role in learning, memory, and attention [88–90], and there is substantial evidence that impairments in basal forebrain cholinergic function contribute to cognitive decline [91–94]. Cholinergic cell loss also contributes to TBI-induced cognitive dysfunction [79,95]. Importantly, the attenuation of cholinergic deficits enhances functional outcome [82,95–97]. Clinically, trials have been conducted using CDP-choline, with favorable results in stroke, and are currently ongoing in TBI [98,99].

Serotonin_{1A} (5-HT_{1A}) receptor agonists

It is known that serotonergic pathways originating in the raphe nuclei project extensively to brain areas involved in cognition, and that serotonin (5-HT) receptor agonists and antagonists alter these processes [100,101]. Of the 5-HT receptors characterized so far (5-HT₁ – 5-HT₇), the 5-HT_{1A} is the most studied. 5-HT_{1A} receptors are abundantly expressed in brain regions, such as the cortex and hippocampus that, while susceptible to neuronal damage [102–104], play critical roles in learning and memory. Thus, this receptor has been targeted for pharmacotherapies after TBI.

Results of several studies from our laboratory have shown that 5-HT_{1A} receptor agonists, such as 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) and buspirone enhance spatial learning and attenuate histological damage after cortical injury. The benefits are observed whether the treatment is provided acutely or chronically. Acute treatment, given 15 minutes after TBI, with 8-OH-DPAT attenuated cognitive deficits in a water maze task, decreased cortical lesion volume, and conferred hippocampal neuron survival [105,106]. In an effort to define the therapeutic window of opportunity after a single administration of 8-OH-DPAT, a subsequent study evaluated three time points (i.e., 15 min, 1 hr and 2 hr after TBI). The study showed that only the 15 min administration group exhibited a significant functional benefit [107], which replicated previous studies [105,106]. That no benefit was observed with treatments administered at 1 and 2 hrs after TBI suggests that an early and narrow critical period exists for the behavioral recovery afforded by a single 8-OH-DPAT treatment paradigm. The critical window corresponds to the well documented TBI-induced glutamate increase [108], suggesting that 8-OH-DPAT may confer neuroprotection by attenuating excitotoxicity.

Although, acute administration of 8-OH-DPAT after TBI was effective, we investigated the potential efficacy of a chronic treatment regimen, with once daily administration of 8-OH-DPAT beginning 24 hr after TBI. The data showed that this regimen enhanced motor skills, spatial learning abilities, and memory retention [109,110]. These data replicated previous acute administration findings from our laboratory and extended those results by demonstrating that the benefits could be achieved even when treatment was delayed for 24 hrs, making this treatment regimen clinically feasible.

Inflammation and plasticity

TBI initiates a complex cascade of inflammatory processes such as the synthesis and upregulation of pro-inflammatory cytokines, chemokines, and endothelial-leukocyte adhesion molecules that may contribute to secondary tissue damage [111–113]. Specific inflammatory molecules such as interleukin-1 β , tumor necrosis factor- α , and interleukin-6 (IL-6) have been well studied after TBI because they are believed to contribute to the disruption of the blood brain barrier, cerebral edema, and neuronal death [114–116]. Because of their potential deleterious effects on functional outcome after brain trauma, several studies investigating various therapeutic strategies have been conducted targeting these molecules. One approach that has shown success in the laboratory is the use of statins. Simvastatin and atorvastatin have been reported to enhance neurobehavioral and cognitive performance, attenuate hippocampal degeneration, and improve cerebral blood flow [117]. It is possible that the improvement in cerebral blood flow may have facilitated the resolution of diasthesis as discussed earlier, which contributed to the behavioral benefits. Reduced inflammation and improved functional outcome has also been observed after experimental brain trauma with lovastatin treatment [118]. Thus, the administration of statins appears to be a viable therapeutic approach after brain trauma.

Although the administration of the anti-inflammatory agent IL-10 has been shown to enhance neurological recovery after TBI [119], the benefits have not been consistent, as demonstrated by findings from our laboratory that show the combination of IL-10 plus moderate hypothermia was ineffective in attenuating functional and histological deficits with a dose that prevents neutrophil accumulation in injured tissue [120]. Anti-inflammatory therapies can represent a dual-edged sword, exhibiting both beneficial and detrimental effects, and thus underscore the importance of timing and dosing of anti-inflammatory agents as well as the duration of the anti-inflammatory effect.

Hormones and Plasticity

Although it is becoming more evident that systemic endogenous sex steroids circulating in the acute phases after TBI are not linked with favorable outcomes [121], the sex steroid progesterone is showing significant promise as a biologic treatment for TBI neuroprotection [122,123]. The neuroprotective effects of progesterone across multiple models of neurological injury are well described elsewhere in this supplement [124,125], however, long term use may lead to a depression in neuroplastic potential in the post acute phases. Estrogen, when studied using *in vitro* systems and some *in vivo* injury models shows the capacity for neuroprotection through multiple mechanisms. Estrogen has been reported to maintain CBF post injury [126,127], function as an antioxidant [128], ameliorate excitotoxic injury [129], and promote the neuronal utilization of lactate [130]. However, in the acute clinical TBI setting, endogenous elevation in estrogen is strongly indicative of mortality [121], a finding corroborated in other trauma populations [131–134]. However, in the post acute phase, estrogen has significant potential to augment the neurorecovery process by facilitating several mechanisms of adaptive plasticity. Specifically, there is evidence that in several brain regions controlling cognition, estrogen may mediate stress-induced synapse formation and dendrite remodeling via genomic and nongenomic pathways [135]. In addition, estrogen exerts important effects on signaling and excitability within these regions' networks [136]. Our clinical work corroborates this phenomenon, in part, by showing that men in the postacute phase and who have persistent hypogonadism during the first year after injury also have low serum estrogen levels and score poorly on cognitive function tests and other measures of outcome (in preparation). Future work will be required to determine the specificity and efficacy of estrogen, and/or its precursor testosterone, as a biologic treatment to facilitate long-term plasticity in this population.

Agents that impair recovery after TBI

Typically the term “plasticity” is associated with beneficial effects. However, the reality is that some plastic changes can be considered maladaptive because of their negative influence on recovery. In this section we discuss 2 classes of drugs, namely, antipsychotic drugs (APD) and anticonvulsants, that are frequently used in the clinic, but that fit the maladaptive plasticity model.

The few studies that have investigated APDs after experimental TBI show that these drugs generally impair the recovery process, and in some instances, exacerbate TBI-induced behavioral deficits. A seminal study by Feeney and colleagues showed that a single administration of haloperidol (HAL) provided after sensorimotor cortex lesions in adult rodents delayed motor recovery assessed on a beam-walk task. Moreover, the administration of HAL *after* the animals were recovered, led to a reinstatement of the deficits [137]. Similar findings have been reported by Goldstein and Bullman [138] and our group [139]. In contrast to these studies, more recent data from our laboratory revealed that neither HAL nor the atypical APD, risperidone (RISP) negatively impacted functional outcome when only a single administration was provided. However, a significant reinstatement of motor and cognitive deficits was observed after once daily administrations for 5 days [139]. Moreover, chronic administration of HAL and RISP, impeded recovery [140,141]. Furthermore, these negative findings with APDs are observed in other clinically relevant models of TBI as shown by Wilson and colleagues following a fluid percussion brain injury [142]. These findings suggest that the deleterious effects of APDs after TBI on neurobehavioral outcome may be related to their actions as D₂ receptor antagonists.

Although experimental studies, albeit quite limited in number, show consistent negative impacts on recovery after TBI, particularly with those APDs with high affinity for D₂ receptors [143,144], this approach is still often used in the management of TBI-induced agitation and aggression. Our laboratory is currently evaluating the role of APDs with minimal or no D₂ receptor antagonism properties on functional recovery after TBI.

Anticonvulsants also have the potential to produce negative effects on outcome after TBI. A recent study from our group evaluating the effects of acute (15 minutes after TBI and again at 24 hours) or chronic (i.e., once daily for 21 days) administration of a clinically relevant dose of dilantin following cortical impact injury revealed that the chronic administration paradigm produced spatial learning deficits and increased hippocampal cell loss compared to controls. Furthermore, chronic treatment with this common anticonvulsant also decreased GAP-43, a marker of neuroplasticity. In contrast, acute dilantin treatment did not adversely affect spatial learning and promoted hippocampal plasticity, specifically GAP-43 expression. A modest enhancement in exploratory performance was also observed with acute treatment [145]. These data suggest that plasticity associated changes, namely GAP-43 expression, may have contributed, in part, to the findings on functional outcome. Specifically, decreases in GAP-43 significantly impaired the recovery process, while increases promoted modest recovery.

Phenytoin can also exert negative effects on cognition clinically. Previous randomized clinical trials with either phenytoin or placebo after severe or moderate TBI showed that the severely injured patients who received phenytoin exhibited more cognitive impairment compared with control subjects who received placebo when assessed at one month. This effect did not translate to the moderately injured TBI group that received phenytoin [146].

Drugs with anticonvulsant properties like benzodiazapines, carbamazepine, and phenobarbital are sedating and can also be used to address other medical rehabilitation problems, such as behavioral dysfunction and spasticity. Some work shows that transient use

of a GABA-A receptor agonist with a benzodiazepine just prior to experimental TBI can be neuroprotective [147]. Not surprising, daily use of the benzodiazepine, diazepam, delays recovery in an anteromedial cortex (AMC) lesion model of brain injury. Interestingly, when diazepam was delayed for 3 weeks after the AMC lesion, the deficits observed were transient (i.e., 2 days) [148]. In other studies of AMC lesions and somatosensory function, rats receiving daily administration of phenobarbital did not show recovery even at 2 months after injury [149]. Furthermore, the deleterious effects correlated with decreases in basic fibroblast growth factor, an important marker of plasticity for recovery after brain trauma [149,150]. Taken together, these data suggest that plasticity associated events occurring after brain trauma can be significantly affected by anticonvulsant use, thus leading to functional impairments. Hence, judicious use of anti-convulsants, as recommended by the American Academy of Neurology, for a limited period of seizure prophylaxis is encouraged. Additionally, care should be taken when considering the use of related drugs for neurobehavioral management, and benzodiazepines should be considered for seizure and spasticity management only after other pharmacological interventions have been unsuccessfully.

Conclusions

We have presented evidence highlighting that TBI or therapy-induced plasticity contributes to neurobehavioral consequences. The therapies discussed and their subsequent plasticity changes can positively impact the recovery process, as it appears to be the case when augmenting cholinergic, dopaminergic, and serotonergic systems as well as several markers of plasticity. Other commonly used treatments can have negative effects, as is the case when antagonizing D2 receptors or attenuating synaptic plasticity. Additional research is necessary to translate the experimental data and inform clinical rehabilitation practices after TBI.

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