

Invited Review

Post-Traumatic Neural Depression and Neurobehavioral Recovery after Brain Injury

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ABSTRACT

There are an estimated 2 million traumatic brain injuries (TBIs) each year in the United States, making the yearly incidence eight times greater than that of breast cancer and 34 times greater than HIV/AIDS. Still, it remains a “silent epidemic” because TBI results in persistent neurobehavioral impairment, without necessarily imparting a physical scar. The present review is a comparative analysis of TBI research, both basic and applied, outlining the evidence that at least one component of the brain’s innate response to insult (e.g., post-traumatic neural depression) is sufficiently well understood to be the target of additional clinical studies and therapeutic strategy development.

Key words: anti-convulsant drugs; pharmacotherapy; plasticity; seizures

INTRODUCTION

TRAUMATIC BRAIN INJURY (TBI) affects both mundane and complex behaviors through which we interact with our ever-changing environment. Following TBI, there is a well-orchestrated cascade of intra- and extracellular events that lead to cell death and dysfunction. At the same time, this cascade also includes responses that limit local and distal toxicity, and promote healing, plasticity, and reorganization (Cotman et al., 1996; Pennypacker et al., 2000; Meythaler et al., 2001; Keyvani and Schallert, 2002; Butler et al., 2003; Liou et al., 2003). Given the simultaneous processes aimed at cell death and survival, it is not surprising that functional recovery is variable, unpredictable, and often incomplete.

An important aspect of the post-injury neural response cascade is post-traumatic neural depression, which is a

period of quiescence or hypometabolism that occurs after a variety of injury types. The present review focuses on the basic and clinical evidence for post-traumatic neural depression, as well as how modulating the functional depression can affect recovery in a positive or negative way. The results of basic and clinical studies will be reviewed, and new directions for clinical research will be proposed. The information contained in this review may provide a rational basis for managing TBI, so as to improve the prospects of functional recovery.

Each year, there are an estimated 1.5–2 million TBIs in the United States (Goldstein, 1990; Sosin et al., 1996). The yearly incidence of TBI is eight times greater than that of breast cancer and 34 times greater than HIV/AIDS (according to the Centers for Disease Control). Almost one-half of TBIs are associated with motor vehicle accidents and alcohol is a contributing factor much of the

time (NIH, 1999). Males are two to three times as likely as females to sustain a TBI, especially during the high-risk years (ages 15–24 and >75) (Thurman, 2001). Because of its predominance in the young, the TBI survivor faces a potential lifetime of living with deficits and disability, making TBI a leading disabler of young adults (Marr and Coronado, 2002). The United States is not unique, in that there are many countries worldwide within which TBI is of significant concern (Thurman, 2001; Das-Gupta and Turner-Stokes, 2002).

Commonly seen functional limitations following TBI are in the cognitive, emotional, physical, and psychosocial domains, with interactions amongst these (Dikmen et al., 1995; Arciniegas et al., 2000; Arciniegas et al., 2002). The post-injury temporal pattern of change within each domain has not been well characterized. Still, it is believed that most individuals sustaining a mild TBI will recover within about 1 year (Whyte, 1999), though there are a percentage of these for whom deficits and disability persist beyond this time (Das-Gupta and Turner-Stokes, 2002; Rees, 2003). In contrast, the functional recovery time course associated with moderate or severe TBI is significantly longer in duration, with deficits still being present many years, and in some instances decades, later (Thomsen, 1992; Spikman et al., 2000).

In addition to injury severity, differences in progression to and eventual level of recovery may also stem from more subtle issues such as the post-injury neural response cascade specific to the individual, whether or not the response cascade was modulated after injury, as well as how it was modulated (e.g., drug treatment, physical therapies). Traditionally, rehabilitation efforts in the physical or cognitive domains tend to rely on *compensation* rather than *true recovery* to achieve functional gains and minimize disability. Pharmacotherapeutic interventions in the clinic have been disappointing, despite their emphasis on promoting neuroprotection and plasticity, each of which should be beneficial to the recovering brain and the functions it subserves (Narayan et al., 2002; Phillips et al., 2003; Tolia and Bullock, 2004). Unfortunately, currently available treatment strategies are of limited efficacy, though recent clinical trials with progesterone (Stein, personal communication) and scheduled telephone counseling/education (Bell et al., 2005) show promise.

There is an apparent disconnect between actual experimental outcome in the clinic and expected outcome based on data generated from the basic science. This may stem from the interventions not optimally coinciding with (Cristofori et al., 2001) or capitalizing on the human brain's innate response to insult, much of which is still being delineated (Tolia and Bullock, 2004). Alternatively, that which is found beneficial in animal studies

may be so only because of the careful control of all variables that can be controlled within this type of basic research, yet may not be possible to control in the clinic. Nonetheless, an extensive body of work has accumulated (Narayan et al., 2002; Phillips et al., 2003; Tolia and Bullock, 2004) and therefore laid the essential groundwork for future research to identify and characterize treatments strategies that improve neurobehavioral outcome (Lu et al., 2004).

TARGETING THE POST-INJURY NEURAL RESPONSE CASCADE

The present review centers on one aspect of the post-injury neural response cascade, post-traumatic neural depression, as a worthy target for therapeutic intervention. Post-traumatic neural depression fits several criteria that render it a viable candidate for study, understanding and therapeutic manipulation. First, it has early, though not immediate onset. Beginning hours to days after insult is useful in that it affords sufficient time for intervention to be initiated and the consequences measured. Second, it is enduring, but not without end, providing multiple opportunities over time to intervene, as opposed to a process that begins seconds after insult and lasts only minutes to hours. Designing clinical interventions for the latter process would pose quite a challenge. Third, it is measurable in multiple ways, in that it can be correlated with behavioral deficits, as well as metabolic dysfunction via imaging. This affords both external and internal validation of its presence, as well as the delineation of its time course and the functional consequences to the individual.

POST-TRAUMATIC NEURAL DEPRESSION

Basic Animal Models

Post-traumatic neural depression was first described as *diaschisis* (e.g., *shock*) in 1914 by von Monakow (von Monakow, 1914) and later as *remote functional depression* (Feeney et al., 1985). Evidence that “post-traumatic neural depression” (term to be used in the present review) occurs after brain injury has been well established with measures of blood flow, metabolism, electrical activity and neurotransmitter levels (Kempinsky, 1958; Meyer et al., 1970; Boyeson and Feeney, 1985; Hovda et al., 1987; Yoshino et al., 1991). Moreover, this functional depression has been correlated with post-injury behavioral deficits, and restoration of normal activity with behavioral recovery (Glassman and Malamut, 1976; Deuel and Collins, 1984; Hovda, 1996). The temporal pattern of post-traumatic neural depression, its resolution and the

accompanying behavioral change have been well characterized in animal models of TBI (Hovda, 1996): within the first 24 h (and evident as early as 6 h) post-injury, glucose metabolism is significantly depressed and this correlates with the presence of a motor deficit; within 10 days, the neural depression recovers to at or near pre-injury level, as does the motor deficit.

Clinical Studies

Post-traumatic neural depression has been studied not only in basic animal models of TBI, but in humans as well. The use of positron emission tomography (PET) has made it possible to measure the presence and evolution of post-traumatic neural depression clinically. Cerebral glucose metabolism clearly shows a state of depression as early as 2 days after TBI and the persistence of hypometabolism correlates with injury severity (as assessed by the Glasgow Coma Scale [GCS]): hypometabolism persisted up to 17 days after mild-moderate injury and 28 days following severe injury (Bergsneider et al., 2000, 2001).

When assessing neurobehavioral function over time, its exact relationship with neural metabolism appears to depend on timing and type of behavioral measure utilized. For example, the severity of glucose hypometabolism correlates well with *initial* injury severity (Bergsneider et al., 2000, 2001), while measures other than the GCS provide only some agreement with the basic research findings. Both PET and SPECT (single positron emission tomography) assessments of neural depression correlate with dysfunction on certain cognitive tasks, with greater depression being associated with greater dysfunction (Goldenberg et al., 1992; Ricker et al., 2001a,b). Measures of psychosocial function (Goldenberg et al., 1992; Oder et al., 1992) and disability (Bergsneider et al., 2001) show a similar relationship with post-injury neural metabolic rate. Lastly, persistent metabolic disturbance post-TBI, especially within critical periods, has been linked to poorer outcome (Vespa et al., 2003).

Taken together, the basic and clinical findings support that the level of post-traumatic neural depression is commensurate with the precipitating insult and correlates with outcome: the more severe the insult, the greater the post-traumatic neural depression, and the greater the post-traumatic neural depression, the greater the behavioral dysfunction. In terms of its potential as a therapeutic target, it would be predicted that when post-traumatic neural depression was made more profound or prolonged (as would be seen with a more severe injury), functional recovery would be deterred. Conversely, if less profound or prolonged (as would be seen with a milder injury), recovery should be promoted. Is there evidence in the lit-

erature showing that modulating post-traumatic neural depression is of neurobehavioral consequence?

TARGETING POST-TRAUMATIC NEURAL DEPRESSION FUNCTIONAL CONSEQUENCES OF ATTENUATION: RECOVERY PROMOTERS

Basic Animal Models

There are several means by which post-traumatic neural depression could be attenuated, with many types of CNS (central nervous system) stimulation having been studied. For example, stimulant drugs and peri-lesional electrical stimulation have each been a means of eliciting activation *without* seizure activity. Alternatively, seizure activity evoked in a variety of ways, including generalized and focal onset with and without propagation, has also been studied. The results show that the type and timing of post-injury CNS stimulation influence how recovery is affected.

In studies using CNS stimulant drugs without seizure activity, amphetamine administration with motor experience of the task minimizes the degree of post-traumatic neural depression *and* at the same time, this correlates with improved functional recovery (Feeney et al., 1982; Hovda, 1996; Queen et al., 1997). Similarly, peri-lesional electrical stimulation appears to improve functional recovery (Adkins-Muir and Jones, 2003). Stimulation of the CNS induced by external events such as motor activity or behavioral experience, has been linked to improved outcome, with the caveat that the activity or experience not be too intense or initiated too soon after injury. Specifically, functional benefit was associated with “moderate” limb use, as opposed to forced overuse of a limb (Kleim et al., 2003), while behavioral impairment was associated with activities initiated “too soon” after the injury, such as running-wheel exercise immediately post-lesion (Griesbach et al., 2004). The methods of CNS stimulation described thus far have done so *without* seizures. What are the functional consequences of post-injury CNS stimulation *with* seizures?

Seizures per se have not been determined to be necessarily harmful to the recovery process, nor are they always associated with poor outcome in animal or clinical studies. Instead, data from both the bench and the bedside suggest that the effects of post-injury seizures depend upon a variety of factors, including type and timing. Though our understanding of the exact parameters of this relationship remains incomplete, it is an extremely important area of continued investigation given that post-traumatic seizures (PTS) are common after TBI, and oc-

cur even more frequently than once thought: chronic EEG monitoring following TBI detected seizure activity in 22% of the patients, with one-half of these individuals experiencing non-convulsive seizures, detectable only via EEG (Vespa et al., 1999).

Almost two decades ago, it was postulated that the occurrence of seizures after brain injury might serve as an *adaptive* response against profound or prolonged post-traumatic neural depression (Schallert et al., 1986); the same profound and prolonged post-traumatic neural depression that has been associated with poor outcome. If seizures *diminish* post-traumatic neural depression, then their occurrence after brain injury should be associated with improved functional recovery. At the same time, if seizures merely *counteract* post-traumatic neural depression, preventing it from becoming more profound or prolonged, then post-injury seizures should be “functionally neutral”. There are data supporting both of these possibilities. Certain types of generalized, seizure-induced CNS stimulation are associated with *improved* functional recovery in animals (Feeney et al., 1987; Hernandez and Schallert, 1988; Hamm et al., 1995). Faster recovery was shown in studies in which electroconvulsive shock (Feeney et al., 1987) or pentylenetetrazol (Hernandez and Schallert, 1988) were administered beginning in the first week after cortex lesion.

Other types of seizure-induced CNS stimulation (focal seizure activity without convulsive behavior) appear to be functionally neutral in their impact on recovery. This has been shown using an animal model of post-traumatic epilepsy (PTE) in which focal, cortical injury is combined with amygdala-kindled seizures (Hernandez and Warner, 1995). Specifically, unilateral lesions of the anteromedial cortex (AMC) produce an ipsilateral somatosensory deficit and recovery from this deficit is vulnerable to manipulation during the post-lesion critical period, which has been defined as beginning 12 h and lasting for 6 days following lesion (Schallert et al., 1986; Hernandez et al., 1989; Hernandez and Warner, 1995; Kline et al., 2000). Non-convulsive, Stage 0 kindled seizures administered during this 6-day critical period neither facilitate, nor hinder the recovery process. That certain types of seizures may be neutral in their impact on the recovery process is a significant consideration when deciding whether or not to administer drugs prophylactically against seizures in the clinic.

Clinical Studies

While there are no clinical data to support that seizures may improve recovery, there are data showing that certain types of seizures are neutral and therefore correlate with an overall recovery pattern similar to that seen in

patients with no seizure activity. Vespa et al. (1999) found no difference in outcome when comparing individuals with early (within the first week) seizure activity and those without seizures. Even though both groups experienced increased intracranial pressure (ICP) after brain injury, the overall ICP was actually *greatest* in the non-seizure group. Cerebral perfusion pressure (CPP) was significantly lower in the non-seizure group. In terms of mortality, there was a non-significant trend towards a *lower* mortality rate in the seizure group when patients with status epilepticus were removed from the analysis. When controlling for injury severity, this resulted in similar mortality rates in individuals with and without early seizures (Haltiner et al., 1999). No differences were observed in length of stay or in GOS (Glasgow Outcome Scale) (Vespa et al., 1999): both good and poor outcomes were equally likely regardless of whether there had been seizures or not. The contribution of injury severity to this finding is unknown.

Attempting to draw exact parallels between the basic and clinical studies is challenging, because in the animals studies, the exact timing and type of seizure activity can be controlled, which is not possible in the clinic. The most parsimonious statement would be that while there is no clinical evidence to suggest that seizures might improve recovery as has been found in animals, there is clinical evidence to support seizures being neutral in their impact on neurobehavioral function and this has been shown using a variety of measures.

FUNCTIONAL CONSEQUENCES OF AUGMENTATION: RECOVERY BARRIERS

Basic Animal Models

When the degree of post-traumatic neural depression is prolonged or made more profound, the resulting level of neural depression is larger than the precipitating insult would dictate, and associated with greater impairment and/or a more enduring deficit. Examples of this can be seen in studies of drugs that augment post-traumatic neural depression, where recovery is delayed and in some instances, there is enhanced atrophy in regions of diaschisis. Chronic administration of the CNS depressant diazepam initiated within the first 24 h after unilateral frontal cortex lesion, correlates with enhanced striatal atrophy ipsilateral to the lesion, as well as sustained somatosensory impairment in rats months after lesion and strikingly, even months after diazepam discontinuation (Schallert et al., 1986; Jones and Schallert, 1992). Though post-traumatic neural depression was not measured specifically in these animals, diazepam is a known CNS depressant. Drugs that exacerbate post-traumatic neural

depression such as haloperidol (Feeney et al., 1982; Goldstein and Bullman, 2002), have been similarly found to delay recovery, as have GABAergic agonists (Watson and Kennard, 1945; Hernandez and Schallert, 1990; Hernandez and Holling, 1994), phenytoin (Watson and Kennard, 1945; Brailowsky et al., 1986a,b) and several commonly used sedative/anesthetics (Statler et al., 2006).

Clinical Studies

There is evidence that some of the CNS depressants drugs studied in animal models may be similarly detrimental clinically, serving as recovery barriers. For example, Bergsneider and colleagues (Bergsneider et al., 2000) reported that brain injured patients receiving *both* benzodiazepines and morphine exhibited significantly lower metabolic rates than did those individuals receiving neither. Because outcome and atrophy were not assessed, the functional relevance of drug-associated hypometabolism in this study remains unknown. The anti-convulsant drugs phenytoin and carbamazepine have each been associated with adverse effects on psychomotor function following brain injury, though these effects were reversible upon drug discontinuation (Smith et al., 1994). Problematic for drawing clear conclusions is that individuals were included who had been given carbamazepine and phenytoin prophylactically following a brain injury or post-injury surgical procedure and seizure history was not reported (though they were seizure-free for at least 4 months pre-entry into the study) (Smith et al., 1994). The most extensive and elegant study of these issues can be found in the placebo-controlled clinical trial of phenytoin prophylaxis (Dikmen et al., 1991; Temkin et al., 1990). As with the Smith study, the negative neurobehavioral effects of phenytoin were seen relatively early while the drug was being administered. Though the negative effect was no longer significant by 1 year, analyses of change from 1 to 2 years revealed greater within subject improvement in the phenytoin group. This change from 1 to 2 years was concluded by the authors to suggest phenytoin had a negative effect on neurobehavioral function after TBI, at least while the drug was in the system (Dikmen et al., 1991).

That anti-convulsant drugs after TBI may be harmful is less than surprising when considered in light of the facts that drug sensitivity is raised in individuals with TBI (Silver and Yudofsky, 1994) and anticonvulsant drugs can adversely affect cognition in non-brain injured individuals (Massagli, 1991; Meador et al., 1995, 2001), as well as those with epilepsy (Ortinski and Meador, 2004). Such issues are particularly important given a high percentage of TBI patients receive these (and other) potentially harmful drugs in hospital after

injury (40% received benzodiazepines and 48% neuroleptics [Goldstein, 1995]) and anti-convulsant drugs are given prophylactically. Indeed, it has been said that despite TBI carrying only an approximate 5% risk of PTE, many of the remaining 95% needlessly receive anti-convulsant medication (Pellock, 1989). In an attempt to minimize the adverse effects of anti-convulsant drugs, it has been recommended that anti-convulsant prophylaxis be utilized in high-risk patients (e.g., those with severe brain injury) and only for the first week after injury (Group, 1998; Chang and Lowenstein, 2003). Still, it is worth determining whether even short exposure to any of these CNS depressants or depressant-like compounds could possibly result in a more profound or prolonged injury-associated post-traumatic neural depression, as well as in sustained deficits and disability.

MECHANISMS UNDERLYING RECOVERY PROMOTERS AND BARRIERS

There are several putative mechanisms by which the attenuation or augmentation of post-traumatic neural depression becomes a recovery promoter or barrier, respectively. Seizure-inducing drugs, such as bicuculline, increase certain growth factors in non-injured brain (Zafra et al., 1991). Seizures also have been found to increase angiogenic and neuroprotective factors, such as FGF-2 (Newton et al., 2003), as well as markers of plasticity and neurogenesis (Madsen et al., 2000, 2003). For example, multiple, noninjurious electroconvulsive seizures have been found to increase FGF-2 (Gwinn et al., 2002; Kondratyev et al., 2002) and glial cells (Madsen et al., 2005) in some brain regions, as well as provide neuroprotection against subsequent injurious seizures (e.g., status epilepticus) (Kondratyev et al., 2001). Taken together, the attenuation of post-traumatic neural depression via activation from seizures or other CNS stimulants may promote recovery because of the potential for plasticity and neuroprotection. In order to promote recovery, however, the seizure activity may need to be sufficient to diminish post-traumatic neural depression and/or evoke plasticity markers. Short of this, seizures may instead be functionally neutral. Examples of this include post-lesion Stage 0 seizures which did not affect functional recovery, nor upregulate FGF-2 (Kline et al., 2000). Similar types of seizures have not been associated with neurogenesis (Parent et al., 1998; Scott et al., 1998). As a caveat, more intense levels of seizure activity (status epilepticus, convulsive-partially kindled) have been associated with poor outcome (Hernandez and Warner, 1995; Vespa et al., 1999; Kline et al., 2000), which may

be due to significant amounts of post-ictal depression of neural activity (Brailowsky et al., 1986a,b; Namba et al., 1989; Hernandez and Schallert, 1990) or the disruption of lesion-induced FGF-2 expression (Kline et al., 2000).

Clinically, the mechanisms of seizure-associated effects are just beginning to be characterized. In a study of two patients (one with and one without status), there was a correlation between a rise in extracellular glutamate and seizure activity, but a similar rise in glutamate was also seen in a group of seizure-free patients when CPP was low (Vespa et al., 1998). Similarly, elevated glycerol, a marker of membrane damage, was reported in one patient with post-traumatic status epilepticus and in another patient with post-traumatic electrographic events without status (Vespa et al., 2002). It remains unclear whether these results are only specific to instances of post-injury status epilepticus or generalizable to other types of recurrent seizure events. Moreover, what any of these findings mean for functional outcome has yet to be determined.

When considering the mechanisms by which augmentation of post-traumatic neural depression leads to sustained impairment, growth factors seem to play a role. Diazepam inhibits growth factors in vivo (Zafra et al., 1991) and leads to degeneration in the substantia nigra when administered after cortical lesion (Schallert et al., 1986; Jones and Schallert, 1992). Phenobarbital administration prior to kindled seizure stimulation blocks the functionally neutral state of Stage 0 seizures and alters FGF-2 expression (Montanez et al., 2000). This effect was distinct from that of phenobarbital alone which only *delayed* recovery (Hernandez and Holling, 1994). Augmenting post-traumatic neural depression via GABergic drugs may serve as a recovery barrier because of ion-associated (Cl^- or Ca^{2+}) toxicity and/or GABA-receptor dependent excitotoxicity, both of which have been found to occur via GABA or GABA agonist administration, especially after injury (Erdö et al., 1991; van den Pol et al., 1996, 1997; Lucas et al., 1997; Chen et al., 1999). Individually or together, these potentially toxic and aplastic conditions may be the means by which augmented post-traumatic neural depression results in atrophy and sustained deficits and disability (Gale et al., 1995; Bigler et al., 1996, 1999; Arciniegas et al., 2001).

It is noteworthy that the exact impact of drugs (and seizures for that matter) is significantly influenced by post-lesion sensitive periods, a full discussion of which is beyond the scope of this review. That said, because a damaged brain is still “damaged” even when there is recovery, this creates a persistent state of vulnerability that extends well beyond the precipitating insult. Evidence for this persistent vulnerability includes studies showing that certain benzodiazepines reinstate deficits long after in-

sult, even when “recovery” is supposedly stable (Schallert et al., 1986; Lazar et al., 2002). Because of this, there may be no completely safe or invulnerable time after brain injury. Instead, there may be differing degrees of vulnerability, each of which must be considered in the treatment of TBI.

DISCUSSION

A comparative analysis of TBI research, both basic and applied, provides evidence that at least one component of the brain’s innate response to insult (e.g., post-traumatic neural depression) is sufficiently well understood to be the target of additional clinical studies and eventual therapeutic strategy development. The timing of its onset and resolution is sufficient to allow intervention, as is the evidence for post-traumatic neural depression in animal models of and humans with TBI. Post-traumatic neural depression appears to be temporally bound to behavioral change: soon after injury, both behavioral and neural function are impaired, with each changing, in parallel, over time. The diminution of behavioral deficits proceeds in a manner commensurate with the degree of damage. Movement or a shift in the pattern of post-traumatic neural depression has behavioral consequences. When made more profound or prolonged (e.g., via certain CNS depressants), there is sustained functional impairment. On the other hand, when the degree of post-traumatic neural depression is attenuated (e.g., via certain CNS stimulants/stimulation), as if the amount of damage were similarly attenuated, functional recovery may be improved. There are limits, however, insofar as more intense levels of seizure activity, as well as seizures in the presence of anti-convulsant drugs have been associated with poor outcome.

Our current understanding of post-traumatic neural depression, its modulation and neurobehavioral consequences is sufficient in the basic sciences to warrant further clinical research. For maximal impact, the research should be aimed at the identification of recovery promoters and barriers, while controlling for important variables that contribute to outcome, such as injury severity. Also important would be a more extensive delineation of the clinical time course for post-traumatic neural depression, including the timing of its onset and persistence, as each relate to injury severity. These types of studies could be accomplished by assessing blood flow or metabolic rate following TBI, as well as short- and long-term outcome. Important independent variables would include the timing and type of anti-convulsant drugs and sedative/anesthetics, as well as seizure activity. Results from such studies could highlight the most common correlates of good and poor outcomes. This could, in turn, lead to the

tailoring of pharmacological interventions to optimize outcome by taking into account post-traumatic neural depression. For example, strategies targeting ligand-gated ion channels and the promotion of cerebral blood flow might be useful (Statler et al., 2006). There may also be a need to re-evaluate the use (or prolonged use) of GABAergic agonists, sedative/anesthetics (Statler et al., 2006), benzodiazepines (Goldstein, 1995), and anti-convulsants prophylactically (Hernandez, 1997; Schallert and Hernandez, 1998; Hernandez et al., 2004), particularly during early “critical periods.” Findings may also support that anti-convulsant prophylaxis should not be utilized uniformly, and instead be replaced with treating in response to seizures (Naritoku and Hernandez, 1995; Hernandez, 1997; Hernandez and Naritoku, 1997; Richard et al., 1998). Alternatively, in cases where anti-convulsant treatment is necessitated post-injury, novel drugs could be developed to minimize neurotoxicity and undesirable side effects (Meldrum, 2002). In an instance where enhanced atrophy is likely, attempting to counter this by administering a drug that stimulates growth factors (Buytaert-Hoefen et al., 2002; Butler et al., 2003) might be of neural and functional benefit. Such a concerted clinical research effort could greatly improve the evidence-based management of TBI and optimize neurobehavioral outcome.

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