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Traumatic brain injury and its effects on synaptic plasticity

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Animal models have been used to simulate the effects of human head trauma. Some of these models have been further utilized to explore how trauma affects specific mechanisms of synaptic plasticity, a cellular model for memory consolidation. Unfortunately, these studies have been more limited in number in spite of their importance for understanding alterations in synaptic plasticity and memory impairments in trauma patients. Research in this area includes well characterized trauma models, genetically engineered animals and neuroprotective studies. One largely ignored but important idea that is entertained here is that trauma may be a crucial aetiological factor for the loss of potassium homeostasis. Moreover, high extracellular potassium has been shown to promote abnormal expression of hippocampal synaptic plasticity due to K^+-induced glutamate release, thus showing important relationships among trauma, glia, potassium and synaptic plasticity. Collectively, this mini review surveys investigations of head trauma involving altered mechanisms of synaptic plasticity and how trauma may be related to increased risk for dementia.

Introduction

A number of animal models of traumatic brain injury (TBI) have been designed to simulate pathologic conditions seen in human TBI [1, 2]. The importance of these models cannot be overstated, since there is currently no standardized neuroprotective therapy available for human use. Most TBI models use rodents due to their low cost and small size [3]. *In vivo* TBI models include lateral fluid percussion [4] (see figure 1), cortical freeze, weight drop, acceleration and controlled cortical impact [5]. *In vitro* TBI models also exist, but will not be discussed in this short review. From a clinical viewpoint [6], some TBI models are more relevant than others; however, the most clinically useful models also appear to suffer from too much variability, whereas models that are more uniform often have little resemblance to human TBI [7]. As one might guess, no one model by itself is adequate to simulate the complex changes observed in human TBI.

Genetically-engineered animals have also been utilized in trauma studies, but these investigations have been more limited in number [3]. Genotypes for testing molecules involved with the inflammatory response and signal transduction pathways have included intracellular adhesion molecule 1 (ICAM-1), tumour

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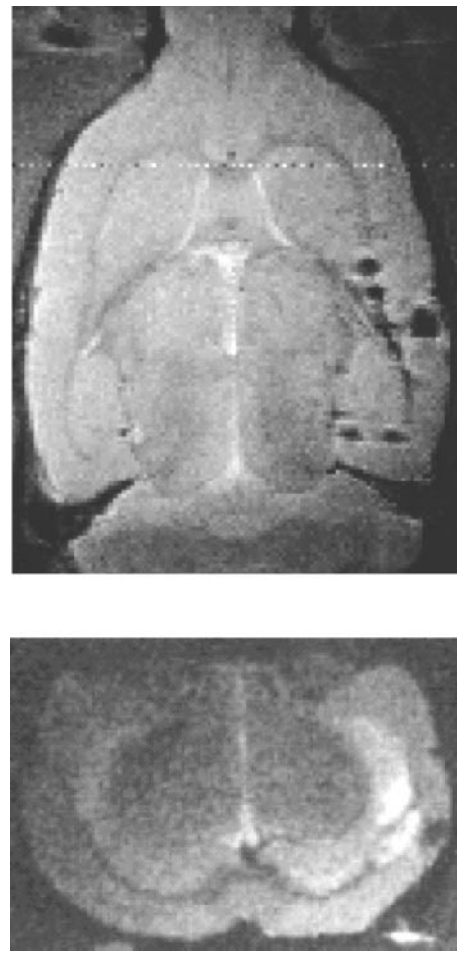

Figure 1. MRI Scans of a rat subjected to lateral fluid percussion TBI. The top panel shows an horizontal scan at 3–4 hours post-TBI. Notice the anterior-to-posterior extent of the lesion (hypointense regions) in the cortex and how it borders the corpus callosum. The bottom panel shows a coronal scan imaged at 2 weeks post-TBI, where both hypointense and hyperintense MR signal changes are evident in the hippocampal formation and in the cortex. These MR signal changes are indicators of oedema formation (hyperintense) and cavitation (hypointense) characteristic of this model and human TBI. Astrocytic swelling via K^+ channels is likely to mediate brain oedema after TBI. Modified from Albensi et al. [51].

necrosis factor (TNF), copper zinc superoxide dismutase (CuZn SOD) and apoE to highlight a few. Studies utilizing genetically-engineered mice have many advantages for examining specific molecular mechanisms, but the approach also comes with a number of pitfalls. For example, permanent alterations in target genes may cause responses to TBI in engineered strains that are different than those found in controls. Moreover, investigators have found [8] that different background strains of mice demonstrate various responses to TBI that indicates the proper choice of background strain is critical when using genetically altered mice for TBI. Also, the polymorphism inherent in the genetic background of genetically altered strains can, at times, make the results troublesome to evaluate. Finally, investigations concerning the inflammatory cytokine, TNF, have resulted

in a complex mixture of both neuroprotective and neurodegenerative effects. Therefore, over-expressing or deleting certain genes that code for enzymes or receptors found in pathways involving TNF may be too simplistic for some studies where results will need to be interpreted with caution.

Animal models have been further utilized to explore specific mechanisms of how trauma affects synaptic plasticity [4, 9–13] and cognition [14]. Post-traumatic amnesia is a typical outcome after head injury where, for a period of time, information about ongoing events is not stored [15].

Synaptic plasticity

In 1949, Hebb [16] published a book entitled *The Organization of Behaviour*, where he put forward a theory on synaptic modification. Central to this theory was the idea that, in response to external and internal stimulation, information is stored in the brain by way of synaptic modification. Hebb [16] proposed that the storage of information, the engram of memory, was found in the synapse and that synapses were strengthened between cells when cells were active at the same time. In 1973, Bliss and Lomo [17] demonstrated evidence for Hebb's theory when they described that brief trains of high frequency stimulation resulted in a persistent and long-lasting increase in the efficiency of synaptic transmission. They called this observation long-term potentiation (LTP). Increasing literature [18–20] suggests that LTP and long-term depression (LTD) responses are manifestations of long-lasting synaptic plasticity related to memory consolidation. Moreover, LTP and LTD processes may have inter-related mechanisms [21], where LTD may function as the inverse of LTP. Conditions modulating LTP/LTD responses include prior synaptic history, learning, development, ageing, stress, disease and brain injury [21, 22].

In light of these studies, investigators [9–13] have attempted to analyse the effects of TBI on LTP and LTD responses in hippocampal regions. Results appear to be similar across studies with regard to TBI attenuating LTP responses; however, TBI's effects on LTD responses were more variable (i.e. when tested), and so many questions remain unanswered. On the whole, investigations do appear to point to disrupted mechanisms regulating glutamate receptor activation, intra-cellular calcium levels, extracellular potassium levels and GABA-mediated inhibition.

For example, Miyazaki *et al.* [11], using a fluid-percussion model of TBI in combination with *in vivo* electrophysiologic recordings, found that, in hippocampal CA1, the excitatory post-synaptic potential (EPSP) was significantly smaller in injured animals at 2–3 hours post-TBI. Furthermore, they found that LTP of population spike responses and EPSPs in the injured animals was markedly suppressed. Since LTP may be related to processes associated with memory formation, the impairment in LTP may be a correlate of an enduring memory deficit. In another *in vivo* electrophysiologic study by Reeves *et al.* [23], LTP of the Schaffer collaterals was tested in rats on days 2, 7 and 15 post-TBI (fluid-percussion injury). Here, they found that TBI significantly increased cellular excitability on day 2 and that LTP was impaired in rats subjected to TBI.

The cholinergic pathway has also been implicated in processes of cognition, arousal and attention, where acute and chronic changes in this pathway may contribute to the cognitive deficits seen following TBI [24]. Verbois *et al.* [24] tested this idea using a model of controlled cortical impact in rats. In this study, they evaluated TBI on the expression of brain nicotinic acetylcholine receptor (nAChr)

sub-types using quantitative autoradiographic methods. The effects of TBI (48 hours post-TBI) on brain nAChrs were compared to effects of the injury on muscarinic cholinergic receptors, NMDA receptors and calcium channel expression. They found that TBI significantly reduced $\alpha 7$ nicotinic cholinergic receptor binding. These results suggest that $\alpha 7$ nicotinic receptors are sensitive targets for TBI-induced down-regulation. These data are interesting, since most other studies involving changes in the cholinergic system following TBI have been focused on muscarinic rather than nicotinic cholinergic receptor systems.

Pathology of trauma and neuronal excitability

TBI results in a plethora of disrupted mechanisms (figure 2) and disturbances to homeostatic processes that include synaptic depression, the possible loss of neurons in specific regions and/or hyperexcitability. In fact, trauma-induced seizure activity is a condition that affects a rather large number of trauma patients [25].

Perhaps at the heart of this activity are shifts in the balance of neuronal excitation to inhibition [26]. Some excitability changes may be due to pre-synaptic mechanisms [27]. In addition to neurochemical modifications, studies have shown structural evidence for the hippocampal involvement in persistent seizure susceptibility after TBI [28]. Furthermore, it has recently been shown that a single episode of

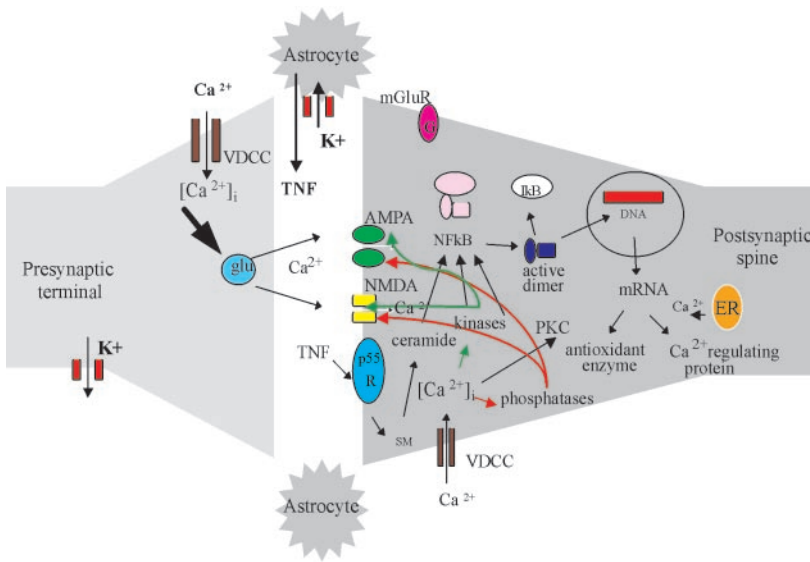

Figure 2. Signalling pathways in synaptic transmission, plasticity and trauma. The illustration shows some of the overlapping pathways that are utilized during synaptic transmission, synaptic plasticity and also following trauma. Central to all processes (large arrows) are: (1) the release of glutamate, (2) NMDA activation, and (3) changes in intra-cellular calcium levels and calcium sources, where concentrations and/or durations are critical for normal vs pathologic events. Additionally, neuronal-glial interactions are emerging as important for responding to brain injury via K^+ channels and for regulating synaptic strength through TNFα [52, 53]. There are of course hundreds of mechanisms and pathways activated as a result of synaptic processes and brain injury, but the cartoon has only enough space to highlight some key points of interest. Also note that GABAergic mechanisms (not shown) are important in the regulation of neuronal excitability and temporal and spatial summation of electrical potentiation. Modified from Albensi, Drug News Perspect **15***(4), 2002.*

experimental closed head trauma induces long-lasting alterations in the hippocampus and in persistent increases in neuronal excitability [29]. The astute reader, however, will notice that synaptic depression (e.g. decreased EPSP slope) is at odds with increased hyperexcitability (e.g. electrical bursting, etc.), which further suggests that the effects of trauma is complex and are likely time- and region-dependent.

TBI-induced damage to the hippocampus has frequently been demonstrated to be selectively restricted to the dentate hilus [30]. Loss of neurons in this area is thought to be a causative factor in trauma-induced hyperexcitability. Furthermore, TBI-induced injury may lead to disturbances in GABAergic mediated inhibition in dentate granule cells. To test this idea, Toth *et al.* [31] used whole cell patch clamp methods to evaluate neurons after moderate lateral fluid percussion injury (FPI) in adult rats. They found that, 1-week after FPI, injured rats showed that feed-forward inhibitory control of dentate granule cell discharges was compromised and the frequency of IPSCs was decreased. The results also showed that TBI affects the dentate neuronal network in a unique way where the pattern of injury is selective. In fact, small tightly packed granule cells appeared in this study to suffer little physical stress from the FPI pressure pulse as opposed to larger neurons located in the granule cell layer.

Trauma, glia and synaptic plasticity

During trauma, pre-synaptic terminals appear to release excessive glutamate in response to abnormal increases in extracellular potassium. High levels of extracellular potassium have also been shown to promote abnormal hippocampal synaptic plasticity due to K^+-induced glutamate release. Since the homeostatic control of extracellular glutamate depends on the preservation of the neuronal and glial resting potential, it stands to reason that failure of Na/K ATP-ase and excessive extracellular potassium may enhance excitatory neurotransmission and alter synaptic plasticity.

The concentration of potassium in the extracellular matrix increases during trauma. It also temporarily increases after seizures, from direct stimulation of afferent pathways, during anoxia and/or from spreading depression [32–35]. Interestingly, K^+ values return to normal levels in a relatively short period of time after these conditions. Several theories have been proposed to explain the rapid clearance of potassium from the extracellular space, including uptake by glia, passive diffusion and neuronal re-uptake. Experimental evidence has suggested that potassium uptake by glia may be primarily responsible for reducing excessive potassium during trauma.

The theory of *spatial buffering* [36] provides an hypothesis to explain some of the observations associated with potassium uptake in the extracellular space. The spatial buffering mechanism is based on several electrophysiological measurements that include that the glial resting membrane potential closely follows the potassium equilibrium potential (i.e. glial cells are permeant to K^+ and that glial cells form a complex by tight electrotonic coupling via gap junctions).

Present-day orthodoxy maintains that glial cells lack regenerative, action potential-like responses. However, glial cells express a number of voltage-, second messenger- and agonist-operated channels [37–39]. *Potassium channels* are the most common electrophysiological feature of both cultured and *in situ* astrocytes and can

be categorized as follows: channels that allow inward but not outward current flow (*inward rectifiers*, K_{IR}); channels that allow outward but not inward current flow (*delayed rectifier*, I_{DR}; *transient outward current*, I_A); channels that are opened by intracellular calcium ($I_{K(Ca)}$). Glial potassium channels differ in their sensitivity to blockers: inward rectifiers are blocked by sub-millimolar concentrations of external Cs^+ and Ba^{++}; outward I_{DR} and I_A are both sensitive to tetraethylammonium (TEA) and 4-amino-pyridine (4-AP). Voltage dependent, TTX-sensitive and insensitive *sodium channels* are also expressed in both cultured and *in situ* glial cells [40]. While astrocytes are incapable of producing action potential-like responses [39], possibly due to the relatively low Na^+ current densities in these cells, a role of Na^+-channels in spatial buffering has been proposed. According to this hypothesis, Na^+ influx sustains the Na^+/K^+-ATPase pump, resulting in net K^+ uptake. Finally, *calcium channels* are represented sparingly in glial cells and require either neuronal or otherwise differentiating factors for expression [37]. Whether I_{Ca} can be recorded from *in situ* hippocampal astrocytes is still unknown, but release of calcium from intra-cellular stores in response to neurotransmitters acting on astrocytes has been clearly demonstrated. Relevant to spatial buffering, micromolar levels of $[Ca^{+2}]_i$ can cause opening of $I_{K(Ca)}$ and may, thus, participate in the generation of outward potassium fluxes.

Several years ago, Sastry *et al.* [41, 42] suggested a connection between astrocytic resting potential and hippocampal synaptic plasticity. Sastry *et al.* [41, 42] showed a unique form of LTP mediated by depolarization of glial cells. This form of LTP is sensitive to APV and removal of extracellular Ca^{++}, thus resembling synaptically evoked LTP. Other studies support this hypothesis, where increased extracellular potassium has been shown to induce LTP.

Neuroprotection

Neuroprotection therapy for TBI has resulted in a search that so far has not yielded results that can be used routinely in the clinic or the emergency room [43]. However, there is still great hope among scientists and clinicians that the delayed events of TBI, also known as *secondary injury*, are events that can be therapeutically targeted that could reduce cell loss and diminish the impairments seen in memory following TBI.

Experimental drugs (table 1) that have been tested so far in animal models of TBI include several classes ranging from anti-epileptic compounds to thyrotropin-releasing hormone analogues. Additionally, a number of drugs have also been tested in pre-clinical animal models to treat dementia associated with Alzheimer's disease (AD) (table 2) that may or may not have benefits in trauma-induced memory impairment. Various forms of TBI appear to be a risk factor for AD, so there is some rationale for testing AD drugs in models of TBI. Unfortunately, many experimental drugs appear to be highly promising in animal models; however, when following up on results from Phase III clinical trials these drug candidates have generally been disappointing [44]. In one study by Albensi *et al.* [9], cyclosporin A was tested in a controlled cortical impact model of TBI. Here, one was interested in determining if cyclosporin, a compound known to stabilize mitochondrial function, was able to reverse alterations in synaptic plasticity induced by TBI. Prior studies have shown that cyclosporin A reduces brain damage caused by ischemia. Increasing data also support a role for mitochondrial dysfunction as part of the neurodegenerative

Table 1. Classes of experimental drugs used previously in animal models of TBI

Agent	Mechanism of action
Catecholamines	Antagonists of dopamine and norepinephrine receptors
Gangliosides	Membrane stabilization
Antioxidants	Free-radical scavengers
Calcium channel antagonists	Blockers of calcium channels
NMDA antagonists	Blockers of glutamate receptors
Steriods	Inhibition of lipid peroxidation
Arachidonic acid (AA) modulators	Inhibition of AA metabolism
Platelet-activating factor (PAF) antagonists	Antagonists of PAF
Anti-epileptic drugs	Various mechanisms affecting excitability
Thyrotropin-releasing hormone (TRH) analogues	Antagonists to select actions of opioids

Table 2. Examples of experimental drugs tested in animal models of dementia and memory impairment

Agent	Mechanism of action
Vitamin E	Antioxidant
Nifedipine	Blocker of calcium channels
MK-801	NMDA antagonist
Phenytoin	Sodium channel blocker
Valproic acid	GABA agonist
Chromakalim	Potassium channel opener
Congo red	Prevents peptide aggregation

process in TBI. It was reasoned that, since cyclosporin inhibits mitochondrial membrane permeability transition (MPT) in isolated mitochondria and since MPT plays a role in synaptic dysfunction, applications of cyclosporin would inhibit MPT and be beneficial in the model of TBI and synaptic plasticity. It was found that administration of 20 mg/kg at 15 min post-TBI was effective at ameliorating the TBI-induced impairment of LTP and completely removing the TBI-induced enhancement of LTD (figure 3) in hippocampal brain slices tested at 48 hours post-TBI. Collectively, these data suggest that cyclosporin A may be effective at relieving synaptic dysfunction in head trauma patients. Previously, cyclosporin has been used in the clinic as an immunosuppresant agent in transplant patients and is, therefore, already well suited for clinical studies.

L-Deprenyl, a dopamine enhancer, has also been shown to improve cognitive function and enhance neuroplasticity after fluid-percussion induced TBI [45]. In this study, it was demonstrated that the MAO inhibitor, L-deprenyl, administered in a daily dose of 1 mg/kg significantly attenuated cognitive dysfunction induced by either fluid percussion TBI, bilateral entorhinal cortical lesion (BEC) alone, or combined TBI and BEC lesion. These data suggest that dopaminergic/noradrenergic enhancement facilitates cognitive recovery after brain injury. However, the exact mechanism of action for the beneficial effects of L-deprenyl in TBI is still unclear, since four different mechanisms of action have been proposed

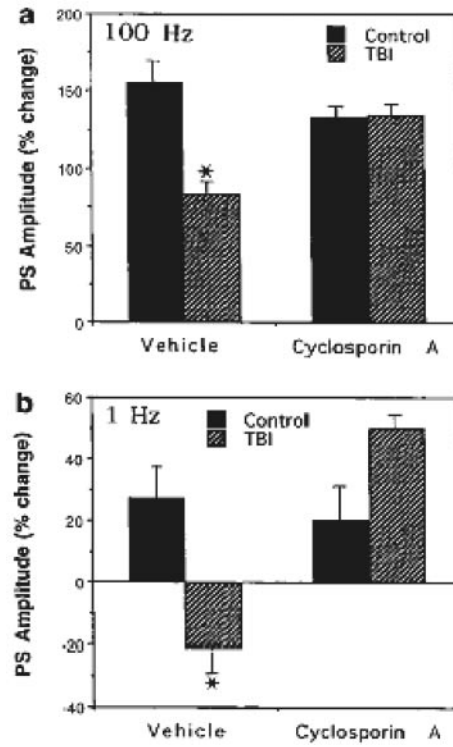

Figure 3. Cyclosporin preserves synaptic plasticity: (a) Moderate controlled cortical impact induced TBI was found to impair LTP as measured by population spike (PS) responses (100 Hz) in CA1 region hippocampal brain slices at 48 hours post-TBI. Applications of cyclosporin A (20 mg/kg) administered IP at 15 minutes post-TBI removes impairment. (b) TBI was also found to enhance LTD PS responses (1 Hz) where similar applications of cyclosporin removed the LTD enhancement. Modified from Albensi et al. [9].

based on data from *in vitro* and *in vivo* models. These include, MAO inhibition, the reduction of free radicals via scavenging by superoxide disumutase, stabilization of the mitochondrial membrane potential and by enhanced neurotrophic activity protecting against neuronal cell death.

TBI as a risk factor for cognitive impairment in Alzheimer's disease

Increasing epidemiological data suggest that TBI may be a risk factor for Alzheimer's disease (AD) later in life [46, 47]. However, the biological mechanisms for how TBI may lead to AD are still unclear and are highly controversial. Mesulam [48] has recently put forth an hypothesis concerning plasticity burden and its relationship to the pathogenesis of AD. He states in his hypothesis that the premature development of neurofibrillary tangles and Aβ deposits in the brains of ex-boxers provides support for the idea for an heightened state of neuroplasticity (TBI-induced) that can trigger the neuropathological changes seen in AD. He goes on to postulate that AD-promoting factors create a setting where neurons must work harder to meet plasticity demands at their axonal and dendritic terminals.

Others have proposed that mechanisms linking TBI to AD may include damage to the blood–brain barrier (creates a situation where plasma proteins leak into the brain and also increases the permeability of toxins and viruses), neuronal loss and the liberation of free radicals. In particular, the epsilon 4 allele of apolipoprotein E appears to be a major risk factor for AD [49]; more recent evidence indicates a link with a poor outcome after TBI and intracerebral haemorrhage. Other investigators have shown [50] a strong association between the APOE-epsilon 4 allele and a poor clinical outcome, implying genetic susceptibility to the effect of TBI.

Conclusions

The complex relationships among TBI, alterations in synaptic plasticity and cognitive impairment are slowly being unraveled. Animal models have been shown to be important for exploring how trauma affects specific mechanisms of synaptic plasticity. Investigations, in general, do seem to point to disrupted mechanisms regulating glutamate receptor activation, calcium and potassium levels and changes in GABA mediated inhibition. Furthermore, glial cells may be playing an important role in regulating potassium homeostasis.

Moreover, many drugs have been tested in pre-clinical models targeting altered mechanisms where preliminary results have been quite promising, however, in Phase III clinical trials, results from drug candidates have generally not been as fruitful. Finally, increasing literature points to the possibility that TBI is a risk factor for Alzheimer's disease, which further complicates the understanding of how TBI affects synaptic plasticity in the short term and also over great periods of time. Therefore, the effect of TBI on synaptic plasticity still remains a major scientific challenge that awaits the efforts of curious and talented investigators.

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