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What are the effects of prolonged seizures in the brain?

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Abstract

Convulsive status epilepticus is the most common neurological emergency in children and is associated with significant morbidity and mortality. The morbidities include later development of epilepsy, cognitive impairment, and psychiatric impairments. There has been a long-standing hypothesis that these outcomes are, at least in part, a function of brain injury induced by the status epilepticus. There is evidence from animal models and prospective human studies that the hippocampus may be injured during febrile status epilepticus although this pathophysiological sequence remains uncommon. Potential mechanisms include excitotoxicity, ischaemia, and inflammation. Neuroprotective drugs reduce brain injury but have little impact on epileptogenesis or cognitive impairments. Anti-inflammatory treatments have given mixed results to date. Broad-spectrum anti-inflammatory agents, such as steroids, are potentially harmful, whereas prevention of leucocyte diapedesis across the blood brain barrier appears to have a positive outcome. Therefore, more studies dissecting the inflammatory process are required to establish the most effective strategies for translation into clinical practice. In addition to neuronal loss, cognitive impairments are related to neuronal re-organisation and disruption of neural networks underpinning cognition. Further understanding of these mechanisms may lead to novel therapies that prevent brain injury, but also therapies that may improve outcomes even if injury has occurred.

Keywords

convulsive status epilepticus; seizure; cognition; hippocampus; outcome

Convulsive status epilepticus (CSE) is the most common medical neurological emergency (DeLorenzo *et al*., 1996; Chin *et al*., 2006). For the purposes of this review, CSE is defined as a seizure, or series of seizures during which full consciousness does not return, that lasts for at least 30 minutes. Although shorter time definitions have also been suggested, these definitions largely apply to treatment rather than to brain injury. The incidence in childhood is 17-21/100,000 children per year in London (Chin *et al*., 2006), 108/100,000 children/year in Kilifi (Sadarangani *et al*., 2008), and 38/100,000 children/year in Okayama (Nishiyama *et al*., 2007), reflecting important geographical differences in the nature of CSE. These

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differences are likely to be related to differences in aetiology of CSE. Significant mortality and morbidity has been reported. Mortality is almost exclusively in children with significant pre-existing brain abnormalities. However, morbidity, at least in part, may be related to direct effects of seizures (Pujar *et al.*, 2011). The aim of this review is to describe the relationships between CSE, brain injury, and cognitive outcomes, and to discuss potential mechanisms for these outcomes.

CSE and hippocampal injury

There is a long-standing hypothesis that CSE, and particularly prolonged febrile seizures, are associated with hippocampal injury which gives rise to the most common justification for epilepsy surgery; mesial temporal sclerosis (MTS) (Babb and Brown, 1993; Honovar and Meldrum, 1997). This hypothesis was generated from observations made in epilepsy surgery programs *i.e.* in retrospect. More recently, there has been an emphasis on prospectively identifying children with prolonged febrile seizures (PFS) and assessing whether these children have evidence of hippocampal injury, how any observed injury matures, and how this injury may impact cognition. It is recognised that these relationships may take many years and therefore these issues have not yet been fully resolved in humans.

Animal models have widely been used to investigate whether CSE can cause hippocampal injury (Ben Ari, 1985; Lothman *et al.*, 1989; Meldrum, 1991; Cavalheiro, 1995). This has been extensively reviewed elsewhere (Lothman and Bertram, 1993; Cavalheiro, 1995) and will not be covered in detail here. In brief, there are several well-established models in which the generation of CSE, using chemical means (*e.g.* bicuculline, pilocarpine, kainate) and electrical stimulation approaches, leads to hippocampal injury that closely resembles the histological features of MTS in humans (Babb and Brown, 1993). The outcomes from these animals include spontaneous recurrent limbic seizures and cognitive impairments. These studies have been used to justify human prospective studies.

There are two main studies in the literature which have used MRI to evaluate the relationship between prolonged febrile seizures and hippocampal injury. The London group have shown that there is evidence for bilateral hippocampal oedema 48 hours after a PFS (Scott *et al.*, 2002). None of these children had visually-identified abnormalities which were identified using quantitative analysis tools (Scott *et al.*, 2002). This peak in hippocampal oedema has been confirmed in an animal model and in addition, the T2 relaxation time at 48 hours predicts the severity of the final hippocampal volume loss (Choy *et al.*, 2010a). Subsequently, these hippocampi return to normal size six months later, although there is an increase in right-left asymmetry when compared to controls (Scott *et al.*, 2003). The relationship between early T2 and final hippocampal volume was not confirmed in this cohort and it is likely that a larger sample size is required for this. No child developed MTS in that timeframe.

A subsequent study by the London group evaluated hippocampal growth over the first year following CSE. As it has been established that PFS is associated with acute hippocampal changes, the children in the next cohort were investigated 1, 6 and 12 months after CSE with the assumption that acute hippocampal oedema would have gone by one month after the

event. In total, 20-30% of the children had evidence for reduction in hippocampal growth, further supporting the view that CSE may cause hippocampal injury in some children (Yoong *et al.*, 2013). This cohort included children with PFS as well as children with other forms of CSE. It is important to note that this growth failure was identified at a similar frequency across all types of CSE.

The FEBSTAT study in the USA has recruited 199 children with PFS and therefore has greater power to identify later MTS than the London studies (Scott and Neville, 2009). FEBSTAT has revealed that there are approximately 10% of children that have visually identified increases in T2 unilaterally in the hippocampus (Shinnar *et al.*, 2012). There is some suggestion that this increase in T2 can predict final volume as in our animal models (Provenzale *et al.*, 2008) and in the recently reported results from FEBSTAT (Lewis *et al.*, 2014). Therefore, it is clear that PFS is associated with acute hippocampal change and that it is possible that this leads to adverse seizure and cognitive outcomes. Understanding the mechanisms of this injury could lead to novel treatments that minimize the chances of these adverse outcomes. It is extremely difficult to establish a mechanism and therefore animal models are required.

The mechanism that has received the most attention is excitotoxicity (Meldrum, 1991; Haglid *et al.*, 1994). Prevention of brain injury and epileptogenesis is possible with pre-administration of the NMDA receptor blocker, MK-801, supporting the hypothesis that excitotoxicity is an important mechanism driving adverse outcomes from CSE (Stafstrom *et al.*, 1993). Unfortunately, administration of MK-801 after termination of CSE, which is the more clinically relevant experiment, fails to prevent epileptogenesis even though brain injury is lessened. This suggests that either the mechanisms downstream of NMDA receptor activation or modulators of those mechanisms could be potential therapeutic targets. The time course of oedema identified in both humans and animal models is consistent with an inflammatory process, and given that the degree of oedema is related to the severity of brain injury, it is possible that modulation of inflammation could improve outcomes from CSE.

There is increasing evidence that CSE in rodents elicits brain inflammation and that blocking inflammatory cascades can improve outcomes. CSE induced electrically, with convulsant drugs or with high temperatures, results in rapid activation of glial cells and concomitant production of inflammatory molecules. Interleukin-1βis induced within one hour of CSE and is observed in the area of seizure origin (Dhote *et al.*, 2007; Ravizza *et al.*, 2008). The release of this and other cytokines (*e.g.* tumour necrosis factor [TNF] and interleukin-6 [Il-6]) (Vezzani and Granata, 2005; Dubé *et al.*, 2005; Vezzani *et al.*, 2011) results in up-regulation of selectins, adhesion molecules (including vascular cell adhesion molecule-1 [VCAM-1]) (Jung *et al.*, 2006; Fabene *et al.*, 2008) and integrins (Fabene *et al.*, 2008). These latter molecules allow the rolling and arrest of leukocytes along the endothelium and subsequently enable the transmigration of those leukocytes across the endothelium. These processes are believed to be important in the modulation of brain injury and epileptogenesis. Global gene expression studies in animal models of CSE and traumatic brain injury have shown prominent up-regulation of immune response genes at multiple time points from the acute insult. If inflammatory processes are modulating the mechanisms underpinning brain injury and epileptogenesis, then the fact that inflammation continues

throughout the time course of injury and epileptogenesis makes inflammatory molecules very attractive therapeutic targets. It is also possible to image evidence of inflammation using a contrast agent targeted to VCAM-1 (Duffy *et al.*, 2012). Therefore, it is clear that there is a relationship between CSE and inflammation, although it remains uncertain whether these changes are causatively related to brain injury and adverse outcomes.

The pharmacological experiments that have attempted to address the relationships between inflammation and adverse outcomes from CSE have explored the effects of cyclooxygenase-2 (COX-2) inhibitors, erythropoietin, disruption of leukocyte-endothelial interactions, and corticosteroids. There is controversial evidence that reducing inflammation following CSE with COX-2 inhibitors can reduce the severity of subsequent epilepsy. Administering the COX-2 inhibitor celecoxib following CSE reduces the severity of hippocampal injury and the frequency of spontaneous recurrent seizures in the pilocarpine model (Jung *et al.*, 2006). The COX-2 inhibitor parecoxib also reduces the severity of brain injury, but does not alter the frequency or duration of spontaneous recurrent seizures when administered following pilocarpine-induced CSE (Serrano *et al.*, 2011). However, the severity of the seizures is reduced.

Erythropoietin is known to have neuron and astroglial protective effects *via* several mechanisms including the reduction of tissue-injuring molecules, such as reactive oxygen species, glutamate, and inflammatory cytokines. Administration of erythropoietin for seven days, commencing immediately after termination of status epilepticus, reduces hippocampal injury as well as the frequency and severity of subsequent spontaneous recurrent seizures (Chu *et al.*, 2008; Jung *et al.*, 2011). This suggests that a broad spectrum antiinflammatory agent has positive effects on outcomes from CSE. Another broad spectrum anti-inflammatory is dexamethasone. When this is administered soon after CSE and then daily for five days, brain injury is greater than in controls with CSE, and mortality is greater (Duffy *et al.*, 2014). Thus, a greater understanding of the inflammatory mechanisms to disentangle advantageous from disadvantageous processes may provide insight on treatment.

The fourth approach that has been tested is the disruption of leukocyte-endothelial interactions. CSE leads to up-regulation of VCAM-1, which is important in the rolling and arrest of leukocytes. This effect is mediated by P-selectin glycoprotein ligand-1 (PSGL-1, encoded by Selplg) and leukocyte integrins $\alpha 4\beta 1$ and $\alpha_L\beta 2$. Genetically interfering with PSGL-1, using blocking antibodies to $\alpha 4$, and depleting leukocytes all result in reduced brain injury and reduced epileptogenesis (Fabene *et al.*, 2008). This suggests an extremely important role for leukocyte vascular interactions in injury and epileptogenesis.

Another possible mechanism of brain injury is related to blood flow. During pilocarpine-induced status epilepticus, there are increases in blood flow across many parts of the brain. This is hypothesised to be in order for the brain to meet the metabolic demand of the seizure, thereby minimizing brain injury. However, the increase in blood flow to the hippocampus does not increase as much as in the cortex, despite the hippocampus having marked epileptic changes (Choy *et al.*, 2010b). Thus, there is a relative hyporaemia in the hippocampus which may, at least in part, lead to hippocampal injury. It is probable that there is no one

predominant mechanism of injury and injury is likely to be a result of an interaction between all of the processes described as well as possible mechanisms not yet described.

Cognitive outcomes

Brain injury associated with status epilepticus could result in long-term cognitive impairment. The London group has been exploring this issue and have shown that one month following CSE, there are reductions in cognitive and language abilities (Martinos *et al.*, 2013). One year following CSE, there were no further changes to cognition, suggesting that the identified cognitive impairments were fixed within one month of the event. These findings are confounded by the aetiology of the CSE which is also a major driver of impairment and therefore the outcomes could be a result of a pre-existing condition. Children with non-febrile CSE often have important neurological illness and have more impairment than those with febrile seizures who are usually considered to be neurologically normal. Nevertheless, children with PFS also have a reduction in cognitive and language ability when compared to controls. Although this may be a result of the mechanisms that predispose a human to having PFS, it is also possible that this reduction of approximately 10 DQ points is a direct effect of the seizure. As the hippocampus is integral to memory function, we also investigated this. Children with PFS have abnormalities in memory retention one month after PFS (Martinos *et al.*, 2012).

There are many potential mechanisms underlying these observed cognitive changes. It is commonly attributed to neuronal loss and thus insufficient neural machinery to adequately process information. However, there are other potential processes that could lead to cognitive impairments. A common observation after hippocampal injury is mossy fibre sprouting in the dentate gyrus (Buckmaster *et al.*, 2002). This phenomenon is thought to increase excitability of the hippocampus and thus predispose to seizures, and it is likely that this disruption of the neural system could also impair cognition. Alterations in signalling processes including AKT/MToR (Talos *et al.*, 2012), as well as increased neurogenesis with abnormal migration and integration, may also contribute to cognitive outcomes (Danzer, 2008). Thus, there are many factors that could lead to adverse cognitive outcomes and the net effects of these events are likely to disrupt the neural networks underpinning cognition. Behaviourally, it has been shown that after CSE, animals have marked impairments in the Morris water maze which is a test of spatial memory in rodents.

There are several lines of evidence supporting the view that the function of neural networks is impaired following brain injury associated with CSE. Changes in long-term potentiation have been identified in hippocampal slices and this may be important as a mechanism for the marked spatial memory impairments seen following CSE-induced brain injury (Cornejo *et al.*, 2007). Cognitive networks can also be interrogated *in vivo* by looking at individual cells, EEG oscillations, and functional connectivity between cells. Place cells are hippocampal pyramidal neurons that exhibit location-specific firing which can be recorded in freely moving rodents. Parameters from those recordings give insight into the fidelity with which these cells fire, *i.e.* a cell that fires very precisely with location specificity is thought to encode spatial information with high fidelity and predicts hippocampal function. Place cells are impaired following brain injury, but importantly, are also disrupted in a PFS model in

which there is no overt neuronal loss (Dubé *et al.*, 2009). Place cells also show the phenomenon of phase precession which describes the way a place cell fires with respect to EEG oscillations (Lenck-Santini and Holmes, 2008). This phenomenon which describes how a place cell functions within its network is also abnormal post CSE. Direct correlations between how well an animal performs in a maze and these parameters have not been attempted.

It has been recognised for decades that the frequency and size of oscillations in the theta frequency (4-12 Hz) in the rodent hippocampus are important for information processing. These oscillations are also known to fluctuate with respect to running speed. In animals with CSE-induced hippocampal injury, the speed modulation of theta frequency is less precise and the degree of imprecision predicts how well an animal performs in a figure-8 alternation task (Richard *et al.*, 2013). The evaluation of EEG oscillations gives some information about neural networks. An alternative way to evaluate neural networks is to build functional connectivity networks from single unit recordings in which multiple neurons are recorded simultaneously. Following CSE-induced hippocampal injury, there is increased functional connectivity between hippocampal pyramidal cells and the level of connectivity predicts performance in the same alternation task as above (Tyler *et al.*, 2012). The networks that form during the running phase of the task are expected to reactivate when the animal rests at the feeder. The level of reactivation also predicts performance in the spatial task. Therefore, spatial cognition impairments following CSE are related to the way surviving neurons are organised into networks and not simply to the number of neurons. If it were possible to modulate the networks of remaining neurons then this may lead to strategies that improve cognition.

In conclusion, status epilepticus is likely to cause some brain injury although the frequency at which this leads to MTS and epilepsy remains uncertain. Mechanisms of injury include excitotoxicity, inflammation, and relative reductions in hippocampal blood flow. There is evidence for cognitive impairment following CSE in humans and in animal models and this may be related to disruptions in the neural networks underpinning cognition. Further understanding of these mechanisms may lead to novel therapies that prevent brain injury, but also therapies that may improve outcomes even if injury has occurred.

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