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Review

Pathophysiology of convulsive status epilepticus

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ABSTRACT

Purpose: To summarize the pathophysiology of convulsive status epilepticus (SE) with a focus on practical implications for treatment.
Method: Narrative review of the medical literature on the pathophysiology of convulsive SE. We considered both animal models of SE and clinical studies.
Results: Convulsive SE is an emergency in which prolonged convulsive seizures are associated with cardiorespiratory instability, hypoxia, hypoglycemia, and hyperthermia. Supportive treatment helps correct these physiological imbalances. When treatment is delayed, the ability of first line seizure suppressing medications to terminate the seizure can be reduced. Animal studies have suggested that $GABA_A$ receptor trafficking may contribute to the failure of the first line therapies and that NMDA receptor antagonists such as ketamine may become more effective as seizures last longer. Potential strategies to take advantage of these changes in pathophysiology include a rapid escalation from benzodiazepines to non-benzodiazepine antiepileptic drugs (AEDs), early polytherapy and use of NMDA antagonists such as ketamine for refractory convulsive SE. Despite the importance of a timely treatment of convulsive SE, major treatment delays are frequent in clinical practice. Policies to improve time to treatment, especially in convulsive SE that starts outside the hospital, may improve response to treatment and convulsive SE outcomes.
Conclusions: Convulsive SE is a time-sensitive emergency in which the underlying pathophysiology may provide targets for improving treatment strategies. A timely transition from benzodiazepines to other AEDs may help reduce treatment resistance in convulsive SE.

1. Introduction

Convulsive status epilepticus (SE) is a common neurological emergency that disproportionately affects young children and older adults [1–3]. SE is associated with a mortality of approximately 0–3% in children [1,4–7], 20–30% in older adults [7–9], and survivors often have neurological and cognitive deficits. Although these outcomes have been attributed to convulsive SE itself, etiology is a primary predictor of long-term outcome. The pathophysiological changes underlying SE are only partially understood [10,11], but an evaluation of the underlying pathophysiology may help optimize treatment strategies. In this review, we aim to provide a practical overview of the pathophysiology of convulsive SE with a focus on practical implications for treatment.

2. Effects of status epilepticus on body physiology

2.1. Animal studies

SE is defined as a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures [12]. Prolonged convulsive seizures are associated with altered body physiology including major changes in blood pressure, heart rate, respiratory function, electrolyte concentrations, glycemia, and body temperature [11,13]. During the first 20–40 min of convulsive SE, homeostatic mechanisms act to compensate for the extreme metabolic demands of the seizing brain and the contracting muscles [11,13]. There is an initial increase in cerebral blood flow with tachycardia, increased blood pressure, and dilatation of the cerebral blood vessels [13]. Increased peripheral vasoconstriction prioritizes adequate perfusion and

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oxygenation to the most metabolically active organs: brain and muscles [11,13]. Glycemia increases shortly after seizure onset, but a high demand for energy leads to increased anaerobic metabolism with rising lactate levels and acidosis [13]. In non-human, non-mechanically ventilated primates, there is a progressive failure of these compensatory mechanisms commencing approximately 20–40 min after seizure onset [13]. Blood pressure, cerebral perfusion, brain oxygenation, and glycemia progressively decrease [13]. Hypoventilation, hypoxia, and pulmonary edema lead to respiratory acidosis which worsens the already existing lactic acidosis [13]. Repetitive muscular contraction can lead to rhabdomyolysis and hyperthermia [13]. Repetitive muscular contraction and hyperthermia increase the metabolic demands and rhabdomyolysis worsens the electrolytic imbalances [13]. At this stage in convulsive SE, after compensatory mechanisms have failed, non-human, non-mechanically ventilated primates show frequent arrhythmias and cardiovascular collapse [13]. Importantly, the progressive failure of compensatory mechanisms starts 20–40 min after seizure onset in previously healthy animals with a normal cardiorespiratory reserve. It can be speculated that some epilepsy patients who have a compromised cardiorespiratory reserve at baseline because of limited exercise, marked scoliosis, or other reasons may suffer an earlier failure of compensatory mechanisms.

2.2. Human studies

Although most literature on physiologic changes during convulsive SE comes from animal models, human studies suggest a similar chain of events [14–16]. In a series of 17 patients with tonic-clonic seizures, plasma epinephrine and norepinephrine were elevated within 30 min of the end of the seizure with the maximum elevations occurring within 10 min of seizure end [15]. The norepinephrine level increased to approximately 12 times normal and epinephrine increased to approximately 40 times normal [15]. Such increases were expected to exert a direct vasoconstrictor effect and increase the risk for cardiac arrhythmias [15]. In an unusual study that would not meet modern ethical standards, seizures were provoked with pentylenetrazol infusion in patients with epilepsy [16]. Heart rate and blood pressure rose rapidly after seizure onset and increases in cerebrospinal fluid pressure suggested an increase in cerebral blood flow during seizures [16]. In a series of 98 patients with convulsive SE, 70 patients had arterial blood gases measured while not on a ventilator [14]. The pH was within the normal range of 7.35–7.45 in 10 patients, alkalotic in 1 patient, and acidotic in the other 59 patients, including a pH value of less than 7 in 23 patients [14]. In the same study of convulsive SE, rectal temperature was available for 90 patients and showed that most patients had hyperthermia, even though only 4 patients had an infectious etiology of SE [14]. In summary, the available literature on the physiological changes during prolonged seizures and convulsive SE suggest that humans undergo similar compensatory responses to those documented in animal models. There is less evidence supporting the view that decompensation occurs in a similar time frame to that observed in animal models.

2.3. Brain injury in SE

The degree of cerebral hypoxia during convulsive SE is probably not capable of causing brain injury on its own [17], but it might be a contributor in the presence of other factors disturbing brain function such as hyperthermia, hypotension, hypoglycemia, and acidosis [17]. These factors are particularly relevant after the compensatory mechanisms have failed [17]. In non-human primates, prolonged convulsive seizures lead to lesions in the cortex, cerebellum, and hippocampus with a pattern similar to that seen in circulatory arrest, systemic hypotension, or hypoglycemia [17].

A characteristic neuropathology that has been associated with prolonged convulsive SE is hippocampal sclerosis which consists of a loss of neurons in the dentate nucleus and the pyramidal layer of the hippocampus with variable gliosis [18]. The first detailed description of hippocampal sclerosis in the brains of epileptic patients is attributed to Sommer in 1880 [19]. Since then, the controversy on whether hippocampal sclerosis is the cause or the consequence of SE remains with evidence supporting both hypotheses [11]. While the relationship of prolonged seizures with hippocampal sclerosis is well established in animal models, the evidence that SE causes hippocampal sclerosis in humans is less robust [20]. The North London and FEBSTAT studies show that only a small proportion of children with febrile status epilepticus develop hippocampal sclerosis and that seizure characteristics such as seizure length or seizure type do not predict injury. Therefore, it is likely that hippocampal sclerosis is both cause and consequence of convulsive SE with a predominance of one over the other in different clinical scenarios [18].

Although most of the literature on neuropathology of brain injury in SE refers to convulsive seizures, there is evidence that non-convulsive seizures also cause brain injury. When prolonged seizures are induced in paralyzed and artificially ventilated non-human primates, the neuronal injury is less severe, especially in the cerebellum [21]. Some neuronal injury is secondary to physiological dysregulation, but injury still occurs even in the physiologically stable but seizing brain [18]. Epileptic activity alone leads to neuronal injury and neuronal death, mainly through the excessive activation of glutamate receptors and subsequent Ca^{2+} influx into the neuron [22]. Although clear in animals, the additional impact, over and above the effect of etiology, remains uncertain in the human.

2.4. Clinical relevance

Protecting the airway, maintaining adequate oxygenation, circulation, and serum glucose are recommended by most convulsive SE treatment guidelines [23]. While maintenance of cardiorespiratory function, prevention of hypoglycemia, body temperature control, and muscular paralysis may potentially reduce brain injury, the most effective way to prevent brain injury in animal models is early seizure control [21]. Detection and prompt treatment of ongoing seizures in patients with non-convulsive SE or in patients with convulsive SE after convulsive seizures have been controlled may also help minimize brain injury.

3. Neurotransmitter receptor changes during status epilepticus

Studies of receptor trafficking during convulsive SE induced by the chemoconvulsant pilocarpine in isolation or in combination with lithium have demonstrated rapid changes in the surface expression of the receptors studied and changes in receptor composition. It has been proposed that these changes could contribute to the self-sustaining nature of convulsive SE as well as potentially underlie the failure of medications to terminate SE.

3.1. Synaptic $GABA_A$ receptor internalization and NMDA receptor accumulation in the synaptic membrane during convulsive SE

Early clinical observations suggested that convulsive SE became progressively more refractory to treatment the longer the seizures lasted [24,25]. In a study in which information on the duration of convulsive SE was available for 120 adults, treatment was effective in 80% of patients who received first-line therapy within 30 min of seizure onset and effectiveness progressively declined to less than 40% for patients who received first-line therapy after seizing for 2 h [25]. In a series of 157 children with convulsive SE, a delay of more than 30 min to the first antiepileptic drug (AED) was independently associated with worse response to treatment [24]. In a series of 182 children with convulsive SE, the use of several doses of benzodiazepines was associated with a more prolonged convulsive SE episode [26].

These clinical observations were confirmed in several studies using the lithium-pilocarpine convulsive SE rat model [27–29]. One study showed that the ability of diazepam to stop seizures progressively decreased from 6 of 6 rats when diazepam was administered early (mean: 7.3 min since seizure onset) to 1 of 6 rats when diazepam was administered late (mean: 36.7 min since seizure onset) [29]. In a similar study, diazepam terminated seizures in 3 of 3 rats when administered 10 min after seizure onset but did not terminate seizures in any of 3 rats when administered 45 min after seizure onset [28]. A different study showed that the dose required to achieve seizure control in half of the rats was 10 times higher when diazepam was administered 45 min after seizure onset compared to when it was administered 10 min after seizure onset [27]. The progressive loss of sensitivity to diazepam was attributed to an alteration of the functional properties of $GABA_A$ receptors [28].

In 2005, 2 different groups discovered that $GABA_A$ receptors internalize and decrease their density in the synapse with prolonged seizures or prolonged seizure-like activity [30,31]. An experimental model of SE using cultures of hippocampal pyramidal neurons showed that GABA-mediated synaptic inhibition was reduced after prolonged epileptiform activity [30]. In the experimental preparation, the intracellular accumulation rate constant of the $GABA_A$ receptors was approximately 65% greater in neurons with repetitive bursting than in controls [30]. The internalization of $GABA_A$ receptors was modulated by neuronal activity: recurrent bursting enhanced it and blockade of neuronal activity reduced it [30]. Internalization of $GABA_A$ receptors was associated with a reduced response to GABA while inhibition of internalization was associated with increased response to GABA [32]. Therefore, an increase in the proportion of $GABA_A$ receptors that are internalized may, in part, explain the reduction of response to the benzodiazepines, $GABA_A$ receptor allosteric modulators [30]. A different study showed that there was a decrease in the number of functional postsynaptic $GABA_A$ receptors during SE [31]. In granule and pyramidal hippocampal control cells, the $GABA_A$ receptors were mostly located in the synaptic membrane; but after 1 h of SE much of the $GABA_A$ receptors relocated to the cell interior [31]. This relocation was demonstrated with two different markers of the $GABA_A$ receptor: the β2/β3 subunit and the γ2 subunit [31]. The authors estimated that after 1 h of *in vivo* SE, dentate granule cells have a 50% decrease in the number of functional $GABA_A$ receptors per granule cell synapse [31]. The decrease in functional $GABA_A$ receptors may promote self-sustaining seizures and SE [31].

$GABA_A$ receptors are Cl^- channels that communicate the intracellular and extracellular space when opened. Therefore, GABAergic neuronal inhibition is critically dependent on the activity of K^+/Cl^- transporter KCC2 which allows neurons to maintain low intracellular Cl^- levels [33]. KCC2 activity is enhanced by phosphorylation of residue serine 940, which is rapidly dephosphorylated during SE [33] which may contribute to higher intracellular Cl- levels and more resistance to $GABA_A$ allosteric modulators like benzodiazepines. In an experimental model, compromising the activity of KCC2 resulted in longer and more severe seizure-like events [34].

While $GABA_A$ receptors internalize during SE, NMDA receptors accumulate in the synapse [35]. A study of dentate gyrus granule cells and CA3 pyramidal cells showed that NMDA receptors appear to relocate from the cell interior to the synaptic membrane [35]. This relocation was observed for NR1 subunit-containing NMDA receptors and was observed in two distinct SE animal models: convulsive SE induced by lithium-pilocarpine and with the neurokinin B [35]. The authors estimated that after 1 h of SE dentate granule cells show a 38% increase in the number of functionally active NMDA receptors per somatic synapse [35] (Fig. 1).

Another potential target for refractory convulsive SE is AMPA receptors. In an animal study of SE-treated CA1 pyramidal neurons and dentate granule cells, the proportion of AMPA receptors lacking GluA2 subunits increased in the membrane during SE [36]. In these animals, benzodiazepine-resistant convulsive SE was terminated with an AMPA receptors antagonist [36].

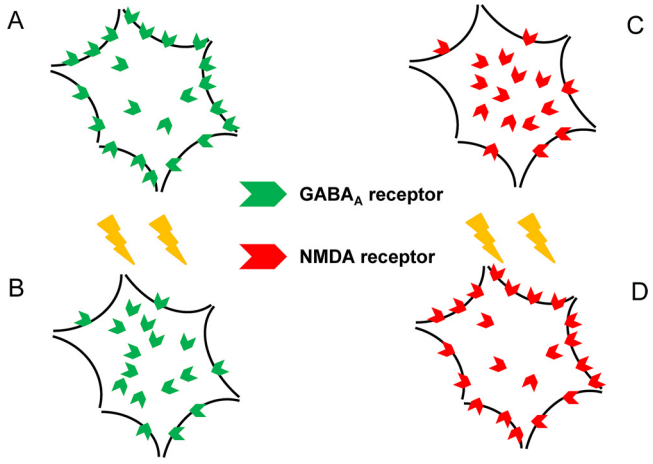

Fig. 1. Schematic representation of the distribution of neurotransmitter receptors in control neurons and in neurons with frequent epileptiform activity. **A and B.** Markers of $GABA_A$ receptors are predominantly distributed in the cellular membrane in control neurons (A) but tend to internalize after prolonged seizures and status epilepticus (B). **C and D.** Markers of NMDA receptors are predominantly distributed in the interior of the cell in control neurons (C) but accumulate in the cell membrane after prolonged seizures and status epilepticus (D).
Legend: GABA: Gamma-amino-butyric acid. **NMDA:** *N*-methyl-D-aspartate.

In summary, rapidly after SE onset there is a progressive decrease in functionally active $GABA_A$ receptors and a progressive increase in functionally active NMDA receptors in the postsynaptic membrane [30,31,35]. These changes may explain the progressive pharmacoresistance to $GABA_A$ receptor allosteric modulators and the progressive pharmacosensitivity to NMDA antagonists documented in animal models [27–29,37,38]. In a rat model where convulsive SE was achieved with electrical stimulation of the hippocampus, phenobarbital, another $GABA_A$ positive allosteric modulator, controlled convulsive SE in 4 of 6 rats when administered 15 min after seizure onset but controlled convulsive SE in only 1 of 4 rats when administered 60 min after seizure onset [37]. In contrast, ketamine did not control convulsive SE in any of 4 rats when administered 15 min after seizure onset and controlled convulsive SE in 3 of 4 rats when administered 60 min after seizure onset [37]. In a rat model where convulsive SE was achieved with brief intermittent electrical stimulation of the perforant path blocking the NMDA receptor with MK-801 or ketamine rapidly and reversibly aborted convulsive SE [38].

3.2. Clinical relevance

Understanding the time-dependent evolution of neurotransmission in SE may help tailor treatment to the specific stage of SE. Benzodiazepines are widely recommended and used as the first-line treatment for convulsive SE as they are safe and relatively easy to administer [23,39]. However, when one or two doses of benzodiazepines fail to control convulsive SE, then an escalation to non-benzodiazepine AEDs is the recommended best next step [23,40] because the effectiveness of benzodiazepines decreases rapidly. Unfortunately, repeated doses of benzodiazepines are common and lead to marked delays in the time to non-benzodiazepine AEDs [41]. Cl^- homeostasis also influences the severity of SE in experimental preparations [33,34] and increasing the intracellular concentration of Cl^- through targeting the NKCCl transporter with bumetanide has proven effective in restoring the potency of diazepam in a mouse model [42]. SE modifies neurotransmission and susceptibility to AEDs over time and future convulsive SE treatment algorithms would benefit from incorporating that knowledge into their recommendations.

4. Treatment Strategies to target the underlying pathophysiology

4.1. Cardiovascular and metabolic support

Maintaining physiologic stability may potentially contribute to minimizing brain injury until seizure control is obtained. The initial treatment for seizures includes ensuring airway patency, appropriate ventilation and oxygenation, monitoring and supporting an adequate blood pressure, correcting hypoglycemia, and avoiding hyperthermia [23]. These supportive measures should be established as soon as possible [23]. After 5 min of convulsive seizures, treatment with rescue medications should be added to the supportive measures [23].

4.2. Minimize treatment delays

Basic science and clinical studies show that convulsive SE is a time-sensitive emergency where the longer the seizures last in animal models and in humans the worse the prognosis [13,17,43] although other studies cannot find a relationship between seizure characteristics and outcomes [44,45]. In particular, administration of the first-line treatment beyond 10 min is independently associated with higher mortality, greater use of continuous infusions, longer convulsive duration, and more frequent hypotension [43]. Despite this fact, major delays in time to treatment occur frequently [41,46]. In a retrospective study of 889 patients (625 adults and 264 children) with convulsive SE, approximately 60% of the patients received their first AED after 30 min of seizure onset and approximately 25% after 60 min [46]. In a series of 161 children with febrile convulsive SE and information on time to treatment, most children experienced a significant delay initiating treatment with a median time from seizure onset to the first AED of 30 min [47]. In a series of 81 children with refractory convulsive SE the median (p_{25}–p_{75}) time elapsed from seizure onset to administration of AEDs was 28 (6–67) min for the first AED, 40 (20–85) min for the second, and 59 (30–120) min for the third [41]. Delays are mainly driven by patients with onset of convulsive SE out of the hospital, with more than half of these patients not receiving any AED until hospital arrival [41]. Delays in time to treatment occur even in patients who are known to have a diagnosis of epilepsy and should have a rescue plan readily available [48]. In summary, current literature suggests that there is much room for improving time to treatment. In particular, emphasizing the importance of a rescue plan in patients with a diagnosis of epilepsy may greatly reduce time to treatment when convulsive SE starts out of the hospital.

4.3. Early switch from benzodiazepines to other AEDs

As seizures last longer, benzodiazepines become less potent and effective; in contrast, the situation for NMDA antagonists may be reversed [30,31,35]. Although current convulsive SE treatment guidelines recommend a benzodiazepine as first-line treatment [23], multiple doses of benzodiazepines and major delays to non-benzodiazepine AEDs occur [41]. Based on the underlying pathophysiology of SE, future guidelines may need to further emphasize a timely transition to non-benzodiazepine AED. A randomized trial showed similar efficacy of benzodiazepines and non-benzodiazepine antiepileptic drugs for the treatment of convulsive SE [49]. Also, NMDA antagonists such as ketamine may be a better option when seizures are prolonged. A timely switch from benzodiazepines may prevent treating seizures with AEDs to which seizures have already become resistant. In summary, future convulsive SE treatment guidelines may further consider the underlying pathophysiology of SE, as these considerations may potentially improve treatment success and convulsive SE outcomes.

4.4. Targeting extrasynaptic GABA receptor: allopregnanolone

While synaptic $GABA_A$ receptors are progressively internalized with prolonged seizures, the extrasynaptic $GABA_A$ tonic currents augment during SE [31]. Neurosteroids increase tonic inhibition via their allosteric modulation to extrasynaptic $GABA_A$ receptors containing a δ subunit [50]. Considering these findings, neuroactive steroids, especially allopregnenolone, have been successfully used to stop convulsive SE in several animal models [51,52]. Several case reports describing the resolution of super-refractory SE with allopregnanolone in humans [53,54] fueled a clinical trial with brexanolone, a proprietary aqueous formulation of allopregnanolone [55]. The initial open label phase 1/phase 2 trial with 25 patients showed promising results with good tolerability and a high rate of weaning from anesthetic agents for SE (control of SE) [55]. Unfortunately, SAGE therapeutics recently reported that the phase 3 STATUS trial did not meet the primary endpoint with a frequency of weaning from anesthetic agents (control of SE) similar between brexanolone and placebo (43.9% versus 42.4%; $p = 0.8775$) [56]. Although this result is discouraging, it can potentially reflect multiple potential confounders such as other treatments and delays to neurosteroid administration, different etiologies, and different comorbidities obscuring results.

4.5. Early polytherapy

The stepwise treatment of convulsive SE is mainly based on expert opinion and the need to balance benefits (seizure control) and risks (unnecessary side effects, especially respiratory depression). However, given that convulsive SE represents an emergency in which the continued seizure can represent a barrier to treatment, it may be appropriate to consider a polytherapy protocol [57]. Currently, there are limited studies comparing monotherapy with polytherapy as first-line treatment for convulsive SE [58]. In an animal model of convulsive SE, combinations of a benzodiazepine with ketamine and valproate or with ketamine and brivaracetam were more effective and less toxic than benzodiazepine monotherapy [57]. These combinations aim to leverage ketamine's NMDA antagonism to target the increase in the surface expression of NMDA receptors with prolonged seizures [57]. In a different animal model the combination of diazepam, phenobarbital, and scopolamine effectively stopped prolonged SE [59].

The clinical literature on polytherapy as first-line for convulsive SE is even more limited. In a double-blind trial 107 patients with out-of-hospital convulsive SE onset were randomized to receive intravenous clonazepam with placebo and 96 were randomized to receive intravenous clonazepam with intravenous levetiracetam [60]. The trial was stopped early because an interim analysis showed no difference in outcome [60]. Among the 68 patients included in each arm in the intention-to-treat analysis at the time the study was halted, seizure control within 15 min of administration occurred in 84% of patients receiving clonazepam and placebo and in 74% of patients receiving clonazepam and levetiracetam [60]. Mortality, heart failure, respiratory failure, and the need for cardiac, respiratory, or hemodynamic assistance were similar between the 2 groups [60]. Despite the lack of clinical evidence supporting early polytherapy with clonazepam and levetiracetam in humans, future clinical studies may consider the efficacy of first-line polytherapy including anti-NMDA drugs.

5. Conclusions

Convulsive SE is a common neurological emergency, especially in children and the elderly, in whom cardiorespiratory stability and electrolyte balance are compromised. Supportive treatment to correct or minimize the effects of hypoxia, hypoglycemia, hypotension, and hyperthermia may reduce brain injury from convulsive SE. However, the most effective measure is to stop seizures as early as possible. Convulsive SE is a time-sensitive emergency where response to AEDs varies over time. The $GABA_A$ receptor allosteric modulators such as benzodiazepines or phenobarbital can progressively lose their potency as synaptic $GABA_A$ receptors internalize. In contrast, NMDA receptor

antagonists such as ketamine can become progressively more effective as surface expression of NMDA receptors increases with seizure duration. Improving time to treatment, tailoring convulsive SE treatment recommendations to target the neurotransmitter changes occurring in the synapse during SE, and early polytherapy are potential approaches to try to improve treatment success and outcomes in convulsive SE.

Conflicts of interests

None.

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