**Status Epilepticus**

*Mary L. Zupanc, MD*

*Professor, Dept of Neurology and Pediatrics*

*Division Chief, Pediatric Neurology*

*Director, Pediatric Comprehensive Epilepsy Program*

*University of California—Irvine/Children’s Hospital of Orange County*

The International League Against Epilepsy (ILAE) taskforce on classification of status epilepticus recently redefined status epilepticus and its classification1. Status epilepticus is now 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 (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.

It has long been recognized that convulsive SE is a dynamic and rapidly evolving condition 2. Ongoing seizures rapidly modify neuronal activity and synaptic function 3. This rapid neuronal plasticity is manifest in changes in behavioral seizures, EEG patterns, sensitivity to drugs, and evolution of neuronal injury and death. Although these changes are continuous, it is convenient to divide SE in to “stages” for the purposes of investigation and treatment.

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|  | **Early** | **Established** | **Refractory** |
| **Treatment** | Lorazepam/ Diazepam/Midazolam effective | Benzodiazepines fail: 2nd line AEDs used | Second line agents fail/Anesthetics are often used |
| **Clinical manifestation** | Generalized Convulsions | convulsions interspersed with stupor and focal or subtle motor manifestations | Coma |
| **EEG** | Discrete seizures separated by normal background | Seizures merge with waxing and waning spike wave discharges | Seizures with suppression and Periodic discharges |
| **Systemic effects** | Hyperventilation, Hypertension |  | Respiratory depression, |
| **Brain Damage** | No evidence | Starting | Increases with time |
| **Mortality (adults)** | 19.6%1 | ? | 31.4%1 |
| **Animal models: behavior** | Stage 1-2 seizures | 10 minutes after first stage 5 | 60 minutes first stage 5 |
| **Animal models EEG** | Discrete seizures | Continuous seizures | Seizures with suppression |

Table1: Characteristics, clinical manifestations and treatment of SE 4. 1 DeLorenzo, 1996.

**Experimental models of SE:** Animal models and *in vitro* cell culture models have proved very useful in understanding the cellular and molecular mechanisms underlying seizures of SE. In the experimental animals, SE can be induced either by administration of chemo-convulsants or through electrical stimulation of limbic structures. Activation of muscarinic receptors by administration of the cholinergic agonist pilocarpine 5 alone or in combination with lithium 6;7, or by organophosphates, which inhibit the enzyme cholinesterase. SE can also be produced by stimulation of glutamatergic receptors by kainic acid. In addition, prolonged self-sustaining seizures of SE can be induced by electrical stimulation of limbic structures such as the hippocampus, entorhinal cortex or amygdala 8;9.

The behavioral seizures and EEG in the animal models of SE evolve over time with many similarities to the progression of human SE. Furthermore, efficiency of benzodiazepines in controlling seizure diminishes with seizure duration 10-15, which validates their use in understanding pathophysiology of SE.

Two *in vitro* models that mimic repeated bursting characteristic of SE include incubation of cell cultures in an external environment in which either external magnesium has been reduced or eliminated or external potassium has been increased (i.e. Reducing magnesium below physiological levels induces recurrent bursting in hippocampal slices and cultured neurons 16-19. Elevating extracellular potassium resulting in prolonged depolarization also induces spontaneous seizures 20. )

**Neuronal circuits sustaining SE**

Febrile status epilepticus study suggests that the hippocampus is involved and affected by generalized convulsive SE21-23. EEG and metabolic mapping studies during experimental animal models demonstrate activation of the hippocampus and subiculum, entorhinal cortex, parts of the thalamus and the cortex during SE 24. The circuitry between the hippocampus, entorhinal cortex and subiculum forms a reentrant path facilitating recurrent seizures. The entorhinal cortex is connected to the hippocampal dentate granule neurons via the perforant path, which project to the CA3 pyramidal neurons via mossy fibers. CA3 pyramidal neurons in turn project to CA1 pyramidal neurons via Schaffer collaterals 25. The axons of CA1 pyramidal neurons innervate subiculum, which connects to layer IV and II of entorhinal cortex, thus forming a loop resulting in self-sustaining seizures. Neurons in the CA1 region and entorhinal cortex are capable of generating recurrent bursting patterns characteristic of seizures 26;27. Therefore, many studies aimed at understanding the cellular and molecular mechanisms underlying the prolonged seizures of SE have focused on hippocampus. Dentate granule cells play a key role in regulating seizure entry into the hippocampus, and this gating function breaks down during SE28. Studies on break down of dentate gate are also important for understanding the development of benzodiazepine resistance during SE.

**Role of GABA(A) receptors: Impact on therapy Benzodiazepines Neurosteroids and anesthetics**

Multiple clinical trials have demonstrated efficacy of benzodiazepines in the treatment of early SE29-32. Despite their efficacy in the early stages of SE, SE may become refractory to benzodiazepine therapy. In the Veterans Affairs cooperative study 29 the benzodiazepines were largely ineffective in the treatment of the more prolonged subtle SE, controlling the seizure in less than 20% of these patients.

Benzodiazepine pharmacoresistance has also been consistently observed in experimental models of SE33. There is a substantial reduction of benzodiazepine potency for seizure termination with the passage of time. Seizures readily terminated by diazepam when administered early during the seizures (ten minutes of seizure but when they had lasted 45 minutes, much higher doses of diazepam were necessary to terminate the seizures demonstrated by a dramatic rightward shift and 10-fold change in the dose required to terminate seizures in 50% of animals (ED50). This pharmacoresistance is closely related to clinical and EEG stage of SE and also occurs in young animals34-36.

Reduced inhibitory neurotransmission mediated by GABA(A) receptors is proposed to be one of the underlying mechanisms for self-sustaining and progressive nature of SE. Benzodiazepines, such as diazepam and lorazepam are the preferred drugs to treat seizures of SE 37; they act on GABA ( amino-butyric acid) type A receptors, which mediate the majority of inhibitory neurotransmission in the forebrain. In addition to the first line drugs, phenobarbital, pentobarbital, midazolam and propofol used in the intensive care units to treat refractory SE 38 also modulate GABA(A) receptors.

GABA(A) receptors are pentameric ligand-gated anion channels. The subunits are derived from  andεgene families, some of which have multiple members such as 1-6, 1-3, 1-3. Majority of the receptors appear to be composed of 2 and  or subunits. The sensitivity of the receptor to many of these modulators depends on their subunit composition 39. Subunit composition-dependent properties of GABARs relevant to status epilepticus and epilepsy include their sensitivity to benzodiazepines such as diazepam, Zn2+ and neurosteroids. Diazepam sensitivity requiresthe presence of a 2 subunit and the relative affinity also depends on the  subtype incorporatedinto the receptor 40;41. The presence of a  subunit confers higher GABA and neurosteroid affinity to the receptors 42;43. Presence of a 2 subunit is necessary for synaptic localization of the GABA(A) receptors 44;45, whereas GABA(A) receptors composed of the subunit remain exclusively in the peri- and extra-synaptic membrane 46;47. Synaptic GABA(A) receptors mediate fast inhibition in response to the high concentration of GABA released in the synaptic cleft, whereas the extra-synaptic receptors respond to GABA spilled over from the synapses and contribute to the persistent background inhibition called tonic inhibition 48-51.

GABA -mediated inhibition is reduced in the hippocampi of animals in SE. The GABA evoked currents recorded from the dentate granule neurons and CA1 pyramidal neurons were smaller in animals 45 min after onset of SE than those in naïve animals 12;52. Size and frequency of inhibitory postsynaptic currents (IPSCs) recorded from granule cells or CA1 pyramidal neurons are diminished during SE 53-55. Reduced frequency and amplitude of mIPSCs recorded from DGCs of animals in SE suggest pre-synaptic and post-synaptic changes. Biochemical studies have revealed a decrease in the number of functional GABA(A) receptors on the post-synaptic membrane in the hippocampi of animals in SE. Internalization of synaptic GABA (A) receptors increased in *in vitro* models of SE 19;53. Studies in vivo animal models of SE also suggested that increased internalization of GABARs likely reduced their surface expression.

In contrast to synaptic inhibition, tonic inhibition recorded from granule cells of animals in SE remained unaltered or increased 53;54 . In accordance, the number of surface expressed  subunit-containing receptors either remained unchanged or increased in the hippocampi of animals in SE 53;55. Surface expression and internalization of the  subunit-containing GABA(A) receptors also remained unaltered in cultured hippocampal neurons incubated in medium containing high extracellular potassium 53. Preserved surface expression of the  subunit-containing receptors during SE is clinically significant. GABARs containing a  subunit have higher sensitivity to neurosteroids, which are endogenous regulators of seizures 56 and can be used to treat SE after benzodiazepine resistance has set in. In one study neurosteroids were effective in treating pilocarpine and kainate induced SE 57. In these rats, neurosteroids were potent in controlling SE when pre-administered before pilocarpine. Furthermore, allopregnanolone was effective in aborting ongoing SE. These studies form the basis of clinical trial to test the effectiveness allopregnanolone in super-refractory SE.

**Excitatory transmission and SE:** A large body of evidence suggests that excitatory transmission is enhanced during SE. We focus on NMDA and AMPA receptors, which are potential targets for ther5apy.

**Role of NMDA receptors:**  A large number of studies indicate that NMDA receptor activation during SE leads to cell loss observed as a consequence of SE58;59. Prolonged SE results in loss of CA1, CA3 pyramidal neurons, hilar neurons in the dentate gyrus in most animal models of SE58. Blocking NMDA receptors during experimental SE or prior to seizure onset protects against epileptogenesis, prevents cell loss and may convert refractory SE to benzodiazepine sensitive SE60-63.

There is likely to be increased activation of NMDA receptors during SE64. Glutamate release from presynaptic terminals is increased in certain models of SE and chronic epilepsy. Prolonged seizures and SE enhance the activity of calcium phospholipid-dependent kinase (PKC) in the hippocampus which can modulate gating and trafficking of NMDA receptors. Finally, NMDA receptors undergo tyrosine phosphorylation during SE, which may alter their trafficking and surface availability. There are many case reports of the efficacy of NMDA receptor antagonist ketamine in terminating refractory SE. However, there are no blinded, randomized clinical trials documenting efficacy.

**AMPA receptors in SE**: There is growing evidence that AMPA receptor-mediated transmission is altered during SE. AMPA receptor mediated transmission is enhanced during SE 65. AMPA receptors become calcium permeable during refractory SE 66. In addition, AMPA receptor antagonists effectively terminate refractory SE67;68. These initial observations suggest that enhanced AMPA receptor-mediated inhibition could sustain refractory SE, however more evidence is necessary to determine the precise role of AMPA receptor plasticity during SE.

In addition to the plasticity of GABA(A) receptors and excitatory transmission, multiple other systems are impacted during SE including calcium homeostasis, second messenger systems, neuropeptides, potassium channels.

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