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Mechanistic and pharmacologic aspects of status epilepticus and its treatment with new antiepileptic drugs

*†‡Claude G. Wasterlain and *†James W. Y. Chen

*Epilepsy Research Laboratories and the †Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, California, U.S.A.; and ‡The Brain Research Institute, David Geffen School of Medicine at UCLA, Los Angeles, California, U.S.A.

Summary

We review recent advances in our understanding and treatment of status epilepticus (SE). Repeated seizures cause an internalization of γ-aminobutyric acid $(GABA)_A$ receptors, together with a movement of *N*-methyl-D-aspartate (NMDA) receptors to the synapse. As a result, the response of experimental SE to treatment with GABAergic drugs (but not with NMDA antagonists) fades with increasing seizure duration. Prehospital treatment, which acts before these changes are established, is finding increased acceptance, and solid evidence of its efficacy is available, particularly in children. Rational polypharmacy aims at multiple receptors or ion channels to increase inhibition and simultaneously reduce excitation. Combining $GABA_A$ agonists with NMDA antagonists and with agents acting at other sites is successful in treating experimental SE, and in reducing SE-induced brain damage and epileptogenesis. The relevance of these experimental data to clinical SE is actively debated. Valproate and levetiracetam have recently become available for intravenous use, and the use of ketamine and of other agents (topiramate, felbamate, etc.) have seen renewed interest. A rapidly increasing but largely anecdotal body of literature reports success in seizure control at the price of relatively few complications with the clinical use of those agents in refractory SE.

KEY WORDS: Acute seizures, Status epilepticus, Receptor trafficking, $GABA_A$ receptors, NMDA receptors, Valproate, Levetiracetam, Ketamine.

Basic Concepts and Therapeutic Principles

The nature of the beast: What is status epilepticus?

Humans and other animals alike have very effective mechanisms to stop seizures: After a single tonic–clonic seizure, coma (defined by the inability of physiologic stimulation to arouse the subject) often lasts several minutes, during which seizure thresholds are massively elevated. These changes are adaptive, since they tend to restore homeostasis and stop runaway excitation. Yet during status epilepticus (SE) those mechanisms fail, and seizures occur in rapid succession or even become self-sustaining. The development of self-sustaining seizures is seen in many animal models: it is a feature of SE caused by electrical stimulation of the whole brain or of many brain regions, including perforant path, ventral hippocampus, pre-piriform cortex, or amygdala. It also occurs with chemoconvulsants (for references see Wasterlain & Treiman, 2006): Once seizures are established, if the initial chemical trigger is blocked, seizures continue despite the complete removal of their initial cause. The observations that seizures become ''more or less incessant'' (Bourneville, 1876, ref. in Shorvon, 1994), ''subintrant'' (Clark & Prout, 1903), increasingly difficult to treat (Treiman et al., 1998), and less likely to stop spontaneously (DeLorenzo et al., 1999) as time elapses, support the extension of this concept to clinical SE.

The reason that seizures become independent of their original cause in SE, is unknown, but recent advances have suggested potential explanations (Chen & Wasterlain, 2006). γ-Aminobutyric acid $(GABA)_A$–mediated inhibition becomes less effective, whereas glutamate's excitatory actions are enhanced (Fig. 1).

Address correspondence to Claude G. Wasterlain, MD, VA Medical Center (127), 11301 Wilshire Boulevard, West Los Angeles, CA 90073, U.S.A. E-mail: wasterla@ucla.edu

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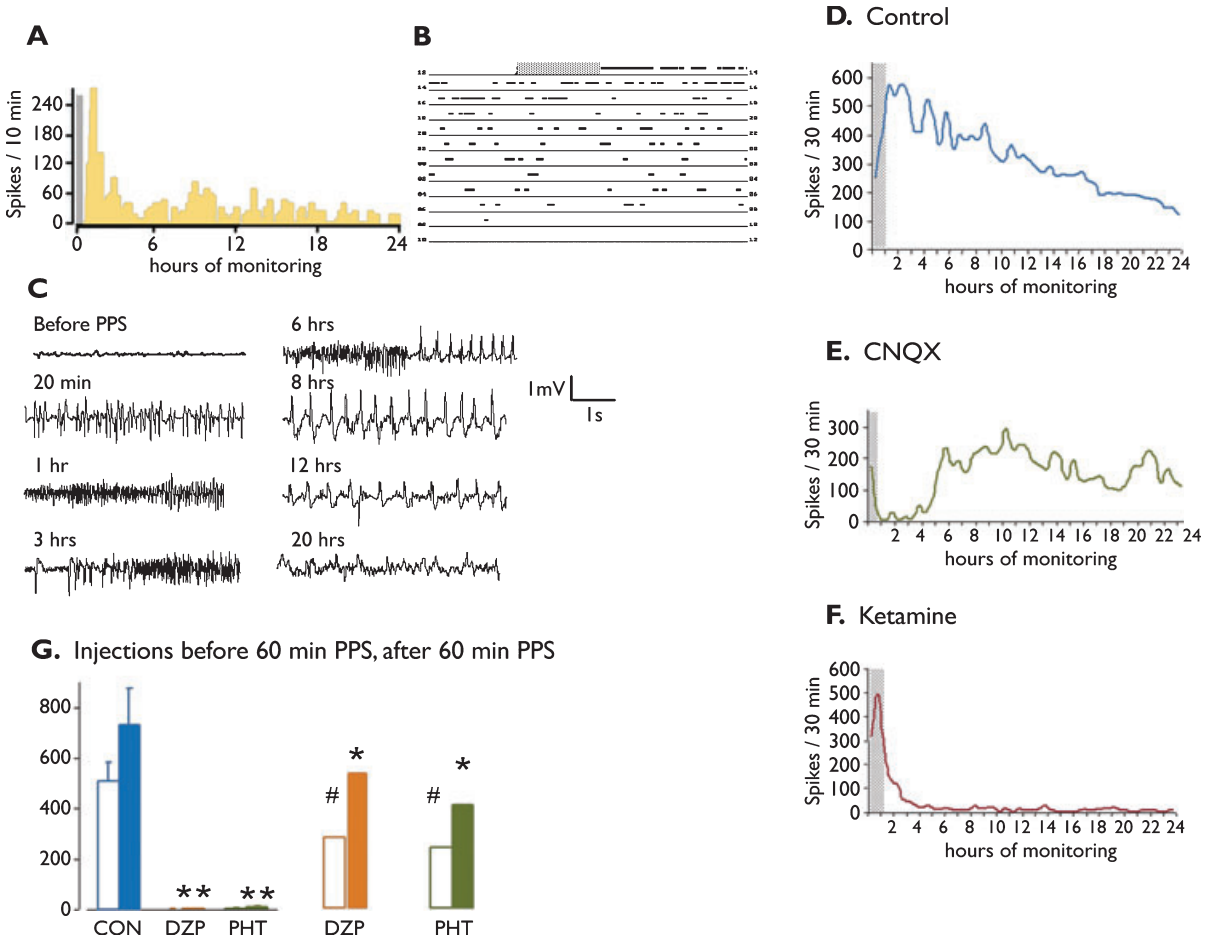

Figure 1.

Features of self-sustaining status epilepticus (SE) induced by stimulation of the perforant path for 30 min [perforant path stimulation (PPS)]. (**A**) Representative time course of spikes. (**B**) Twenty-four hour distribution of seizures (black bars). PPS is indicated by the gray bar on top. Each line represents 2 h of monitoring. (**C**) Electrographic activity in the dentate gyrus during SE. Individual seizures blend into continuous polyspike activity, which later is interrupted by slow waves, evolving progressively into semiperiodic spike bursts separated by low amplitude activity. (**D**–**F**) The effects of an *N*-methyl-D-aspartate (NMDA) receptor blocker (**F**) and an Aα-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate antagonist (**E**), administered 10 min after the end of PPS, on SE induced by 30-min PPS. Each graph shows the number of spikes per 30-min epoch, plotted against time during the course of SE. PPS is indicated by gray bars. Notice that the NMDA antagonist ketamine (10 mg/kg, i.p.) irreversibly aborted SE. The AMPA/kainate receptor antagonist CNQX (10 nmol into the hilus) induced only transient suppression of seizures, which reappeared within 2–4 h as the drug was eliminated. (**G**) Time-dependent development of pharmacoresistance in SE induced by 60-min PPS. Open bars show cumulative seizure time, and colored bars show the duration of SE. *Blue bar graphs on the left:* When administered before PPS, both diazepam (DZP) and phenytoin (PHT) effectively blocked the development of SSSE. *Brown/green bar graphs on the right:* When injected 10 min after the end of PPS, neither drug aborted SSSE, although they shortened its duration slightly. *$p < 0.05$ versus control. #$p < 0.05$ versus DZP and PHT pretreatment, respectively. (Modified from Chen & Wasterlain, 2006).

Initiation and maintenance of SE

Experimental self-sustaining SE is hard to get going, but once established, it is even harder to stop (Table 1), and clinical SE shares some of these features. It is easy to trigger self-sustaining SE by repeatedly stimulating excitatory pathways (Vicedomini & Nadler, 1987). However, the process is easily stopped by many agents that increase inhibition or decrease excitation (Table 1) through many different transmitter systems (GABAergic, glutamatergic, cholinergic, peptidergic of many types), or

Table 1. Initiation and maintenance of SE

Initiators	Blockers of initiation phase	Blockers of maintenance phase
Low Na_o^+, High K_o^+	Na^+ channel blockers	NMDA antagonists
$GABA_A$ antagonists	$GABA_A$ agonists	Tachykinin antagonists
Glutamate agonists: NMDA, AMPA, kainate, low Mg_o^{++}, low Ca_o^{++}, stimulation of glutamatergic pathways	NMDA antagonists, high Mg_o^{++}	Galanin
Cholinergic muscarinic agonists, stimulation of muscarinic pathways	AMPA/kainate antagonists	Dynorphin
Tachykinins (SP, NKB)	Cholinergic muscarinic antagonists	
Galanin antagonists	SP, Neurokinin B antagonists	
Opiate δ agonists	Galanin	
Opiate κ antagonists	Somatostatin	
	NPY	
	Opiate δ antagonists	
	Dynorphin (κ agonist)	

AMPA, Aα-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; GABA, γ-aminobutyric acid; NKB, neurokinin B; NMDA, *N*-methyl-D-aspartate; NPY, neuropeptide Y; SP, substance P.

that alter cells' ionic balance in many different ways (e.g. through changes in $[Na^+]$, $[K^+]$, $[Ca^{2+}]$, $[Mg^{2+}]$). The development of SE seems to require the activation of an excitatory circuit involving many ions, transmitters, and modulators, in which all systems must be in the ''go'' position. Obviously, the system is strongly biased against the initiation of SE, and that is not surprising, given the fact that SE can be life-threatening.

However, once self-sustaining seizures have become established, the list of effective agents becomes much shorter (Table 1). Most agents become minimally effective and require much higher concentrations to block the maintenance of SE than they did to alter its initiation. Many agents that effectively stop the maintenance of SE block glutamate synapses, or presynaptically inhibit glutamate release (Table 1).

Clinical definition and sequential phases of SE

Gastaut (1983) suggested that the diagnosis of SE requires a ''fixed and enduring epileptic condition,'' but he did not include time parameters in his definition. In the guidelines of the Epilepsy Foundation of America (1993), the duration of repetitive seizures that is accepted as SE was 30 min, which is also a pivotal time for the development of SE-induced neuronal injury and pharmacoresistance. To find a definition of SE that does not delay therapeutic intervention, even if not all such patients are in a true ''enduring epileptic condition,'' the time required to define SE was reduced to 20, 10, and, recently, to 5 min (references in Wasterlain & Treiman, 2006). A modern definition should be statistical, and should take into account the different stages, types, and age-specific features of SE. The average tonic–clonic seizure lasts about a minute [mean 59.9 s, standard deviation (SD) 12; Theodore et al., 1994] whereas the average complex partial seizure lasts nearly 2.5 min (mean 145 s, SD 94; J. W. Y. Chen, unpublished data). Continuous seizure activity lasting 5 min is most unusual for tonic–clonic (20 SDs removed from the mean), but not for complex partial seizures (1 SD away from the mean).

Clark and Prout's (1903) description of three sequential phases of SE is still valid. We call these phases impending SE, established SE, and subtle SE (Chen & Wasterlain, 2006; Wasterlain & Chen, 2006).

Impending status epilepticus is defined as continuous or intermittent seizures lasting more than 5 min without full recovery of consciousness between seizures. Impending SE should be treated as SE, to prevent adverse consequences of prolonged seizures, but a significant proportion of such patients will stop short of developing full-blown SE (DeLorenzo et al., 1999).

Established status epilepticus is defined as clinical or electrographic seizures lasting more than 30 min without full recovery of consciousness between seizures.

In *subtle status epilepticus*—called the ''stuporous'' stage by Clark and Prout (1903)—during this late, ''burned-out'' stage of SE, the motor and EEG expression of seizures become less florid (Wasterlain & Treiman, 2006).

The basic science of SE

Repeated seizures produce complex pathophysiologic and biochemical changes in the brain. The first milliseconds to seconds are dominated by the release of neurotransmitters and modulators, the opening and closing of ion channels, receptor phosphorylation, and desensitization. In seconds to minutes, receptor trafficking, mainly of the GABA and glutamate receptors, is responsible for key adaptations. Receptors can move from the synaptic membrane into endosomes where they are inactive but ready

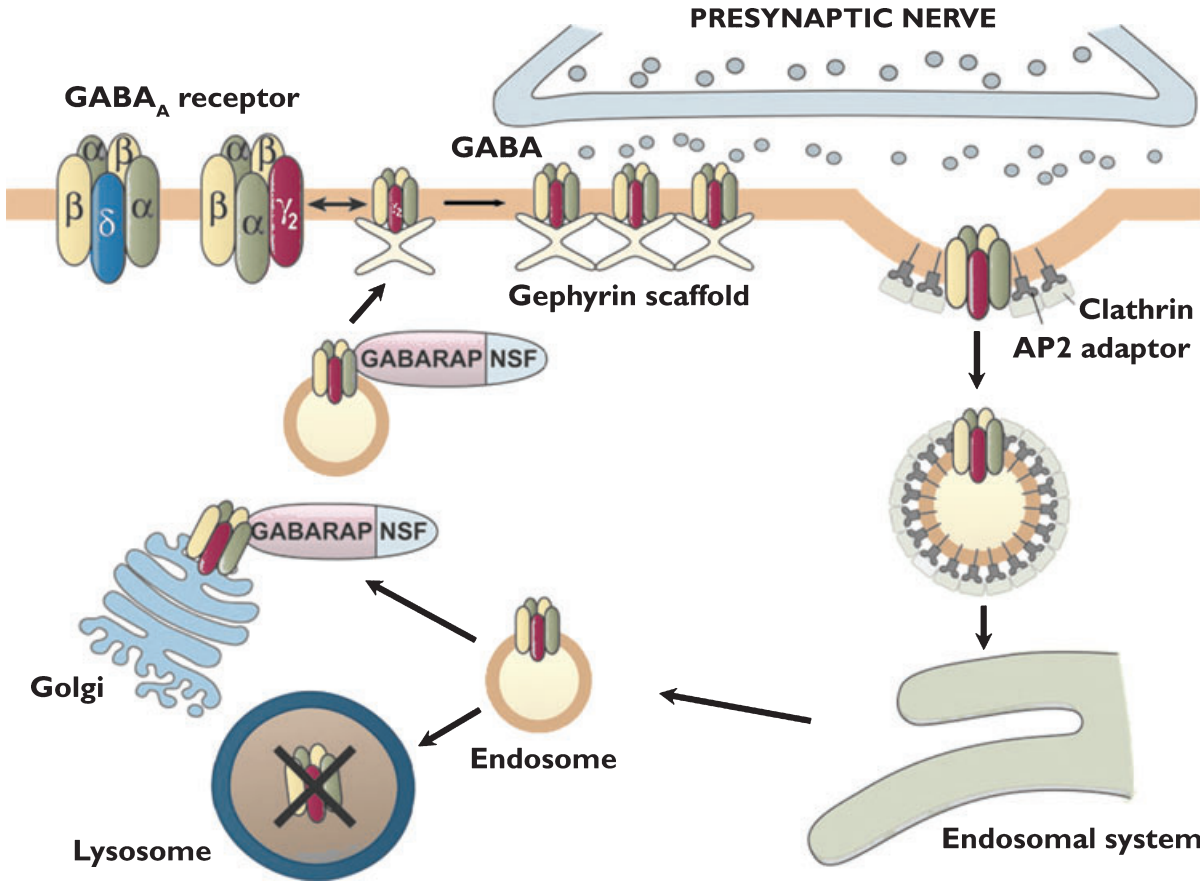

Figure 2.
Cartoon summarizing our model of the role of receptor trafficking in the transition from single seizures to status epilepticus (SE). After repeated seizures, and massive γ-aminobutyric acid (GABA) release, the synaptic membrane of $GABA_A$ receptors forms clathrin-coated pits (CI), which internalize. This inactivates the receptors, which are no longer within reach of the neurotransmitter. These vesicles evolve into endosomes (E), and reach a phosphorylation-dependent decision point where they are transported toward the soma to lysosomes (L) where the receptors are destroyed, or to the Golgi apparatus (G) from where they are recycled to the membrane.
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for recycling (Fig. 2), or be mobilized from storage sites to the synaptic membrane where they become active. This changes brain excitability by decreasing the number of inhibitory receptors and increasing the number of excitatory receptors in the synaptic membrane (Fig. 3) (Goodkin et al., 2005; Naylor et al., 2005; Goodkin et al., 2008; Hu et al., 2008). In minutes to hours, depletion of molecular reserves and changes in gene expression increase some proconvulsant neuropeptides and decrease the availability of some inhibitory neuropeptides (referenced in Wasterlain & Treiman, 2006), further enhancing excitability, whereas the development of neuronal injury and depletion of energy reserves work in the opposite direction. Finally, in the hours, days, and weeks following SE, long-term changes in gene expression take place as a late result of repeated seizures, of seizure-induced neuronal death, and of reorganization.

Transition from single seizures to SE

Trafficking of GABA and glutamate receptors

Hippocampal $GABA_A$ receptors move from the synaptic membrane to the cell interior as a result of repetitive seizures (Fig. 2): During the transition from single seizures to self-sustaining SE, the number of $GABA_A$ receptors per dentate granule cell synapse declines from 36 ± 11 in controls to 18 ± 4 after 1 h of SE (Naylor et al., 2005). The γ_2 and β_{2-3} subunits on the $GABA_A$ receptors decrease in number on the synaptic membrane, and increase in number in the interior of the cell (Naylor & Wasterlain, 2005; Naylor et al., 2005). This may in part explain the failure of $GABA_A$ inhibition and the development of pharmacoresistance to benzodiazepines (Kapur & MacDonald, 1997; Mazarati et al., 1998). Extrasynaptic $GABA_A$

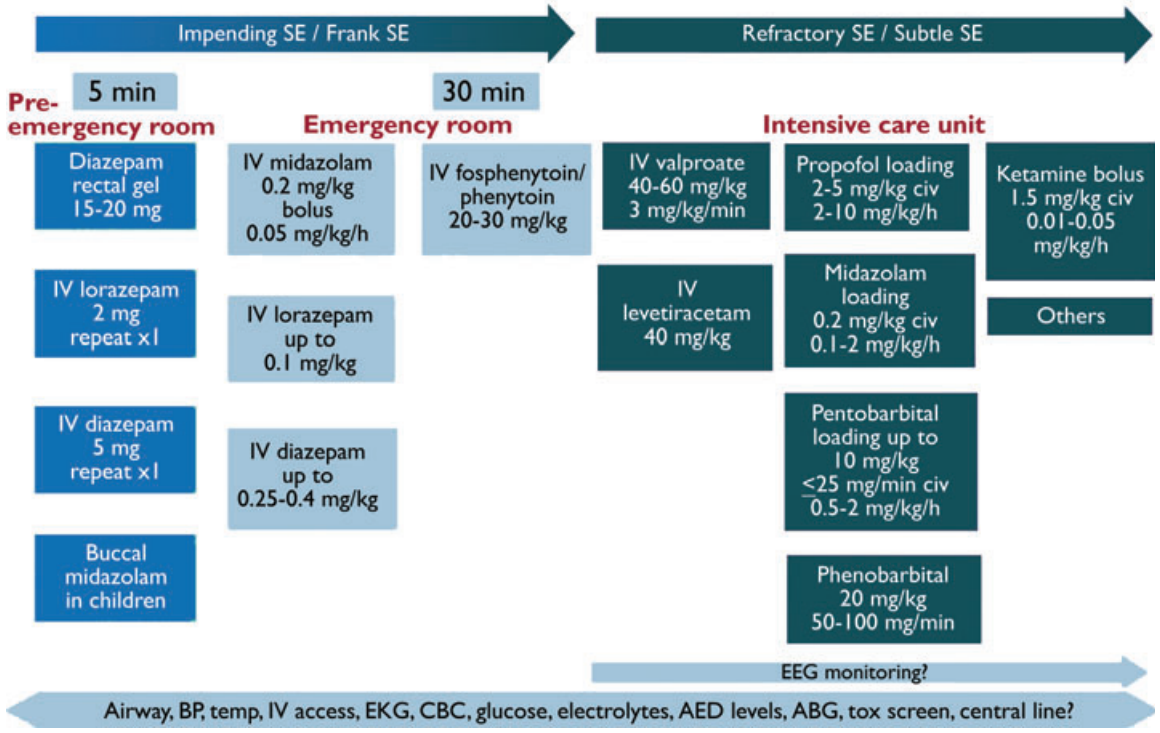

Figure 3.
Flowchart describing our recommendations for the treatment of generalized convulsive status epilepticus (SE) in adults. *Impending or established SE*: start with 20 mg/kg PE of fosphenytoin, and if SE persists, give an additional 10 mg/kg. Follow the flow chart UNLESS there is a history of drug intolerance (e.g., allergy to phenytoin or benzodiazepine) and then replace by intravenous (i.v.) valproic acid 40–60 mg/kg or i.v. phenobarbital 20 mg/kg; UNLESS treatment-induced hypotension slows rate of delivery; UNLESS history of progressive myoclonic epilepsy (PME) or juvenile myoclonic epilepsy (JME) (phenytoin/fosphenytoin harmful in PME, ineffective in JME, replace with i.v. valproic acid or i.v. phenobarbital); UNLESS tonic status epilepticus with Lennox-Gastaut syndrome (might be worsened by benzodiazepines), replace with i.v. valproic acid or i.v. phenobarbital; UNLESS, acute intermittent porphyria, avoid P450 inducers, replace by i.v. levetiracetam; UNLESS, focal SE without impairment of consciousness, i.v. treatment not indicated, load anticonvulsants orally or rectally. *Refractory SE*: i.v. valproic acid—start with 40 mg/kg and, if SE persists, give an additional 20 mg/kg. Continuous intravenous infusion (c.i.v.) usually starts with the lower dose, which is titrated to achieve seizure suppression and is increased as tolerated if tachyphylaxis develops. Ketamine: rule out increased intracranial pressure before administration. Other drugs: felbamate, topiramate, lidocaine, inhalation anesthetics, etc. Dosage and pharmacokinetics of most anticonvulsants must be adjusted appropriately in patients with hepatic or renal failure, or with drug interactions. Some patients in refractory SE will need systemic and pulmonary artery catheterization, with fluid and vasopressors as indicated to maintain blood pressure. CBC, complete blood count; AED, antiepileptic drug; ABG, arterial blood gas; PE, phenytoin equivalents.

receptors, which contain δ instead of $\gamma 2$ subunits, do not internalize during SE, raising the possibility that stimulation of those extrasynaptic receptors with neurosteroids might be useful in the treatment of SE.

Excitatory synapses show changes in the opposite direction from those of GABA synapses. *N*-methyl-D-aspartate (NMDA) receptor subunits are recruited to the synaptic membrane, where they form additional receptors (Mazarati & Wasterlain, 1999; Wasterlain et al., 2002a). This further enhances excitability and helps to maintain SE.

Other maladaptive changes during SE

Other changes in synaptic activity may increase glutamate release; reduce the chloride gradient across the neuronal membrane; and deplete stores of the predominantly inhibitory hippocampal neuropeptides dynorphin, galanin,

somatostatin, and neuropeptide Y; whereas expression of the proconvulsant tachykinins, substance P and neurokinin B, increases; and all of these proconvulsant changes may play a role in maintaining SE. Galanin-overexpressing mice and substance P-KO (knockout) mice are resistant to the development of SE, whereas galanin KO mice are very susceptible to it (Wasterlain & Treiman, 2006).

Clinical implications of those changes

Because seizures generate a transient but severe loss of synaptic inhibitory receptors and peptides, and an increase in synaptic excitatory receptors and peptides, we have a putative explanation for the tendency of seizures to become self-sustaining, and for the time-dependent development of pharmacoresistance to GABAergic drugs. This implies that prehospital treatment of SE should become routine, since it has the potential of preventing seizure-induced receptor trafficking and pharmacoresistance. It also suggests that rapid and vigorous treatment should be given, to stop seizures as soon as possible and avoid the development of time-dependent complications such as pharmacoresistance and brain damage (Fig. 3). Failure of one treatment should immediately be followed by initiation of the next therapy. Finally, the progressive loss of synaptic GABA receptors with increasing seizures suggests that benzodiazepines should be combined to another drug acting at a different site, in the initial treatment of SE. Type 1 evidence (Treiman et al., 1998) shows lorazepam alone to be at least as good as other treatments tested, in the treatment of generalized convulsive SE. However, only a very limited number of choices were tested, and pathophysiology suggests that waiting for a first drug to fail before administering the second drug may allow greater pharmacoresistance to develop and lose precious time.

Fig. 3 summarizes our approach to treating generalized convulsive SE in adults, as discussed in detail in previous publications (Chen & Wasterlain, 2006; Wasterlain & Treiman, 2006).

Pharmacology of Newly Available Intravenous Antiepileptic Drugs

Valproate and levetiracetam are now available for intravenous administration, but in the USA, neither is approved for use in SE. Table 2 shows that both agents are neuroprotective and slow the development of kindling. Valproate has a very broad anticonvulsant spectrum, whereas levetiracetam has an unusual spectrum, being nearly inactive in some classical seizure models, but very potent in some genetic models and in models of complex partial seizures, with a very high therapeutic index for acute use.

Both agents have low protein binding and linear kinetics, but levetiracetam has the advantage of a low hepatic metabolism, and of having few drug interactions. Valproate is metabolized by mixed function oxidases in liver microsomes, and as a result has multiple drug interactions. Valproate has rare, but severe hematologic and hepatic toxicity, whereas levetiracetam has low acute toxicity but has been associated with increased aggressiveness and psychiatric complications. The teratogenicity of valproate is also a concern in women of reproductive age (Vajda et al., 2007).

Table 2. Basic pharmacology of "new" injectable AEDs

	Valproate	Levetiracetam
Kindling devlpt inh.	+	+
Neuroprotective	+	+
ED50 PTZ (mg/kg)	106	>540
ED50 PTZ kindling	147	7
ED50 Kainic A	>600	54
TD50 Rotarod	206	1,060
Therap. index KA	<0.3	20
Therap. index PTZ	0.94	?
Therap. index PTZ Kind.	1.4	151
Protein binding	10–20%	<10%
Metabolism	Liver P450	Minor
Half-life	16 h	6–8 h
Kinetics	Linear	Linear
Drug interactions	Cbz, Ph, PB ↓ V V ↑ Cbz Epoxide, Ltg, PB, Lz, Dz, Ph	None
Toxicity	Liver, pancreatitis, thrombocytopenia, teratogenicity	Psychiatric

Cbz, carbamezepine; Dz, diazepam; Ltg, lamotrigine; Lz, lorazepam; PB, pentobarbital; Ph, phenobarbital; PE, phenytoin equivalents; V, valproate.

Use of Valproate and Levetiracetam in SE and Acute Seizures

Despite the lack of an FDA-approved indication, a rapidly growing body of literature (recently reviewed, Trinka, 2007) reports their use in SE. These studies are largely favorable, and describe impressive efficacy at the price of only a few, generally mild side effects. However, one has to beware of publication bias: Physicians are far more likely to report favorable results of treatment than they are to publish insignificant or unfavorable results. In the case of valproate, which has been used in Europe as an injectable preparation since 1993 (Giroud et al., 1993), several controlled but unblinded studies are available. Levetiracetam, which became available in injectable form in the USA in 2006, has generated only case reports and uncontrolled studies.

Valproate: Experimental data

Valproate treatment has been studied in a few animal models of SE. It is effective in the pilocarpine model (Turski et al., 1989), in the cobalt/homocysteine model (Walton & Treiman, 1992), in SE induced by repeated electro convulsive shock (ECS) (Hönack & Löscher, 1992), and in SE triggered by intrahippocampal 4-aminopyridine (Martín & Pozo, 2003). However, it is ineffective in the intra-amygdala kainate model (Riban et al., 2002). During SE, it seems to display the same time-dependent loss of potency displayed by most antiepileptic drugs (AEDs). It is effective in the lithium–pilocarpine model of SE when it is given before the onset of seizures, but the same dose (300 mg/kg) is ineffective when given 30–60 min after the onset of seizures (Morissett et al. 1987; George & Kulkarni, 1996; see also Sofia et al., 1993; Kim et al., 2007).

Valproate: Clinical studies

Misra et al. (2006) conducted an unblinded randomized trial of intravenous (i.v.) valproate versus i.v. phenytoin as first-line treatment of convulsive SE in 68 patients of various ages (the majority were adults). Valproate (30 mg/kg over 15 min) stopped SE in 66% of patients versus 42% for phenytoin (18 mg/kg at 50 mg/min). This barely reached statistical significance ($p < 0.05$). However, the choice of a one-sided Fisher's exact test has been criticized (Rossetti, 2007), since the authors had no way of predicting which drug would be better. A two-sided test would show no significant difference. When the first drug failed, patients received the second drug. Valproate stopped SE in 79% of patients versus 25% with phenytoin ($p = 0.004$). The number of recurrent seizures during the next 24 h was also smaller. The incidence of side effects did not differ significantly, although the two patients with arterial hypotension and the two patients with respiratory depression were in the phenytoin-treated group. Another weakness of this study was that the choice of phenytoin as first-line treatment does not match standard practice (Hirsch & Claassen, 2002), since phenytoin was the single treatment of SE that was proven inferior to another treatment (lorazepam) in the VA cooperative trial (Treiman et al., 1998).

Mehta et al. (2007) treated children in refractory SE (ages 5–12) with valproate or diazepam infusion ($n = 20$ each). Initial treatment for all subjects was i.v. diazepam (0.2 mg/kg) followed if necessary by i.v. phenytoin (20 mg/kg followed by an additional 5–10 mg/kg if seizures did not stop). Subjects that did not respond to initial treatment were randomized to valproate (30 mg/kg over 2–5 min., followed as needed by a 10 mg/kg bolus 10 min later, then by infusion at 5 mg/kg/h) or diazepam infusion (10 μg/kg/min, increased every 5 min if seizures continued, until control or 100 μg/kg/min was reached). Treatment failures received thiopental. This vigorous protocol controlled seizures in 80% and 85% of patients in the valproate and diazepam groups, respectively. None of the children in the valproate group had arterial hypotension or needed ventilatory support, whereas 60% of those in the diazepam group required ventilation, 50% became hypotensive, and 40% required vasopressors (all $p < 0.01$). Intensive care unit (ICU) admission was needed for 95% of the diazepam group and 55% of the valproate group. This study showed i.v. valproate to be as efficacious as i.v. diazepam in treating refractory childhood SE, with fewer side effects. It was unblinded, however, and one might question whether treating diazepam failure with more diazepam was the best option available.

Agarwal et al. (2007) compared valproate to phenytoin in 100 patients (50 in each group) with SE refractory to benzodiazepines. Their rate of success was high (88% valproate, 84% phenytoin), and they did not find significant differences in efficacy or adverse effects between treatment groups. Many of the problems of the previous studies also apply to this study.

Anecdotal reports

In 139 patients with SE, treatment with i.v. valproate (15–31.5 mg/kg) was successful in 63–77% (Uberall et al., 2000; Jha et al., 2003; Yu et al., 2003). Even postanoxic myoclonic SE showed some response (Sheth & Gidal, 2000; Patel & Jha, 2004). Treatment efficacy was time-dependent: In a study of SE or serial seizures unresponsive to diazepam (Olsen et al., 2007), valproate (25 mg/kg loading dose followed by infusion of 100 mg/h) stopped seizures in 95% of patients when treatment was given within 3 h of seizure onset, but in only 40% when given after 24 h of SE. Respiratory and circulatory depression were uncommon (White & Santos, 1999; Sinha & Naritoku, 2000; Peters & Pohlmann-Eden, 2005), even at high infusion rates (Venkataraman & Wheless, 1999, Wheless et al., 2004; Limdi et al., 2005). However, the potential for hepato- and hematotoxicity exists, particularly in patients with mitochondrial diseases (Schwabe et al., 1997; Krähenbühl et al., 2000). Induction of encephalopathy (Embacher et al., 2006), Fanconi syndrome (Knorr et al., 2004), or SE (Shahar et al., 2002; Velioğlu & Gazioğlu, 2007; Spriet et al., 2007) and increased HIV viral loads (Maggi & Halman, 2007) have been reported.

Levetiracetam: Experimental studies

Levetiracetam was inactive at moderate dose in seizures induced by intracerebroventricular NMDA, AMPA, or kainic acid, by systemic bicuculline or picrotoxin, but was effective in SE triggered by systemic kainic acid (Marini et al., 2004) or pilocarpine (Klitgaard et al., 1999, 2003). In electrical stimulation models of SE, it was very effective when given before SE was established, was

potent at high doses in established SE, but failed when given after very long stimulation, demonstrating that levetiracetam is subject to time-dependent pharmacoresistance (Mazarati et al., 2004; Gibbs et al., 2006). Levetiracetam was particularly effective in those models when combined with benzodiazepines (Mazarati et al., 2004).

Levetiracetam: Clinical studies

No controlled studies are available, but at total of 87 cases of SE treated with levetiracetam have been reported. Most cases had failed to respond to a previous treatment, most often a benzodiazepine (Knake et al., 2008). Doses of i.v. levetiracetam ranged from 500–7,500 mg. Control was achieved in 31–100% of patients. The majority of patients had complex partial SE (Atefy & Tettenborn, 2005; Farooq et al., 2007; Rupprecht et al., 2007; Trabacca et al., 2007; Goraya et al., 2008), but generalized convulsive SE (Rossetti & Bromfield, 2006; Abend et al., 2008) and ''ICU NCSE'' (the unresponsive ICU patients who are found to be in nonconvulsive SE, usually after partially successful treatment of generalized convulsive status epilepticus (GCSE), and which Fujikawa (1996) called the ''ictally comatose'') were also included (Schulze-Bonhage et al., 2007; Alehan et al., 2008). In postanoxic status myoclonicus, both success (Veldkamp & Swart, 2006) and failure (Ruegg et al., 2008) of levetiracetam treatment have been reported.

Specific indications for which the lack of hepatic metabolism and drug interactions were particularly important included a case of posterior leukoencephalopathy with NCSE following liver transplantation (Alehan et al., 2008) and a case of acute intermittent porphyria (Zaatreh, 2005). Because of its lack of induction of hepatic enzymes, levetiracetam should probably be considered the drug of choice for SE associated with acute intermittent porphyria. Successful treatment of myoclonic SE and of SE associated with Lafora disease were reported in unpublished meeting abstracts (2007). Triggering of myoclonic SE in a patient with myoclonic-astatic epilepsy was also reported (Kroll-Seger et al., 2006), suggesting that not all myoclonic SE responds well to levetiracetam. Status gelasticus may also have been triggered by levetiracetam (Pustorino et al., 2007).

Few side effects were noted (but beware of publication bias!). Somnolence was seen in six patients, and among unpublished abstracts, two patients required intubation (without showing arterial hypotension), and one patient showed aggressivity after treatment. Two cases of transient thrombocytopenia were observed (Ruegg et al., 2008).

Topiramate for refractory SE

There have been several case reports, showing that topiramate administrated via nasogastric tube at 300–1,600 mg/day in adults or 3–10 mg/kg/day in children (age 2 months to 11 years) was well tolerated and effective in terminating refractory SE, both generalized and complex partial (Reuber et al., 2002; Bensalem & Fakhoury, 2003; Kahriman et al., 2003; Perry et al., 2003, Towne et al., 2003, Blumkin et al., 2005). A delayed beneficial effect was noted, which usually required 12–48 h of high-dose topiramate treatment. However, the beneficial effect could be observed as early as 6 h in complex partial SE, or as late as 10 days if a low dosage (200 mg/day) was used in refractory generalized SE (Towne et al., 2003). More extended treatment with gradual improvement of the ictal electroencephalography (EEG) pattern and eventual termination of ictal pattern after 5 days of treatment was reported (Bensalem & Fakhoury, 2003). The basic mechanisms of action of topiramate include enhancement of the inhibitory function of $GABA_A$ receptors, inhibition of excitatory AMPA receptors, blockage of sodium and L-type calcium channels, and inhibition of carbonic anhydrase isoenzymes. The efficacy of topiramate in aborting refractory SE might be attributed to a combination of mechanisms. However, the delayed effect, the lack of i.v. formulation and the lack of controlled clinical trials relegate topiramate to a secondary role in the treatment of refractory SE.

Ketamine for refractory SE

Ketamine is metabolized by the cytochrome P450 system in the liver to its active metabolite nor-ketamine. It is a general anesthetic that inhibits NMDA receptors by binding with low affinity to the phencyclidine (PCP) site inside the channel. Other drugs with similar mechanism of action include PCP and MK-801, but their toxicity (e.g., psychosis) precludes clinical use. Experimental data showing an increase in synaptic NMDA receptors during SE, and the high potency of NMDA blockers late in the course of experimental SE (Mazarati et al., 1998), support the use of inhibitors of NMDA receptors in refractory SE. In contrast to other general anesthetics, ketamine increases blood pressure, heart rate, and cardiac output. It is neuroprotective in experimental SE (Fujikawa, 1996). Unfortunately, the possibility that it might raise intracranial pressure requires ruling out an intracranial mass [usually by computed tomography (CT)] before using it, and this has limited clinical applications.

In a retrospective study by Bleck et al., 2002, five of seven patients with refractory SE were controlled with ketamine. An observational study (Mewasingh et al., 2003) showed good responses to 006Fral ketamine treatment (1.5 mg/kg/day) in five cases of nonconvulsive SE in children. No significant side effects were noted. A 13-year-old girl with generalized SE refractory to diazepam, phenytoin, phenobarbital, pentobarbital anesthesia, lorazepam, lidocaine, valproate, and propofol, lasting for 4 weeks, responded to i.v. ketamine within 90 s, but she continued to have several clinical or electrographic

seizures daily. No adverse effects could be attributed to ketamine. The patient recovered with cognitive impairment, short-term memory deficits, and atrophy by magnetic resonance imaging (MRI) 3 months later, all presumably because of SE (Sheth & Gidal, 1998). However, concern for long-term ketamine toxicity was raised in a case report of SE in a 44-year-old patient with neurosyphilis who received 3 days of ketamine infusion with a dose of 7.5 mg/kg/h. SE was aborted, but the patient recovered with global cognitive impairment, aphasia, apathy and depressed affect, and mild to moderate cortical volume loss on brain MRI. (Ubogu et al., 2003).

Conclusions

1. We are making progress in our understanding of the pathophysiology of SE, and experimental data tell us that seizures by themselves (in the absence of any metabolic complications) can injure neurons; that pharmacoresistance is an expected result of prolonged seizure activity, which can be prevented by early treatment; and that treatment should not be limited to drugs acting on $GABA_A$ receptors, which offer a rapidly shrinking therapeutic target.
2. Unfortunately, the new principles derived from animal models have not been tested in controlled clinical trials. The lack of objective evidence in this field is not surprising. In a market of only 150,000 acute cases per year in the USA, the cost of a controlled clinical trial is far higher than the prospective income from intravenous preparations, even if one takes into account the indirect economic benefits of emergency treatment. Therefore, we cannot expect the pharmaceutical industry to fund controlled clinical trials. One solution, based on the ''orphan disease'' model, would be to provide economic incentives to encourage controlled trials for treatments with a modest market (such as SE). Without such incentives, those very expensive trials depend on funding from states or nonprofit organizations, which either lack the means to carry them out or have many competing priorities.
3. The growing acceptance of the new AEDs is reflected in recent consensus statements. The Belgian consensus recommendations for GCSE (van Rijckevorsel et al., 2005) and CPSE (van Rijckevorsel et al., 2006), and the Italian League Against Epilepsy's guidelines for treatment of SE in adults (Minicucci et al., 2006) regard valproate as an acceptable second-line drug. The guidelines of the European Federation of Neurological Societies (Meierkord et al., 2006) do not include the new AEDs in the treatment of GCSE, but find them acceptable for CPSE.
4. The next two communications will discuss the pros and cons of using newer AEDs in the treatment of SE.

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