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Lessons from the Laboratory: The Pathophysiology and Consequences of Status Epilepticus

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Abstract

Status epilepticus (SE) is the most common neurological emergency of childhood. Experimental models parallel several clinical features of SE including: (1) treatment is complicated by an increasing probability that benzodiazepines will fail with increasing seizure duration and (2) outcome varies with age and etiology. Studies using these models demonstrated that the activity-dependent trafficking of $GABA_A$ receptors contributes, in part, to the progressive decline in GABA-mediated inhibition and the failure of the benzodiazepines. Furthermore, laboratory studies have provided evidence that age and inciting stimulus interact to determine the neuronal circuits activated during SE (i.e. functional anatomy), and that differences in functional anatomy can partially account for variations in SE outcome. Future laboratory studies are likely to provide an additional understanding of the cellular and molecular mechanisms that underlie SE and its consequences. Such studies are necessary in the development of rational emergent therapy for SE and its long term outcomes.

The majority of seizures stop spontaneously. However, when the mechanisms that terminate a seizure fail, the result is a prolonged, self-sustaining seizure that can be refractory to treatment. This condition, which has been termed status epilepticus (SE), represents the most common neurological emergency of childhood with an estimated incidence of 10–27/100,000/year for children between the ages of 1 month and 15 years with the majority of episodes occurring in children <4 years.[1–5] Fortunately for many children, SE occurs without apparent consequences; however, for others, SE results in death or long term neurological dysfunction or potentially epilepsy[1, 6–14]

The intent of translational research focused on the pathogenesis and long term outcome of SE is to gain a better understanding of the mechanisms that underlie this childhood emergency with the goal of reducing its associated mortality and morbidity to even lower levels. The ethical and practical limitations of performing such studies in children are well known.[15] Furthermore, current clinical techniques do not yet provide the resolution required to completely address questions at the cellular and molecular levels in human studies. Therefore, many questions regarding basic mechanisms are still best addressed using *in vivo* animal models that, for the

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purposes of SE, also provide the ability to precisely determine the onset and duration of the prolonged seizure in a stable genetic background and developmental state of the central nervous system. Further, the shorter developmental time scale of the central nervous system in murine animal models[16–18] (Table 1) permits the prospective study of long term outcomes to be addressed in an efficient time period.

Murine Models of SE

Acute prolonged seizures can be triggered in the laboratory by a number of varied techniques. The systemic injection of a convulsant substance (i.e. chemoconvulsant) into rodents tends to be favored for its ease as well as the tendency of prolonged seizures in adult animals induced using these substances to consistently trigger long term changes, i.e. epileptogenesis, that results in the development of spontaneous recurrent seizures (SRS), i.e. epilepsy.[19–22]

Of the chemoconvulsant models, the two most commonly used have been the broad spectrum glutamatergic agonist kainic acid (KA model)23 and the muscarinic agonist pilocarpine (Pilo model).19 Frequently pilocarpine is preceded by the administration of lithium (LiPilo model) which allows for the dosage of pilocarpine to be reduced.20, 24–27 A less commonly used chemoconvulsant is pentylenetetrazol (PTZ model),28 a tetrazol derivative that acts by antagonizing GABAergic inhibition.29

Recognizing that it may be difficult to separate the direct toxic effects of the chemoconvulsants from the changes that occur as the result of the seizure, recurrent electrical stimulation models (ES) were developed with the hypothesis that the effects observed following stimulation-induced SE were more likely to be the direct result of the seizure. Although electrical stimulation resulting in self-sustaining SE has been utilized frequently in studies of SE in the developed brain,[30, 31] it has received less attention in the developing brain due to its relative resistance to stimulation-induced SE.[31, 32]

Febrile SE accounts for nearly 25% of SE during childhood and is typically associated with a better outcome and a lower risk of developing epilepsy.33 To model this condition, rodents have been exposed to a steady stream of air heated to 41.5 °C. This exposure produces a seizure that involves the limbic system including the amygdala and hippocampal formation.[34, 35] However, unlike the models described above in which the SE is self-sustaining, induction of a prolonged seizure in this model requires that the animal be maintained in the hyperthermic environment for the duration of the seizure. As with febrile seizures, there is a unique age-specificity as these events are most readily induced in rats when they are approximately postnatal day (P) 10.

Age- and model-dependent differences are observed with respect to seizure induction and mortality (table 1). For example, pilocarpine largely fails to induce seizures in animals <P10 [36, 37] whereas KA at low doses induced robust seizures in these animals.[38] In addition, the behavior and electrographic characterization of SE has also been observed to vary with age and model.[36, 39–44]

SE Pathogenesis: Altered trafficking of $GABA_A$ receptors

Murine models have demonstrated that an important component of the pathogenesis of SE is a progressive reduction in GABA-mediated inhibition.[45, 46] Clinically, this progressive reduction in GABA-mediated inhibition complicates the treatment of SE as medications that are effective in the early treatment of SE often fail to treat SE in its later stages.[47–51] Treiman and colleagues[52] and others [53–55] demonstrated that the $GABA_A$ receptor modulator diazepam also fails to terminate SE in its late stages in both the developed and developing animal. Given the parallel between the human condition and the murine models, the majority of the recent

animal studies investigating the pathogenesis of SE have focused on the changes that occur in GABA-mediated inhibition during SE.

The interaction of the neurotransmitter GABA with the postsynaptic $GABA_A$ receptors is the predominant mediator of inhibitory transmission within the central nervous system. The $GABA_A$ receptor is a heteropentameric structure formed from 16 subunit subtypes.[56, 57] The current consensus is that the majority of native receptors are assembled from two copies of an α, two copies of a β, and one single copy of a γ, δ, or ε subunit. When GABA binds to the receptor, it undergoes a conformational change that results in a chloride conductance. Synaptically-located receptors contain a γ2 subunit in their assembly and are sensitive to benzodiazepines. In contrast, receptors that contain a δ subunit are extrasynaptically-located, are insensitive to benzodiazepines but sensitive to anesthetics, and modulate a persistent (tonic) background inhibition.

Kapur and colleagues[53, 58] provided evidence that a rapid modification in the population of postsynaptic $GABA_A$ receptors occurs during SE. Subsequent studies demonstrated that during SE the reduction observed in GABA-mediated inhibition correlated with a reduction in the surface expression of the benzodiazepine-sensitive $GABA_A$ receptors but not the benzodiazepine-insensitive $GABA_A$ receptors.[59–61] For example, we used a biotinylation pull-down assay to measure the surface expression of benzodiazepine-sensitive γ2-containing and benzodiazepine-insensitive δ-containing $GABA_A$ receptors in hippocampal slices acutely obtained from adolescent animals (P30 and older) in SE (SE-treated) and from age-matched naïve controls.[61] The surface expression of the γ2 subunit in the SE-treated slices was approximately 50% that observed in controls whereas no significant change in the surface expression of the δ subunit was observed. Complementary whole-cell patch clamp recordings from dentate granule cells in SE-treated slices demonstrated a reduction in GABA-mediated synaptic currents but not tonic inhibition. Moss and colleagues 60 demonstrated that this activity-dependent reduction in the $GABA_A$ receptor surface expression corresponded to a reduction in the phosphorylation of the β3 subunit. Dephosphorylation of this subunit unmasks a patch-binding motif for the clathrin adaptor AP2 protein allowing for clathrin-mediated endocytosis of the receptor.

It has been posited that this activity-dependent decrease in benzodiazepine-sensitive receptors is a potential mechanism to explain the failure of benzodiazepines to treat SE in its late stages. Furthermore, these findings provide a biological rationalization to support recent recommendations that SE protocols be modified to provide for the earlier initiation of anesthetics[62] as the δ subunit-containing benzodiazepine-insensitive $GABA_A$ receptors are sensitive to general anesthetics such as propofol and pentobarbital.[63–65]

Early in development, activation of postsynaptic $GABA_A$ receptors can result in neuronal depolarization (i.e. excitation) via relative overexpression of a Na-K-Cl cotransporter (NKCC1).[66–68] To-date, studies of activity-dependent trafficking of $GABA_A$ receptors during SE have been limited to those animals in which GABA is hyperpolarizing (i.e. inhibitory). Whether a similar reduction in the surface expression of these receptors occurs in these younger animals is not known. However, it has been demonstrated that hypoxia-induced seizures [69] caused the downregulation of $GABA_A$ receptors on the CA1 pyramidal neurons of immature animals (P10-P11), a change that was reversed by calcineurin inhibitors. This finding demonstrates that altered receptor trafficking may play a role in the pathogenesis of seizures at this younger developmental age as well.

SE Outcome: An interaction between age and inciting stimulus

Independent of age and etiology, what the prolonged seizures of SE share in common, what distinguishes them from other seizure types, is that they are self-sustaining and the probability

of spontaneous termination in the absence of treatment is low. However, what the prolonged seizures of SE do not share in common is a single outcome at either the neuropathological or behavioral level. In the classic study of Aicardi and Chevrie 6 cataloging the outcome of children ≤ 15 years old following an episode of SE ≥ 1 hour in duration, the number of children with sequelae was approximately 50%. Therefore, almost 50% of children had no obvious sequelae one year after their prolonged seizure. These investigators made the important observation that outcome varied with age and etiology. Subsequent clinical studies (as reviewed by 13) have confirmed their conclusion.

Although the number of studies in which murine models have been used to study the outcome of early life SE is relatively small when compared to studies performed using adult animals (as reviewed by 18), it is evident that outcome at the neuropathological and behavioral levels in these models also reflects a unique interaction between developmental stage and model (as reviewed by 70–73). A summation of age and model dependence of the long term outcomes of SE based on a representative sample of the published literature is provided in Table 2. *In general, with advancing age, the probability of observing permanent neuropathologic, cognitive and emotional deficits in adulthood and the development of spontaneous recurrent seizures increases.*

However, there are variations on this theme. For example, Sankar et al.[32] compared the development of spontaneous recurrent seizures at P21 following SE-induced by either electrical stimulation (ES) or lithium-pilocarpine and P35 animals following SE-induced by ES. They observed that following ES-induced SE, only a single P21 animal (11%; n=1/9) developed spontaneous recurrent seizures compared to 73% (n= 8/11) of the P21 animals in which SE had been induced by lithium-pilocarpine and 100% (n=6/6) of the P35 animals after ES. Similarly, although Pilo, LiPilo, and KA-induced SE between P15 and P20 have been shown to result in cognitive deficits, no long term adverse effects were observed following PTZ-induced SE in this age group.[74]

The functional anatomy of SE - the neuronal circuits recruited during the prolonged seizures of SE - can be determined using several techniques. Common methods include the determination of changes in the local cerebral metabolic rate of glucose utilization using 2-Deoxyglucose (2-DG) method[75, 76] and the mapping of the expression of early intermediate genes, e.g. c-fos and c-jun, as a marker for neuronal activation.[32, 77]

There is good evidence that the functional anatomy of SE is determined by an interaction between developmental stage and inciting stimulus, and that these differences in functional anatomy can partially influence outcome. Multiple studies confirm age-dependent changes in the functional anatomy of SE.[28, 39,41–43, 78–81] A summation of the recruitment of several anatomical regions based the expression of early immediate genes at different ages and using different models is shown in Table 3. This summation demonstrates that not only do age-dependent changes occur within any single model but that there are differences in functional anatomy that occur between models. For example, Nehlig and colleagues[42] induced SE in animals aged P10, P21, and P60-70 using LiPilo and mapped the functional anatomy by characterizing the expression of the immediate early gene c-fos in multiple brain regions 2 hours after the start of SE. They observed widespread c-fos expression throughout the brain with very little variation with age with the exception of the substantia nigra where no activation was observed at P10 but was present at P21 and P60-70. In contrast, Holmes and colleagues [43] mapped the expression of c-fos 2 hours after the start of KA-induced SE in P7, P13, P20, and P60 animals. The activation of c-fos after KA-induced SE in the youngest animals was present in the substantia nigra and isolated to the CA3 region of the hippocampus as well as the central nucleus of the amygdala. In the P20 animals, induction of c-fos was not observed in the substantia nigra, but was observed throughout the entire hippocampus and amygdala.

In an elegant group of studies, Ben-Ari and colleagues[39, 78] provided an explanation for the age-dependent variation of SE within a single model by demonstrating that developmental changes in the expression of KA binding sites mirrored the changes in the functional anatomy of KA-induced SE. It is likely that developmental changes in other neurotransmitter systems [82] result in the age and model dependent differences that occur with other SE-inducing stimuli.

Ben-Ari and colleagues83 also made the observation that the functional anatomy correlated with the neuropathological findings. Even severe SE did not cause significant neuropathology in animals younger than the third week of life, after which there was an age dependent increase in the severity of pathological changes in various limbic regions as well as the hippocampal formation, amygdala, and thalamus among other regions. This age-dependent change in outcome reflected the age at which the amygdala was recruited into the neuronal circuit as reflected by metabolic activation. In addition, these authors, and others,[84] found that SE induced during prepubescence (P30 - 35) caused acute damage to the CA3 region of the hippocampus whereas the pathology was restricted to the hilar cells before this time, suggesting that SE-induced damage to CA3 was a function of the developmental maturation of the connectivity of the region with the dentate gyrus.

Variations in functional anatomy also partially account for the Sankar and colleagues' finding of the differences in the rates of spontaneous recurrent seizures after ES-induced and LiPilo-induced SE at different ages as described above.[32] It may also explain the failure of PTZ-induced SE between P16 to P20 to result in deficits in the performance of an elevated T-maze or result in permanent changes in behavior.[74, 85]

However, although age- and model-dependent differences in the functional anatomy of SE may partially account for some of the variation in outcome, activation of a region during SE as evidenced by expression of an early immediate gene does not necessarily predestine that region to neuropathological changes.[41, 81] For example, despite involvement of the hippocampus in the P10 animal in LiPilo-induced SE,[41] LiPilo-induced SE at this age does not result in obvious hippocampal injury, cognitive deficits or the development of spontaneous recurrent seizures. Therefore, murine models provide evidence that outcome is the result of a multifactorial process that depends on the functional anatomy of the seizure as well as the inherent vulnerability of a region to injury and plasticity at specific ages.[86–88]

Conclusions

The murine models of SE have provided an improved understanding of the cellular and molecular mechanisms that underlie the pathogenesis and long term outcomes of SE. Studies of pathogenesis have suggested that an activity-dependent trafficking of $GABA_A$ receptors contributes to the self-sustaining nature of this neurological emergency. The trafficking of these receptors offers a potential explanation for why benzodiazepine pharmacoresistance develops, as well as providing a basis on which to modify current protocols and to develop future therapies. Studies of long term outcome of SE using the murine models suggest that the functional anatomy of SE as determined by an interaction of the developmental stage and inciting stimulus is one of the factors that determines the long term outcome of SE. Future studies using these models are likely to provide further insights into these mechanisms and serve as a basis for future rational therapies for not only the treatment of status epilepticus but to also the prevention of its long term neurological consequences.

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Table 1

Summary of age dependent changes in status epilepticus susceptibility and associated mortality in common murine models of status epilepticus.

Human Developmental stage	Rat age	SE model	SE susceptibility	Mortality	References
Premature newborn	P3–P8	Pilo	Cannot be induced		36, 37
		Li – Pilo	+		40
		KA	+++	+++	38
Full term newborn	P8 – P10	Pilo	+	--	36, 37
		Li – Pilo	+	--	40, 92
		KA	+++	+++	38, 39
		PTZ	+++	--	80, 96
		Hyperthermia-induced SE	+++	--	34, 35
Infant/toddler/pre-adolescence	P11 – P24	Pilo	++	+	37
		Li – Pilo	++	--	40
		KA	+++	+	38, 39
		ES	++	+	32
Adolescent (Prepubescent/pubescent)	P25 – P35	Pilo	+++	+++	37
		Li – Pilo	+++	+++	40
		KA	++	+	38, 39, 78
		PTZ	+++	--	81
		ES	+++	+++	32
Adult	>P60	Pilo	+++	+++	37
		Li – Pilo	+++	+++	20
		KA	+++	+	20, 21, 23, 38

Note: Onset of puberty is from approximately P32-P38 in the rat.

Table 2

A summation of the consequences of SE based on age and model.

Rat age	SE model	Neuropathology	Behavioral impact in adulthood	Susceptibility to seizures and development of epilepsy in adulthood	Reference
P3 – P8	Pilocarpine	No apparent injury	None	Do not develop epilepsy	36
	KA	No apparent injury	↑ anxiety, deficits in short and long term learning and memory*	Do not develop epilepsy	38, 89, 90, 91
P8 – P10	Pilocarpine	Mild loss in dorsal hippocampus (CA4, CA1), septum, amygdala, thalamus, neocortex, hypothalamus	↑ aggression to handling; deficits in auditory discrimination, and visual spatial memory	Develop epilepsy ++	36, 37, 103, 104, 105
	Li Pilo	No apparent injury		↓ threshold to KA (but not GABAergic antagonist) induced seizures; but do not develop epilepsy	92, 93
	KA	? Reversible – all hippocampal sub fields	↑ anxiety, may have deficits in short and long term memory	Do not develop epilepsy	38, 89, 91, 94, 95
	PTZ	No injury / Mossy fiber sprouting†	None or memory deficits††	Do not develop epilepsy	80, 95, 96, 97
	Hyperthermia induced SE	Reversible – lateral amygdala; hippocampus (CA1, CA3)	Reference and working memory deficits	↓ threshold to KA induced seizures; Develop epilepsy	34, 35, 98, 99, 100, 101, 102
P11 – P24	Pilocarpine	Similar to P11 – P20 animals; but damage extends into the ventral hippocampus	Memory deficits	Develop epilepsy +++	19, 22, 36, 37
	Li Pilo	Similar to pilocarpine; but extensive cell loss in hippocampus (CA1 and DG) and associated mossy fiber sprouting. No CA3 loss	Spatial memory deficits	↑ susceptibility to kindling, develop epilepsy +	32, 106, 107, 108, 109, 110,
	KA	Reversible CA1 injury in pups < P18; in those P18 and above, irreversible CA1–CA3 damage, amygdala, lateral septum, mild damage to thalamus, hypothalamus and neocortex	↑ anxiety, deficits in short and long term memory	Do not (systemic administration) or can develop (focal application) epilepsy	38, 89, 91, 94, 111, 112
	PTZ	No injury	None	Do not develop epilepsy	74, 80
	ES			Develop epilepsy +	33
P25 – P35	Pilocarpine	Similar to P25 – P30 pilocarpine treated animals	↑ aggression, deficits in learning and memory, deficits in auditory discrimination	Develop epilepsy +++	19, 36, 103, 104, 115
	Li – Pilo	Similar to pilocarpine	Memory deficits	Develop epilepsy +++	111
	KA	Similar to P11 – P20 KA treated pups; but with increasing severity of damage	↑ anxiety, deficits in short and long term memory	↑ susceptibility to kindling; and develop epilepsy +++	38, 83, 84, 114

Rat age	SE model	Neuropathology	Behavioral impact in adulthood	Susceptibility to seizures and development of epilepsy in adulthood	Reference
	PTZ	No injury	None	Do not develop epilepsy	95
	ES			Develop epilepsy +++	32
>P60	Li – Pilo	Similar to pilocarpine treated animals		Develop epilepsy +++	20, 22
	KA	Similar to P25 – P30 KA treated animals; but with greater severity	↑ anxiety, deficits in short and long term memory	↑ susceptibility to kindling, and develop epilepsy +++	38, 89
	PTZ	None	None / Transient learning deficit	Do not develop epilepsy	74, 115

*Observed following focal administration of KA (see ref. 90)

†But see ref. 97

††Observed following repeated PTZ induced SE (see ref. 116)

Table 3

Status epilepticus functional anatomy: A summation of the early expression of early immediate genes during status epilepticus.

Model	Marker	Age	Amygdala	Hippocampus			SN	PC	EC	Reference
				CA1	CA3	DG				
LiPilo	c-fos	P10	+++	++	++	++	-	++	++	41
		P21	+++	+++	+++	+++	+++	+++	+++	
		P60-70	+++	+++	++	+++	++	+++	+++	
	c-jun	P21	+	+	+	++	+			32
KA	c-fos	P7	Limited to CeA	-	++	-	+			43
		P13	Limited to CeA	++	++	++	-			
		P20	Widespread	++	++	++	-			
		P60	Widespread	+	+	+++	-			
PTZ	c-fos	P10	+	-	+	++	-	++	++	81
		P21	+	-	+	+++	+	++	++	
	c-fos	P10	+++	-	-	+++	-	+++	++	42
		P21	+++	+	++	++	++	+++	++	
		>P60	+++	+++	+++	+++	++	+++	+++	
ES	c-jun	P21	-	-	-	+	-			32
		P35	+	-	-	+	+			

Key: CeA - central amygdaloid nucleus. DG - dentate gyrus. SN - substantia nigra. PC- piriform cortex. EC - entorhinal cortex.