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Authors

Santana-Gomez, Cesar E
Engel, Jerome
Staba, Richard

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CRITICAL REVIEW

Drug-resistant epilepsy and the hypothesis of intrinsic severity: What about the high-frequency oscillations?

Cesar E. Santana-Gomez[1] | **Jerome Engel Jr.**[1,2,3,4] | **Richard Staba**[1]

[1]Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

[2]Brain Research Institute, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

[3]Department of Neurobiology, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

[4]Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

Correspondence
Cesar E. Santana-Gomez, Department of Neurology, David Geffen School of Medicine, Reed Neurological Research Center, Suite 2155, 710 Westwood Plaza, Los Angeles, CA 90095, USA.
Email: csantanagomez@mednet.ucla.edu

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Abstract

Drug-resistant epilepsy (DRE) affects approximately one-third of the patients with epilepsy. Based on experimental findings from animal models and brain tissue from patients with DRE, different hypotheses have been proposed to explain the cause(s) of drug resistance. One is the intrinsic severity hypothesis that posits that drug resistance is an inherent property of epilepsy related to disease severity. Seizure frequency is one measure of epilepsy severity, but frequency alone is an incomplete measure of severity and does not fully explain basic research and clinical studies on drug resistance; thus, other measures of epilepsy severity are needed. One such measure could be pathological high-frequency oscillations (HFOs), which are believed to reflect the neuronal disturbances responsible for the development of epilepsy and the generation of spontaneous seizures. In this manuscript, we will briefly review the intrinsic severity hypothesis, describe basic and clinical research on HFOs in the epileptic brain, and based on this evidence discuss whether HFOs could be a clinical measure of epilepsy severity. Understanding the mechanisms of DRE is critical for producing breakthroughs in the development and testing of novel strategies for treatment.

KEYWORDS

drug-resistant epilepsy, EEG, epilepsy, epilepsy severity

1 | DRUG-RESISTANT EPILEPSY

Epilepsy is a brain disorder characterized by the enduring predisposition to generate spontaneous and recurrent seizures.[1] The World Health Organization reports epilepsy affects more than 50 million people around the world,[2] though others estimate there are 70 million people with epilepsy worldwide.[3] Approximately 30% of persons diagnosed with epilepsy continue to have seizures despite taking one or more antiseizure medication(s) (ASM), and in these cases, the individuals could be considered to have drug-resistant epilepsy (DRE). Though there is no precise definition of drug resistance, one definition considers DRE as a failure of two adequate trials of a well-tolerated and selected ASM regimen to produce sustained seizure freedom.[4–6]

The current research on drug resistance has focused on cellular and molecular alterations that lead to the reduction in drug sensitivity. Several decades of research

from animals and resected tissue from surgical patients with DRE have led to two major hypotheses to explain ASM resistance.[7–9] The first is the "multidrug transporter hypothesis," which posits that DRE is caused by the overexpression or gain of function of multidrug transporters (such as P-glycoprotein) and members of multidrug resistance–associated proteins in the blood-brain barrier. This condition leads to a decrease in the concentrations of ASMs in the brain parenchyma and consequently a reduction in drug efficacy.[7] The second is the "target hypothesis," which postulates inherited or acquired changes in the structure, function, or localization of the drug targets lead to reduced pharmacodynamic effects of the ASM.[8]

1.1 | The hypothesis of intrinsic severity

Proving the two aforementioned hypotheses has been difficult. Some have noted the basis of these hypotheses, that is, drug resistance develops independently of epilepsy itself, might be constraining research on the mechanisms of drug resistance.[10]

An alternative explanation considers a clinical observation, that is, in treatment studies of patients with newly diagnosed epilepsy, those with a higher frequency of seizures before treatment often have lower likelihood for remission of seizures.[11] This observation is consistent with the progressive aspects of seizures as described by Gowers in the late 19th century,[12] and later by others who observed more seizures or longer duration of epilepsy is associated with lower probability of remission.[13] These data suggest there is a continuum in severity of epilepsy and higher frequency of seizures at the early stage of epilepsy diagnosis indicates future drug resistance. In 2008 and again in 2013, Rogawski organized clinical data and the concept of epilepsy severity into the "intrinsic severity hypothesis," which states "pharmacoresistance is an inherent property of epilepsy related to disease severity."[10,14]

The term severity defines the impact of the illness in the biological, physical, or psychosocial function of the patient and is an often-used descriptive feature for most medical symptoms and conditions, such as in the case of traumatic brain injury where injury can be mild, moderate, or severe.[15] Severity is not commonly used to describe clinical epilepsy, and thus, there is little consensus on metrics to assess severity of epilepsy, and as noted by Rogawski in 2008, there is a need to identify measures of epilepsy severity. Nonetheless, as noted above, seizure frequency could be a measure of epilepsy severity associated with drug nonresponsiveness. In a study of 780 newly diagnosed patients with epilepsy followed in a single center over 20 years, a higher seizure frequency before treatment with ASM was associated with drug resistance.[11] In this same study, the presence of psychiatric comorbidities such as depression, anxiety, and psychosis, as well as recreational drug use, also was associated with DRE.[11] Sillampää and colleagues observed that pediatric patients who had three or more seizures in 24 hours, or a seizure cluster, had a lower likelihood for seizure remission than patients without a seizure cluster during the same period.[16] Other work found patients with 2 or fewer seizures in the first 6 months after epilepsy diagnosis had a 77% probability of being seizure-free for 1 year within 2 years of diagnosis. However, patients with 10 seizures during the first 6 months had a 50% chance of being seizure-free during the same period.[17] Based on this evidence, the authors concluded that the rate of epileptic seizures during the first 6 months after the disease diagnosis could be an important and predictive marker for the development of DRE.[17] Likewise, clinical trials have been shown that the delay in adequate treatment with ASM gradually increases the risk of DRE.[18] However, other studies found patients with a low number of seizures at the beginning of the disease could develop DRE.[17]

Some of these clinical observations are also seen in preclinical studies of epileptogenesis.[19,20] In these rat studies, self-sustained status epilepticus was induced by electrical stimulation of the basolateral amygdala, and then, rats that developed subsequent spontaneous seizures were treated with phenobarbital. Results show rats with a low seizure frequency before initial treatment were more responsive to phenobarbital and rats with a high seizure frequency were less responsive to the same treatment.[19,20] However, some of the unresponsive rats had a low seizure

Key Points

- The hypothesis of intrinsic severity theorizes that DRE is an inherent property of epilepsy related to the severity of the disease.
- Seizure frequency is a relevant marker of the severity, but not the only measure of severity, to predict DRE.
- PIN clusters are proposed to generate pathological HFOs and believed to reflect neuronal disturbances responsible for epilepsy.
- Pathological HFOs correlate with rate of epileptogenesis and, in some types of epilepsy, epileptogenicity of the lesion and propensity for seizures.
- HFOs could be used as an additional clinical marker to evaluate the severity of the disease and the possible development of DRE.

rate similar to responsive rats.[21] These data indicate seizure frequency is a good predictor of DRE, but it does not explain drug response in all cases and thus unlikely to be the only measure of epilepsy severity. Other measures could include occurrence of precipitating injury such as status epilepticus or traumatic brain injury, the type of seizure, a lesion on MRI verified by electrophysiology as epileptogenic and potentially unresponsiveness to medication, and other functional disturbances in the EEG, like high-frequency oscillations (HFOs).

1.2 | Pathologically interconnected neuron clusters in the epileptic brain

Studies in the epileptic brain show an increase in basal concentrations of glutamate in epileptogenic and nonepileptogenic brain areas.[22–26] Once a seizure begins, extracellular glutamate levels increase and remain elevated after the seizure has ended.[22–25] A consequence of this sustained high glutamate level is continuous excitation of neurons, producing abnormally high levels of intracellular calcium, deregulation of signaling pathways and organelle dysfunction, and ultimately cell death.[27] Cell loss changes the tissue architecture and among surviving neurons could induce axonal sprouting and activity-dependent synaptic reorganization.[28,29] These morphological alterations could strengthen excitatory connections between neurons, leading to the formation of pathologically interconnected neuron (PIN) clusters.[30] PIN clusters are hypothesized to be the mechanism for generating pathological synchronous bursts of population spikes, which are recorded as HFOs, and could represent the neuronal disturbances responsible for epilepsy.[31]

1.2.1 | High-frequency oscillations

High-frequency oscillations are local field potentials that correspond to an increase in synchronous neuronal spike bursts.[32] Based on their spectral frequency properties, HFOs are classified into “ripples” (80-200 Hz) and “fast ripples” (FRs, 200-800 Hz).[32] Ripples have been recorded in the normal hippocampus and parahippocampal structures of mammals, including rodents, nonhuman primates, and humans,[33–37] as well as in eloquent cortex of humans.[38] Normal ripples correspond to summated inhibitory postsynaptic potentials (IPSPs) of rhythmically discharging interneurons, which regulate pyramidal cell firing,[33,35] and in the hippocampus, ripples play a key role in the memory formation, reactivation of previous experiences, and information processing (eg, during somatosensory evoked potentials).[39] On the contrary, FRs have been recorded in patients and many animal models of epilepsy.[40–42] FRs reflect as a burst of population spikes generated from the out-of-phase firing of distinct cell clusters consisting primarily of principal cells.[42–50]

In animals and patients with epilepsy, both ripples and FRs have been associated with the seizure-onset zone (SOZ), suggesting some ripple frequency oscillations could also be pathological HFOs.[42,51–53] For example, in the normal dentate gyrus, oscillatory activity is typically lower than 100 Hz.[54,55] However, Bragin and colleagues found ripples >100 Hz in the epileptogenic dentate gyrus of kainic acid–treated rats.[56,57] Several patient studies of epilepsy surgery indicate resection of pathological HFO-generating areas is important for a seizure-free outcome.[58–61]

1.2.2 | High-frequency oscillations and epileptogenesis

In 2000, Bragin and colleagues hypothesized the development of PIN clusters generating pathological HFOs as a mechanism of epileptogenesis (ie, development of epilepsy).[30] Much of the evidence for this hypothesis was derived from the intrahippocampal kainic acid rat model of human temporal lobe epilepsy where rats receive a unilateral injection of kainic acid in posterior hippocampus and status epilepticus begins within 20 minutes of injection and lasts for up to 6 hours. Not all rats that have status epilepticus later develop epilepsy, but between 50% and 75% of them do, indicating there are differences in susceptibility between different strains and between rats within the same strain. In one study, using kainic acid–treated rats, HFOs were found in the dentate gyrus, CA1, and entorhinal cortex ipsilateral to the injection site of rats that later developed epilepsy, but HFOs were not found in rats that did not develop epilepsy.[57] In this same study, the sooner HFOs appeared after status epilepticus, the sooner the first spontaneous seizure occurred, the shorter the interval between first HFOs and first seizure, and the higher the rate of seizures per month.[57] However, the rate of HFOs, when they first appeared, which could be as early as one day after status epilepticus, was unrelated to the rate of subsequent spontaneous seizures. In other studies, higher rates of pathological HFOs were found inside and outside the hippocampus in animals that developed epilepsy than those that did not develop epilepsy.[62,63] It appears pathological HFOs in the epileptic hippocampus can also trigger the occurrence of remote HFOs, as well as spindles,[64] and likely through cross-frequency coupling with slow waves could contribute to epileptogenesis.[65] Recording from epileptic rats shows a greater number of electrodes with FRs correlate with a higher number of seizures per day.[41] Interestingly, an intracranial EEG study involving presurgical patients with focal epilepsy found a greater number

of electrode contacts recording more than 20 FRs per minute correlated with a higher number of seizures per month, especially in cases of temporal lobe epilepsy.[66] In addition to the intrahippocampal kainic acid rat model, pathological HFOs can be recorded in the fluid percussion injury rat model of human traumatic brain injury and posttraumatic epilepsy. Studies recorded pathological HFOs alone or superimposed on EEG spikes within the first two weeks after fluid percussion injury only in rats that later developed focal spontaneous seizures.[67,68] Results from the intrahippocampal kainic acid and fluid percussion injury models suggest pathological HFOs could be an electrophysiological biomarker of epileptogenesis. The neuronal mechanisms of epileptogenesis could be due to the formation of PIN clusters.[69] After an episode of status epilepticus or a traumatic brain injury, PIN clusters could form and, through a kindling-like process, lead to the formation of widespread PIN clusters (Figure 1). A greater number of PIN clusters lead the increase in amplitude and duration of HFOs leading up to seizure onset, and correlating with higher density of the PIN clusters with more frequent seizures.[30,62,70]

1.2.3 | High-frequency oscillations and epilepsy severity

Several studies have identified links between HFOs and aspects of epilepsy that could be associated with severity, such as frequency and type of seizures, MRI pathology, and, in some types of epilepsy, the propensity to generate seizures. In addition to the studies on interictal FRs and seizure frequency in rats and patients with epilepsy noted in Section 1.2.2, a study in children with drug-resistant focal epilepsy showed higher rates of HFOs in preoperative scalp EEG correlate with higher seizure frequency.[71] Results like this are also observed between interictal ripples and number of seizures in cases of childhood epilepsy with centrotemporal spikes (CECTS).[72] With respect to the type of seizures in rats, rates of ripples and FRs are higher during seizures with clonus, rearing and falling or with wild running than rates during seizures with rearing only (no falling) or movements limited to forelimbs, face, mouth, or eyes.[73] A similar analysis performed in patients showed ripple activity in the SOZ is higher during seizures that subsequently evolve with bilateral tonic-clonic movements than during focal seizures without such movements.[74] These latter data are consistent with a previous patient study that showed, during low voltage fast (LVF) seizures, a common ictal EEG pattern associated with regional-onset seizures,[75] that ripples increase in the SOZ and sites of spread.[76] The LVF activity is associated with an increase in inhibitory cell firing and a reduction in excitatory cell firing that subsequently rebounds.[77] One interpretation of these data is that a widespread HFO network generates seizures and can facilitate seizure spread. Alternatively, the ripples could be a mechanism to prevent seizure spread that ultimately fails, which might explain the pattern of inhibitory and excitatory cell firing.

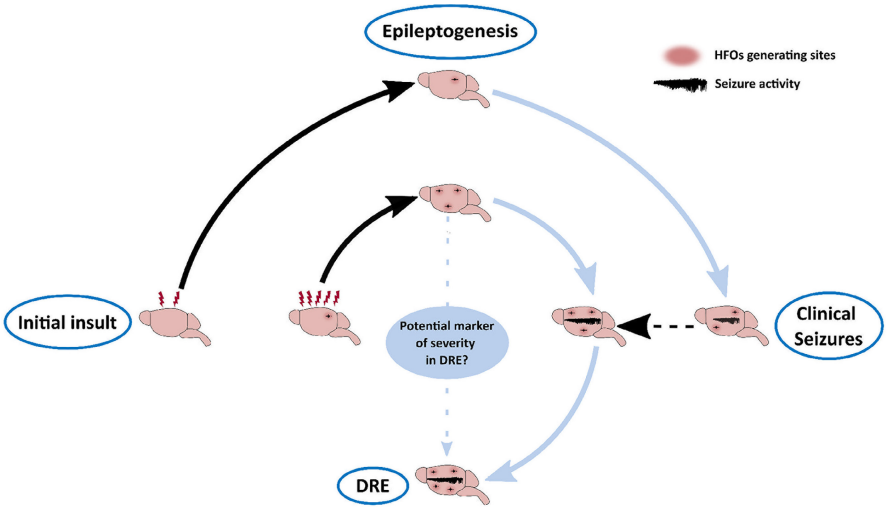

FIGURE 1 High-frequency oscillations (HFOs) as a potential marker of epilepsy severity. After an epileptogenic insult, the appearance of HFOs precedes and contributes to the development of clinical seizures (denoted by outer arc). In some cases, HFOs could appear immediately after injury, and lead to the formation of a more extensive HFO network, and soon thereafter the appearance of clinical seizures (inner arc). Once epilepsy is established, the rate of HFOs or the number of HFO-generating sites or both increases to generate more frequent seizures (denoted by black dashed arrow). If the intrinsic severity hypothesis is correct and HFOs are a measure of epilepsy severity, then a high burden of HFOs would predict a severe form of epilepsy with high seizure frequency (solid blue arrow) that could be unresponsive to medication, that is, drug-resistant epilepsy (DRE) (blue dashed arrow)

In mesial temporal lobe epilepsy, a higher ratio of FR to ripples correlates with reduced hippocampal volume and cell loss associated with hippocampal sclerosis.[78] Similar results can be found in pilocarpine-treated epileptic rats.[46] In a separate patient study, higher rates of FR alone, but not ripples, correlated with local areas of atrophy in hippocampi ipsilateral and contralateral to the SOZ.[79] This latter study included patients who had drug-resistant seizures, and results suggest the extent of atrophy and the size or number of the brain areas generating FR are greater in patients with many years of poorly controlled seizures. This interpretation is consistent with the positive correlation between the number of electrodes with FR and seizure frequency in rats with chronic epilepsy.[41] In cases with focal cortical dysplasia (FCD), patients with FCD type 2 have significantly more seizures and higher rates of HFOs than patients with FCD type 1.[80] Results from these studies suggest HFOs could correspond to the epileptogenicity of the lesion and a measure of epilepsy severity.

Several studies have found HFOs, particularly ripples, either alone or superimposed on spikes (spike ripples) in cases of CECTS. The highest number of ripples is associated with frequent seizures in patients with atypical CECTS and the fewest or absence of ripples in classical CECTS or those patients without seizures.[72,81] Ripples are better than spikes alone for predicting seizures and can help distinguish patients with atypical CECTS from those with few or no seizures. In other work of CECTS, spike ripples are associated with more recent seizures,[82] and rates of spike ripples are higher in patients who have at least one seizure within one year than in patients who are seizure-free for more than one year.[83] Also, a longer duration without a seizure is associated with a lower spike ripple rate. Patients with CECTS and scalp-recorded HFOs have more cognitive deficits than patients without HFOs.[84] These data suggest in some types of epilepsy, HFOs correspond to active epilepsy. In a syndrome such as CECTS with a spectrum of severity of focal seizures and neurocognitive impairments, HFOs indicate a greater propensity for seizures and cognitive deficits.

In surgical pediatric patients with diverse etiologies and focal seizures, high rates of scalp-recorded HFOs over the affected hemisphere are associated with recurrent seizures and rates of HFOs decrease after surgery in patients whose seizures are reduced or eliminated.[71] Another study found in surgical patients, HFOs in pre- and postoperative electrocorticography are associated with recurrent seizures.[85] Interestingly, in some patients, preoperative HFOs outside the resection margins disappear on postoperative recordings, and in a few patients, sites with "new" HFOs could be found in postoperative recordings that were not in preoperative recordings. Of these latter patients, one had recurrent seizures postoperatively, and the other was seizure-free. There could exist HFO "hub" sites that maintain a high number of direct (possibly synaptic) connections with remote HFO sites, and these interconnected sites could coordinate activity through preferred phases of low-frequency EEG rhythms (see Section 1.2.2).[86] In this scenario, severe forms of epilepsy could have several HFO hubs that have a strong modulatory effect on remote sites,[87] and resection of HFO hubs renders remote HFOs sites inactive and abolishes seizures.

1.2.4 | The effect of antiseizure drugs on high-frequency oscillations

A study of the effects of seizures and ASM on spikes and HFOs showed there are higher rates of spikes, but not HFOs, after than before a seizure.[88] The number of electrode contacts with spikes or HFOs is also higher after a seizure. During reduction in ASM, there is no change in the rates of spikes, but there is an increase in the rate and duration of HFOs. In other work on West syndrome, scalp-recorded interictal HFOs were higher in patients with seizures before the start of treatment than in controls without seizures.[89] During treatment, the decrease in hypsarrhythmia and seizures is accompanied by a decrease in number of HFOs. A similar decrease is found in HFOs after treatment in patients with atypical benign partial epilepsy.[81] More recently, a study of interictal HFOs after treatment for epileptic spasms showed a higher incidence of HFOs coupling with the trough-to-peak transition of 2-3 Hz slow waves in patients unresponsive to treatment than those who responded to treatment.[90] Previous studies also found a strong association between HFOs coupling with the trough-to-peak transition of the slow wave in epileptogenic tissue in patients with drug-resistant seizures.[91–93] The mechanism(s) for HFO coupling with slow waves described in these cited studies are not known, but one explanation is that the trough-to-peak transition of the slow wave produces a powerful depolarizing volley that excites PIN clusters and generates pathological HFOs. HFOs correspond to abnormal neuronal activity involved with generating seizures, and lowering the threshold for seizures as in the case of ASM withdrawal increases HFOs and likelihood for seizures.

1.3 | Summary and conclusions

The intrinsic severity hypothesis proposes there is a continuum in severity of epilepsy that corresponds to a likelihood the epilepsy will respond to ASM. A high seizure frequency is a risk factor for refractoriness, though the hypothesis does not explain why patients with infrequent

seizures do not respond to ASM or why seizure control on ASMs can vary over time. Seizure frequency should not be the only measure of severity, and other measures such as pathological HFOs appear to reflect other aspects of epilepsy severity.

PIN clusters are proposed to be the mechanism for generating pathological HFOs and may contribute to the generation of spontaneous epileptic seizures (Figure 1). During the development of epilepsy, the greater the extent of pathological HFO-generating sites in terms of their number and spatial distribution, the sooner seizures appear with greater frequency, indicating pathological HFOs could be a measure of the rate and strength of epileptogenesis.

In patients with medication-resistant epilepsy and some childhood epilepsies, increased irritability within PIN clusters as measured by the rate of HFO discharges corresponds with greater propensity to generate seizures. In CECTS, for example, HFOs (particularly ripples) or spikes with HFOs are better than spikes alone to predict active epilepsy that require ASM treatment.

Pathological HFOs are associated with some types of FCD and histological cell loss and MRI atrophy, especially in cases of hippocampal sclerosis, which could correspond to the extent of structural abnormality and epileptogenicity of these lesions. It appears widespread pathological HFOs indicate a large area of brain capable of generating seizures and could be a mechanism for seizure spread with greater motor and behavioral impairment. Incomplete resection of pathological HFOs reduces the likelihood for seizure-free outcome in many, but not all, surgical patients, which implies there could be hub-like sites generating HFOs. Severe forms of epilepsy could have a greater number of HFO hubs that need to be removed to eliminate seizures.

Invasive EEG is best for recording pathological HFOs, especially in deeper brain areas. Scalp EEG can record HFOs and is used more frequently, carries less risk, and has greater spatial sampling than invasive EEG. In clinical epilepsy, recording HFOs could provide a measure of the risk for developing epilepsy and propensity for spontaneous seizures, and, in some types of epilepsy, the epileptogenicity of a lesion and severity of the disease.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Cesar E. Santana-Gomez https://orcid.org/0000-0001-9163-5615

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