Neuron-specific mechanisms for epilepsy self-termination

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Epilepsy is characterized as the ictal discharges of the cerebral brain in the sudden onset and self-termination for a few minutes. The seizure onset is presumably originated from the synchronous activity of excitatory neurons and the weakness of inhibitory synapses, which guide the suppression of the seizure onset by giving the exogenous reagents to enhance inhibitory synaptic transmission and to block action potentials. After long-term treatment, many epileptic patients become insensitive to such medications and the pathogenesis in the elevated ratio of cortical excitation to inhibition is still present. The lack of long-term therapeutic effectiveness may be reasoned from the facts that the current medication is not neuron-specific and the seizure self-termination has not been taken into account. Therefore, the new therapeutic strategies against epilepsy remains to be explored based on strengthening the endogenous mechanisms of seizure self-termination in a neuron-specific manner. We review the potential mechanisms of seizure self-termination and present our thoughts in anti-epilepsy by strengthening seizure self-termination in different neuronal compartments.

Keywords: epilepsy; neuron; synaptic transmission; excitability; GABA and homeostasis

or delayed emergence within a few minutes. In the cerebral seizure-onset tissues, pathology-induced homeostasis, which is slowly developed in days, months or even a year, includes the upregulation of GABAergic function and the downregulation of glutamatergic function. In the following sections, we will discuss these endogenous factors of seizure self-termination.

The intrinsic homeostasis for seizure self-termination

The intrinsic homeostasis in response to seizure discharges can be initiated instantly and latterly for seizure self-termination. An immediate emergence of the intrinsic homeostasis is based on the natively preset endogenous factors, such as the circuit of inhibitory neurons, the refractory period of voltage-gated sodium channels and the desensitization of glutamate receptors. This immediate homeostasis presumably attenuates synchronous neuron activities during the seizure-onset. The delayed emergence of the intrinsic homeostasis includes activity-induced spontaneous spikes in GABAergic neurons, accumulative proton, glutamate depletion and subcellular compartment coordination. These delayed endogenous factors more or less are able to suppress over-excitation after the seizure onset.

Inhibitory neuronal circuits

In the central nervous system, 10–20% of neurons are inhibitory in function and they are evenly distributed among the excitatory neurons. These inhibitory neurons receive synaptic innervation from the axons of the excitatory neurons, and in turn their inhibitory axonal branches synaptically target onto the excitatory neurons in the feedforward and feedback manners. These mutual innervations between excitatory and inhibitory neurons lead to the facts that the excitatory neurons activate the inhibitory neurons and the inhibitory neurons suppress the excitatory neurons in their functions. Moreover, there are the electrical couplings among the inhibitory neurons through gap junction, which make the inhibitory interneurons to work together coordinately. These inhibitory processes will quickly terminate any over-excitation among the neurons, so that local neuronal circuits are physiologically maintained at homeostasis.

In addition to mutual interactions among the neurons, the efficient and coordinated relationships between the presynaptic axons and their postsynaptic neurons are critical for the stable functions of neural networks. Current study shows that the branches sprouted from inhibitory axons and their target neurons are functionally differentiated, and that the excitability and synaptic transmission at such presynaptic vs. postsynaptic partners are linearly correlated. The innervation of active axonal branches to active neurons, or vice versa, indicate that the inhibitory axonal branches are functionally compatible with their postsynaptic partners. This functional compatibility between inhibitory axonal branches and their postsynaptic partners makes the postsynaptic neurons not being over-inhibition and disinhibition, such that neural networks are maintained in homeostasis.

It has been suggested that the weakness of inhibitory neuronal networks occurs in epileptic tissues, especially epilepsy caused by cortical developmental dystrophy. This pathological change makes the inhibitory neuronal circuits not to sufficiently suppress the cortical over-excitation during synchronous seizure discharges. In fact, seizure automatically stops a few minutes after its onset. Some mechanisms for this seizure self-termination may be present in the epileptic tissues, such as an upregulation in portion of inhibitory neurons, and so on (please see below).

Refractory period of voltage-gated sodium channels

The upstroke of action potentials generates based on the activation of voltage-gated sodium channels, and each of the action potentials is followed by a refractory period when a subsequent action potential cannot be induced. Spike refractory period is due to voltage-gated sodium channels falling into inactivation from activation status. Moreover, the refractory periods of action potentials are prolonged with spiking persistence in the cerebral neurons, i.e., a time-dependent prolongation of spike refractory periods, especially in the excitatory neurons but not the inhibitory neurons. This property restricts spike frequency in the excitatory neurons, so that the strength and persistence of synchronous neuronal excitation are quickly limited. In addition, the refractory period of axon voltage-gated sodium channels attenuates the generation and propagation of high frequency spikes, which benefits to limit the output of sequential spikes for seizure self-termination. Spike refractory period can also be used to explain a hypothesis about seizure termination from the asynchrony to the synchrony of population network neurons. The asynchrony activity among the excitatory neurons makes their positive interactions via recurrent axons reciprocally, whereas the synchrony activity among the excitatory neurons confers them to simultaneously enter spike refractory periods, leading to seizure self-termination.

Based on this view, the exploration of reagents that prolong spike refractory periods or strengthen voltage-gated sodium channel inactivation should be an avenue against seizure onset and persistence, i.e., accelerate seizure self-termination. In fact, phenytoin as epileptic suppressor is an antagonist of voltage-gated sodium channels. Because
it blocks voltage-gated sodium channels on both excitatory and inhibitory neurons, searching the reagents that specifically prolong the refractory period of voltage-gated sodium channels on excitatory neurons will benefit to prevent seizure persistence. It is noteworthy that spike refractory period appears intensity-dependent shortening, in which an increased input intensity shortens spike refractory period [16], such that the effort to shorten spike refractory periods should be combined with lowering excitatory synaptic inputs.

The desensitization of glutamate receptors

In the synapses of the central neurons, the glutamate receptors that mediate fast synaptic transmission express receptor desensitization in response to glutamate actions prolonged more than a few seconds [43, 44]. This property gives the possibility for the excitatory synaptic transmission to be downregulated in massive glutamate release during seizure discharges. Although this hypothesis remains to be examined, the enhancers of glutamate receptor desensitization is likely an approach to shorten the persistent status of seizure.

Activity-induced spontaneous spikes in GABAergic neurons

It has been found that the intensive activity in cortical GABAergic neurons for 2~3 minutes induces them firing spontaneous spikes, activity-induced spontaneous spike (AISS) [45, 46]. AISS demonstrates zero threshold potential for its initiation, which may be based on the activation of axonal voltage-independent sodium channels [45]. Through the axonal branches of these GABAergic neurons, AISS inhibits the excitatory neurons in local circuits by feedforward and feedback mechanisms. Through the synaptic connections in local neural circuits (Figure 1), the synchronous activity of
the excitatory neurons will trigger AISS in GABAergic
neurons, and AISS in turn inhibits synchronous discharges in
the cortical excitatory neurons.

It is noteworthy that this AISS can be induced in the
functionally upregulated inhibitory neurons in the
seizure-onset cortices (Figure 2). The upregulation of the
inhibitory neurons [47] and the AISS in these neurons will
work together coordinately for seizure self-termination. In
this regard, the reagents that turn on voltage-independent
sodium channels [45] on the GABAergic neurons are expected
to accelerate seizure self-termination, which remain to be
explored.

Activity-induced change in biochemical environment

It is assumed that intensive activities in a population of
neurons lead to the changes of cellular biochemical
environment, such as the accumulation of intracellular proton
[48], the elevation of extracellular potassium [49] and the
depletion of glutamates in presynaptic terminals [50]. Acidosis
and glutamate depletion may inhibit neuronal activity or
reduce excitatory initiation, and in turn cause seizure
self-termination. It is noteworthy that some of these changes
are not specific to excitatory and inhibitory neurons, and the
decreased activities in both excitatory and inhibitory neurons
may not be major reasons for seizure self-termination.

Homeostasis via coordination among subcellular compartments

It has been found that neuronal excitability can be
maintained at a homeostasis by coordinating the activities
among different subcellular compartments [16]. The
upregulated excitatory synaptic activity is associated with the
upregulated inhibitory synaptic activity and the
downregulated cellular excitability on the same excitatory
neurons. The changes of the somatic and axonal excitability
go toward opposite direction. These changes confer neuronal
encodings to be constant, which are regulated by intracellular
calcium signal pathways [16]. Through this mechanism, the
hyperactivity in any compartment can be balanced by
hypoactivity in other compartments, so that over-excitation
in the excitatory neurons is self-terminated.

Pathology-related homeostasis for seizure
self-termination

Previous studies are mainly focused on elucidating the
pathology of seizure onset, especially the dysfunction of
inhibitory synapses and neurons, in animal models [2-4, 28, 51].
These data provide invaluable information for understanding
epilepsy mechanism, but antiepileptic strategies based on
these data have not completely made the patients cured [11, 52,
53]. The findings in animal models are expected to be
examined in the seizure-onset cerebral cortices from epileptic
patients [54-57], which may help to reveal the mechanisms
underlying seizure onset and self-termination as well.

The upregulation of GABAergic functions

The study from the patients suffering from temporal lobe
epilepsy indicates that inhibitory neurons and synapses are
functionally differentiated [47]. Compared to the cortical
inhibitory neurons in non-epilepsy individuals, the inhibitory
neurons in seizure-onset cortex demonstrate two populations

![Figure 2. The functional upregulated inhibitory neurons express activity-induced spontaneous spikes. A) shows input-output curves for an interneuron in cortical tissue from non-epileptic individual (black curve and symbols) and for an interneuron in seizure-onset cortical tissue from epileptic patient. B) shows the induction of activity-induced spontaneous spikes from this functional upregulated interneuron in seizure-onset cortical tissue from epileptic patient.](image)
in their abilities of responding to excitatory synaptic input, producing spikes and influencing downstream cells. Two third of inhibitory neurons and synapses are functionally downregulated, while one third of them are functionally upregulated. The computational modeling shows that the patch-like disinhibition facilitates an onset of neuronal synchronous discharges, and the upregulated inhibitory neurons and synapses synergistically promote the termination of seizure discharges by shortening seizure duration, attenuating seizure strength and reducing seizure propagation. Automatic seizure termination is likely due to a fact that a portion of the inhibitory neurons and synapses are upregulated in the seizure-onset cortices.

Pathophysiological changes in the upregulation of inhibitory neurons and synapses from seizure-onset cortices may be the consequence induced by long-time epilepsy. Molecular mechanisms underlying their upregulation remain to be studied. The increases in the portions of upregulated inhibitory synapses and neurons reinforce cortical inhibitory networks to terminate seizure discharge. Inhibitory neuron-based therapy for epilepsy has been proposed [58]. Synergistically upregulating inhibitory neurons and synapses for seizure self-termination suggests that the epilepsy therapy will be benefit from strengthening the functions of multiple subcellular compartments in the inhibitory neurons, such as their synaptic sensitivity, intrinsic property and GABAergic output. In these regards, the therapeutic strategies for the intractable epileptic patients should be to raise the number and function of the inhibitory neurons synergistically. As stem cells are preferentially differentiated to inhibitory neurons, stem cell therapy will be the option to increase the number of inhibitory interneurons.

**The internalization of synaptic receptors**

It has been found that the epileptogenesis leads to the increases of GABA<sub>A</sub> receptor endocytosis that contributes to seizure induction and maintenance [59]. This internalization of GABA<sub>A</sub> receptors is thought be induced by the long-term use of GABA<sub>A</sub> receptor agonists during epileptic treatments [60]. Similarly, glutamate receptors undergo internalization evoked by glutamate or its agonists [61-63]. Long-term action of glutamates in the excitatory synapses during seizure activity may induce the internalization of glutamate receptors, despite lack of experiment evidence. If it is a case, this internalization of glutamate receptors will reduce the number of glutamate receptors in the postsynaptic density, which may benefit seizure self-termination. In these regards, the exploration of reagents that increase glutamate receptor internalization and decrease GABA<sub>A</sub> receptor internalization in the postsynaptic neurons is expected to accelerate the seizure termination.

In summary, we have discussed the endogenous factors including native intrinsic homeostasis and pathology-induced homeostasis that are potentially underlying seizure self-termination. In these factors of seizure termination, some are neuron-specific and others are not, as well as some occur in the late-phase of seizure attack and others are onset early. The goal to accelerate seizure self-termination in the brain is to boost the mechanisms in GABAergic neurons, strengthen excitatory attenuation in excitatory neurons and shift self-termination mechanisms toward the early phase of seizure onset. The suggested processes include the enhancements of glutamate receptor desensitization/internalization in the excitatory neurons, the agonist of voltage-independent sodium channels in the inhibitory neurons, as well as the upregulated number and function of the GABAergic neurons. More importantly, the combined applications of these strategies should boost the therapeutic efficiency and reduce the side-effects.

**Competing interests**

Jin-Hui Wang, Wei Lu and Bo Wen declare no competing interests.

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