# Understanding complexities of synaptic transmission in medically intractable seizures: A paradigm of epilepsy research

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## ABSTRACT

Investigating the changes associated with the development of epileptic state in humans is complex and requires a multidisciplinary approach. Understanding the intricacies of medically intractable epilepsy still remains a challenge for neurosurgeons across the world. A significant number of patients who has undergone resective brain surgery for epilepsy still continue to have seizures. The reason behind this therapy resistance still eludes us. Thus to develop a cure for the difficult to treat epilepsy, we need to comprehensively study epileptogenesis. Although various animal models are developed but none of them replicate the pathological conditions in humans. So the ideal way to understand epileptogenecity is to examine the tissue resected for the treatment of intractable epilepsy. Advanced imaging and electrical localization procedures are utilized to establish the epileptogenic zone in epilepsy patients. Further molecular and cytological studies are required for the microscopic analysis of brain samples collected from the epileptogenic focus. As alterations in inhibitory as well as excitatory synaptic transmission are key features of epilepsy, understanding the regulation of neurotransmission in the resected brain specimen to understand the changes in GABAergic and glutamatergic synaptic transmission in epileptogenic zone. We also review evidence pertaining to the proposed role of nicotinic receptors in abnormal synaptic transmission which is one of the major causes of epilepsy cases that cannot me managed pharmacologically.

Key words: GABA, glutamate, intractable seizures, nicotinic receptors, synaptic transmission

# INTRODUCTION

Epilepsy is defined as a state of recurrent unprovoked or spontaneous seizures. Clinical studies on epilepsy and use of anticonvulsants started in the 1800s, but the actual understanding of the state of epilepsy started with the advent of electroencephalogram in the 1900s.<sup>[1]</sup> Electroencephalography (EEG) provided an understanding of electrical basis of sequence of events that leads to epileptic seizures, which helped in the development of new generation of anticonvulsants.<sup>[2]</sup> But there is significant number of epilepsy cases where treatment with antiepileptic drugs is not effective. In

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these medically refractory epilepsy cases, surgery has been established as an effective mode of cure. About 30-40% of patients who have undergone an adequate epilepsy surgery still continue to have seizures.<sup>[3]</sup> To investigate this therapy resistance we need to understand the process of epileptogenesis that leads to generation of hyperexcitable neuronal network.

Various animal models with brain dysfunctions are currently under investigation to get an insight into the processes that leads to epilepsy. Chronic models of epilepsy like, kindling where short electrical stimulations is applied to amygdala or hippocampus and in post-status epilepsy model in which sustained electrical stimulus to hippocampus or amygdala leads to recurrent spontaneous seizures, are widely used to study temporal lobe epilepsy.<sup>[4-6]</sup> Chronic epilepsy could also be induced in animals by chemical convulsants like glutamate analogue kainate or muscarinic receptor agonist pilocarpine.<sup>[5,6]</sup> Genetic animal models with spontaneous mutations as well as induced mutations

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are also used to study molecular mechanisms of epilepsy.<sup>[7,8]</sup> Although all these animal models play an important role in epilepsy research, but unfortunately none of them replicate the human conditions. Thus, we need an epilepsy model which is helpful in understanding the processes underlying epileptogenesis to develop new therapies.

In cases where epileptic seizures cannot be controlled with pharmacological management, also referred as drug-resistant epilepsy (DRE), patients are recommended for epilepsy surgery.<sup>[8]</sup> The examination of resected brain specimen obtained from epilepsy surgery gives an opportunity to explain the abnormalities associated with DREs. Histopathological examination of the surgically resected specimen is helpful in understanding the phenotypic changes associated with epileptogenesis. Various neuropathological lesions have been demonstrated in chronic intractable epilepsy cases.<sup>[9]</sup> Magnetic resonance imaging (MRI), electroencephalography (EEG), video EEG, as well as functional imaging techniques like positron emission tomography (PET), and single photon emission tomography (SPECT) are utilized to locate the epileptogenic area. A non-invasive protocol like magnetoencephalography (MEG) has been very useful for the localization of epileptogenic focus. The well-established epileptogenic zones in the resected brain sample serves as an ideal model to study the mechanism of epileptogenesis. Quantification of abnormalities in these tissues based on various morphological, cellular/molecular, and electrical properties may define the extent of damage caused. These demonstrated properties may help resolve the issue of therapy resistance in intractable epilepsy cases. For control experiments normal brain samples are not available due to ethical reasons thus, non-epileptic tissues like that from tumour or trauma is used. Moreover, brain specimens resected during tumor surgery not presenting with epilepsy or seizures, but well within the abnormal perimeter of surgical resection also serves as control.

## ABNORMAL SYNAPTIC TRANSMISSION LEADS TO EPILEPTIFORM ACTIVITY

In resting condition there is a high concentration of potassium inside the neurons and a high sodium ion concentration outside the cell creating a transmembrane potential of -60 mV.<sup>[10]</sup> During seizure this system goes awry leading to depolarization of neurons and excessive discharge of action potentials. One of the reasons behind this uncontrolled neuronal firing is the imbalance between excitatory and inhibitory synaptic transmission, which is a hallmark of epileptic seizures.

Immunohistochemical analysis of brain samples using antibodies against markers that label glutamatergic and GABAergic synaptic terminals indicates modulation of synaptic transmission in epileptogenic zone.<sup>[11-13]</sup> Similarly, gene expression studies on resected tissue revealed changes in the mRNA levels of various glutamate and GABA-receptor subunits.<sup>[14]</sup> Modulation of glutamatergic and GABAergic synaptic transmission has been reported in resected surgery zone obtained from epilepsy cases.<sup>[15]</sup> Comparison of electrophysiological characteristics of neurons in maximally abnormal tissue with that in least abnormal tissue indicates significant alterations in synaptic current kinetics.<sup>[16,17]</sup> These changes in the cellular signaling properties may be responsible for generating epileptogenic focus. There are multiple mechanisms that cause disruption of processes that create a balance between glutamatergic and GABAergic transmission causing the neurons to discharge excessive action potential and uninhibited firing.<sup>[18]</sup> Examining the mechanisms that regulate the glutamatergic and GABAergic transmission at various levels is necessary to conceptualize epileptogenesis.

### DYSFUNCTIONAL GLUTAMATERGIC SYNAPTIC TRANSMISSION LEADS TO SEIZURE GENERATION

Excitatory synaptic transmission mediated by glutamate which is released from pyramidal neurons leads to depolarization and excitation of target neurons through ionotropic receptors N-methyl-D-aspartic acid (NMDA) receptor, α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) receptor, and kainic acid receptor. NMDA receptors, AMPA receptors, and kainic acid receptors have been localized in post-mortem human brains.<sup>[19-21]</sup> NMDA receptors which are tetramers composed of GluN1, GluN2A-CluN2D, and GluN3A-GluN3B<sup>[22]</sup> has been extensively studied for its role in epilepsy. Mutations in the gene encoding GluN2A have been identified in patients with idiopathic epilepsy<sup>[23]</sup> and haplotypes of gene encoding GluN1 have also been associated with epilepsy.<sup>[24]</sup> Decreased GluN2B expression in pyramidal neurons has been shown in TLE patients and upregulation of this receptor subunit was reported in the pyramidal neurons in hippocampal scelerosis.<sup>[12]</sup> NMDA receptor-mediated excitatory postsynaptic potentials recorded from dentate granule cells in brain specimens obtained from epileptic patients had increased duration and amplitude.<sup>[25,26]</sup> NMDA channel opening was enhanced even in the dissociated dentate granule cells from human epileptic hippocampus.<sup>[27]</sup> Moreover, NMDA-subtype glutamate receptor-mediated excitatory postsynaptic current (EPSC) response is prolonged in slice preparations of surgically resected tissues obtained from temporal lobe epilepsy patients.<sup>[28]</sup> Thus, abnormal regulation of NMDA receptor-mediated glutamate receptor activity could be a major contributor for epileptogenesis. Further evidences indicate that NMDA receptors are involved in epileptogenesis and in epileptic tissues upregulation of NMDA receptor subunits has been shown to contribute to hyperexcitability.<sup>[29]</sup> Even though the role of glutamate receptor in hyperexcitability has been reported in human brain tissue, its involvement in seizure generation is complicated. Glutamate neurons on one hand synapse onto other glutamate neurons and on the other side it also impinges onto GABAergic neurons. Thus, it is difficult to predict if glutamate-induced seizure generation is due to excessive glutamate receptor activity or it is because of the increased GABA release through depolarization of GABAergic neurons [Figure 1].



**Figure 1:** Abnormal synaptic transmission in epileptogenesis. This simplified scheme illustrates the changes in synaptic transmission associated with epileptogenesis. For ease of understanding only nicotinic receptors are shown to be present on the pyramidal neurons and interneurons. Two models have been proposed to explain regulation of synaptic transmission during epileptogenesis. In the first model it is hypothesised that decreased nicotinic receptor function leads to reduced inhibitory transmission. Reduction in the nicotinic receptor activity also causes inhibition of excitatory input to the GABAergic neuron which in turn impairs the inhibitory transmission impinging onto pyramidal neurons. The other model shows that increased cholinergic function causes entrainment of inhibitory transmission. Moreover, it is also plausible that upregulation of nicotinic receptor activity leads to increased excitatory input to the interneurons, thereby causing excessive GABA release. The contribution of enhanced cholinergic stimulation on glutamatergic transmission causing hyperexcitabilty should also be considered

# ROLE OF ALTERED INHIBITORY NEUROTRANSMISSION IN EPILEPTOGENESIS

There are considerable amount of evidences that suggest altered GABAergic signaling leads to seizure generation. Dysfunction in GABAergic input causing reduced inhibition might contribute to epileptogenesis. Impaired inhibitory synaptic transmission causes neuronal hyperexcitability [Figure 1]. GABAergic inhibition regulates the spread of epileptic discharges<sup>[30,31]</sup> and intrinsic burst-firing properties of neurons.<sup>[32]</sup> In tissues resected from TLE patients' loss of interneuron density has been shown to cause reduced GABAergic synaptic transmission.<sup>[33]</sup> There are also evidences suggesting reduction in paravalbumin-positive interneurons in tissues resected from TLE patients.<sup>[34]</sup> In samples received from focal cortical dysplasia (FCD) patients there was reduction in the inhibitory (IPSC) frequency due to changes in the distribution of interneurons.<sup>[35]</sup> It is also found that the duration of GABA-evoked IPSCs is increased in FCD brain specimen indicating decreased release of GABA from the GABAergic terminals.<sup>[35]</sup> Quantitative changes in the subunits of GABA receptor,<sup>[36]</sup> modulation of GABA by other neurotransmitters and second messengers,<sup>[37,38]</sup> and phenotypic changes in GABA receptor types that create depolarizing rather than hyperpolarizing reactions to GABA<sup>[39]</sup> are also associated with epileptic deregulation. Thus, decrease in the GABA signaling allowing uncontrolled glutamate signaling cannot be solely implicated for epileptogenesis [Figure 1].

An immature GABAergic inhibitory system has been linked to intractable epilepsy. A predominant GABAergic synaptic transmission in an immature neuronal network can cause depolarization leading to excessive cell firing, where GABA may be acting as an excitatory neurotransmitter<sup>[40,41]</sup> [Figure 1]. It is represented by higher frequency of spontaneous IPSCs and lower frequency of EPSCs as observed in dysmature cerebral development in severe cortical dysplasia.<sup>[42]</sup> Higher GABA inputs could also be contributed by cytomegalic interneurons<sup>[43]</sup> and by supernumerary cells in superficial layers and white matter observed in severe cortical dysplasia cases.<sup>[44]</sup> There is also possibility of increased GABA release and higher number of neurotransmitter release site in severe CD cases.<sup>[45]</sup> An increased GABA receptor activity relative glutamate receptor activity has been so far reported in severe CD cases and not in non-CD or mild-CD.<sup>[15,46]</sup> Histopathological features of tuberous scelerosis complex (TSC) cases are similar to severe CD cases, but the morphological and electrophysiological characteristics of neurons in resected brain samples from these two disorders vary significantly.<sup>[45]</sup> This indicates that molecular characteristics of TSC more closely resemble non-CD and mild-CD. These differences indicate that mechanism of epileptogenesis varies in patients with different epileptic syndromes. This necessitates that these facts should be taken into consideration while deciding therapies against different epileptic disorders.

#### ROLE OF NICOTINIC RECEPTOR-DEPENDENT SYNAPTIC TRANSMISSION IN EPILEPTOGENESIS

In human brain nicotinic acetylcholine receptors (nAChRs) are known to control excitatory and inhibitory synaptic transmission mediated by glutamate and GABA, respectively. It has been shown that interneurons present in human cerebral cortex express  $\alpha$ 7 and  $\alpha$ 4 $\beta$ 2 subtypes of nAChRs and that  $\alpha 4\beta 2$  nAChRs present on the preterminal regions of the interneurons contributes to GABA-release process.<sup>[47]</sup> Evidence exists that suggest the role of  $\alpha$ 7 and  $\alpha$ 4 $\beta$ 2nAChRs in nicotine-induced seizures.<sup>[48]</sup> Reduction in the nAChR function in the interneurons that synapse onto pyramidal neurons could contribute to the process of epileptogenesis. Nicotinic receptors enhance the release of glutamate in case of nicotine-induced seizures through activation of NMDA receptors.<sup>[49]</sup> Mutations in the genes encoding for  $\alpha$ 7 and  $\alpha 4\beta 2nAChR$  subtypes are known to be related to various forms of epilepsy.<sup>[50-52]</sup> An understanding of the mechanisms by which nAChRs regulate the inhibitory tonus in the resected brain specimens is likely to provide new insights into the involvement of these receptors in epileptogenesis. Nicotinic receptors are known to provide excitatory input to the interneurons which in turn inhibit excitatory pyramidal neurons. Inhibition of nicotinic cholinergic input to interneurons reduces GABAergic transmission to pyramidal neurons leading to increased excitability and seizures.<sup>[47]</sup> In mice nicotinic receptor desensitization inhibited nicotine-induced GABA release and seizures.<sup>[48]</sup> This suggests epileptic activity could be result of disinhibition of pyramidal neurons<sup>[47,48]</sup> [Figure 1]. Another model describing the role of nicotinic receptor-mediated GABAergic inhibition is based on the fact that high doses of nicotine causes synchronous activation of interneurons.<sup>[48]</sup> Under physiological conditions interneurons generate synchronous oscillations, but during seizure there is entrainment of synchronous activity leading to activation of large populations of pyramidal neurons. It has been shown that  $\gamma$ -oscillations during ictal events caused by widespread synchronous activity were blocked by GABA, receptor antagonist bicuculline,<sup>[53,54]</sup> suggesting that epileptiform activity was induced by increased GABAergic transmission [Figure 1]. In animal models it has been reported that  $\alpha$ 7 antagonist methyl lycaconitine (MLA) inhibited nicotine-induced seizures.<sup>[48,49]</sup> Moreover, a7 nAChR antagonists are known to block electroshock-induced seizures in mice and kindling-induce seizures in rats<sup>[55]</sup> further indicating that upregulation of  $\alpha$ 7 nAChR activity is involved in epileptogenesis. Under resting conditions in rat hippocampal slice preparations  $\alpha$ 7 nAChR function contributes to inhibitory<sup>[56]</sup> and excitatory<sup>[57]</sup> synaptic transmission. This indicates that basal levels of choline or ACh activate  $\alpha$ 7nAChRs, which in turn regulates GABAergic and glutamatergic synaptic transmission. Another relevant finding suggests that kynurenic acid, a tryptophan metabolite, inhibits α7 nAChR-mediated spontaneous glutamatergic currents<sup>[57,58]</sup> as well as α7 nAChR-mediated spontaneous GABAergic currents.<sup>[56,58]</sup> Endogenously synthesised kynurenic acid is known to suppress epileptiform activity in *in vitro* slice preparations<sup>[59]</sup> and *in vivo* microdialysis<sup>[60,61]</sup> in rat models of epilepsy. It is possible that the anticonvulsant effects of kynurenic acid are mediated by its action on  $\alpha$ 7 nAChR-dependent GABAergic and glutamatergic synaptic transmission. Altogether these evidences implicate the role of nicotinic receptor-mediated synchronous GABAergic transmission and nicotinic receptor mediated-excitatory activity in epileptogenesis [Figure 1]. Most of these evidences are based on experiments performed on animal models, so it is of utmost importance to perform similar investigations on resected brain samples from epilepsy patients. The possible involvement of nicotinic receptors in seizure activity might constitute a useful new direction for the treatment of intractable epilepsy.

#### **SUMMARY**

It is noteworthy that abnormal GABAergic and glutamatergic synaptic transmission significantly contributes to epileptogenesis. Recording of synaptic currents in slices obtained from diseased surgical specimen serves as model to investigate mechanisms of seizure generation. Impairment in regulation of excitatory and inhibitory synaptic transmission could be a cause of epileptiform activity in various forms of epilepsy. Evidences suggest involvement of nicotinic receptors in epileptogenesis through regulation of inhibitory and excitatory synaptic transmission. Although resected brain samples serves as an ideal model system to study epileptogenesis, we would like to emphasize that as epilepsy patients are on anticonvulsant medication, the possible effects of these drugs on synaptic transmission cannot be ruled out. Thus parallel investigations on animal models will help interpret the human data to advance our understanding of epileptogenesis.

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