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 surgery zone is of immense importance. Here we summarize various modalities of *in vitro* slice analysis from 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 epileptiform activity. Elucidation of current concepts in regulation of synaptic transmission will help develop therapies for 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.[1] 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.[2] But there is significant number of epilepsy cases where treatment with antiepileptic drugs is not effective. In 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.[3] To investigate this therapy resistance we need to understand the process of epileptogenesis that leads to generation of hyperexcitable neuronal network.

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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.[4-6] Chronic epilepsy could also be induced in animals by chemical convulsants like glutamate analogue kainate or muscarinic receptor agonist pilocarpine.[5,6] Genetic animal models with spontaneous mutations as well as induced mutations

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are also used to study molecular mechanisms of epilepsy.[7,8] 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.[8] 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.[9] 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.[10] 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.[11-13] Similarly, gene expression studies on resected tissue revealed changes in the mRNA levels of various glutamate and GABA-receptor subunits.[14] Modulation of glutamatergic and GABAergic synaptic transmission has been reported in resected surgery zone obtained from epilepsy cases.[15] Comparison of electrophysiological characteristics of neurons in maximally abnormal tissue with that in least abnormal tissue indicates significant alterations in synaptic current kinetics.[16,17] 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.[18] 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.[19-21] NMDA receptors which are tetramers composed of GluN1, GluN2A-CluN2D, and GluN3A-GluN3B[22] has been extensively studied for its role in epilepsy. Mutations in the gene encoding GluN2A have been identified in patients with idiopathic epilepsy[23] and haplotypes of gene encoding GluN1 have also been associated with epilepsy.[24] 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.[12] NMDA receptor-mediated excitatory postsynaptic potentials recorded from dentate granule cells in brain specimens obtained from epileptic patients had increased duration and amplitude.[25,26] NMDA channel opening was enhanced even in the dissociated dentate granule cells from human epileptic hippocampus.[27] Moreover, NMDA-subtype glutamate receptor-mediated excitatory postsynaptic current (EPSC) response is prolonged in

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slice preparations of surgically resected tissues obtained from temporal lobe epilepsy patients.[28] 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.[29] Even though the role of glutamate receptor in hyeprexcitability 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].

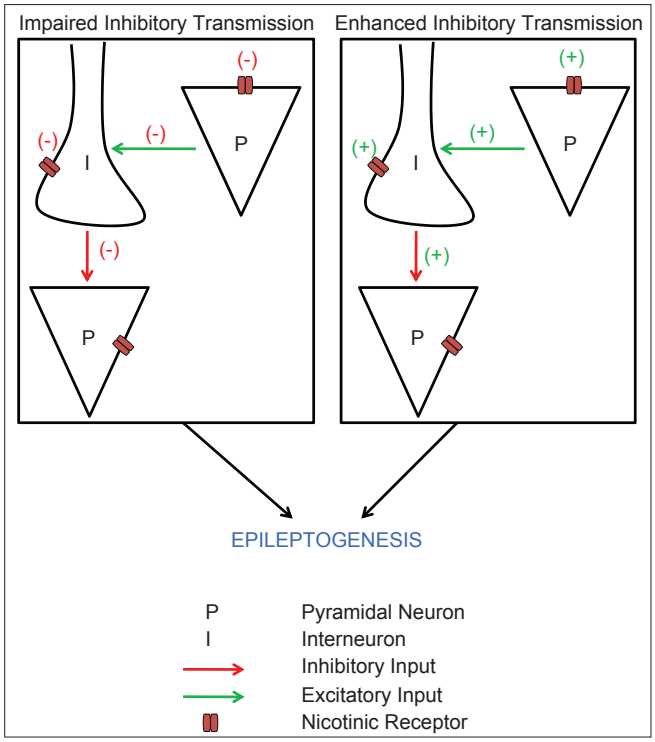

Figure 1: Abnormal synaptic transmission in epileptogenesis. This simplified scheme illustrates the changes in synaptic transmission associated with epileptogenesis. For ease of understanding only nicotinic receptors are shown to be present on the pyramidal neurons and interneurons. Two models have been 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[30,31] and intrinsic burst-firing properties of neurons.[32] In tissues resected from TLE patients' loss of interneuron density has been shown to cause reduced GABAergic synaptic transmission.[33] There are also evidences suggesting reduction in paravalbumin-positive interneurons in tissues resected from TLE patients.[34] 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.[35] 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.[35] Quantitative changes in the subunits of GABA receptor,[36] modulation of GABA by other neurotransmitters and second messengers,[37,38] and phenotypic changes in GABA receptor types that create depolarizing rather than hyperpolarizing reactions to GABA[39] 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[40,41] [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.[42] Higher GABA inputs could also be contributed by cytomegalic interneurons[43] and by supernumerary cells in superficial layers and white matter observed in severe cortical dysplasia cases.[44] There is also possibility of increased GABA release and higher number of neurotransmitter release site in severe CD cases.[45] 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.[15,46] 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.[45] This indicates that

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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 α7 and α4β2 subtypes of nAChRs and that α4β2 nAChRs present on the preterminal regions of the interneurons contributes to GABA-release process.[47] Evidence exists that suggest the role of α7 and α4β2nAChRs in nicotine-induced seizures.[48] 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.[49] Mutations in the genes encoding for α7 and α4β2nAChR subtypes are known to be related to various forms of epilepsy.[50-52] 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.[47] In mice nicotinic receptor desensitization inhibited nicotine-induced GABA release and seizures.[48] This suggests epileptic activity could be result of disinhibition of pyramidal neurons[47,48] [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.[48] 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 γ-oscillations during ictal events caused by widespread synchronous activity were blocked by $GABA_A$ receptor antagonist bicuculline,[53,54] suggesting that epileptiform activity was induced by increased GABAergic transmission [Figure 1]. In animal models it has been reported that α7 antagonist methyl lycaconitine (MLA) inhibited nicotine-induced seizures.[48,49] Moreover, α7 nAChR antagonists are known to block electroshock-induced seizures in mice and kindling-induce seizures in rats[55] further indicating that upregulation of α7 nAChR activity is involved in epileptogenesis. Under resting conditions in rat hippocampal slice preparations α7 nAChR function contributes to inhibitory[56] and excitatory[57] synaptic transmission. This indicates that basal levels of choline or ACh activate α7nAChRs, 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[57,58] as well as α7 nAChR-mediated spontaneous GABAergic currents.[56,58] Endogenously synthesised kynurenic acid is known to suppress epileptiform activity in *in vitro* slice preparations[59] and *in vivo* microdialysis[60,61] in rat models of epilepsy. It is possible that the anticonvulsant effects of kynurenic acid are mediated by its action on α7 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.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

REFERENCES

1. Scharfman HE. Pedley TA. Temporal lobe epilepsy. In: Gilman A, editor. The neurobiology of disease. New York: Academic Press; 2006.
2. Penfield W, Jasper H. In: Penfield W, Jasper H, editors. Epilepsy and the functional anatomy of the human brain. Boston: Little, Brown and Co; 1954.
3. Scott RA, Lhatoo SD, Sander JW. The treatment of epilepsy in developing countries: Where do we go from here? Bull World Health Organ 2001;79:344-51.
4. Sato M, Racine RJ, McIntyre DC. Kindling: Basic mechanisms and clinical validity. Electroencephalogr Clin Neurophysiol 1990;76:459-72.
5. Löscher W. Animal models of epilepsy and epileptic seizures. In: Eadie MJ, Vajda F, editors. Antiepileptic drugs, Handbook of experimental pharmacology. Berlin: Springer; 1999. p. 19-62.
6. Goodman JH. Experimental models of status epilepticus. In: Peterson SL, Albertson TE, editors. Neuropharmacology methods in epilepsy researchb Boca raton: CRC Press; 1998. p. 95-125.
7. Prasad AN, Prasad C, Stafstrom CE. Recent advances in the genetics of epilepsy: Insights from human and animal studies. Epilepsia 1999;40:1329-52.
8. Chandra PS, Trpathi M. Epilepsy surgery: Recommendations for India. Ann Indian Acad Neurol 2010;13:87-93.
9. Sarkar C, Sharma MC, Deb P, Singh VP, Chandra PS, Gupta A, *et al*. Neuropathological spectrum of lesions associated with intractable epilepsies: A 10-year experience with a series of 153 resections. Neurol India 2006;54:144-50.
10. McCormick DA, Huguenard, JR. In: McCormick DA, Huguenard, JR, editors. Electrophysiology of the neuron: An interactive tutorial. Oxford: Oxford University Press; 1994.
11. Mathern GW, Babb TL, Pretorius JK, Leite JP. Reactive synaptogenesis and neuron densities for neuropeptide Y, somatostatin, and glutamate decarboxylase immunoreactivity in the epileptogenic human fascia dentata. J Neurosci 1995;15:3990-4004.
12. Mathern GW, Pretorius JK, Leite JP, Kornblum HI, Mendoza D, Lozada A, *et al*. Hippocampal AMPA and NMDA mRNA levels and subunit immunoreactivity in human temporal lobe epilepsy patients and a rodent model of chronic mesial limbic epilepsy. Epilepsy Res 1998;32:154-71.
13. Mathern GW, Mendoza D, Lozada A, Pretorius JK, Dehnes Y, Danbolt NC, *et al*. Hippocampal GABA and glutamate transporter immunoreactivity in patients with temporal lobe epilepsy. Neurology 1999;52:453-72.
14. Crino PB, Duhaime AC, Baltuch G, White R. Differential expression of glutamate and GABA-A receptor subunit mRNA in cortical dysplasia. Neurology 2001;56:906-13.
15. Cepeda C, André VM, Flores-Hernández J, Nguyen OK, Wu N, Klapstein GJ, *et al*. Pediatric cortical dysplasia: Correlations between neuroimaging, electrophysiology and location of cytomegalic neurons and balloon cells and glutamate/GABA synaptic circuits. Dev Neurosci 2005;27:59-76.
16. Cepeda C, Hurst RS, Flores-Hernández J, Hernández-Echeagaray E, Klapstein GJ, Boylan MK, *et al*. Orphological and electrophysiological characterization of abnormal cell types in pediatric cortical dysplasia. J Neurosci Res 2003;72:472-86.
17. Cepeda C, André VM, Yamazaki I, Hauptman JS, Chen JY, Vinters HV, *et al*. Comparative study of cellular and synaptic abnormalities in brain tissue samples from pediatric tuberous sclerosis complex and cortical dysplasia type II. Epilepsia 2010;51:160-5.
18. Scharfman HE. The neurobiology of epilepsy. Curr Neurol Neurosci Rep 2007;7:348-54.
19. Hosford DA, Crain BJ, Cao Z, Bonhaus DW, Friedman AH, Okazaki MM, *et al*. Increased AMPA-sensitive quisqualate receptor binding and reduced NMDA receptor binding in epileptic human hippocampus. J Neurosci 1991;11:428-34.
20. Breese CR, Leonard SS. Glutamate receptor subtype expression in human postmortem brain. J Mol Neurosci 1993;4:263-75.
21. Bockers TM, Zimmer M, Muller A, Bergmann M, Brose N, Kreutz MR. Expression of the NMDA R1 receptor in selected human brain regions. Neuroreport 1994;5:965-9.
22. Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, *et al*. Glutamate receptor ion channels: Structure, regulation, and function. Pharmacol Rev 2010;62:405-96.
23. Endele S, Rosenberger G, Geider K, Popp B, Tamer C, Stefanova I, *et al*. Mutations in GRIN2A and GRIN2B encoding regulatory subunits of NMDA receptors cause variable neurodevelopmental phenotypes. Nat Genet 2010;42:1021-6.
24. Ding YX, Zhang Y, He B, Yue WH, Zhang D, Zou LP. A possible association of responsiveness to adrenocorticotropic hormone with specific GRIN1 haplotypes in infantile spasms. Dev Med Child Neurol 2010;52:1028-32.
25. Urban L, Aitken PG, Friedman A, Somjen GG. An NMDA-mediated component of excitatory synaptic input to dentate granule cells in 'epileptic' human hippocampus studied *in vitro*. Brain Res 1990;515: 319-22.
26. Isokawa M, Avanzini G, Finch DM, Babb TL, Levesque MF. Physiologic properties of human dentate granule cells in slices prepared from epileptic patients. Epilepsy Res 1991;9:242-50.
27. Lieberman DN, Isokawa M, Fried I, Mody I. Properties of single NMDA channels in dentate granule cells of temporal lobe epilepsy patients. Epilepsia 1996;37:79.
28. Isokawa M, Levesque M, Fried I, Engel J Jr. Glutamate currents in morphologically identified human dentate granule cells in temporal lobe epilepsy. J Neurophysiol 1997;77:3355-69.
29. de Moura JC, Tirapelli DP, Neder L, Saggioro FP, Sakamoto AC, Velasco TR, *et al*. Amygdala gene expression of NMDA and GABA (A) receptors in patients with mesial temporal lobe epilepsy. Hippocampus 2012;22:92-7.
30. Miller JW, Ferrendelli JA. Characterization of GABAergic seizure regulation in the midline thalamus. Neuropharmacology 1990;29:649-55.
31. Telfeian AE, ConnorsBW. Layer-specific pathways for the horizontal propagation of epileptiform discharges in neocortex. Epilepsia 1998; 39:700-8.
32. Isokawa-Akesson M, Wilson CL, Babb TL. Inhibition in synchronously firing human hippocampal neurons. Epilepsy Res 1989;3:236-47.
33. de Lanerolle NC, Kim JH, Robbins RJ, Spencer DD. Hippocampal interneuron loss and plasticity in human temporal lobe epilepsy. Brain Res 1989;495:387-95.
34. Marco P, Sola RG, Pulido P, Alijarde MT, Sanchez A, Ramon y Cajal S, *et al*. Inhibitory neurons in the human epileptogenic temporal neocortex. An immunocytochemical study. Brain 1996;119:1327-47.
35. Calcagnotto ME, Paredes MF, Tihan T, Barbaro NM, Baraban SC. Dysfunction of synaptic inhibition in epilepsy associated with focal cortical dysplasia. J Neurosci 2005;25:9649-57.
36. Fritschy JM, Kiener T, Bouilleret V, Loup F. GABAergic neurons and $GABA_A$-receptors in temporal lobe epilepsy. Neurochem Int 1999;34:435-45.
37. Chamberlain SE, Jane DE, Jones RS. Pre-and post-synaptic functions of kainate receptors at glutamate and GABA synapses in the rat entorhinal cortex. Hippocampus 2012;22:555-76.
38. Oliveira MS, Skinner F, Arshadmansab MF, Garcia I, Mello CF, Knaus HG, *et al*. Altered expression and function of small-conductance (SK) Ca21-activated K1 channels in pilocarpine-treated epileptic rats. Brain Res 2010;1348:187-99.
39. Galanopoulou AS. Developmental patterns in the regulation of chloride homeostasis and GABAA receptor signaling by seizures. Epilepsia 2007; 48:14-8.
40. Cherubini E, Gaiarsa JL, Ben-Ari Y. GABA: An excitatory transmitter in early postnatal life. Trends Neurosci 1991;14:515-9.
41. Cepeda C, André VM, Wu N, Yamazaki I, Uzgil B, Vinters HV, *et al*. Immature neurons and GABA networks may contribute to epileptogenesis in pediatric cortical dysplasia. Epilepsia 2007;48:79-85.
42. Cepeda C, André VM, Levine MS, Salamon N, Miyata H, Vinters HV, *et al*. Epileptogenesis in pediatric cortical dysplasia: The dysmature cerebral developmental hypothesis. Epilepsy Behav 2006;9:219-35.
43. André VM, Wu N, Yamazaki I, Nguyen ST, Fisher RS, Vinters HV, *et al*. Cytomegalic interneurons: A new abnormal cell type in severe pediatric cortical dysplasia. J Neuropathol Exp Neurol 2007;66:491-504.
44. Chandra PS, Salamon N, Nguyen ST, Chang JW, Huynh MN, Cepeda C, *et al*. Infantile spasm-associated microencephaly in tuberous sclerosis complex and cortical dysplasia. Neurology 2007;68:438-45.
45. Cepeda C, André VM, Hauptman JS, Yamazaki I, Huynh MN, Chang JW,

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et al. Enhanced GABAergic network and receptor function in pediatric cortical dysplasia type IIB compared with tuberous sclerosis complex. Neurobiol Dis 2012;45:310-21.
46. André VM, Cepeda C, Vinters HV, Huynh M, Mathern GW, Levine MS. Pyramidal cell responses to gamma-aminobutyric acid differ in type I and type II cortical dysplasia. J Neurosci Res 2008;86:3151-62.
47. Alkondon M, Pereira EF, Eisenberg HM, Albuquerque Ex. Nicotinic receptor activation in human cerebral cortical interneurons: A mechanism for inhibition and disinhibition of neuronal networks. J Neurosci 2000;20: 66-75.
48. Dobelis P, Hutton S, Lu Y, Collins AC. GABAergic systems modulate nicotinic receptor-mediated seizures in mice. J Pharmacol Exp Ther 2003;306:1159-66.
49. Damaj MI, Glassco W, Dukat M, Martin BR. Pharmacological characterization of nicotine-induced seizures in mice. J Pharmacol Exp Ther 1999;291:1284-91.
50. Elmslie FV, Rees M, Williamson MP, Kerr M, Kjeldsen MJ, Pang KA, *et al*. Genetic mapping of a major susceptibility locus for juvenile myoclonic epilepsy on chromosome 15q. Hum Mol Genet 1997;6:1329-34.
51. Kuryatov A, Gerzanich V, Nelson M, Olale F, Lindstrom J. Mutation causing autosomal dominant nocturnal frontal lobe epilepsy alters Ca^{2+}permeability, conductance, and gating of human $\alpha4\beta2$ nicotinic acetylcholine receptors. J Neurosci 1997;17:9035-47.
52. Adams CE, Yonchek JC, Schulz KM, Graw SL, Stitzel J, Teschke PU, *et al*. Reduced Chrna7 expression in mice is associated with decreases in hippocampal markers of inhibitory function: Implications for neuropsychiatric diseases. Neuroscience 2012;207:274-82.
53. Avoli M, Barbarosie M, Lucke A, Nagao T, Lopantsev V, Köhling R. Synchronous GABA-mediated potentials and epileptiform discharges in the rat limbic system *in vitro*. J Neurosci 1996;16:3912-24.
54. Köhling R, Vreugdenhil M, Bracci E, Jefferys JG. Ictal epileptiform activity is facilitated by hippocampal GABAA receptor-mediated oscillations. J Neurosci 2000;20:6820-9.
55. Löscher W, Potschka H, Wlaz P, Danyz W, Parsons CG. Are neuronal nicotinic receptors a target for antiepileptic drug development? Studies in different seizure models in mice and rats. Eur J Pharmacol 2003;466:99-111.
56. Banerjee J, Alkondon M, Pereira EF, Albuquerque Ex. Regulation of GABAergic inputs to CA1 pyramidal neurons by nicotinic receptors and kynurenic acid. J Pharmacol Exp Ther 2012;341:500-9.
57. Banerjee J, Alkondon M, Albuquerque Ex. Kynurenic acid inhibits glutamatergic transmission to CA1 pyramidalneuronsviaα7 nAChR-dependent and-independent mechanisms. Biochem Pharmacol 2012; 15;84:1078-87.
58. Albuquerque EX, Schwarcz R. Kynurenic acid as an Antagonist of α7 nicotinic acetylcholine receptors in the brain: Facts and challenges. Biochem Pharmacol 2013;85:1027-32.
59. Scharfman HE, Ofer A. Pretreatment with L-kynurenine, the precursor to the excitatory amino acid antagonist kynurenic acid, suppresses epileptiform activity in combined entorhinal/hippocampal slices. Neurosci Lett 1997;224:115-8.
60. Wu HQ, Rassoulpour A, Goodman JH, Scharfman HE, Bertram EH, Schwarcz R. Kynurenate and 7-chlorokynurenate formation in chronically epileptic rats. Epilepsia 2005;46:1010-6.
61. Scharfman HE, Hodgkins PS, Lee SC, Schwarcz R. Quantitative differences in the effects of de novo produced and exogenous kynurenic acid in rat brain slices. Neurosci Lett 1999;274:111-4.

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