Annals of Epilepsy and Seizures

Editorial
Published: 22 Jan, 2018

From Single Acute Seizure to Chronic Epilepsy in Experimental Animals: The Role of Glutamate Receptors and Brain Damage

*András Imre Mihály**

Department of Anatomy, University of Szeged, Hungary

Editorial

The pathogenesis of epilepsy is poorly understood; therefore it is necessary to identify the critical processes that link an initial brain defect or an early convulsive insult to the subsequently manifesting spontaneous seizures. These critical processes need 1 year to 20 years in man, or 2 weeks to 5 weeks in rodents [1]. Clinical observations prove that repeated, unprecedented convulsions increase the risk of the development of epilepsy [2]. Some forms of epilepsy arise as an imbalance between excitatory and inhibitory neurotransmission in different regions of the CNS, where local neuroplasticity changes are induced by the seizures [3]. Therefore, it is fundamentally important to understand the molecular and cellular processes underlying local neuronal plasticity, which push the accidental seizures to a chronic, recurrent disease [1-3]. Apart from local neuroplasticity from repeated excitatory episodes, repeated brain swelling [4] and brain vascular damage [5,6] could also contribute to chronic, degenerative epilepsies. Glutamate Receptors (GluRs) mediate the majority of excitatory responses in the central nervous system and they are involved in the induction and maintenance of epileptic states [7]. The establishment and activity induced refinement of glutamatergic synaptic connections depend on the concerted actions of the ionotropic α-Amino-3-Hydroxy-5-Methylisoxazole-4-Propionate (AMPA), N-Methyl-D-Aspartate (NMDA) and Kainate Acid (KA) type Glutamate Receptors (iGluRs). The most is known about the mechanisms by which the iGluR subtypes are expressed, targeted and the way this is influenced by synaptic activity on both short and long time scales [8]. Changes in iGluR subunit compositions are input specific and regulated by the neuronal activity [8,9]. Several studies reported changes in NMDA and AMPA receptor subunit expression following deafferentation [9] and following repeated seizures [10] (Table 1). The aim of the present editorial is to point out to the possible pathogenic importance of the changes in the expression and molecular organization of iGluRs in acute and chronic models of epileptogenesis. The reference experiments with combinations of biochemical, electrophysiological and immunocytochemical methods were performed in our laboratories [9-19]. We tested the hypothesis that repeated, acute seizures lead to the redistribution of iGluR subunits in cerebrocortical tissues. The alterations of the subunit composition of the iGluRs served the adapting of the neuronal circuits to the increase of the excitatory inputs – but the alterations may also cause the permanent increase in the vulnerability of the neurons. Some changes of the iGluRs could have been contributed to the recurrence of the increased excitation seizures. Using the pilocarpine epilepsy model in mice, we investigated whether a similar rearrangement in iGluR subunit composition could have been caused by the chronic, recurrent epileptic fits [11,20]. The potassium channel blocker 4-Aminopyridine (4-AP) was used to induce acute Generalized Tonic Clonic Seizures (GTCS) in rats and mice [12]. Our research group contributed to the characterization of the acute 4-AP epilepsy with the autoradiography densitometry and magnetic resonance analysis of the strong increase of regional cerebral blood flow [13,15]. We also detected the seizure-concomitant increase of glutamate release in the striatum with in vivo micro dialysis [14]. The GTCS precipitated by 4-AP resulted in widespread nuclear c-Fos expression in principal neurons and parvalbumin-positive interneurons of the cerebral neocortex and hippocampus [15,16], indicating the involvement of NMDA receptors in the gene expression regulation [21]. Furthermore, the pharmacological analysis of the GTCS, using NMDA- and AMPA receptor antagonists proved, that the pharmacological antagonism of the NMDA- and AMPA receptors decreased the neuronal expression of c-Fos significantly [17,18]. Daily administration of 4-AP to Wistar rats caused repeated GTCS events for 12 days: the repeated GTCS events changed the hippocampal iGluR subunit composition permanently [10]. Most prominently, we observed the down regulation of the AMPA receptor subunit GluR2,

OPEN ACCESS

Correspondence:
András Imre Mihály, Department of Anatomy, Histology and Embryology, Faculty of Medicine, University of Szeged, H-6724 Szeged, Kossuth Lajos sgt. 44, Hungary, E-mail: mihaly.andras@med.u-szeged.hu

Received Date: *03 Jan 2018*
Accepted Date: *17 Jan 2018*
Published Date: *22 Jan 2018*

Citation:
Mihály AI. From Single Acute Seizure to Chronic Epilepsy in Experimental Animals: The Role of Glutamate Receptors and Brain Damage. Ann Epilepsy Seizure. 2018; 1(1): 1001.

Table 1: Comparison of the receptor subunit alterations of iGluR's in the dentate gyrus in chronic deafferentation.

Receptor density alterations in the molecular layer of the dentate gyrus of rats and mice	Chronic deafferentation [9]	Daily generalized 4-AP convulsions for 12 days [10]	Chronic pilocarpine seizures (2 months after pilocarpine treatment [11])
NMDA receptors (GluN1 subunit)	significant increase	no alteration	significant decrease
AMPA receptors (GluA2 subunits)	no alteration	significant decrease	significant decrease
Kainate receptors (GluK2 subunit)	no alteration	no alteration	significant increase

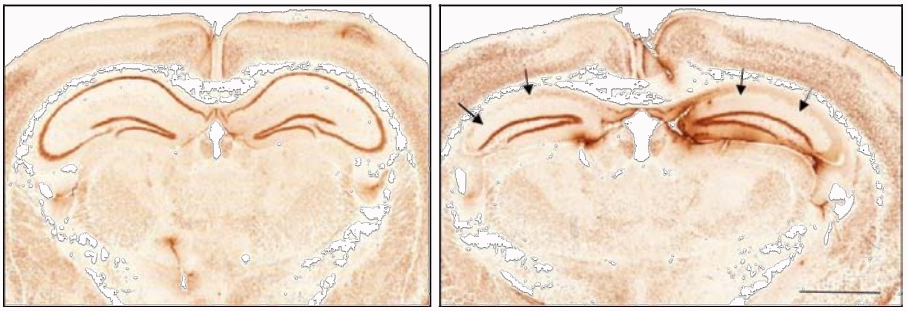

Figure 1: Polyclonal Neu-N antibody immunostaining of the coronal brain sections of the control NMRI mouse (A) and the pilocarpine-treated animal (B). The animals were sacrificed three months following the pilocarpine treatment. Note that the hippocampus of the pilocarpine treated mouse displays widespread neurodegeneration (arrows) in the Ammon's horn (CA 1, CA 2, CA 3, CA 4). This is hippocampal sclerosis [23]. Bar: 500 µm.

and a concomitant increase of the kainic acid stimulated in vitro Co^{2+} uptake in the CA1 region of the Ammon's horn and in the dentate gyrus [10]. The down regulation of the GluR2 subunit indicated that following the repeated seizures neuronal AMPA receptors became permeable to cations, because the GluR2 subunit was responsible for the control of Ca^{2+} influx [10]. In pilocarpine epilepsy, neuronal degeneration and synaptic rearrangement take place in the Ammon's horn and in the dentate gyrus [21,22]. The rodent pilocarpine epilepsy model was used to induce chronic, recurrent motor convulsions [11,17]. Several (3-7) months after the pilocarpine treatment, the reacting mice were characterized by the degeneration of the neurons of the Ammon's horn (Figure 1), proliferation of astrocytes and microglia [23]. Immunohistochemistry of the iGluR subunits proved the significant down regulation of the AMPA subunits GluA1 and GluA2 in the dentate gyrus and in the synaptic layers of the Ammon's horn [11]. The question arose whether the repeated convulsions in these pilocarpine-treated animals have been specifically targeting the

1. Rearrangement of the iGluR's.

2. The synthesis of new subunit proteins.

3. The synthesis of regulatory postsynaptic proteins, which finally change the arrangement and insertion of the different subunits in the postsynaptic membrane [8]. Apart from these molecular plasticity events, repeated convulsions caused damage to the Blood-Brain Barrier (BBB) [5,6,24] allowing some T-lymphocytes to enter into the brain [25]. This may trigger a slowly developing chronic inflammatory process, which can maintain the neurodegeneration, and finally result in hippocampal sclerosis [11,19,22]. We think that the repeated GTCS events increased the vulnerability of the neurons in many ways – the vulnerability could have been increased through the down regulation of the GluA2 subunit which normally inhibits the Ca^{2+} influx following synaptic excitation [10]. The increase of the calcium permeability of the iGluRs can lead to slowly developing neuronal death (neurodegeneration) in case of the repeated seizures. The end-result of neurodegeneration will be the hippocampal sclerosis, what we see in some rodents following 3 months to 7 months of recurrent pilocarpine convulsions [11,23] (Figure 1). The BBB damage and T-cell entry [6,24,25] may trigger an ongoing chronic inflammation, which together with the iGluR alterations will result in neuronal damage and severe glial proliferation, gradually decreasing the number of the functioning neurons in some of the CNS regions [11,22]. Comparison of the receptor subunit alterations of iGluR's in the dentate gyrus in chronic deafferentation (ablation of the lateral entorhinal cortex in rats), in repeated 4-AP convulsions in rats and in pilocarpine epilepsy in mice. The subunits were analyzed through densitometry of immunohistochemical tissue sections [11] and histoblot preparations [9,10].

References

1. Pitkänen A, Lukasiuk K, Dudek E, Staley KJ. Epileptogenesis. Cold Spring Harb Perspect Med. 2015;5(10):a022822.
2. Shinnar S, Hauser, WA. Do occasional brief seizures cause detectable clinical consequences? Prog Brain Res. 2002;135:221-35.
3. Scharfman HE. Epilepsy as an example of neuronal plasticity. Neuroscientist. 2002;8(2):155-73.
4. Honavar M, Meldrum, BS. Epilepsy. In: Graham, DJ, Lantos, PL, editors. Greenfield's Neuropathology. London: Arnold. 2002;899-931.
5. Ndode-Ekane XE, Hayward N, Gröhn O, Pitkänen A. Vascular changes in epilepsy: functional consequences and association with network plasticity in pilocarpine-induced experimental epilepsy. Neuroscience. 2010;166(1):312-32.
6. Mihály A, Bozóky B. Immunohistochemical localization of extravasated serum albumin in the hippocampus of human subjects with partial and generalized epilepsies and epileptiform convulsions. Acta Neuropathol. 1984;65(1):25-34.
7. Meldrum BS, Akbar MT, Chapman AG. Glutamate receptors and transporters in genetic and acquired models of epilepsy. Epilepsy Res. 1999;36(2-3):189-204.
8. Collingridge GL, Isaac JTR, Wang YT. Receptor trafficking and synaptic plasticity. Nat Rev Neurosci. 2004;5(12):952-62.
9. Kopniczky Z, Dobo E, Borbely S, Vilagi I, Detari L, Krisztin-Péva B, et al. Lateral entorhinal cortex lesions rearrange afferents, glutamate receptors, increase seizure latency and suppress seizure-induced c-fos expression in the hippocampus of adult rat. J Neurochem. 2005;95(1):111-24.
10. Borbély S, Dobó E, Czégé D, Molnár E, Bakos M, Szűcs B, et al.

Modification of ionotropic glutamate receptor mediated processes in the rat hippocampus following repeated, brief seizures. Neuroscience. 2009;159(1):358-68.

11. Dobó E, Török I, Mihály A, Károly N, Krisztin-Péva B. Interstrain differences of ionotropic glutamate receptor subunits in the hippocampus and induction of hippocampal sclerosis with pilocarpine in mice. J Chem Neuroanat. 2015;64-65:1-11.
12. Mihály A, Bencsik K, Solymosi T. Naltrexone potentiates 4-aminopyridine seizures in the rat. J Neural Transmiss. 1990;79(1-2):59-67.
13. Mihály A, Shihab-Eldeen A, Owunwanne A, Ayesha A, Mathew M, Gopinath S. Acute 4-aminopyridine seizures increase regional cerebral blood flow in the thalamus and neocortex, but not in the allocortex of the mouse brain. Acta Physiol Hung. 2000;87(1):43-52.
14. Kovács A, Mihály A, Komáromi A, Gyengési E, Szente M, Weiczner R, et al. Seizure, neurotransmitter release and gene expression are closely related in the striatum of 4-aminopyridine-treated rats. Epilepsy Res. 2003;55(1-2):117-29.
15. Mihaly A, Szakacs R, Bohata C, Dobo E, Krisztin-Peva B. Time-dependent distribution and neuronal localization of c-fos protein in the rat hippocampus following 4-aminopyridine seizures. Epilepsy Res. 2001;44(2-3):97-108.
16. Mihaly A, Borbely S, Vilagi I, Detari L, Weiczner R, Zador Z, et al. Neocortical c-fos mRNA transcription in repeated, brief, acute seizures: is c-fos a coincidence detector? Internat J Mol Med. 2005;15(3):481-6.
17. Szakács R, Weiczner R, Mihály A, Krisztin-Péva B, Zádor Z, Zádor E. Non-competitive NMDA receptor antagonist drugs moderate seizure-induced c-fos expression in the rat cerebral cortex. Brain Res Bull. 2003;59(6):485-93.
18. Weiczner R, Krisztin-Péva B, Mihály A. Blockade of AMPA-receptors attenuates 4-aminopyridine seizures, decreases the activation of inhibitory neurons but is ineffective against seizure-related astrocytic swelling. Epilepsy Res. 2008;78(1):22-32.
19. Károly N, Mihály A, Dobó E. Comparative immunohistochemistry of synaptic markers in the rodent hippocampus in pilocarpine epilepsy. Acta Histochem. 2011;113(6):656-62.
20. Leite JP, Garcia-Cairasco N, Cavalheiro EA. New insights from the use of pilocarpine and kainate models. Epilepsy Res. 2002;50(1-2):93-103.
21. Greenberg ME, Ziff EB. Signal transduction in the postsynaptic neuron. Activity dependent regulation of gene expression. In: Cowan WM, Südhof TC, Stevens CF, editors. Synapses. Baltimore: The Johns Hopkins University Press. 2001;357-91.
22. Thom M. Hippocampal sclerosis in epilepsy: a neuropathology review. Neuropath Appl Neurobiol. 2014;40(5):520-43.
23. Mátyás A, Török AI, Dobó E, Morvai M, Mihály A. Neuronal degeneration in the hippocampus of the mouse with spontaneous recurrent seizures following pilocarpine treatment. Rev Argentina de Anat Clin. 2016;8(3):191-2.
24. Fabene PF, Weiczner R, Marzola P, Nicolato E, Calderan L, Andrioli, et al. Structural and functional MRI following 4-aminopyridine-induced seizures: a comparative imaging and anatomical study. Neurobiol Dis. 2006;21(1):80-9.
25. Farkas IG, Czigner A, Farkas E, Dobó E, Soós K, Penke B, et al. Beta-amyloid peptide-induced blood-brain barrier disruption facilitates T-cell entry into the rat brain. Acta Histochem. 2003;105(2):115-25.