Journal of Neurology & Neurophysiology

Shi and Zhang, J Neurol Neurophysiol 2016, 7:3
DOI: 10.4172/2155-9562.1000376

Short Communication Open Access

Protective Effects of Anterior Thalamic Nuclei Stimulation on Hippocampal Neurons: A Promising Direction

Lin Shi[1,2] **and Jian-Guo Zhang**[1-3*]

[1]*Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China*

[2]*Functional Neurosurgery Laboratory, Beijing Neurosurgical Institute, Beijing, China*

[3]*Beijing Key Laboratory of Neurostimulation, Beijing, 100050, China*

[*]**Corresponding author:** Jian-Guo Zhang, Beijing Neurosurgical Institute, Tiantan West No. 6, Dongcheng District, Beijing 100050, China, Tel: +86 10 67096767; Fax: +86 10 67097507; E-mail: zjguo73@126.com

Received date: April 26, 2016; **Accepted date:** May 27, 2016; **Published date:** June 03, 2016

Introduction

Traditionally, patients with partial or generalized epilepsy resort to antiepileptic drugs for seizure control [1]. Albeit many new drugs and compounds have been invented, there are still a large number of patients with drug-resistant epilepsy whose seizures cannot be alleviated by drugs [2]. For these patients, seizure surgery is an apropos choice because some of them can achieve seizure freedom after surgery [3-5]. Many patients, however, are not candidates for resective surgeries for assorted causes, i.e., multiple epileptic foci, involvement of functional cortices, combination of major heart, brain or lung problems that fail general anesthesia, so they have to look for alternative therapies to cure their diseases [5,6].

Neuromodulation is an emerging treatment modality for diseases like epilepsy. Its basic idea is to stimulate specific regions of the neurological system with some forms of power to influence the neural circuit activity, i.e., electricity, light, magnetic force, ultrasound, which may result in various effects including a decrease in seizure frequency. The currently available neuromodulation methods include deep brain stimulation (DBS), vagus nerve stimulation, responsive neurostimulaiton and transcranial magnetic stimulation [7-9]. DBS has aroused increasing interest in the academic field, partly because of its success in the treatment of Parkinson's disease, and it is now being tested as an alternative antiepileptic method for epilepsy [10,11]. Various targets have been experimented with, including anterior thalamic nuclei (ATN), subthalamic nuclei, hippocampus, fornix, brainstem and cerebellum [8,9]. Among these targets, ATN is a promising one for epilepsy because it is an important relay point that has myriads of reciprocal connections with other parts of the brain, including neocortices, basal ganglia, limbic system, and brain stem [12,13]. Besides, the effects of ATN stimulation have been proved by several antecedent studies. In 1980, Cooper et al. first reported their experimental application of ATN stimulation in man [14,15]. Subsequently, ATN stimulation has been tested as an antiepileptic method in a number of clinical trials [16-21]. Most clinical studies showed positive antiepileptic results. Although the seizure reduction rate varied in different studies, ranging from 20-70% [16-21], its effectiveness on intractable epilepsy has been gradually established. Based on these pilot studies, Fisher et al. [22] conducted a multi-center, double-blind, randomized controlled clinical trial, i.e., the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) study. 110 participants with partial or generalized intractable epilepsy went through a long-term observation with bilateral ATN stimulation. Results showed that the 2 year seizure reduction rate was 56% [22], and that the 5 year seizure reduction rate was 69% [23]. On the other hand, in laboratory animal studies (rats, dogs and monkeys) the effects of ATN stimulation on chemical-induced epileptic models were also under investigation, and seizure inhibition was observed [24-31]. These findings suggested that ATN stimulation is antiepileptic and may be applied in epilepsy treatment.

While definite effectiveness is observed, our knowledge of the mechanisms underlying the antiepileptic effects of ATN stimulation is insufficient. In previous literatures, electrophysiological alterations induced by DBS were considered to be related to the mechanisms. In chemical-induced epilepsy models, decreased neuronal excitability caused by negative slow potential shifts was detected when high frequency DBS was initiated [32,33]. The reason why stimulation of ATN nuclei resulted in potential shift in a remote brain area was assumed to be associated with the depolarization inhibition through fiber connection between the two sites [34,35]. As is mentioned above, ATN is an important anatomical relay station in the Papez circuit which has bi-directional fiber connection with new cortex, the limbic system, basal ganglia and many other regions of the brain [12]. On the other hand, some studies focused on its influences on neurotransmitters and glucose metabolism, and found that ATN stimulation induced complicated modulation on neurotransmitters and glucose metabolism in epileptic animals [36-40]. We have also done research in this field. Our results showed that short-term and long-term ATN stimulation resulted in a decrease in the excitatory neurotransmitters and an increase in the inhibitory neurotransmitters [26,41], and that ATN stimulation inhibited glycolysis in epileptic animals, which were consistent with previous literatures [42].

Recently, we have further investigated the antiepileptic effects of ATN stimulation from histological and molecular aspects. We applied chronic ATN stimulation on the kainic acid-induced epileptic monkeys and rats, and observed a significant seizure reduction in these models [13,27,43]. Then we conducted immunohistochemical staining, including Nissl staining, NeuN staining and microtubule-associated protein-2 staining on the hippocampal slices to see if hippocampus could be influenced by ATN stimulation since it is a downstream structure in the Papez circuit relative to ATN. Results showed that ATN stimulation reduced the hippocampal neuronal loss, especially in the CA1-CA3 regions [13,27]. Molecular examinations were performed to detect alterations in the injury and apoptosis markers, i.e., heat shock protein 70, caspase-3, B-cell lymphoma-2, and Bcl2-associated X. Results showed that the hippocampal injury was attenuated by chronic ATN stimulation, which was in line with our pathological findings [13,27]. In temporal lobe epilepsy, progressive hippocampal neuronal loss occurred with the process of epileptogenesis [44]. In previous literatures, the hippocampal CA1 and

CA3 regions were considered to be more vulnerable to injuries [27,45]. In our studies, significant neuronal loss was observed in the CA1-CA3 regions. ATN stimulation reduced the neuronal loss, as revealed by pathohistological staining and molecular findings. These results demonstrated that chronic ATN stimulation is protective for the hippocampal neurons in epileptic animals. Such effects might be an important mechanism underling ANT DBS in the treatment of epilepsy. However, there is still work to be done before we can confirm such protective effects exist in humans. Future studies should focus on more thorough evaluation of the potential protective effects, e.g. is chronic ATN stimulation accompanied by elevation of genes related to neuronal survival and decrease of genes related to neuronal apoptosis, is ATN stimulation associated with neuronal genesis, what are the direct effector molecules of its protective effects? If answers to these questions can be found in future studies, then attempts to reverse epileptogenesis with ATN stimulation or other forms of neurostimulation might become worthwhile and reasonable.

Acknowledgement

The Special Funding for Clinical Medicine Development from the Beijing Municipal Administration of Hospitals (ZYLX201305) and the Scientific Research Common Program of Beijing Municipal Commission of Education (KZ201510025029).

References

1. Sillanpää M, Jalava M, Kaleva O, Shinnar S (1998) Long-term prognosis of seizures with onset in childhood. N Engl J Med 338: 1715-1722.
2. Hauser WA, Annegers JF, Rocca WA (1996) Descriptive epidemiology of epilepsy: Contributions of population-based studies from Rochester, Minnesota. Mayo Clin Proc 71: 576-586.
3. Kohno R, Abe H, Akamatsu N, Benditt DG (2016) Long-term follow-up of Ictal Asystole in Temporal Lobe Epilepsy: Is permanent pacemaker therapy needed? J Cardiovasc Electrophysiol.
4. Murphy M, Smith PD, Wood M, Bowden S, O'Brien TJ, et al. (2010) Surgery for temporal lobe epilepsy associated with mesial temporal sclerosis in the older patient: A long-term follow-up. Epilepsia 51: 1024-1029.
5. Nakase H, Tamura K, Kim YJ, Hirabayashi H, Sakaki T, et al. (2007) Long-term follow-up outcome after surgical treatment for lesional temporal lobe epilepsy. Neurol Res 29: 588-593.
6. Bien CG, Scheffer IE (2011) Autoantibodies and epilepsy. Epilepsia 52 Suppl 3: 18-22.
7. Jaseja H (2015) Deep brain stimulation in intractable epilepsy: Role of pulse width in neuromodulation. Clin EEG Neurosci 46: 268-269.
8. Krishna V, Sammartino F, King NK, So RQ, Wennberg R (2016) Neuromodulation for epilepsy. Neurosurg Clin N Am 27: 123-131.
9. Nune G, DeGiorgio C, Heck C (2015) Neuromodulation in the treatment of epilepsy. Curr Treat Options Neurol 17: 375.
10. Pollo C, Villemure JG (2007) Rationale, mechanisms of efficacy, anatomical targets and future prospects of electrical deep brain stimulation for epilepsy. Acta Neurochir Suppl 97: 311-320.
11. Graber KD, Fisher RS (2012) Deep brain stimulation for epilepsy: Animal models. Deep Brain Stimulation for Epilepsy: Animal Models.
12. Papez JW (1995) A proposed mechanism of emotion. 1937. J Neuropsychiatry Clin Neurosci 7: 103-112.
13. Meng DW, Liu HG, Yang AC, Zhang K, Zhang JG (2016) Stimulation of anterior thalamic nuclei protects against seizures and neuronal apoptosis in hippocampal CA3 region of kainic acid-Induced epileptic rats. Chin Med J (Engl) 129: 960-966.
14. Cooper IS, Upton AR, Amin I (1980) Reversibility of chronic neurologic deficits. Some effects of electrical stimulation of the thalamus and internal capsule in man. Appl Neurophysiol 43: 244-258.
15. Cooper IS, Upton AR, Amin I, Garnett S, Brown GM, et al. (1984) Evoked metabolic responses in the limbic-striate system produced by stimulation of anterior thalamic nucleus in man. Int J Neurol 18: 179-187.
16. Sussman NM Jr (1988) Stimulation of thalamic anterior nucleus in medically intractable epilepsy: II preliminary clinical results. Epilepsia 29: 1.
17. Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, et al. (2004) Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 45: 346-354.
18. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43: 603-608.
19. Lee KJ, Jang KS, Shon YM (2006) Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy. Acta Neurochir Suppl 99: 87-91.
20. Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, et al. (2007) Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. Epilepsia 48: 342-347.
21. Osorio I, Overman J, Giftakis J, Wilkinson SB (2007) High frequency thalamic stimulation for inoperable mesial temporal epilepsy. Epilepsia 48: 1561-1571.
22. Fisher R, Salanova V, Witt T, Worth R, Henry T, et al. (2010) Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 51: 899-908.
23. Salanova V, Witt T, Worth R, Henry TR, Gross RE, et al. (2015) Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 84: 1017-1025.
24. Mirski MA, Rossell LA, Terry JB, Fisher RS (1997) Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res 28: 89-100.
25. Zhang Q, Wu ZC, Yu JT, Zhong XL, Xing YY, et al. (2012) Anticonvulsant effect of unilateral anterior thalamic high frequency electrical stimulation on amygdala-kindled seizures in rat. Brain Res Bull 87: 221-226.
26. Shi L, Yang AC, Li JJ, Meng DW, Jiang B, et al. (2015) Favorable modulation in neurotransmitters: effects of chronic anterior thalamic nuclei stimulation observed in epileptic monkeys. Exp Neurol 265: 94-101.
27. Yang AC, Shi L, Li LM, Li JJ, Jiang Y, et al. (2015) Potential Protective Effects of Chronic Anterior Thalamic Nucleus Stimulation on Hippocampal Neurons in Epileptic Monkeys. Brain Stimul 8: 1049-1057.
28. Lado FA (2006) Chronic bilateral stimulation of the anterior thalamus of kainate-treated rats increases seizure frequency. Epilepsia 47: 27-32.
29. Takebayashi S, Hashizume K, Tanaka T, Hodozuka A (2007) Anti-convulsant effect of electrical stimulation and lesioning of the anterior thalamic nucleus on kainic acid-induced focal limbic seizure in rats. Epilepsy Res 74: 163-170.
30. Hamani C, Hodaie M, Chiang J, del Campo M, Andrade DM, et al. (2008) Deep brain stimulation of the anterior nucleus of the thalamus: Effects of electrical stimulation on pilocarpine-induced seizures and status epilepticus. Epilepsy Res 78: 117-123.
31. Covolan L, de Almeida AC, Amorim B, Cavarsan C, Miranda MF, et al. (2014) Effects of anterior thalamic nucleus deep brain stimulation in chronic epileptic rats. PLoS One 9: e97618.
32. Durand D (1986) Electrical stimulation can inhibit synchronized neuronal activity. Brain Res 382: 139-144.
33. Gluckman BJ, Neel EJ, Netoff TI, Ditto WL, Spano ML, et al. (1996) Electric field suppression of epileptiform activity in hippocampal slices. J Neurophysiol 76: 4202-4205.
34. Dostrovsky JO, Lozano AM (2002) Mechanisms of deep brain stimulation. Mov Disord 17 Suppl 3: S63-68.
35. Boon P, Raedt R, de Herdt V, Wyckhuys T, Vonck K (2009) Electrical stimulation for the treatment of epilepsy. Neurotherapeutics 6: 218-227.

36. Darbin O, Risso JJ, Carre E, Lonjon M, Naritoku DK (2005) Metabolic changes in rat striatum following convulsive seizures. Brain Res 1050: 124-129.
37. Wasterlain CG, Thompson KW, Suchomelova L, Niquet J (2010) Brain energy metabolism during experimental neonatal seizures. Neurochem Res 35: 2193-2198.
38. Slais K, Vorisek I, Zoremba N, Homola A, Dmytrenko L, et al. (2008) Brain metabolism and diffusion in the rat cerebral cortex during pilocarpine-induced status epilepticus. Exp Neurol 209: 145-154.
39. Guo J, Liu J, Fu W, Ma W, Xu Z, et al. (2008) The effect of electroacupuncture on spontaneous recurrent seizure and expression of GAD(67) mRNA in dentate gyrus in a rat model of epilepsy. Brain Res 1188: 165-172.
40. Rajasekaran K, Joshi S, Sun C, Mtchedlishvilli Z, Kapur J (2010) Receptors with low affinity for neurosteroids and GABA contribute to tonic inhibition of granule cells in epileptic animals. Neurobiol Dis 40: 490-501.
41. Liu HG, Yang AC, Meng DW, Chen N, Zhang JG (2012) Stimulation of the anterior nucleus of the thalamus induces changes in amino acids in the hippocampi of epileptic rats. Brain Res 1477: 37-44.
42. Liu HG, Yang AC, Meng DW, Zhang K, Zhang JG (2012) Effect of anterior nucleus of thalamus stimulation on glucose metabolism in hippocampus of epileptic rats. Chin Med J (Engl) 125: 3081-3086.
43. Chen N, Liu C, Yan N, Hu W, Zhang JG, et al. (2013) A macaque model of mesial temporal lobe epilepsy induced by unilateral intrahippocampal injection of kainic Acid. PLoS One 8: e72336.
44. Snyder JS, Kee N, Wojtowicz JM (2001) Effects of adult neurogenesis on synaptic plasticity in the rat dentate gyrus. J Neurophysiol 85: 2423-2431.
45. Lévesque M, Avoli M (2013) The kainic acid model of temporal lobe epilepsy. Neurosci Biobehav Rev 37: 2887-2899.