Cell J
Cell Journal(Yakhteh)
Homepage: https://www.celljournal.org/
Original Article
Vol 25, No 4, April 2023, Pages: 273-286

Effect of Deep Brain Stimulation in The Ventral Tegmental Area on Neuronal Activity in Local and Remote Brain Regions in Kindled Mice

Parisa Esmaeili Tazangi, M.Sc.[1#], Faisal Alosaimi, Ph.D.[2, 3#], Fatemeh Bakhtiarzadeh, M.Sc.[1], Amir Shojaei, Ph.D.[1], Ali Jahanshahi, Ph.D.[2*], Javad Mirnajafi-Zadeh, Ph.D.[1, 4*]

1. Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
2. Department of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands
3. Department of Physiology, Faculty of Medicine, King Abdulaziz University, Rabigh, Saudi Arabia
4. Institute for Brain Sciences and Cognition, Tarbiat Modares University, Tehran, Iran

Abstract

Objective: The mechanisms behind seizure suppression by deep brain stimulation (DBS) are not fully revealed, and the most optimal stimulus regimens and anatomical targets are yet to be determined. We investigated the modulatory effect of low-frequency DBS (L-DBS) in the ventral tegmental area (VTA) on neuronal activity in downstream and upstream brain areas in chemically kindled mice by assessing c-Fos immunoreactivity.

Materials and Methods: In this experimental study, 4-6 weeks old BL/6 male mice underwent stereotaxic implantation of a unilateral stimulating electrode in the VTA followed by pentylenetetrazole (PTZ) administration every other day until they showed stage 4 or 5 seizures following 3 consecutive PTZ injections. Animals were divided into control, sham-implanted, kindled, kindled-implanted, L-DBS, and kindled+L-DBS groups. In the L-DBS and kindled+L-DBS groups, four trains of L-DBS were delivered 5 min after the last PTZ injection. 48 hours after the last L-DBS, mice were transcardially perfused, and the brain was processed to evaluate c-Fos expression by immunohistochemistry.

Results: L-DBS in the VTA significantly decreased the c-Fos expressing cell numbers in several brain areas including the hippocampus, entorhinal cortex, VTA, substantia nigra pars compacta, and dorsal raphe nucleus but not in the amygdala and CA3 area of the ventral hippocampus compared to the sham group.

Conclusion: These data suggest that the possible anticonvulsant mechanism of DBS in VTA can be through restoring the seizure-induced cellular hyperactivity to normal.

Keywords: Deep Brain Stimulation, Epilepsy, Pentylenetetrazole, Ventral Tegmental Area

Citation: Esmaeili Tazangi P, Alosaimi F, Bakhtiarzadeh F, Shojaei A, Jahanshahi A, Mirnajafi-Zadeh J. Effect of deep brain stimulation in the ventral tegmental area on neuronal activity in local and remote brain regions in kindled mice. Cell J. 2023; 25(4): 273-286. doi: 10.22074/CELLJ.2023.557500.1058.

Introduction

Epilepsy is a prevalent neurological disorder that affects 1-2% of the population worldwide. It is characterized by unprovoked seizures caused by significant changes in the activities of different brain areas (1). Despite major progress in defining the mechanisms behind epileptic seizures, there is no safe and effective treatment for seizure suppression. About 20-30% of epileptic patients remain resistant to current pharmacological therapeutics and require surgical intervention if an epileptic focus can be identified (2).

Deep brain stimulation (DBS) has been used to reduce disease burden in several neurological disorders. Nevertheless, there is no consensus on the optimal stimulus paradigms and DBS target (3). Low-frequency DBS (L-DBS), is shown to be effective in suppressing seizure severity in animal models (4) and reducing seizure frequency in patients (5). However, there are lots of limitations in using DBS as a therapeutic manner in epilepsy patients including finding the best pattern of stimulation and the best brain target for inducing its therapeutic effects. In addition, the exact mechanism(s) underlying the anticonvulsant effects of L-DBS remains to be determined.

Different hypotheses including synaptic modulation and changes in different neurotransmitters or neuromodulators controlling neural hyperexcitability have been suggested as underlying mechanisms (6). The hyperexcitable state of epilepsy is thought to be due to an imbalanced excitatory (glutamatergic) and inhibitory (GABAergic) synaptic activity. However, neuromodulators such as dopamine (DA) can also affect this ratio by altering

Received: 10/July/2022, Revised: 07/January/2023, Accepted: 11/January/2023
# These authors equally contributed to this study.
*Corresponding Addresses: Department of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands
P.O.Box: 14115-111, Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
Emails: a.jahanshahi@maastrichtuniversity.nl, mirnajaf@modares.ac.ir

Royan Institute
Cell Journal (Yakhteh)

the glutamatergic and/or GABAergic activity (7, 8). A growing body of evidence suggests that epilepsy coincides with impaired DA-ergic neurotransmission in humans and laboratory animals (9, 10).

The mesolimbic DA-ergic projections are mainly from the DA-ergic neurons of the ventral tegmental area (VTA). It governs a range of non-motor behavioursbehaviours (11) as it widely projects both to limbic and neocortical areas (12). Given dense DA-ergic projections from the VTA to those brain areas that are involved in seizure propagation, such as the hippocampus (13), we sought to investigate the VTA as a potential target for DBS in a pentylenetetrazole (PTZ)-induced kindled mice. In support of this hypothesis, our recent studies have revealed that altered activity in the VTA DA-ergic neurons in the PTZ mouse model of epilepsy was associated with cognitive deficits (14). In addition, our recent studies show that applying DBS at low frequency in the VTA exerts anticonvulsant effects on PTZ-kindled seizures (15).

To address whether L-DBS in the VTA may change the activity of brain areas involved in seizure activity, we assessed c-Fos expression using a specific antibody, which is designed to measure chronic neuronal activity (16). c-Fos is a molecular marker for determining the neuronal activity in the central nervous system (17). The expression of this molecule increases following seizures (18).

Materials and Methods

42 male BL/6 mice aged 4-6 weeks were used in this study. The animal house had standard conditions (22-25°C, 12-h light/dark cycle). Animals had free access to food and water. The experimental procedures and the animals' handling were according to the Animal Ethics Committee's guidelines of the Faculty of Medical Sciences, Tarbiat Modares University (IR.Modares.52D/1178).

Experimental groups and design

Animals were randomly assigned into control, sham-implanted, kindled, kindled-implanted, L-DBS, and kindled+L-DBS (KL-DBS) groups. Animals in the Kindled group were administered with PTZ (37 mg/kg, i.p.) on alternating days until achieving three consecutive stages of 4 or 5 seizures (fully kindled). In the KL-DBS group, mice were implanted with unilateral stimulating electrodes in the VTA and received L-DBS after being fully kindled. In the L-DBS group, animals were handled similarly to the KL-DBS group but received only L-DBS (without PTZ administrations). In the sham-implanted group, animals were implanted with an electrode in the VTA and received saline. In the kindled-implanted group, animals were implanted with a stimulating electrode in the VTA and received PTZ. Animals were transcardially perfused at the end of experiments. Their brains were removed and processed for immunohistochemistry (Fig.1).

Electrode implantation

A mixture of ketamine/xylazine (100/10 mg/kg, 10/1 mg/ml) was injected intraperitoneally to anaesthetize the animals. Then, animals were fixed in a stereotaxic frame and their skull was exposed. Body temperature was maintained at 37ºC using a heating pad throughout the surgery. Two stainless Teflon-coated electrodes were twisted to make a bipolar stimulating electrode, which was isolated except at its tips. This bipolar electrode was implanted unilaterally in the right VTA (0.5 mm lateral, 3.5 mm posterior, and 4.5 mm ventral from bregma (19). Teflon was removed from one end of the electrodes that were connected to the pins of a plastic socket. The socket was fixed to the skull with dental acrylic as the head stage.

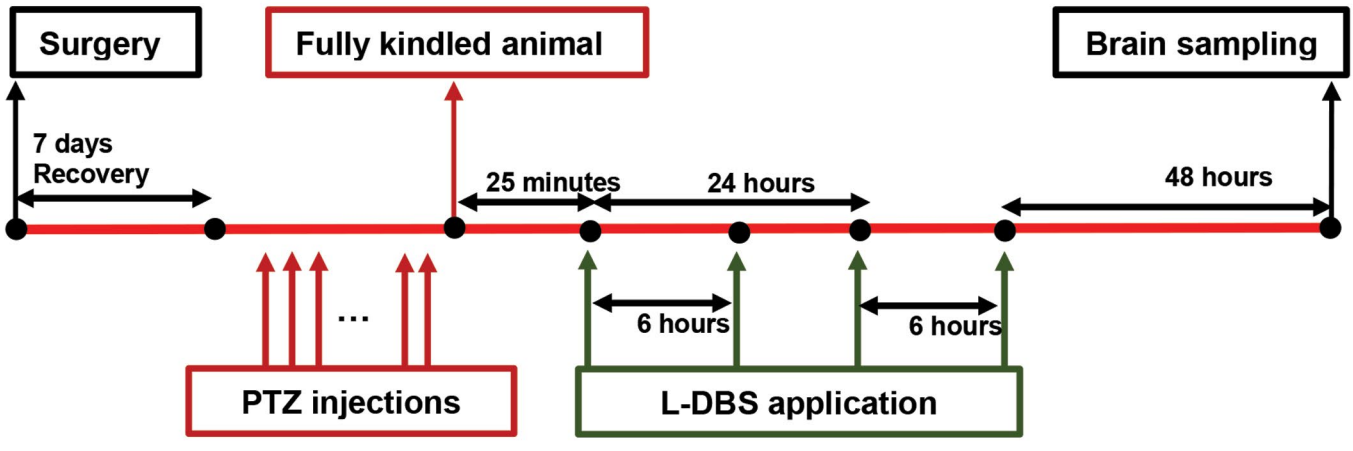

Fig.1: The timeline showing the experimental procedure. Please see the text for more explanation. PTZ; Pentylenetetrazol and L-DBS; Low frequency-deep brain stimulation.

Pentylenetetrazole (PTZ) kindling

After a recovery period of 10 days, mice received saline or PTZ. To induce the kindled seizure behaviours, subjects received sub-threshold dose of freshly prepared PTZ (37 mg/Kg, i.p.) at normal pH every other day while the animals were in their home cage (14). Bodyweight measured before each injection. Subjects in the sham group received PTZ vehicle (saline) and handled exactly similar to animals in the kindled group.

The mice's behaviour monitored for 20 minutes Immediately after PTZ injection and the convulsive seizures were scored follows stage 1: ear and facial contractions; stage 2: myoclonic jerks; stage 3: forelimb clonus; stage 4: tonic-clonic seizures and stage 5: generalized tonic-clonic seizure (20).

Low-frequency deep brain stimulation

L-DBS was applied using a digital stimulator and stimulus isolators (BIODAC ES1721, TRITA Health Technology CO., Tehran, Iran) for four sessions. The first stimulation session was administered 5 minutes after the last seizure behaviour observation in a fully kindled animal and the second session was applied 6 hours later. The third and fourth sessions were similarly applied on the next day (Fig.1). Each session lasted 20 minutes and consisted of 4 trains with 5 minutes intervals. 200 monophasic square wave pulses (with 0.1 ms pulse duration at 1 Hz) existed in each train. L-DBS parameters were designed based on our previous studies (21). L-DBS was applied through the bipolar electrode implanted in the VTA.

Tissue collection

48 hours after the last stimulation (or the equivalent time in animal groups that did not receive stimulation), mice were deeply anaesthetized with a ketamine/xylazine mixture (100/10 mg/kg, 10/1 mg/ml, i.p.) and were perfused with Tyrone's solution and Somogyi fixative solution [4% paraformaldehyde, picric acid, phosphate-buffered saline (PBS), glutaraldehyde] respectively (22). The removed brains were placed in fresh fixative solution (4% paraformaldehyde, 15% picric acid, and 0.05% glutaraldehyde in 0.1 M phosphate buffer (pH=7.6) at 4ºC for 2 hours. Then, brains were moved to 1% NaN_3 at 4ºC for long-term storage.

For preparing the brain slices, mice brains were embedded in 10% gelatin from porcine skin (Sigma-Aldrich, Zwijndrecht, The Netherlands), and then 30 µm coronal slices were prepared using a vibratome (Leica®, Wetzlar, Germany). Slices were immediately transferred into 1% NaN_3 and kept at 4ºC.

c-Fos Immunohistochemistry

Sections from 5 randomly selected mice per group were selected for immunohistochemistry. An indirect immunohistochemical (3,3′-Diaminobenzidine, DAB) staining method was used and amplification was employed using streptavidin and nickel-diaminobenzidine chromogen enhancement (23).

In brief, after overnight incubation of sections with polyclonal rabbit anti-c-Fos (K-25) (16); at first primary antibody (1:2000; Santa Cruz Biotechnology) and then biotinylated donkey anti-rabbit secondary antibody (1:800; Jackson Immunoresearch Laboratories) followed by avidin-biotin-peroxidase complex (1:800, Elite ABC-kit, Vestastatin, Burlingame, CA, USA) were applied. The stained brain slices were visualized by 3,3´-Diaminobenzidine (DAB) combined with $NiCl_2$ intensification. In the next step, the mounting and dehydrating of slices were done and samples were cover slipped with Pertex (Histolab Products ab, Goteborg, Sweden). All sections were stained in the same session and were kept in equal conditions to avoid variability.

For semi-quantitative analysis, photographs of the stained sections were taken from two sections (rostrocaudally) at 10x magnification through an Olympus DP70 digital camera connected to an Olympus AX 70 microscope (Olympus, Zoeterwoude, The Netherlands) and the Cell P software (Olympus Soft Imaging Solutions, Münster, Germany). Using ImageJ software [version 1.52; National Institutes of Health (NIH), Bethesda, USA], the number of c-Fos–positive cells was counted in the area of interest. The c-Fos immunopositive cells were counted manually, and the mean number of cells was corrected for surface area and expressed as cells/mm^2. If the staining intensity of the cell was significantly higher than the surrounding background, the cell was regarded as positive. The average value of two sections was used for statistical analysis in each subject.

In all cases, the delineation was based on standard anatomical landmarks for different brain areas and the anatomical descriptions of these regions according to the Mouse Brain Atlas (19).

Electrode trajectory verification

To verify the position of electrodes, the brain sections with the electrode trajectories were stained by hematoxylin-eosin and then sections were photographed under bright field microscopy (Fig.2).

Statistics

Data were presented as mean ± SEM values. A two-way ANOVA was used to compare the difference in kindling rate between the experimental groups. In addition, a one-way ANOVA was used to compare the parameters among different experimental groups. Bonferroni's post hoc test was run to compare the values between different experimental groups. All statistical analyses were conducted using GraphPad Prism 8 (GraphPad Software, Inc, USA). A $P<0.05$ was considered a significant difference.

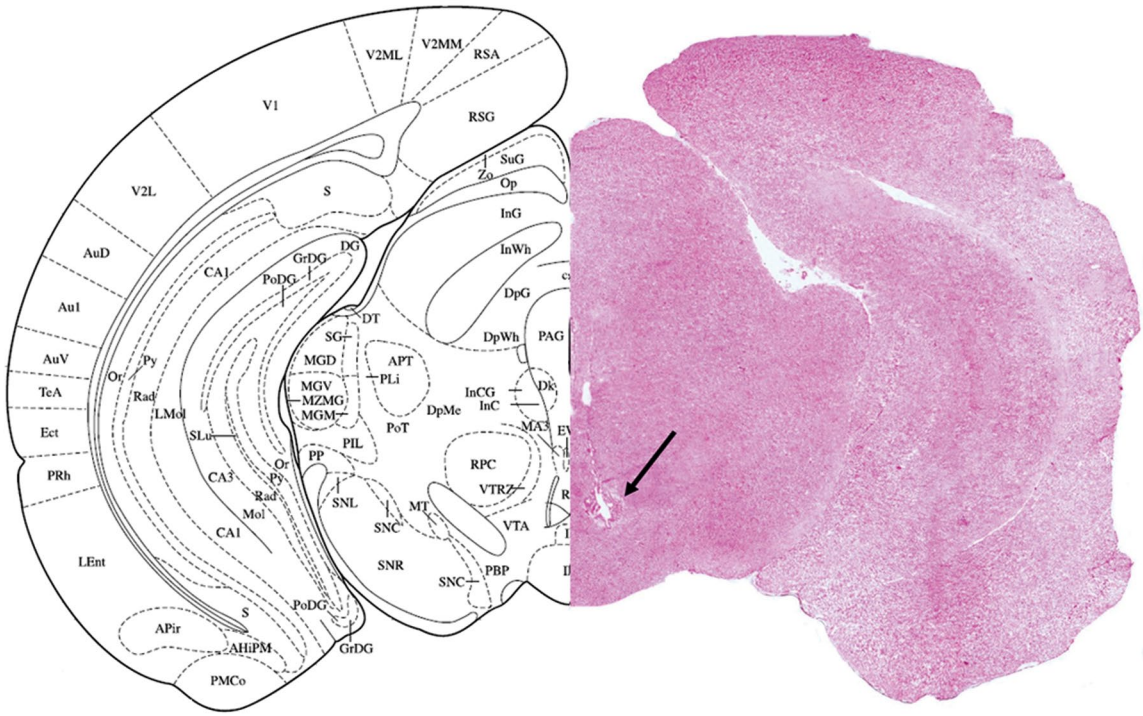

Fig.2. Verification of electrode placement in the ventral tegmental area (VTA). On the right side, a coronal histology section of the Nissl-stained is shown (40x). Arrow indicates the location of the electrode tip in the VTA. In the left, the corresponding slice of the stereotaxic atlas (-5.3 mm caudal to the Bregma) is showing.

Results

Repeated PTZ administration resulted in an increasingly tonic and clonic seizure. The number of PTZ injections in kindled and KL-DBS groups was 8.22 ± 0.72 and 8.38 ± 0.75, respectively and about 6 and 10 injections were required to induce full kindling (Fig.3). A two-way ANOVA showed that there was no significant difference in kindling rate between the two experimental groups ($F_{(1,80)}$=0.8674, P=0.3545). In addition, no significant difference was observed between control and sham-implanted groups in the expression of c-Fos. Therefore, data of these groups were merged and regarded as a sham group. Similarly, data of kindled and kindled-implanted groups were also merged and considered as a kindled group.

A one-way ANOVA and post-hoc Bonferroni test revealed that PTZ-induced kindling enhanced c-Fos expression in the inspected brain areas including CA1 ($F_{(3,19)}$=15.5, P=0.0018) and CA3 ($F_{(3,16)}$=7.41, P=0.0025) regions of the dorsal hippocampus, dorsal dentate gyrus (DG) ($F_{(3,19)}$=16.55, P=0.0009), CA1 ($F_{(3,16)}$=18.84, P=0.0001) and CA3 ($F_{(3,19)}$=16.08, P=0.0011) of ventral hippocampus, ventral DG ($F_{(3,19)}$=16.71, P=0.0008) (Fig.4) and basolateral amygdaloid nucleus (BLA) ($F_{(3,19)}$=15.47, P=0.0014), entorhinal cortex (EC) ($F_{(3,16)}$=34.63, P=0.00001), DRN ($F_{(3,19)}$=12.66, P=0.0054), VTA ($F_{(3,19)}$=12.12, P=0.007) and SNc ($F_{(3,19)}$=13.74, P=0.0033) (Fig.5).

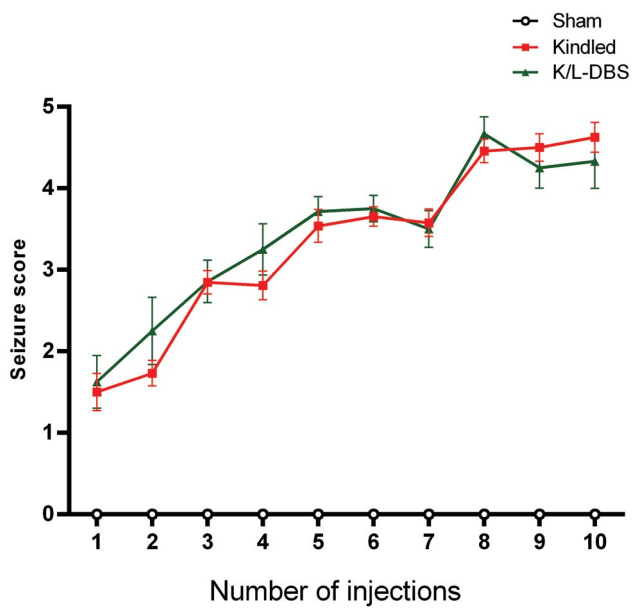

Fig.3: Pentylenetetrazole (PTZ) kindling procedure in experimental groups.

L-DBS in kindled animals (KL-DBS group) restored the observed increase in c-Fos expression in all the above-mentioned brain regions. A one-way ANOVA and post-hoc Bonferroni's test showed a significant difference between KL-DBS and kindled groups (P values being reported in Fig.5) except in the basolateral amygdala (Figs.4, 5).

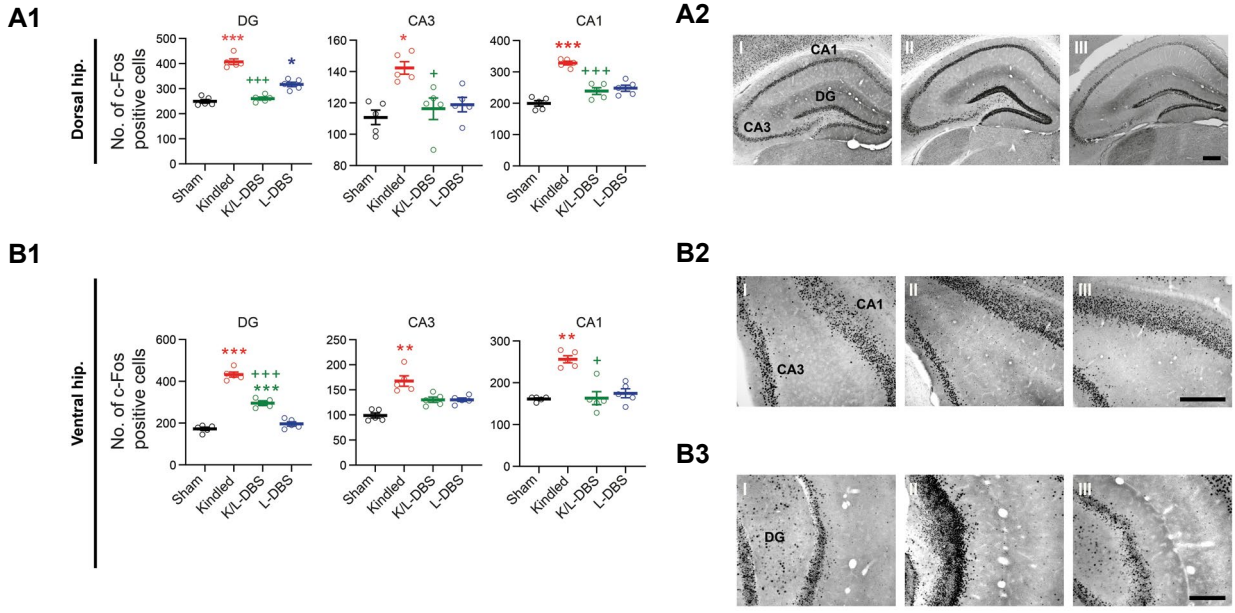

Fig.4: Effect of L-DBS on c-Fos neural activity. On the left, **A1.** The number of c-Fos positive cells is showing in the CA1, CA3, and DG of the dorsal hippocampus, **B1.** The CA1, CA3 and DG of the ventral hippocampus. Values are mean ± SEM, *; P<0.05, **; P<0.01, ***; P<0.001 compared to sham and +; P<0.05 and +++; P<0.001 compared to kindled group by one-way ANOVA. In right, **A2.** The distribution of c-Fos immunohistochemical staining of 30 -µm-thick sections of the above-mentioned areas is shown in the sham (I), kindled (II), and KL-DBS (III) groups for the dorsal hippocampus at the bregma level of -1.94 mm, **B2, B3.** The ventral hippocampus at the bregma level of -2.92 mm. The small dark dots represent c-Fos positive cells at 4x magnification power. L-DBS; Low frequency-deep brain stimulation, CA; Cornu ammunis, and DG; Dentate gyrus.

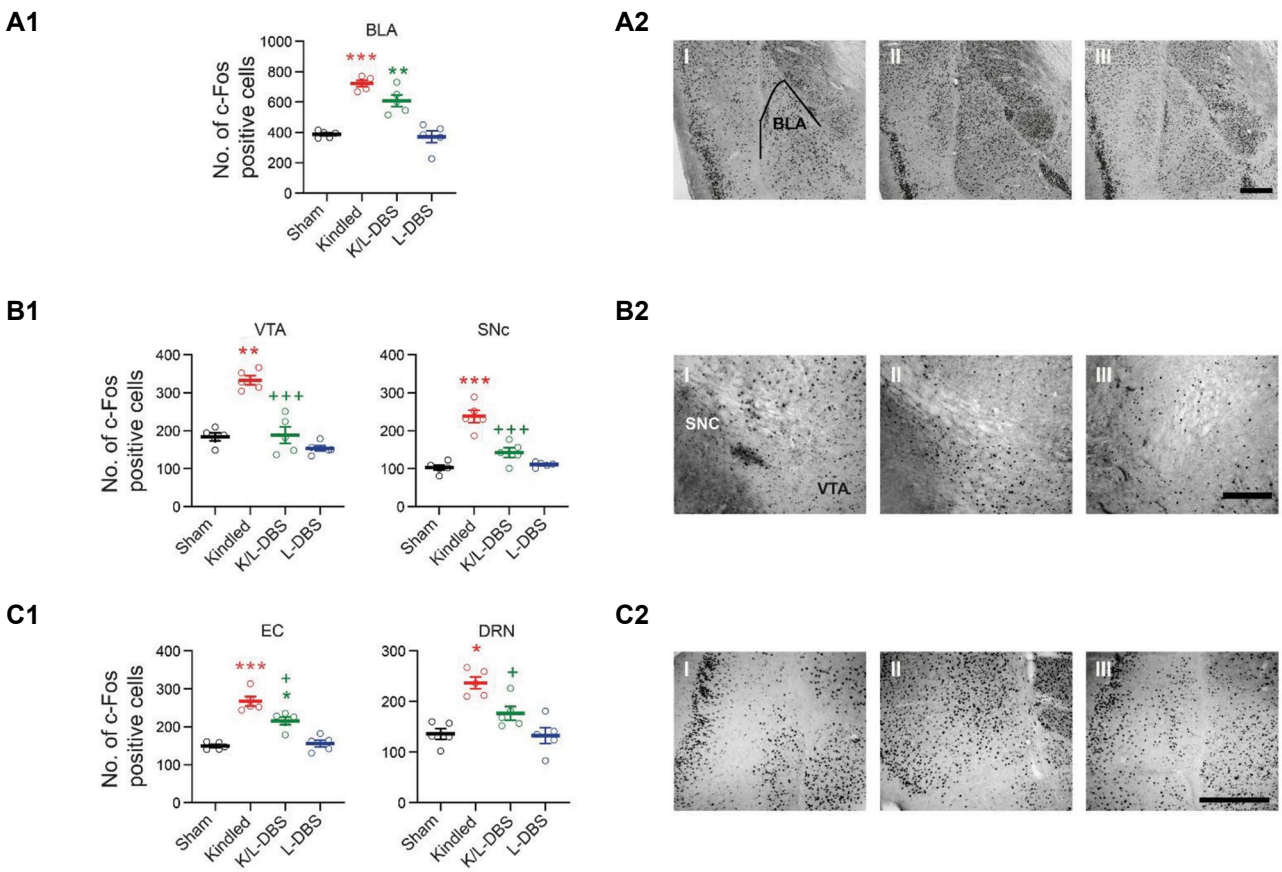

Fig.5: Effect of low frequency-deep brain stimulation (L-DBS) on c-Fos neural activity. On left, **A1.** The number of c-Fos positive cells is showing in the basolateral amygdala (BLA), **B1.** The ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), **C1.** The entorhinal cortex (EC) and the dorsal raphe nucleus (DRN). Values are mean ± SEM, *; P<0.05, **; P<0.01, ***; P<0.001 compared to sham and +; P<0.05 and +++; P<0.001 compared to kindled group by one-way ANOVA. On right, **A2.** The distribution of c-Fos immunohistochemical staining of 30 -µm-thick sections of the above-mentioned areas is shown in the sham (I), kindled (II), and KL-DBS (III) groups for the BLA at the bregma level of -1.34 mm, **B2.** The VTA and the SNc at the bregma level of -3.16 mm, **C2.** The EC at the bregma level of -1.94 mm. The small dark dots represent c-Fos positive cells at 4x magnification power.

Discussion

Modulation of the DA-ergic system in managing epileptic seizures is gaining attention again. Unlike the nigrostriatal DA-ergic pathway, which primarily involves motor control, the mesolimbic DA-ergic pathway regulates non-motor functions. Herein we addressed whether the VTA could be targeted for seizure control. Our data suggest that VTA-DBS could reduce neuronal hyperactivity in different brain areas especially those involved in seizure generation and propagation and restore the kindling-induced increase in c-Fos expression (K-25, a chronic neuronal activity marker (16). To our knowledge, this is the first study that targets the VTA as a brain region for DBS in an animal model of epilepsy.

All regions of interest including the hippocampus, amygdala, entorhinal cortex, DRN, SNc and VTA showed a significant increase in neuronal activity (identified as a significant increase in c-Fos expression) in epileptic mice. Whereas, applying L-DBS in VTA restored the neuronal activity in all aforementioned areas to normal levels.

Altered DA neurotransmission has implications in a variety of brain disorders including epilepsy (9, 24). Furthermore, DA plays a key role in controlling cell excitability in different brain regions innervated by DA-ergic fibers, such as the prefrontal cortex and hippocampus (25). The VTA, as a major DA-ergic region, is made up of a heterogeneous population of DA (60%), GABA (35%), and glutamate (2-5%)-releasing neurons (26, 27). Two primary DA-ergic projections originate from the VTA, including mesocortical and mesolimbic pathways (12). We have recently shown that applying L-DBS in PTZ-kindled rats restores seizure-induced increase in firing of VTA DA-ergic neurons to the control level (21). VTA projects to the limbic areas that are involved in the generation and propagation of seizures. Therefore, it is an interesting area to investigate the mechanisms involved in neuromodulation in epilepsy.

DA-ergic neurons exert phasic burst activity accompanied by a transient and high-concentration DA release. Whilst, during the tonic pattern of activity, these neurons generate spikes at low frequency which results in tonic and low-concentration DA release (28). It has been suggested that encountering salient stimuli and reward is associated with a shift from a tonic firing pattern, an increase in D_2-like activity, to a burst firing mode, a rise in D_1-like activity (29). Moreover, D_2-like receptors exert an inhibitory and anticonvulsant effect while, D_1-like receptors involve an excitatory and proepileptic action (10, 25). The opposite action of D_1- and D_2-like receptors is thought to be due to a DA-glutamate interaction. This hypothesis has been supported both in epileptic and healthy animals (30, 31).

Based on this evidence, one may suggest that low-frequency DBS would enhance the tonic activity of DA neurons in the VTA in favour of D_2-like receptor activity. This is an important characteristic of VTA neurons, making it a suitable target for DBS compared to other brain areas.

The activity of the DA-ergic system increases in the epileptic brain (32, 33). An increase in the firing rate of DA-ergic neurons (21) and extracellular DA level during epilepsy have been reported (34). Therefore, a probable L-BDS-induced shift in the activity of the VTA DA-ergic neurons from phasic in kindled mice to a tonic in the K/L-BDS group could shift the excitation to inhibition ratio towards inhibition. Lower c-Fos expression following L-DBS in the VTA is in line with this hypothesis. However, electrophysiological recordings need to confirm this hypothesis.

The exact mechanism behind the effects of L-DBS is not clear. However, it has been hypothesized that L-DBS exerts excitatory effects at local neuronal element, and drive the neural pathways (35), unlike HFS which has been shown to induce ablative-like effects (6). Here we suggest that the observed DBS effects were probably caused by the modulatory effect of L-DBS on the pattern of DA-ergic cells activity. Based on this, the activity of DA-ergic cells in the VTA may be driven by the stimulation frequency of L-DBS. This would change the spontaneous activity of those neurons from phasic in epileptic mice to the tonic pattern that could shift the network from excitatory to inhibitory. We observed a significant increase in c-Fos expressing cells in the VTA in kindled mice, which was restored following L-DBS. VTA DA-ergic projections mainly innervate the ventral hippocampus (33). Nevertheless, we found that the effect of L-DBS was similar in both dorsal and ventral hippocampal areas.

The amygdala, the SNc (36), the DRN (37) and the hippocampus receive DA-ergic inputs from the VTA (38). L-DBS in the VTA would drive these projections towards a tonic firing mode. As a result of the tonic firing pattern, there will be an increase in the D_2-like dependent pathways which can reduce neuronal excitability (39). Our data showed that PTZ kindled mice exhibit high levels of c-Fos expression in the SNc, the DRN, the amygdala, the VTA, and the hippocampus. Subsequently, L-DBS restored those changes except in the amygdala. These changes in neuronal activity could be related to the different patterns of VTA projections or diverse distribution of DA-ergic receptors in different brain areas.

Herein we explained the outcomes based on the assumption that VTA-DBS would result in DA release in downstream areas following the tonic activity of DA-ergic neurons. However, other neurotransmitters are known to be involved in the complex VTA circuitry, which could play a role by sending long-range projections (38).

Owing to the preliminary nature of these results, this c-Fos mapping study would be a basis for further immunofluorescence assessment to unravel the cell types and a number of c-Fos expressing cells in the VTA. Moreover, additional research is needed to determine the mechanism of how L-DBS makes the VTA effective in reducing the activity of cells in different brain regions.

Conclusion

Given the current insights on the mechanism of DBS, we suggest that the firing of DA-ergic cells in the VTA is time-locked to the stimulation frequency. This would change the spontaneous activity of those neurons from phasic in epileptic mice to the tonic pattern that could shift the network from excitatory to inhibitory.

Acknowledgements

This research was supported by a grant (#957513) from National Institute for Medical Research Development (NIMAD) and a grant #IG-39709 from Tarbiat Modares University, Tehran, Iran. The authors declare no conflict of interest.

Authors' Contributions

P.E.T.; Participated in data collection and evaluation, drafting and statistical analysis. F.A.; Contributed to data collection, evaluation and analysis. F.B.; Contributed to histological experiments, preparing histological graphs and data analysis. A.S.; Participated in data evaluation, drafting and statistical analysis. A.J., J.M-Z.; Contributed to study design, interpretation of the data and the conclusion. All authors edited and approved the final version of this manuscript for submission, participated in the finalization of the manuscript and approved the final draft.

References

1. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005; 46(4): 470-472.
2. Wiebe S, Blume WT, Girvin JP, Eliasziw M. Effectiveness and efficiency of surgery for temporal lobe epilepsy study group. a randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001; 345(5): 311-318.
3. Sunderam S, Gluckman B, Reato D, Bikson M. Toward rational design of electrical stimulation strategies for epilepsy control. Epilepsy Behav. 2010; 17(1): 6-22.
4. Rashid S, Pho G, Czigler M, Werz MA, Durand DM. Low frequency stimulation of ventral hippocampal commissures reduces seizures in a rat model of chronic temporal lobe epilepsy. Epilepsia. 2012; 53(1): 147-156.
5. Koubeissi MZ, Kahriman E, Syed TU, Miller J, Durand DM. Low-frequency electrical stimulation of a fiber tract in temporal lobe epilepsy. Ann Neurol. 2013; 74(2): 223-231.
6. Jakobs M, Fomenko A, Lozano AM, Kiening KL. Cellular, molecular, and clinical mechanisms of action of deep brain stimulation-a systematic review on established indications and outlook on future developments. EMBO Mol Med. 2019; 11(4): e9575.
7. Gonzalez-Islas C, Hablitz JJ. Dopamine enhances EPSCs in layer II-III pyramidal neurons in rat prefrontal cortex. J Neurosci. 2003; 23(3): 867-875.
8. Slaght SJ, Paz T, Mahon S, Maurice N, Charpier S, Deniau JM. Functional organization of the circuits connecting the cerebral cortex and the basal ganglia: implications for the role of the basal ganglia in epilepsy. Epileptic Disord. 2002; 4 Suppl 3: S9-S22.
9. Bozzi Y, Dunleavy M, Henshall DC. Cell signaling underlying epileptic behavior. Front Behav Neurosci. 2011; 5: 45.
10. Starr MS. The role of dopamine in epilepsy. Synapse. 1996; 22(2): 159-194.
11. Waddington JL, Jenner P. D1: D2 dopamine receptor interactions: neuroscience and psychopharmacology (neuroscience perspectives). 1st ed. Academic Press; 1993.
12. Koob GF. Dopamine, addiction and reward. Semin Neurol. 1992; 4(2): 139-148.
13. Goto Y, Araki T, Kato M, Fukui M. Propagation of hippocampal seizure activity arising from the hippocampus: a local cerebral blood flow study. Brain Res. 1994; 634(2): 203-213.
14. Ahmadi M, Dufour JP, Seifritz E, Mirnajafi-Zadeh J, Saab BJ. The PTZ kindling mouse model of epilepsy exhibits exploratory drive deficits and aberrant activity amongst VTA dopamine neurons in both familiar and novel space. Behav Brain Res. 2017; 330: 1-7.
15. Rezaei M, Raoufy MR, Fathollahi Y, Shojaei A, Mirnajafi-Zadeh J. Tonic and phasic stimulations of ventral tegmental area have opposite effects on pentylenetetrazol kindled seizures in mice. Epilepsy Res. 2022; 189: 107073.
16. Budzikowski AS, Vahid-Ansari F, Leenen FH. Chronic activation of brain areas by high-sodium diet in Dahl salt-sensitive rats. Am J Physiol. 1998; 274(6): H2046-H2052.
17. Chung L. A brief introduction to the transduction of neural activity into Fos signal. Dev Reprod. 2015; 19(2): 61-67.
18. Malhi SM, Jawed H, Hanif F, Ashraf N, Zubair F, Siddiqui BS, et al. Modulation of c-Fos and BDNF protein expression in pentylenetetrazole-kindled mice following the treatment with novel antiepileptic compound HHL-6. Biomed Res Int. 2014; 2014: 876712.
19. Paxinos G, Franklin K. Paxinos and Franklin's the mouse brain in stereotaxic coordinates. 5th ed. Academic press; 2019.
20. Van Erum J, Van Dam D, De Deyn PP. PTZ-induced seizures in mice require a revised Racine scale. Epilepsy Behav. 2019; 95: 51-55.
21. Sadeghian A, Salari Z, Azizi H, Raoufy MR, Shojaei A, Kosarmadar N, et al. The role of dopamine D_2-like receptors in a "depotentiation-like effect" of deep brain stimulation in kindled rats. Brain Res. 2020; 1738: 146820.
22. Somogyi P, Takagi H. A note on the use of picric acid-paraformaldehyde-glutaraldehyde fixative for correlated light and electron microscopic immunocytochemistry. Neuroscience. 1982; 7(7): 1779-1783.
23. Tang Y, Liu L, Xu D, Zhang W, Zhang Y, Zhou J, et al. Interaction between astrocytic colony stimulating factor and its receptor on microglia mediates central sensitization and behavioral hypersensitivity in chronic post ischemic pain model. Brain Behav Immun. 2018; 68: 248-260.
24. Rasheed N, Alghasham A. Central dopaminergic system and its implications in stress-mediated neurological disorders and gastric ulcers: short review. Adv Pharmacol Sci. 2012; 2012: 182671.
25. Gangarossa G, Di Benedetto M, O'Sullivan GJ, Dunleavy M, Alcacer C, Bonito-Oliva A, et al. Convulsant doses of a dopamine D1 receptor agonist result in Erk-dependent increases in Zif268 and Arc/Arg3.1 expression in mouse dentate gyrus. PLoS One. 2011; 6(5): e19415.
26. Nair-Roberts RG, Chatelain-Badie SD, Benson E, White-Cooper H, Bolam JP, Ungless MA. Stereological estimates of dopaminergic, GABAergic and glutamatergic neurons in the ventral tegmental area, substantia nigra and retrorubral field in the rat. Neuroscience. 2008; 152(4): 1024-1031.
27. Taylor SR, Badurek S, Dileone RJ, Nashmi R, Minichiello L, Picciotto MR. GABAergic and glutamatergic efferents of the mouse ventral tegmental area. J Comp Neurol. 2014; 522(14): 3308-3334.
28. Ellwood IT, Patel T, Wadia V, Lee AT, Liptak AT, Bender KJ, et al. Tonic or phasic stimulation of dopaminergic projections to prefrontal cortex causes mice to maintain or deviate from previously learned behavioral strategies. J Neurosci. 2017; 37(35): 8315-8329.
29. Dreyer JK, Hounsgaard J. Mathematical model of dopamine autoreceptors and uptake inhibitors and their influence on tonic and phasic dopamine signaling. J Neurophysiol. 2013; 109(1): 171-182.
30. Gangarossa G, Di Benedetto M, O'Sullivan GJ, Dunleavy M, Alcacer C, Bonito-Oliva A, et al. Convulsant doses of a dopamine D1 receptor agonist result in Erk-dependent increases in Zif268 and Arc/Arg3.1 expression in mouse dentate gyrus. PLoS One. 2011; 6(5): e19415.
31. Tseng KY, O'Donnell P. Dopamine-glutamate interactions controlling prefrontal cortical pyramidal cell excitability involve multiple signaling mechanisms. J Neurosci. 2004; 24(22): 5131-5139.
32. Floresco SB, West AR, Ash B, Moore H, Grace AA. Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. Nat Neurosci. 2003; 6(9): 968-973.
33. Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron. 2005; 46(5):

703-713.
34. Cifelli P, Grace AA. Pilocarpine-induced temporal lobe epilepsy in the rat is associated with increased dopamine neuron activity. Int J Neuropsychopharmacol. 2012; 15(7): 957-964.
35. Goodman JH, Berger RE, Tcheng TK. Preemptive low-frequency stimulation decreases the incidence of amygdala-kindled seizures. Epilepsia. 2005; 46(1): 1-7.
36. Ferreira JG, Del-Fava F, Hasue RH, Shammah-Lagnado SJ. Organization of ventral tegmental area projections to the ventral tegmental area-nigral complex in the rat. Neuroscience. 2008; 153(1): 196-213.
37. Kalén P, Skagerberg G, Lindvall O. Projections from the ventral tegmental area and mesencephalic raphe to the dorsal raphe nucleus in the rat. Evidence for a minor dopaminergic component. Exp Brain Res. 1988; 73(1): 69-77.
38. Fields HL, Hjelmstad GO, Margolis EB, Nicola SM. Ventral tegmental area neurons in learned appetitive behavior and positive reinforcement. Annu Rev Neurosci. 2007; 30: 289-316.
39. Cousineau J, Lescouzères L, Taupignon A, Delgado-Zabalza L, Valjent E, Baufreton J, et al. Dopamine D2-like receptors modulate intrinsic properties and synaptic transmission of parvalbumin interneurons in the mouse primary motor cortex. eNeuro. 2020; 7(3): ENEURO.0081-20.2020.