Basic and Clinical
NEUROSCIENCE

January & February 2023, Volume 14, Number 1

Review Paper

Neurostimulation as a Putative Method for the Treatment of Drug-resistant Epilepsy in Patient and Animal Models of Epilepsy

Fatemeh Bakhtiarzadeh[1], Meysam Zare[1], Zahra Ghasemi[2], Samaneh Dehghan[3, 4], Azam Sadeghin[1], Mohammad Taghi Joghataei[5, 6], Nooshin Ahmadirad[6*]

1. Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.
2. Lunenfeld-Tanenbaum Research Institute, Toronto, Canada.
3. Stem cell and Regenerative Medicine Research Center, Iran University of Medical Sciences, Tehran, Iran.
4. Eye Research Center, The Five Senses Health Institute, Rasool Akram Hospital, Iran University of Medical Sciences, Tehran, Iran.
5. Department of Anatomy and Neuroscience, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
6. Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran, Iran.

Use your device to scan and read the article online

Citation Bakhtiarzadeh, F., Zare, M., Ghasemi, Z., Dehghan, S., Sadeghin, A., & Joghataei, M. T., et al. (2023). Neurostimulation as a Putative Method for the Treatment of Drug-resistant Epilepsy in Patient and Animal Models of Epilepsy. *Basic and Clinical Neuroscience, 14*(1), 1-18. http://dx.doi.org/10.32598/bcn.2022.2360.4

http://dx.doi.org/10.32598/bcn.2022.2360.4

Article info:
Received: 06 Jul 2022
First Revision: 18 Oct 2022
Accepted: 26 Oct 2022
Available Online: 01 Jan 2023

Keywords:
Drug-resistant epilepsy, Vagus nerve stimulation, Trigeminal nerve stimulation, Responsive stimulation system, Deep brain stimulation

ABSTRACT

A patient with epilepsy was shown to have neurobiological, psychological, cognitive, and social issues as a result of recurring seizures, which is regarded as a chronic brain disease. However, despite numerous drug treatments, approximately, 30%-40% of all patients are resistant to antiepileptic drugs. Therefore, newer therapeutic modalities are introduced into clinical practice which involve neurostimulation and direct stimulation of the brain. Hence, we review published literature on vagus nerve stimulation, trigeminal nerve stimulation, applying responsive stimulation systems, and deep brain stimulation (DBS) in animals and epileptic patient with an emphasis on drug-resistant epilepsy.

*** Corresponding Author:**
Nooshin Ahmadirad, PhD.
Address: *Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran, Iran.*
Tel: *+98 (21) 86704725*
E-mail: *ahmadiyerad@gmail.com*

Highlights

- Epilepsy is a chronic neurological disease followed by cognitive impairment and social problems.
- 30% of patients with epilepsy are drug resistant.
- Neurostimulation concluded vagus nerve stimulation, trigeminal nerve stimulation, responsive focused stimulation and deep brain stimulation.
- Deep brain stimulation is one of the newest ways to treat drug-resistant epilepsy.

Plain Language Summary

Neurostimulation is a new approach with many advantages for drug-resistant epileptic patients. It typically involves low-frequency stimulation and high-frequency stimulation, and apply through vagus nerve stimulation, trigeminal nerve stimulation, responsive focused stimulation and deep brain stimulation. The effect of electrical high and low-frequency stimulation on neuronal excitability and seizure occurrence has been demonstrated in experimental models, but the precise mechanism has not been well-known. The protective effect of neurostimulation seems mediated through desynchronization of neural activity.

1. Introduction

One of the most common neurological diseases is epilepsy, with abnormal electrical activity causing recurrent unprovoked seizures (Sirven, 2015). Effective drug treatment results in seizure freedom in about 70% of epileptic patients, although 30% of individuals are resistant to anti-epileptic drug therapy (Neligan et al., 2011). It is essential to identify patients with drug-resistant epilepsy to maximize drug therapy and start the evaluation process to see if they are candidates for surgery or other non-pharmacological alternatives. The International League Against Epilepsy (ILAE) describes drug-resistant epilepsy as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (P. Kwan et al., 2010). Seizure freedom is declared when a patient has been seizure-free for more than a year or has alternate seizures that are separated by a period three times longer than the largest interval between seizures before treatment, whichever is longer. Over 25% of epileptic patients show signs of drug-resistant epilepsy. (Westover et al., 2012). Poor control of their epileptic seizures increased their risks of early death, trauma, and psychosocial disorders while decreasing their quality of life. Drug-resistant epilepsy may exhibit brief remissions (4% of adult cases annually, with a higher rate in children), although epileptic seizures are frequently seen. (Devinsky et al., 2018). The first step in preparing for a preoperative evaluation and setting up potential treatment options in specialized units or centers is to identify patients with drug-resistant epilepsy. Furthermore, it is never a good idea to surgically eliminate the epileptogenic region. Hence, it is necessary to consider new and different treatments for drug-resistant patients.

2. Pharmacological Treatment for Epilepsy

Seizures are based on an imbalance between stimulation and inhibition. Ion transporters, pumps, and channels at the cellular level regulate the influx and outflow of positively or negatively charged ions into and out of neurons, respectively. In turn, factors, such as voltage or ligands binding directly to or via G protein receptors control these pumps and ion channels. (Bean, 2007; Dascal, 2001; Kandel et al., 2000)

Na^+, K^+, Ca^{2+}, and Cl_2 channels, the targets of many currently available antiepileptic medications, are the key channels in these processes ([automated external defibrillators] AEDs). The excitatory and inhibitory neurotransmitters, in particular glutamate and Gamma-aminobutyric acid (GABA), are another area of attention for AEDs. (Kandel et al., 2000). Other active neurotransmitters that modulate brain activity include monoamines such as serotonin (5-HT), dopamine (DA), and noradrenaline (NA), which may influence the initiation and progression of seizure activity. (Giorgi et al., 2004; Stefulj et al., 2010). However, primarily targeted by any current AED is not observed.

In 1857, Dr. Edward Sieveking introduced potassium bromide as the first antiepileptic drug (Clouston, 1868). With the discovery of the antiepileptic properties of phenobarbital, a new era has begun for the drug therapy of epilepsy (Hauptmann, 1912). In 1938, following the discovery of more effective drugs than phenobarbital, Tracy Putnam et al. introduced phenytoin, which is still used as a treatment for seizures (Merritt & Putnam, 1938). Sodium valproate (VPA) and lamotrigine were established in 1960 (Glauser et al., 2010). Carbamazepine was discovered in the same decade (Meunier, 1963). Sternbach was able to synthesize benzodiazepines in the 1960s (Browne & Penry, 1973). Following this, Henry Gastaut showed the anticonvulsant effects of diazepam (Gastaut,et al., 1965), and with the development of drugs in this category including clonazepam and clobazam, these drugs became the most effective medications in seizure therapy (Aghdash , 2021; Silva et al., 2006).

The National Institute of Neurological Disorders and Stroke (NINDS) in the United States launched a program for anticonvulsant medications in 1975, ushering in a new era of medicinal treatment for seizures. Anticonvulsant drugs are divided into four subgroups based on their possible mechanism of action. The first group affecting sodium channels and reducing the channel activity includes carbamazepine, phenytoin, eslicarbazepine, and rufinamide (Rogawski & Löscher, 2004). The second group includes the agents that block calcium channels, such as ethosuximide, gabapentin, and pregabalin (Meldrum & Rogawski, 2007). The third category consists of drugs that increase GABA activity, including barbiturates, and benzodiazepines (Sills & Brodie, 2002). The fourth class includes several broad-spectrum AEDs that have several mechanisms of action in a wide range of seizures (Kawn & Brodie, 2006). For example, felbamate affects the glutamate receptors, and levetiracetam binds to the synaptic vesicle protein 2A (Meldrum & Rogawski, 2007). But as mentioned, approximately one-third of patients have shown resistance to the current drugs, therefore new medical strategies have been sought for these patients.

3. Neurostimulation and Brain Stimulation History

The history of brain stimulation therapy began in 1936 when Wilder Penfield first used stimulation to treat epilepsy (Penfield, 1936). After that, neurostimulation was used to control seizures in epileptic patients by the Cooper group in 1974 for the first time. Although cerebellar stimulation reduced seizures in 56% of patients (Cooperet al., 1974), other controlled clinical trials showed no advantages (Van Buren et al., 1978; Wright et al., 1984) and the technique was greatly left. But Cooper and his group continued to apply deep brain stimulation (DBS) in seizure patients and finally, they reported that anterior nucleus of the thalamus (ANT) stimulation could suppress abnormal neural discharge within the limbic system. They stimulated ANT bilaterally in six patients with drug-resistant complex partial seizures, which reported significant clinical control of the seizures in four of these patients (Cooper et al., 1980). After that ANT stimulation was used in some clinical research (Hodaie et al., 2002; Kerrigan et al., 2004; Lee et al., 2006a, 2006b; Lim et al., 2007; Lim et al., 2007). In 1948, the first silver electrode was placed into the caudate nucleus of a depressed Parkinson woman and was connected to an implanted induction coil (Pool, 1954).

Pool et al. reported that her mood and appetite improved eight weeks after electrode implantation. The invention of the stereotactic devices led to less invasive and accurate neurosurgery by Spiegel and Wycis in 1947 (Spiegel et al., 1947). The discovery of the levodopa impacts on movement disorders treatment diminished the stereotactic surgery in 1960 for almost two decades (Cotzias et al., 1967). Identification of levodopa side effects, such as dyskinesia as well as resistance to it (Fox et al.), in 1987, led to the re-use of thalamic stimulation by Benabid as a renaissance of brain stimulation to treat movement disorders (Benabid et al., 1987). Different brain regions have been targeted with DBS in preclinical (Wyckhuys et al., 2009) and clinical trials (Sprengers et al., 2017) resulting in variable results. Moreover, many clinical studies including multicenter, double-blind, randomized bilateral stimulation of the anterior nucleus of the thalamus for epilepsy (SANTE) experiment of ANT-DBS in epilepsy also confirm the efficacy (Fisher et al., 2010; Perez- Malagon & Lopez-Gonzalez, 2021). In 2018, the U.S. Food and Drug Administration (FDA) approved the application of DBS in epileptic patients older than 18 years with focal and drug-resistant seizures (Fisher et al., 2010). The results of these studies leading to ANT-DBS have been approved (Conformité Européene) for epilepsy therapy in Europe since 2010. Numerous studies have concluded that hippocampus DBS is a promising treatment option for people with drug-resistant epilepsy as a result of these cases. (Sprengers et al., 2017; Vetkas et al., 2022).

In addition, the crucial areas of the brain undergoing electrotherapy in humans and animals to control seizures are the anterior and central-middle nuclei of the thalamus, hippocampus, caudal nucleus, substantia nigra, locus coeruleus nucleus, cerebellum, thalamic nuclei

and epileptic foci of the cerebral cortex (Theodore & Fisher, 2004; Vetkas et al., 2022). According to previous research, an epileptiform discharge, including epileptic seizures, can be eliminated by electrical stimulation of hippocampal slices both *in vitro* and in patients with temporal lobe epilepsy. Additionally, Lesser et al. reported that in individuals with clinical seizures, neocortical electrical stimulation inhibited evoked after-discharges. (Boon et al., 2007; Velasco et al., 2000). Therefore, applying deep electrical stimulation to control seizures is delivered in two approaches, direct stimulation of the epileptic center, and (a) stimulation of brain areas that impact the excitability of the cerebral cortex and are involved in the spread of seizures. Electrical stimulation is available in a variety of forms, including DBS, VNS, trigeminal nerve stimulation, and stimulation of peripheral nerves. One of the initial methods employed by the FDA was VNS. (Lanska, 2002).

Vagus nerve stimulation (VNS)

One of the essential components of the autonomic nervous system, the vagus nerve regulates the endocrine-immune nerve axis and metabolic homeostasis to maintain homeostasis through its afferent and efferent pathways. (Ruffoli et al., 2011). However, the key function of the vagus nerve is to mediate and convey sensory information from throughout the body to the brain. (Zagon, 2001). The right and left vagus nerves exit the brainstem and traverse the upper chest to the diaphragm and abdominal cavity through the neck. The sensory afferent fibers leave the brainstem in the nucleus tractus solitarius, where they convey fibers directly or indirectly to the different regions of the brain, including the orbitofrontal cortex, dorsal raphe nuclei, locus coeruleus, amygdala, hypothalamus, and thalamus. (Krahl, 2012).

Any kind of vagal stimulation technique is called VNS. The ability of carotid artery compression and manual massage to prevent seizures was first discovered in the 1880s. Vagal activation was the cause of this outcome. (Lanska, 2002). In the 1930s and 1940s, vagal stimulation was used to study how VNS affected the brain system. Studies in cats and monkeys have shown that VNS affects brain function. Additionally, research in dogs showed that VNS had anticonvulsant effects on dogs that had experimentally produced seizures. (Zabara, 1992). The VNS was approved in 1997 by the FDA as a treatment strategy for refractory partial-onset seizures (Schachter & Saper, 1998). The success of this approach in treating epileptic patients was proven by data gathered during the first ten years of VNS application in drug-resistant patients. After receiving VNS treatment for two to three years, almost 40% of patients demonstrated a 50% reduction in seizures. (Bonaz et al., 2013). The frequency of vagal nerve stimulation was a crucial factor that was considered by researchers in the early years. According to Ben Menachem et al., stimulation of the vagus nerve at low frequencies reduced seizure frequency by 6%, while stimulation at high frequencies reduced seizure frequency by 25%. (Ben-Menachem & Manon-Espaillat, 1994). Since a reduction in seizure frequency of at least 50% compared to the typical patient is typically considered when VNS is recognized as an effective treatment. (Englot et al., 2011a).

According to a research conducted in 1998 by Handforth et al., patients who received high-frequency VNS experienced a 28% reduction in seizure frequency, while those who received sham stimulation had a 15% reduction (Handforth et al., 1998). Amar et al implanted VNS in 17 patients to further demonstrate the impact of VNS. The findings showed that 57% of patients had achieved respondent status. (Amar et al., 1998). In the earlier decades, the short-term effects of vagal stimulation on seizures were sought; however, long-term studies on vagal stimulation have shown that a gradual increase in vagal stimulation appears following an increase in implantation time (Englot et al., 2011a; Englot et al., 2011b; Englot, etal., 2016). Table 1 presents a summary of studies on vagal stimulation.

The closed-loop system in VNS has received more attention in recent years. The heart rate is more noticeable during vagal stimulation. AutoStim, a closed-loop feature on more recent responsive VNS (rVNS) devices, can identify ictal tachycardia. Then, using this quick increase in heart rate as a substitute indicator, clinicians may identify seizures and administer more predetermined stimulations. (Boon et al., 2015;Fisher et al., 2016). Despite the limitation of studies in this area, 36% to 71% of patients have reported decreases in seizure frequency. (Datta et al., 2020; Hamilton et al., 2018; Rabenstein et al., 2019; Ryvlin et al., 2021).

Trigeminal nerve stimulation

The trigeminal nerve is the largest cranial nerve with three main branches and significant connections to the brainstem and other brain regions including the nucleus tractus solitarius (NTS), locus coeruleus, and reticular formation, which are crucial for preventing seizures. (Caous et al., 2001; Krout et al., 2002; Reeves, 2007). An especially prominent non-invasive treatment for drug-resistant epilepsy is external trigeminal nerve stimulation. Numerous investigations demonstrated that the trigemi-

nal nerve and its components have anticonvulsant effects in animals with epilepsy. (Hoskin et al., 2001; Krout et al., 2002; Walker et al., 1999). Trigeminal nerve stimulation has been shown to have antiepileptic benefits on individuals or animals, and the frequency of stimulation affects its success. (DeGiorgio et al., 2011; Fanselow et al., 2000).

In 2001, a pilot study began on seven people with seizures. Preliminary findings in the first three months after implantation of the trigeminal nerve stimulation showed a 66% reduction in seizure frequency. Additionally, the mean seizure frequency decreased by 59% twelve months after implantation (DeGiorgio et al., 2009; DeGiorgio et al., 2006). Other studies in humans also confirmed that trigeminal nerve stimulation reduces seizure frequency. In the first phase, 13 people showed that 42% of responders to these stimuli in the first 6 and 12 months. In the second phase, in 50 patients, the average responders reached 40.5% in 18 months after implantation (DeGiorgio et al., 2013; Pop et al., 2011). In 2015, Jason Soss et al. evoked the trigeminal nerve of 35 people with seizures as follows, the 30s on, 30s off, pulse duration of 250 s, and frequency of 120 Hz. Their results showed that the average frequency of seizures decreased significantly to 34.8% during one year after nerve stimulation (Soss et al., 2015). See Table 2 for more studies on trigeminal nerve stimulation and seizure treatment.

4. Responsive Focused Stimulation

In 2013, responsive neurostimulation (RNS) was approved as a therapeutic method for drug-resistant focal epilepsy in the United States. In this method, the electrodes are implanted in the center of the seizure and the programmed stimuli are applied by the physician (Heck et al., 2014). Consequently, responsive neurostimulation suppresses the subsequent seizures (Lesser et al., 1984). RNS also delivers electrical stimulation supported by identified patterns which can reduce subsequent discharges and prevent seizures (Motamedi et al., 2002a). Responsive neurostimulation is considered in patients with a known seizure focus who are not surgical candidates. In patients with multiple foci such as bipolar epilepsy, the RNS is implanted and scheduled for electrical stimulation.

The first clinical trial for RNS was a controlled trial that lasted twelve weeks in 191 adult patients. The outcomes demonstrated a considerable decrease in seizure frequency in the treatment group (37.9% decreases as opposed to 17.3% in the control group). Initial response rates were 29% in the treatment group and 27% in the control group (defined as 50% or fewer seizures). (M. J. Morrell, 2011). Another research of 111 patients with temporal lobe epilepsy revealed 66.5% fewer seizures during a six-year follow-up period, 45% of patients had been seizure-free for at least three months, and 29% of the patients' seizures were spaced more than six months apart. (Geller et al., 2017). Jobst et al. administered the RNS system to 126 patients with neocortical epilepsy, and the results showed that the mean seizures attenuated to 51-70%. A total of 26% of this group has been seizure free for 6 months or more. These favorable long-term outcomes indicate that RNS results improve over time (Jobst et al., 2017).

The diagnosis of seizures before they happen has received more attention in recent years. The so-called closed-loop excitation device, responsive or adaptive Deep brain stimulation (DBS), depends on functional brain feedback such an aberrant non-electrographic discharges. The excitation settings may be changed using these closed-loop methods. DBS research has recently concentrated on how to read brain activity and use it as feedback to regulate therapeutic stimulation. (Chang et al., 2013; Morrell, 2006). Various studies seek to find the best algorithm (Salam, Sawan, & Nguyen, 2010; Zare et al., 2020)

5. Deep Brain Stimulation (DBS)

DBS has been successful in treating neurodegenerative illnesses, such as tremors, dystonia, obsessive-compulsive disorder, chronic pain, Tourette's syndrome, headache, eating disorders, depression, and epilepsy. It was authorized to control specific epileptic seizure types. The FDA has also certified and approved the deep stimulation of the lateral nucleus of the thalamus, hippocampus, and cortical regions in some epileptic situations. (Theodore & Fisher, 2004).

Based on the frequency range, deep brain stimuli are defined in terms of use as high-frequency stimuli (50 to 200 Hz), and low-frequency stimuli (1-7 Hz). Data revealed that high-frequency stimulation (HFS) led to a reduction in seizure incidence and interictal spikes in epileptic patients (Laxpati, et al., 2014).

High-frequency stimulation (HFS)

To treat neurodegenerative diseases, high-frequency electrical stimulation of the deep brain network has been established. For instance, administering HFS to the subthalamic nucleus in Parkinson's disease or the thalamus in tremors has been shown to have a local inhibitory effect that reduces symptoms. (Milosevic et al., 2018).

Table 1. Evidence of VNS efficacy in epilepsy treatment

Study	n	Seizure Type	Notes	Follow Up	Mean Seizure Reduction, %
Ben-Menachem & Manon-Espaillat, 1994	114	Partial	High vs low stim	3 m	25 (high) vs 6 (low)
Handforth et al., 1998	196	Partial	High vs low stim	3 m	28 (high) vs 15 (low)
Amar et al., 1998	17	Partial	High vs low stim	3 m	71 (high) vs 6 (low)
Parker et al., 1999	15	Mixed	Children with encephalopathy	1 y	17
Labar et al., 1999	24	Generalized		3 m	46
Ben-Manachem et al., 1999	64	Mixed		3-64 m	NR
DeGiorgio et al., 2000	195	Mixed		12 m	45
Scherrmann et al., 2001	28	Mixed	2 Stim. paradigms	NR	30 (overall)
Westerveld & Spencer, 2003	29	Partial		1-2 y	53
Vonck et al., 2004	118	Mixed		6 m<	55
DeGiorgio et al., 2005	61	Partial	3 Stim. paradigms	3 m	26 (overall)
Majoie et al., 2005	19	Mixed	Children with encephalopathy	2 y	20.6
Huf et al., 2005	40	NR	Low IQ adults	2 y	26
Kang et al., 2006	16	Mixed	Children	1 y<	50
Ardesch et al., 2007	19	Partial		2 y<	25 (at 2 y)
Elliott et al., 2011	65	NR	Adult and children	10 y<	76.3 and 80
Klinkenberg et al., 2012	41	Mixed	High vs low stim	3 m	16 (high) vs 21 (low)
Ryvlin et al., 2014	112	Partial		2 y	23 (at 1 y)
Boon et al., 2015	31	Mixed	AutoStim trial	1 y	NR
Fisher et al., 2016	20	Mixed	AutoStim trial	1 y	47.3
Pakdaman et al., 2016	44	Partial		5 y	67
Liu et al., 2018	63	NR	Drug-resistant epilepsy	1 y	53.97
Marti et al, 2020	46	Lennox–Generalized Gastaut Syndrome (LGS). Epilepsy (GGE)		5 y	LGS=41.7 GGE=64.7
Muthiah et al., 2020	99	NR	Children	1 y 2 y 4 y	55 60 52
Russo et al., 2021	89	Resistant-drug Epilepsy	Children	1 y 5 y	25.8 31.5

Abbreviations: GGE: Genetic generalized epilepsy; LGS: Lennox-gastaut syndrome; M: Months; NR: Not reported. NEUROSCIENCE

Rats' spontaneous absence seizures were prevented when rats were given HFS (130 Hz) in a bilateral subthalamic nucleus injection. Additionally, bilateral subthalamic nuclei excitotoxic injuries partially reduced absence seizures. As a result, because the basal ganglia system is involved in controlling generalized seizures, HFS was developed to be utilized in the treatment of specific types of seizures. (Vercueil et al., 1998). According to Hamani et al., status epilepticus and pilocarpine-induced seizures may be prevented by bilaterally administering HFS of the anterior thalamic nucleus (the thalamus plays a critical role in the secondary generalization of seizures). (Hamani et al., 2004). In addition, giving patients with inoperable temporal lobe epilepsy high-frequency responsive stimulation to the epileptogenic zone or the anterior nucleus of the thalamus reduced spontaneous seizures. (Osorio et al., 2005). After that, in response to the afterdischarges, brief pulse stimulation bursts were used to terminate or abbreviate them. (Motamedi et al., 2002b) and seizures were suppressed by responsive cortical stimulation in patients (Kossoff et al., 2004). When used on anticipated spontaneous episodes in the status epilepticus rat model, high-frequency hippocampus stimulation increased seizure-free periods and decreased seizure occurrence during the preictal interval. (Nair et al., 2006).

Application of HFS (130 Hz) and (100 Hz) in the hippocampus of moderately epileptic rats evoked afterdischarge properties and blocked the axonal conduction, respectively, resulting in suppression of seizure activity (Chiang, , 2013; Wyckhuys et al., 2007). Also, HFS applying to the thalami reticular nucleus significantly increased latency for tonic-clonic generalized seizure and status epilepticus (Pantoja-Jiménez et al., 2014).

High-frequency stimulation (HFS) mechanism

Based on the studies, HFS is useful in seizure treatment. Nevertheless, the mechanism of seizure improvement has not been fully determined. DBS, especially high-frequency hippocampal stimulation, led to seizure control in patients (Velasco et al., 2000; Vonck et al., 2004) and animal models (Cuellar-Herrera et al., 2006; Staba et al., 2002). The association between HFS performance and desynchronized neural activity, which may have therapeutic consequences, is the logical explanation for the phenomenon. (Boon et al., 2007).

Enhancing GABAergic neurotransmission in the ventral hippocampus via HFS has been shown to improve the effectiveness of low-dose antiepileptic drugs in lithium-pilocarpine-induced status epilepticus. (Cuellar-Herrera et al., 2006). These findings revealed that HFS enhances GABAergic neurotransmission (Cuellar-Herrera et al., 2006).

GABA and glutamate extracellular concentration fluctuations during seizures can be attributed to a deficiency in the amino acid transporters caused by epilepsy. (Rakhade & Loeb, 2008). Typically, astrocytes play a fundamental part in clearing the synapses of neurotransmitters. As a result, astrocytes may help control glutamate and GABA concentrations during interictal discharges. Through a Ca^{2+}-dependent mechanism, astrocytes in epileptic tissue increase extrasynaptic glutamate and reduce glutamate uptake, often resulting in transporter-mediated GABA release. (Héja et al., 2009). Therefore, drug-resistant epilepsy may modify processes involved in the efflux of GABA and glutamate from synapses to the blood. (Terasaki & Hosoya, 1999). Findings demonstrated that applying HFS in the ventral hippocampus decreased seizure susceptibility by increasing extracellular GABA following the ictal episode. (Luna-Munguia et al., 2011). Accordingly, the HFS effect is strongly impacted by GABA release and GABA receptor activation. (Wang et al., 2016).

Delivering HFS is thought to have inactivated presynaptic GABA transporters, which inhibited GABA reuptake and elevated GABA levels in the synaptic cleft. (Li, Qadri, & Moser, 2004).

Findings indicated that subthalamic nucleus HFS initially increased postsynaptic glutamate receptors, including ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, ionotropic kainate receptors, ionotropic NMDA receptors, and metabotropic glutamate receptors activation. AMPA/kainate receptor activation quickly opens Na^{+} channels and causes 5-enolpyruvylshikimate-3-phosphate (EPSPs) to occur. However, a prolonged increase of glutamate concentration following subthalamic nucleus HFS caused immediate desensitization of AMPA/kainate receptors and eventually desensitize local AMPA/kainate receptors (Lee et al., 2006a). Subthalamic nucleus HFS also led to a blockade of voltage-gated Ca^{2+} channels, persistent Na^{+} channels, and transient depression of T- and L-type Ca^{2+} channels (Beurrier et al., 2001).

Studies showed that HFS can alter synaptic responses by affecting the inhibitory postsynaptic currents (IPSC) and excitatory postsynaptic currents (EPSC). Applying HFS to inhibitory interneurons in CA1 hippocampal slices through depolarization of interneuron and GABA release led to IPSP elicitation (Jackson et al., 1999).

Table 2. Evidence of trigeminal nerve stimulation efficacy in epilepsy treatment

Study	Subject	Model	Follow Up	Parameter Stim	Mean Seizure Reduction, %
Fanselow et al., 2000	Long-Evans hooded rats (n=8)	Pentylenetetrazole (PTZ)		Square current pulses (duration of 500 µsec, current 3 to 11 mA, Frequency 1 to 333 Hz)	78
Wang et al., 2016	Sprague-Dawley rats	Pilocarpine		frequency (140 Hz), intensity (10 mA), duty cycle (1 min on: 4 min off), and pulse width (0.5 ms)	NR
Mercante et al., 2017	Sprague-Dawley rats (n=40)	Pentylenetetrazole (PTZ)		-(3-hour session; 30s 92 on, 5 min off; 30 Hz; 500 µs; 2mA)	Mean seizure frequency decrease compared with control
DeGiorgio et al., 2003	Human (n=2)	Generalized		Current (device setting=0 to 1, <8 mA) current to 8 to 25 mA	39 76
DeGiorgio et al., 2006	Human (n=5)	Partial or generalized	3-6 m	Biphasic square wave pulse (120 Hz, 250 µs, ≤30 s on and 30 s off, current 0 to 100 mA)	57
DeGiorgio et al., 2009	Human (n=5)	Complex-partial/ generalized	1 y	Biphasic square wave pulse (120 Hz, 250 µs, ≤30s on and 30 s off)	50
Pop et al., 2011	Human (n=14)	Complex-partial/ generalized	Safety of external TNS	NR	NR
DeGiorgio et al., 2013	Human (n=50)	Complex partial or tonic-clonic	6 m	Frequency=120 Hz and pulse duration , 250 ms. Active control settings were frequency 2 Hz, duty cycle 2 s on and 90 s off, and pulse duration 50 ms	40.5
Soss et al., 2015	Human (n=50)	Complex partial and/or secondarily generalized tonic-clonic seizures	1 y	(30 s on, 30 s off, pulse duration of 250 s, frequency of 120 Hz	50
Gil-López et al., 2020	Human (n=50)	Focal to generalized	6-12 m	Bipolar (intensity <10 mA, frequency 120 Hz, pulse duration 250 µs, and duty cycle 30 s on and 30 s off)	50

NEUROSCIENCE

High-frequency electrical stimulation through 5-enol-pyruvylshikimate-3-phosphate (EPSPs) depression reduced the excitability of neurons responsible for the antiepileptic effect. The antiepileptic function of HFS is mediated mostly through the short-term synaptic depression of excitatory neurotransmission (Schiller & Bankirer, 2007). Depletion of synaptic vesicles from the pool appears to be the most significant process relating to synaptic depression. (Zucker & Regehr, 2002). Presynaptic metabotropic glutamate receptors activation, AMPA receptors desensitization, presynaptic voltage-gated calcium channels inactivation, and saturation of glutamate receptors are pre- and postsynaptic feasible mechanisms contributing to synaptic depression (Schneggenburger et al., 2002; von Gersdorff & Borst, 2002). High-frequency electrical stimulation has also been demonstrated to reduce the excitability of neurons by deactivating voltage-gated sodium channels. (Beurrier et al., 2001).

In summary, the possible mechanisms involving the HFS action on the epileptic activity included HFS increases the extracellular potassium concentration and results in neuronal depolarization blockade (Bikson et al., 2001; Lian et al., 2003). Elevated potassium concen-

tration gradually inactivates Na^+ channels and leads to the inhibition of action potentials initiation (Traub et al., 1991). Also, the lasting period of after-hyperpolarization decreases the excitability of axons. This hyperpolarization is produced by increased activity of the Na^+/K^+-pump following HFS application in the hippocampus (Feng et al., 2014; Lu & Gean, 1998), in addition to increased release or activation of inhibitory neurotransmitters, such as GABA (Windels et al., 2000). Furthermore, desynchronization of the network has a negative impact on the synchronization and spread of paroxysmal activity. (Mirski & Fisher, 1994; Velasco et al., 1987).

Despite the favorable and anticonvulsant effects of HFS in epileptic patients, it also has adverse effects (Feddersen et al., 2007; Lado, 2006). Repeated application of HFS neutralizes its anticonvulsant effect and can even cause seizures. In addition, laboratory and clinical studies demonstrated prolonged HFS administration causes tissue damage and subsequent dysfunction of the stimulated area. Numerous studies have demonstrated that low-frequency electrical stimulation (LFS) can significantly reduce neuronal activity. Following the administration of LFS, no tissue damage has been documented thus far.

Low-frequency stimulation (LFS)

In 1980, Gaito reported that the application of LFS (1-3 Hz) before or after kindling stimuli induces strong and sustained inhibition of seizure activity in the amygdala kindling model and these effects last for about one month (Gaito, 1980). In 2005, Goodman et al. demonstrated the reduced incidence of seizures in kindled animals following applying LHS (1Hz) during the amygdala kindling process. They suggested LFS as a suitable treatment method to prevent seizures in epileptic patients (Goodman et al., 2005). The anticonvulsant effects of applying LFS in epileptic patients have also been shown. Lim et al. found a decrement in seizures occurrence following hippocampal stimulation by LFS (5 Hz, 90 μs) (Lim et al., 2016).

The anticonvulsant effect of LFS has been observed in different seizure animal models and various areas of the brain. For example, 1 Hz stimulation of the hippocampus or perforated pathway during 2 hours attenuated seizures; however, it did not affect the spontaneous seizure rate (Bragin et al., 2002). After electrotherapy of the caudate nucleus with 4 to 6 Hz, the reduction of interictal spikes and cessation of focal seizures occurred. Improving effects in the lithium-pilocarpine model indicated following subiculum electrical stimulation with 1 Hz frequency, 0.1 ms pulse duration, and 300 μA intensity (Zhong et al., 2012). Inhibition of epileptiform activity (high K^+, Low Mg^{2+} models) reported following Schaefer collateral electrical stimulation with a frequency lower than 5 Hz (Ghasemi et al., 2018a; Ghasemi et al., 2019; Ghasemi et al., 2018b). Besides, a decrement in the occurrence and duration of seizures was demonstrated following LFS (1-3 Hz) delivery to the dorsal hippocampus in the genetic model of epilepsy and bilaterally to the thalamus in the pilocarpine model (Kile et al., 2010).

LFS mechanism

Evidence showed that LFS is effective in controlling seizures and improving the associated cognitive impairments. However, the mechanisms involved in these effects have not been fully identified. Applying low-frequency stimulation appears to result in reduced neuronal spike firing, synaptic activity alteration, and changes at the molecular levels.

LFS can alter synaptic potentiation, synaptic strength affected by synapses activity. Synaptic activity increases strongly following the occurrence of a seizure, consequently, leading to increased synaptic strength, a phenomenon similar to long-term potentiation. By considering the similarities between LFS anticonvulsant effects and LFS-induced long-term depression (LTD), it has been hypothesized that one of the most important mechanisms involved in LFS anticonvulsant effects may be LTD-like or depotentiation. After determining the LFS anticonvulsant effect in 1950, for the first time, the hypothesis of similarity between LFS performance and depotentiation was proposed and the phenomenon of quenching was introduced. According to the definition of quenching, it is a physiological manipulation that has no significant effect on behavior but has a long-term inhibitory effect on seizure severity and epileptogenesis. Meanwhile applying LFS increases the after-discharge threshold, which can be sustained for several weeks. The depotentiation effect of LFS has been demonstrated in the hippocampus of consciousness and anesthetized animals and also in brain slices (Weiss et al., 2012).

LFS modifies the neuronal function to induce LTD or depotentiation by altering the permeability of the neuronal membrane to calcium ions through NMDA receptors or voltage-gated calcium channels in postsynaptic neurons (Pi & Lisman, 2008). LFS by activating the CaMKII enzyme and calcineurin causes dephosphorylation of the AMPA receptor GluR1 subunit, which leads to synaptic activity reduction via reducing the permeability

or downregulation of these receptors. However, the process of depotentiation heavily depends on the activation of the NMDA receptor and the metabotropic receptor (mGluR5) (Lee et al., 2000).

On the other hand, the anticonvulsant effects of LFS are mediated by known neuromodulators, such as adenosine (Fujii et al., 2000) and endocannabinoids (Zhu-Ge et al., 2007). In this regard, research has demonstrated that the anticonvulsant effects of LFS in kindled animals required the activity of adenosine A1 receptors and that LFS impact on seizures was suppressed by A1 receptors antagonist. (Mohammad-Zadeh et al., 2009). In addition, after LFS is applied to the CA1 region of the hippocampus, adenosine receptor expression rises. Adenosine inhibits epileptogenesis and seizure-induced potentiation in the kindling seizure model. (Jahanshahi et al., 2009). It has been demonstrated that some of the anticonvulsant functions of LFS involve endocanbionide receptors; hence administering CB1 antagonists reduced the inhibitory effects of LFS on seizures (Mardani et al., 2018). Another investigation showed the significance of dopamine D2-like receptors in the anticonvulsant effects of LFS. (Sadeghian et al., 2020). Gal1 and Gal3 receptors have also been shown to contribute to the anticonvulsant effects of LFS. (Sadegh et al., 2007).

It is noteworthy that factors involved in the LFS performance act through Gi protein and reduce cAMP (Mohammad-Zadeh et al., 2009). Besides, it has been discovered that LFS impacts gene expression of regulator G protein signaling (RGS). LFS decrease and increase gene expression of RGS4, RGS10, and RGS2 respectively (RGS4 and RGS10 decrease the Gi activity whereas RGS2 decreases the Gs activity) (Namvar et al., 2017).

Accordingly, ERK signaling also mediates the LFS anticonvulsant effect. Given the wide range of the Gi and ERK signaling pathways functions and the role of many other signaling pathways in controlling them, it can be argued that actions to produce LFS anticonvulsant effects include a wide range of signaling molecules that require extensive research (Mardani et al., 2018).

In addition to the aforementioned actions, LFS can alter synaptic responses by affecting the inhibitory postsynaptic currents (IPSC) and excitatory postsynaptic currents (EPSC). It was demonstrated that applying LFS in kindled rats increased the GABAergic currents (Asgari et al., 2016). Furthermore, LFS application increased the interaction between GABA receptors and phenobarbital so that even ineffective doses of phenobarbital could significantly increase the GABAergic currents (Asgari et al., 2016). Decreased glutamatergic currents have also been observed in CA1 region of the hippocampus following LFS application (Yang et al., 2005). Applying LFS in kindled rats reduced neuronal hyperexcitability. Electrophysiological properties assessment showed that applying LFS in epileptic animals attenuated the seizure-inducing neuronal hyperexcitability in CA1 pyramidal neurons. In this circumstance, the threshold of action potential firing was increased and the frequency of action potential occurrence was decreased following depolarized current application (Ghotbedin et al., 2013). Recently, *in vitro* studies revealed that group 1 metabotropic glutamate receptors and alpha-adrenergic receptors mediate the inhibitory effect of LFS applying on epileptiform activity in CA1 rat hippocampal slices (Ahmadirad et al., 2021; Ghasemi et al., 2021; Rezaei et al., 2021) LFS applying improved synaptic plasticity impairment following epileptiform activity, this effect mediated by alpha1 adrenergic receptor (Ahmadirad et al., 2019). Considering the role of different ion channels in action potential occurrence, it seems that LFS application has anticonvulsant effects by changing the activity of different types of ion channels, including GABA receptors and ionotropic glutamatergic receptors.

5. Conclusion

For drug-resistant epilepsy, neurostimulation is an effective treatment option, with improvements over time and few major complications. Long-term follow-up research on RNS and DBS is promising, while VNS data are limited. ANT DBS is more effective for focal seizures and hippocampal DBS is more effective for temporal lobe seizures. Successful ANT DBS in patients with epilepsy increases connectivity in the default mode network, increasing the threshold for seizure propagation. In addition, increased hippocampal GABA concentration may suppress seizures through an inhibitory effect on the hippocampus. These findings will be confirmed by future studies. The electrode position, stimulation parameters, epilepsy type, and stimulation duration all affect the clinical result of DBS for epilepsy. DBS for epilepsy may result in better results and fewer abrupt, unexpected deaths due to recent developments in anatomical targeting, functional neuroimaging, responsive neurostimulation, and sensing of local field potentials. DBS for epilepsy still needs to be thoroughly assessed in confirmatory pilot studies and pivotal randomized controlled trials before it can be made available to a larger patient population. Determining the ideal targets and stimulation parameters is still important. DBS may be useful for patients who are not good candidates for epi-

lepsy surgery. VNS has been demonstrated to be somewhat safe, similar to new AEDs, and effective to treat epilepsy. There is a consensus regarding efficacy that one-third of patients experience a significant improvement in seizure control with a reduction of seizure frequency of at least 50%, one-third of patients experience a significant reduction of seizure frequency between 30% and 50%, and one-third experience little or no effect. It has been observed that the efficacy of VNS treatment is improved with prolonged treatment, up to 18 months postoperatively, unlike treatment with AEDs. Identifying the best responders and finding optimal stimulation parameters will become easier after further analysis of larger patient groups and understanding the mode of action.

The mechanisms behind the antiepileptic impact of stimulation are still unknown, despite the growing interest in the possible utility of electrical stimulation to treat a variety of neurological illnesses, including intractable epilepsy. Reduced excitability of neurons, enhanced inhibitory neurotransmission, and depression of excitatory neurotransmission are the three main putative processes that have been proposed.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization and supervision: Nooshin Ahmadirad, Fatemeh Bakhtiarzadeh and Mohammad Taghi Joghataei; Writing, original draft: Nooshin Ahmadirad and Fatemeh Bakhtiarzadeh; Writing, review, and editing: Meysam Zare, Zahra Ghasemi, Samaneh Dehghan and Azam Sadeghin.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

We woould like to thank Cellular and Molecular Research Center of Iran University of Medical Sciences for their support.

References

Aghdash S. N. (2021). Herbal medicine in the treatment of epilepsy. *Current Drug Targets, 22*(3), 356–367. [DOI:10.2174/1389450121999201001152221] [PMID]

Ahmadirad, N., Fathollahi, Y., Janahmadi, M., Ghasemi, Z., Shojaei, A., & Rezaei, M., et al. (2021). The role of α adrenergic receptors in mediating the inhibitory effect of electrical brain stimulation on epileptiform activity in rat hippocampal slices. *Brain Research, 1765,* 147492. [DOI:10.1016/j.brainres.2021.147492] [PMID]

Ahmadirad, N., Fathollahi, Y., Janahmadi, M., Shojaei, A., Ghasemi, Z., & Barkley, V., et al. (2019). Low-frequency electrical stimulation reduces the impairment in synaptic plasticity following epileptiform activity in rat hippocampal slices through α1, But Not α2, adrenergic receptors. *Neuroscience, 406,* 176–185. [DOI:10.1016/j.neuroscience.2019.03.007] [PMID]

Amar, A. P., Heck, C. N., Levy, M. L., Smith, T., DeGiorgio, C. M., & Oviedo, S., et al. (1998). An institutional experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy: Rationale, technique, and outcome. *Neurosurgery, 43*(6), 1265–1280. [DOI:10.1227/00006123-199812000-00001] [PMID]

Ardesch, J. J., Buschman, H. P., Wagener-Schimmel, L. J., van der Aa, H. E., & Hageman, G. (2007). Vagus nerve stimulation for medically refractory epilepsy: A long-term follow-up study. *Seizure, 16*(7), 579- 585. [DOI:10.1016/j.seizure.2007.04.005] [PMID]

Asgari, A., Semnanian, S., Atapour, N., Shojaei, A., Moradi-Chameh, H., & Ghafouri, S., et al. (2016). Low-frequency electrical stimulation enhances the effectiveness of phenobarbital on GABAergic currents in hippocampal slices of kindled rats. *Neuroscience, 330,* 26–38. [DOI:10.1016/j.neuroscience.2016.05.038] [PMID]

Bean, B. P. (2007). The action potential in mammalian central neurons. *Nature Reviews Neuroscience, 8*(6), 451-465. [DOI:10.1038/nrn2148] [PMID]

Ben-Menachem, E., Hellström, K., Waldton, C., & Augustinsson, L. E. (1999). Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years. *Neurology, 52*(6), 1265-1265. [DOI:10.1212/WNL.52.6.1265] [PMID]

Ben-Menachem, E., Mañon-Espaillat, R., Ristanovic, R., Wilder, B. J., Stefan, H., & Mirza, W., et al. (1994). Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. *Epilepsia, 35*(3), 616–626. [DOI:10.1111/j.1528-1157.1994.tb02482.x] [PMID]

Benabid, A. L., Pollak, P., Louveau, A., Henry, S., & de Rougemont, J. (1987). Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Applied Neurophysiology, 50*(1-6), 344–346. [DOI:10.1159/000100803] [PMID]

Beurrier, C., Bioulac, B., Audin, J., & Hammond, C. (2001). High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. *Journal of Neurophysiology, 85*(4), 1351–1356. [DOI:10.1152/jn.2001.85.4.1351] [PMID]

Bikson, M., Lian, J., Hahn, P. J., Stacey, W. C., Sciortino, C., & Durand, D. M. (2001). Suppression of epileptiform activity by high frequency sinusoidal fields in rat hippocampal slices. *The Journal of Physiology, 531*(Pt 1), 181-191. [DOI:10.1111/j.1469-7793.2001.0181j.x] [PMID] [PMCID]

Bonaz, B., Picq, C., Sinniger, V., Mayol, J. F., & Clarençon, D. (2013). Vagus nerve stimulation: From epilepsy to the cholinergic anti-inflammatory pathway. *Neurogastroenterology & Motility, 25*(3), 208-221. [DOI:10.1111/nmo.12076] [PMID]

Boon, P., Vonck, K., De Herdt, V., Van Dycke, A., Goethals, M., & Goossens, L., et al. (2007). Deep brain stimulation in patients with refractory temporal lobe epilepsy. *Epilepsia, 48*(8), 1551- 1560. [DOI:10.1111/j.1528-1167.2007.01005.x] [PMID]

Boon, P., Vonck, K., van Rijckevorsel, K., El Tahry, R., Elger, C. E., & Mullatti, N., et al. (2015). A prospective, multicenter study of cardiac-based seizure detection to activate vagus nerve stimulation. *Seizure, 32,* 52-61. [DOI:10.1016/j.seizure.2015.08.011] [PMID]

Bragin, A., Wilson, C. L., & Engel, J., Jr (2002). Rate of interictal events and spontaneous seizures in epileptic rats after electrical stimulation of hippocampus and its afferents. *Epilepsia, 43* (Suppl 5), 81-85. [DOI:10.1046/j.1528-1157.43.s.5.22.x] [PMID]

Browne, T. R., & Penry, J. K. (1973). Benzodiazepines in the treatment of epilepsy. A review. *Epilepsia, 14*(3), 277-310. [DOI:10.1111/j.1528-1157.1973.tb03965.x] [PMID]

Caous, C. A., de Sousa Buck, H., & Lindsey, C. J. (2001). Neuronal connections of the paratrigeminal nucleus: A topographic analysis of neurons projecting to bulbar, pontine and thalamic nuclei related to cardiovascular, respiratory and sensory functions. *Autonomic Neuroscience, 94*(1-2), 14-24. [DOI:10.1016/S1566-0702(01)00338-1]

Chang, S. Y., Kimble, C. J., Kim, I., Paek, S. B., Kressin, K. R., & Boesche, J. B., et al. (2013). Development of the Mayo investigational neuromodulation control system: Toward a closed- loop electrochemical feedback system for deep brain stimulation. *Journal of Neurosurgery, 119*(6), 1556-1565. [DOI:10.3171/2013.8.JNS122142] [PMID] [PMCID]

Chavel, S. M., Westerveld, M., & Spencer, S. (2003). Long-term outcome of vagus nerve stimulation for refractory partial epilepsy. *Epilepsy & Behavior, 4*(3), 302-309. [DOI:10.1016/S1525-5050(03)00109-4] [PMID]

Chiang, C. C., Lin, C. C., Ju, M. S., & Durand, D. M. (2013). High frequency stimulation can suppress globally seizures induced by 4-AP in the rat hippocampus: An acute in vivo study. *Brain Stimulation, 6*(2), 180–189. [DOI:10.1016/j.brs.2012.04.008] [PMID] [PMCID]

Clouston, T. S. (1868). Experiments to determine the precise effect of bromide of potassium in epilepsy. *Journal of Mental Science, 14*(67), 305-321. [DOI:10.1192/bjp.14.67.305]

Cooper, I. S., Amin, I., Gilman, S., & Waltz, J. M. (1974). The effect of chronic stimulation of cerebellar cortex on epilepsy in man. In I. S., Cooper, M. Riklan, & R. S. Snider (Eds.). *The cerebellum, epilepsy, and behavior* (pp. 119-171). Boston: Springer. [DOI:10.1007/978-1-4613-4508-4_6]

Cooper, I. S., Upton, A. R., & Amin, I. (1980). Reversibility of chronic neurologic deficits. Some effects of electrical stimulation of the thalamus and internal capsule in man. *Applied neurophysiology, 43*(3-5), 244–258. [DOI:10.1159/000102263] [PMID]

Cotzias, G. C., Van Woert, M. H., & Schiffer, L. M. (1967). Aromatic amino acids and modification of parkinsonism. *The New England Journal of Medicine, 276*(7), 374–379. [DOI:10.1056/NEJM196702162760703] [PMID]

Cuellar-Herrera, M., Neri-Bazan, L., & Rocha, L. L. (2006). Behavioral effects of high frequency electrical stimulation of the hippocampus on electrical kindling in rats. *Epilepsy Research, 72*(1), 10–17. [DOI:10.1016/j.eplepsyres.2006.07.002] [PMID]

Dascal, N. (2001). Ion-channel regulation by G proteins. *Trends in Endocrinology & Metabolism, 12*(9), 391-398. [DOI:10.1016/S1043-2760(01)00475-1] [PMID]

Datta, P., Galla, K. M., Sajja, K., Wichman, C., Wang, H., & Madhavan, D. (2020). Vagus nerve stimulation with tachycardia detection provides additional seizure reduction compared to traditional vagus nerve stimulation. *Epilepsy & Behavior, 111,* 107280. [DOI:10.1016/j.yebeh.2020.107280] [PMID]

DeGiorgio, C., Heck, C., Bunch, S., Britton, J., Green, P., & Lancman, M., et al. (2005). Vagus nerve stimulation for epilepsy: randomized comparison of three stimulation paradigms. *Neurology, 65*(2), 317-319. [DOI:10.1212/01.wnl.0000168899.11598.00] [PMID]

DeGiorgio, C. M., Schachter, S. C., Handforth, A., Salinsky, M., Thompson, J., & Uthman, B., et al. (2000). Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. *Epilepsia, 41*(9), 1195-1200. [DOI:10.1111/j.1528-1157.2000.tb00325.x] [PMID]

DeGiorgio, C. M., Fanselow, E. E., Schrader, L. M., & Cook, I. A. (2011). Trigeminal nerve stimulation: Seminal animal and human studies for epilepsy and depression. *Neurosurgery Clinics of North America, 22*(4), 449–v. [DOI:10.1016/j.nec.2011.07.001] [PMID]

DeGiorgio, C. M., Murray, D., Markovic, D., & Whitehurst, T. (2009). Trigeminal nerve stimulation for epilepsy: Long-term feasibility and efficacy. *Neurology, 72*(10), 936-938. [DOI:10.1212/01.wnl.0000344181.97126.b4] [PMID]

DeGiorgio, C. M., Shewmon, A., Murray, D., & Whitehurst, T. (2006). Pilot study of trigeminal nerve stimulation (TNS) for epilepsy: A proof-of-concept trial. *Epilepsia, 47*(7), 1213-1215. [DOI:10.1111/j.1528-1167.2006.00594.x] [PMID]

DeGiorgio, C. M., Shewmon, D. A., & Whitehurst, T. (2003). Trigeminal nerve stimulation for epilepsy. *Neurology, 61*(3), 421-422. [DOI:10.1212/01.WNL.0000073982.42650.57] [PMID]

DeGiorgio, C. M., Soss, J., Cook, I. A., Markovic, D., Gornbein, J., & Murray, D., et al. (2013). Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. *Neurology, 80*(9), 786-791. [DOI:10.1212/WNL.0b013e318285c11a] [PMID] [PMCID]

Devinsky, O., Vezzani, A., O'Brien, T. J., Jette, N., Scheffer, I. E., & de Curtis, M., et al. (2018). Epilepsy. *Nature Reviews. Disease Primers, 4,* 18024. [DOI:10.1038/nrdp.2018.24] [PMID]

Elliott, R. E., Morsi, A., Tanweer, O., Grobelny, B., Geller, E., & Carlson, C., et al. (2011). Efficacy of vagus nerve stimulation over time: Review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS> 10 years. *Epilepsy & Behavior, 20*(3), 478-483. [DOI:10.1016/j.yebeh.2010.12.042] [PMID]

Englot, D. J., Chang, E. F., & Auguste, K. I. (2011). Efficacy of vagus nerve stimulation for epilepsy by patient age, epilepsy duration, and seizure type. *Neurosurgery Clinics, 22*(4), 443–v. [DOI:10.1016/j.nec.2011.07.002] [PMID]

Englot, D. J., Chang, E. F., & Auguste, K. I. (2011). Vagus nerve stimulation for epilepsy: A meta-analysis of efficacy and predictors of response. *Journal of Neurosurgery, 115*(6), 1248-1255. [DOI:10.3171/2011.7.JNS11977] [PMID]

Englot, D. J., Rolston, J. D., Wright, C. W., Hassnain, K. H., & Chang, E. F. (2016). Rates and predictors of seizure freedom with vagus nerve stimulation for intractable epilepsy. *Neurosurgery, 79*(3), 345-353. [DOI:10.1227/NEU.0000000000001165] [PMID] [PMCID]

Fanselow, E. E., Reid, A. P., & Nicolelis, M. A. (2000). Reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation. *The Journal of Neuroscience: The Official Journal of The Society for Neuroscience, 20*(21), 8160–8168. [PMID] [PMCID]

Feddersen, B., Vercueil, L., Noachtar, S., David, O., Depaulis, A., & Deransart, C. (2007). Controlling seizures is not controlling epilepsy: A parametric study of deep brain stimulation for epilepsy. *Neurobiology of Disease, 27*(3), 292–300. [DOI:10.1016/j.nbd.2007.05.005] [PMID]

Feng, Z., Yu, Y., Guo, Z., Cao, J., & Durand, D. M. (2014). High frequency stimulation extends the refractory period and generates axonal block in the rat hippocampus. *Brain Stimulation, 7*(5), 680–689. [DOI:10.1016/j.brs.2014.03.011] [PMID] [PMCID]

Fisher, R., Salanova, V., Witt, T., Worth, R., Henry, T., & Gross, R., et al. (2010). Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia, 51*(5), 899- 908. [DOI:10.1111/j.1528-1167.2010.02536.x] [PMID]

Fisher, R. S., Afra, P., Macken, M., Minecan, D. N., Bagić, A., & Benbadis, S. R., et al. (2016). Automatic vagus nerve stimulation triggered by ictal tachycardia: clinical outcomes and device performance-the US E-37 trial. *Neuromodulation: Technology at the Neural Interface, 19*(2), 188-195. [DOI:10.1111/ner.12376] [PMID] [PMCID]

Fox, S. H., Katzenschlager, R., Lim, S. Y., Ravina, B., Seppi, K., & Coelho, M., et al. (2011). The movement disorder society evidence-based medicine review update: Treatments for the motor symptoms of Parkinson's disease. *Movement Disorders, 26*(Suppl 3), S2-S41. [DOI:10.1002/mds.23829] [PMID]

Fujii, S., Kuroda, Y., Ito, K. L., Yoshioka, M., Kaneko, K., Yamazaki, Y., et al. (2000). Endogenous adenosine regulates the effects of low-frequency stimulation on the induction of long-term potentiation in CA1 neurons of guinea pig hippocampal slices. *Neuroscience Letters, 279*(2), 121–124. [DOI:10.1016/S0304-3940(99)00980-5] [PMID]

Gaito, J. (1980). The effect of variable duration one hertz interference on kindling. *The Canadian Journal of Neurological Sciences, 7*(1), 59–64. [PMID]

Gastaut, H., Naquet, R., Poire, R., & Tassinari, C. (1965). Treatment of status epilepticus with diazepam (Valium). *Epilepsia, 6*(2), 167-182. [DOI:10.1111/j.1528-1157.1965.tb03786.x] [PMID]

Geller, E. B., Skarpaas, T. L., Gross, R. E., Goodman, R. R., Barkley, G. L., & Bazil, C. W., et al. (2017). Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. *Epilepsia, 58*(6), 994-1004. [DOI:10.1111/epi.13740] [PMID]

Ghasemi, Z., Naderi, N., Shojaei, A., Ahmadirad, N., Raoufy, M. R., & Mirnajafi-Zadeh, J. (2018). Low frequency electrical stimulation attenuated the epileptiform activity-induced changes in action potential features in hippocampal CA1 pyramidal neurons. *Cell Journal, 20*(3), 355–360. [PMID]

Ghasemi, Z., Naderi, N., Shojaei, A., Raoufy, M. R., Ahmadirad, N., & Barkley, V., et al. (2019). The inhibitory effect of different patterns of low frequency stimulation on neuronal firing following epileptiform activity in rat hippocampal slices. *Brain Research, 1706,* 184–195. [DOI:10.1016/j.brainres.2018.11.012] [PMID]

Ghasemi, Z., Naderi, N., Shojaei, A., Raoufy, M. R., Ahmadirad, N., & Barkley, V., et al. (2021). Group I metabotropic glutamate receptors contribute to the antiepileptic effect of electrical stimulation in hippocampal CA1 pyramidal neurons. *Epilepsy Research, 178,* 106821. [PMID]

Ghasemi, Z., Naderi, N., Shojaei, A., Raoufy, M. R., Ahmadirad, N., & Mirnajafi-Zadeh, J. (2018). Effect of low-frequency electrical stimulation on the high-K+-induced neuronal hyperexcitability in rat hippocampal slices. *Neuroscience, 369,* 87–96. [DOI:10.1016/j.neuroscience.2017.11.012] [PMID]

Ghotbedin, Z., Janahmadi, M., Mirnajafi-Zadeh, J., Behzadi, G., & Semnanian, S. (2013). Electrical low frequency stimulation of the kindling site preserves the electrophysiological properties of the rat hippocampal CA1 pyramidal neurons from the destructive effects of amygdala kindling: the basis for a possible promising epilepsy therapy. *Brain Stimulation, 6*(4), 515–523. [DOI:10.1016/j.brs.2012.11.001] [PMID]

Gil-López, F., Boget, T., Manzanares, I., Donaire, A., Conde-Blanco, E., & Baillés, E., et al. (2020). External trigeminal nerve stimulation for drug resistant epilepsy: A randomized controlled trial. *Brain Stimulation, 13*(5), 1245-1253. [DOI:10.1016/j.brs.2020.06.005] [PMID]

Giorgi, F. S., Pizzanelli, C., Biagioni, F., Murri, L., & Fornai, F. (2004). The role of norepinephrine in epilepsy: From the bench to the bedside. *Neuroscience & Biobehavioral Reviews, 28*(5), 507-524. [DOI:10.1016/j.neubiorev.2004.06.008] [PMID]

Glauser, T. A., Cnaan, A., Shinnar, S., Hirtz, D. G., Dlugos, D., & Masur, D., et al. (2010). Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *The New England Journal of Medicine, 362*(9), 790–799. [DOI:10.1056/NEJMoa0902014] [PMID] [PMCID]

Goodman, J. H., Berger, R. E., & Tcheng, T. K. (2005). Preemptive low-frequency stimulation decreases the incidence of amygdala-kindled seizures. *Epilepsia, 46*(1), 1-7. [DOI:10.1111/j.0013-9580.2005.03804.x] [PMID]

Hamani, C., Ewerton, F. I., Bonilha, S. M., Ballester, G., Mello, L. E., & Lozano, A. M. (2004). Bilateral anterior thalamic nucleus lesions and high-frequency stimulation are protective against pilocarpine-induced seizures and status epilepticus. Neurosurgery, 54(1), 191-195; discussion 195-197. [DOI:10.1227/01.NEU.0000097552.31763.AE] [PMID]

Hamilton, P., Soryal, I., Dhahri, P., Wimalachandra, W., Leat, A., & Hughes, D., et al. (2018). Clinical outcomes of VNS therapy with As-pireSR®(including cardiac-based seizure detection) at a large complex epilepsy and surgery centre. Seizure, 58, 120-126. [DOI:10.1016/j.seizure.2018.03.022] [PMID]

Handforth, A., DeGiorgio, C. M., Schachter, S. C., Uthman, B. M., Naritoku, D. K., & Tecoma, E. S., et al. (1998). Vagus nerve stimulation therapy for partial-onset seizures: A randomized active-control trial. Neurology, 51(1), 48-55. [DOI:10.1212/WNL.51.1.48] [PMID]

Hauptmann, A. (1912). Luminal bei epilepsie. Munch Med Wochenschr, 59, 1907-1909. [Link]

Heck, C. N., King-Stephens, D., Massey, A. D., Nair, D. R., Jobst, B. C., & Barkley, G. L., et al. (2014). Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: Final results of the RNS System Pivotal trial. Epilepsia, 55(3), 432-441. [DOI:10.1111/epi.12534] [PMID] [PMCID]

Héja, L., Barabás, P., Nyitrai, G., Kékesi, K. A., Lasztóczi, B., & Toke, O., etal. (2009). Glutamate uptake triggers transporter-mediated GABA release from astrocytes. PLoS One, 4(9), e7153. [DOI:10.1371/journal.pone.0007153] [PMID] [PMCID]

Hodaie, M., Wennberg, R. A., Dostrovsky, J. O., & Lozano, A. M. (2002). Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia, 43(6), 603-608. [DOI:10.1046/j.1528-1157.2002.26001.x] [PMID]

Hoskin, K. L., Bulmer, D. C., Lasalandra, M., Jonkman, A., & Goadsby, P. J. (2001). Fos expression in the midbrain periaqueductal grey after trigemi-novascular stimulation. Journal of Anatomy,198(Pt 1), 29-35. [DOI:10.1046/j.1469-7580.2001.19810029.x] [PMID] [PMCID]

Huf, R. L., Mamelak, A., & Kneedy-Cayem, K. (2005). Vagus nerve stimulation therapy: 2-year prospective open-label study of 40 subjects with refracto-ry epilepsy and low IQ who are living in long-term care facilities. Epilepsy & Behavior, 6(3), 417-423. [DOI:10.1016/j.yebeh.2005.01.009] [PMID]

Jackson, M. F., Esplin, B., & Capek, R. (1999). Activity-dependent enhancement of hyperpolarizing and depolarizing γ-aminobutyric acid (GABA) syn-aptic responses following inhibition of GABA uptake by tiagabine. Epilepsy Research, 37(1), 25-36. [DOI:10.1016/S0920-1211(99)00029-7] [PMID]

Jahanshahi, A., Mirnajafi-Zadeh, J., Javan, M., Mohammad-Zadeh, M., & Rohani, R. (2009). The antiepileptogenic effect of electrical stimulation at different low frequencies is accompanied with change in adenosine receptors gene expression in rats. Epilepsia, 50(7), 1768-1779. [DOI:10.1111/j.1528-1167.2009.02088.x] [PMID]

Jobst, B. C., Kapur, R., Barkley, G. L., Bazil, C. W., Berg, M. J., & Bergey, G. K., et al. (2017). Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas. Epilepsia, 58(6), 1005-1014. [DOI:10.1111/epi.13739] [PMID]

Kandel, E. R., Schwartz, J. H., Jessell, T. M., Siegelbaum, S., Hudspeth, A. J., & Mack, S. (2000). *Principles of neural science*. New York: McGraw-hill. [Link]

Kang, H. C., Hwang, Y. S., Kim, D. S., & Kim, H. D. (2006). Vagus nerve stimulation in pediatric intractable epilepsy: A Korean bicentric study. *Acta Neurochirurgica. Supplement, 99,* 93–96. [DOI:10.1007/978-3-211-35205-2_18] [PMID]

Kerrigan, J. F., Litt, B., Fisher, R. S., Cranstoun, S., French, J. A., & Blum, D. E., et al. (2004). Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. *Epilepsia, 45*(4), 346-354. [DOI:10.1111/j.0013-9580.2004.01304.x] [PMID]

Kile, K. B., Tian, N., & Durand, D. M. (2010). Low frequency stimulation decreases seizure activity in a mutation model of epilepsy. *Epilepsia, 51*(9), 1745-1753. [DOI:10.1111/j.1528-1167.2010.02679.x] [PMID] [PMCID]

Klinkenberg, S., Aalbers, M. W., Vles, J. S., Cornips, E. M., Rijkers, K., & Leenen, L., et al. (2012). Vagus nerve stimulation in children with intractable epilepsy: A randomized controlled trial. *Developmental Medicine & Child Neurology, 54*(9), 855-861. [DOI:10.1111/j.1469-8749.2012.04305.x] [PMID]

Kossoff, E. H., Ritzl, E. K., Politsky, J. M., Murro, A. M., Smith, J. R., & Duckrow, R. B., et al. (2004). Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. *Epilepsia, 45*(12), 1560-1567. [DOI:10.1111/j.0013-9580.2004.26104.x] [PMID]

Krahl, S. E. (2012). Vagus nerve stimulation for epilepsy: A review of the peripheral mechanisms. *Surgical Neurology International, 3*(Suppl 1), S47–S52. [PMID] [PMCID]

Krout, K. E., Belzer, R. E., & Loewy, A. D. (2002). Brainstem projections to midline and intralaminar thalamic nuclei of the rat. *The Journal of Comparative Neurology, 448*(1), 53–101. [DOI:10.1002/cne.10236] [PMID]

Kawn, P., Arzimanoglou, A., Berg, A. T., Brodie, M. J., Allen Hauser, W., & Mathern, G., et al. (2010). Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia, 51*(6), 1069-1077. [DOI:10.1111/j.1528-1167.2009.02397.x] [PMID]

Kwan, P., & Brodie, M. J. (2006). Refractory epilepsy: Mechanisms and solutions. *Expert Review of Neurotherapeutics, 6*(3), 397-406. [PMID]

Labar, D., Murphy, J., & Tecoma, E. (1999). Vagus nerve stimulation for medication- resistant generalized epilepsy. E04 VNS Study Group. *Neurology, 52*(7), 1510-1512. [DOI:10.1212/WNL.52.7.1510] [PMID]

Lado, F. A. (2006). Chronic bilateral stimulation of the anterior thalamus of kainate-treated rats increases seizure frequency. *Epilepsia, 47*(1), 27-32. [DOI:10.1111/j.1528-1167.2006.00366.x] [PMID]

Lanska, D. J. (2002). J.L. Corning and vagal nerve stimulation for seizures in the 1880s. *Neurology, 58*(3), 452-459. [DOI:10.1212/WNL.58.3.452] [PMID]

Laxpati, N. G., Kasoff, W. S., & Gross, R. E. (2014). Deep brain stimulation for the treatment of epilepsy: Circuits, targets, and trials. *Neurotherapeutics, 11*(3), 508-526. [DOI:10.1007/s13311-014-0279-9] [PMID] [PMCID]

Lee, H. K., Barbarosie, M., Kameyama, K., Bear, M. F., & Huganir, R. L. (2000). Regulation of distinct AMPA receptor phosphorylation sites during bidirectional synaptic plasticity. *Nature, 405*(6789), 955–959. [DOI:10.1038/35016089] [PMID]

Lee, K. J., Jang, K. S., & Shon, Y. M. (2006). Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy. *Acta Neurochirurgica. Supplement, 99,* 87–91. [DOI:10.1007/978-3-211-35205-2_17] [PMID]

Lee, K. J., Jang, K. S., & Shon, Y. M. (2006). Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy. In J. W. Chang, Y. Katayama, & T. Yamamoto, (Eds.), *Advances in functional and reparative neurosurgery* (pp. 87-91). Vienna: Springer. [DOI:10.1007/978-3-211-35205-2_17]

Lesser, R. P., Lüders, H., Klem, G., Dinner, D. S., Morris, H. H., & Hahn, J. (1984). Cortical afterdischarge and functional response thresholds: Results of extraoperative testing. *Epilepsia, 25*(5), 615-621. [PMID]

Li, T., Qadri, F., & Moser, A. (2004). Neuronal electrical high frequency stimulation modulates presynaptic GABAergic physiology. *Neuroscience Letters, 37*1(2-3), 117–121. [DOI:10.1016/j.neulet.2004.08.050] [PMID]

Lian, J., Bikson, M., Sciortino, C., Stacey, W. C., & Durand, D. M. (2003). Local suppression of epileptiform activity by electrical stimulation in rat hippocampus in vitro. *The Journal of Physiology, 547*(Pt 2), 427-434. [PMID] [PMCID]

Lim, S. N., Lee, C. Y., Lee, S. T., Tu, P. H., Chang, B. L., & Lee, C. H., et al. (2016). Low and high frequency hippocampal stimulation for drug-resistant mesial temporal lobe epilepsy. *Neuromodulation, 19*(4), 365-372. [DOI:10.1111/ner.12435] [PMID] [PMCID]

Lim, S. N., Lee, S. T., Tsai, Y. T., Chen, I. A., Tu, P. H., & Chen, J. L., et al. (2007). Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: A long-term follow-up study. *Epilepsia, 48*(2), 342-347. [DOI:10.1111/j.1528-1167.2006.00898.x] [PMID]

Liu, H. Y., Yang, Z., Meng, F. G., Guan, Y. G., Ma, Y. S., & Liang, S. L., et al. (2018). Preoperative heart rate variability as predictors of vagus nerve stimulation outcome in patients with drug-resistant epilepsy. *Scientific Reports, 8*(1),3856. [PMID] [PMCID]

Lu, K. T., & Gean, P. W. (1998). Endogenous serotonin inhibits epileptiform activity in rat hippocampal CA1 neurons via 5-hydroxytryptamine1A receptor activation. *Neuroscience, 86*(3), 729-737. [DOI:10.1016/S0306-4522(98)00106-7] [PMID]

Luna-Munguia, H., Orozco-Suarez, S., & Rocha, L. (2011). Effects of high frequency electrical stimulation and R-verapamil on seizure susceptibility and glutamate and GABA release in a model of phenytoin-resistant seizures. *Neuropharmacology, 61*(4), 807–814. [PMID]

Majoie, H. J., Berfelo, M. W., Aldenkamp, A. P., Renier, W. O., & Kessels, A. G. (2005). Vagus nerve stimulation in patients with catastrophic childhood epilepsy, a 2-year follow-up study. *Seizure, 14*(1), 10-18. [DOI:10.1016/j.seizure.2004.02.003] [PMID]

Mardani, P., Oryan, S., Sarihi, A., Alaei, E., Komaki, A., & Mirnajafi-Zadeh, J. (2018). Endocannabinoid CB1 receptors are involved in antiepileptogenic effect of low frequency electrical stimulation during perforant path kindling in rats. *Epilepsy Research, 144,* 71–81. [DOI:10.1016/j.eplepsyres.2018.05.008] [PMID]

Mardani, P., Oryan, S., Sarihi, A., Komaki, A., Shojaei, A., & Dehghan, S., et al. (2018). ERK activation is required for the antiepileptogenic effect of low frequency electrical stimulation in kindled rats. *Brain Research Bulletin, 140,* 132–139. [PMID]

Suller Marti, A., Mirsattari, S. M., MacDougall, K., Steven, D. A., Parrent, A., & de Ribaupierre, S., et al. (2020). Vagus nerve stimulation in patients with therapy-resistant generalized epilepsy. *Epilepsy & Behavior: E&B, 111,* 107253. [PMID]

Meldrum, B. S., & Rogawski, M. A. (2007). Molecular targets for antiepileptic drug development. *Neurotherapeutics, 4*(1), 18-61. [PMID] [PMCID]

Mercante, B., Enrico, P., Floris, G., Quartu, M., Boi, M., & Serra, M. P., et al. (2017). Trigeminal nerve stimulation induces Fos immunoreactivity in selected brain regions, increases hippocampal cell proliferation and reduces seizure severity in rats. *Neuroscience, 361,* 69-80. [PMID]

Merritt, H. H., & Putnam, T. J. (1938). Sodium diphenyl hydantoinate in the treatment of convulsive disorders. *Journal of the American Medical Association, 111*(12), 1068-1073. [DOI:10.1001/jama.1938.02790380010004]

Meunier, H. (1963). [Pharmacodynamic properties of N-dipropylacetic acid (French)]. *Therapie, 18,* 435-438. [PMID]

Milosevic, L., Kalia, S. K., Hodaie, M., Lozano, A. M., Popovic, M. R., & Hutchison, W. D. (2018). Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression. *Brain, 141*(7), 2142-2155. [DOI:10.1093/brain/awy139] [PMID] [PMCID]

Mirski, M. A., & Fisher, R. S. (1994). Electrical stimulation of the mammillary nuclei increases seizure threshold to pentylenetetrazol in rats. *Epilepsia, 35*(6), 1309-1316. [DOI:10.1111/j.1528-1157.1994.tb01803.x] [PMID]

Mohammad-Zadeh, M., Mirnajafi-Zadeh, J., Fathollahi, Y., Javan, M., Jahanshahi, A., & Noorbakhsh, S. M., et al. (2009). The role of adenosine A(1) receptors in mediating the inhibitory effects of low frequency stimulation of perforant path on kindling acquisition in rats. *Neuroscience, 158*(4), 1632-1643. [DOI:10.1016/j.neuroscience.2008.11.008] [PMID]

Morrell, M. (2006). Brain stimulation for epilepsy: Can scheduled or responsive neurostimulation stop seizures? *Current Opinion in Neurology, 19*(2), 164-168. [DOI:10.1097/01.wco.0000218233.60217.84] [PMID]

Morrell, M. J., & RNS System in Epilepsy Study Group (2011). Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology, 77*(13), 1295-1304. [PMID]

Motamedi, G. K., Lesser, R. P., Miglioretti, D. L., Mizuno-Matsumoto, Y., Gordon, B., & Webber, W. R., et al. (2002). Optimizing parameters for terminating cortical afterdischarges with pulse stimulation. *Epilepsia, 43*(8), 836-846. [DOI:10.1046/j.1528-1157.2002.24901.x] [PMID]

Muthiah, N., Zhang, J., Remick, M., Welch, W., Sogawa, Y., & Jeong, J. H., et al. (2020). Efficacy of vagus nerve stimulation for drug-resistant epilepsy in children age six and younger. *Epilepsy & Behavior, 112,* 107373. [DOI:10.1016/j.yebeh.2020.107373] [PMID]

Nair, S. P., Sackellares, J. C., Shiau, D. S., Norman, W. M., Dance, L. K., & Pardalos, P. M., et al. (2006). *Effects of acute hippocampal stimulation on EEG dynamics*. Paper presented at: International Conference of the IEEE Engineering in Medicine and Biology Society, New York, NY, USA, 30 August - 03 September 2006. [DOI:10.1109/IEMBS.2006.260830] [PMID]

Namvar, S., Fathollahi, Y., Javan, M., Zeraati, M., Mohammad-Zadeh, M., & Shojaei, A., et al. (2017). The antiepileptogenic effect of low-frequency stimulation on perforant path kindling involves changes in regulators of G-protein signaling in rat. *Journal of the Neurological Sciences, 375,* 450-459. [DOI:10.1016/j.jns.2017.02.047] [PMID]

Neligan, A., Bell, G. S., Johnson, A. L., Goodridge, D. M., Shorvon, S. D., & Sander, J. W. (2011). The long- term risk of premature mortality in people with epilepsy. *Brain, 134*(Pt 2), 388-395. [DOI:10.1093/brain/awq378] [PMID]

Osorio, I., Frei, M. G., Sunderam, S., Giftakis, J., Bhavaraju, N. C., & Schaffner, S. F., et al. (2005). Automated seizure abatement in humans using electrical stimulation. *Annals of Neurology, 57*(2), 258- 268. [DOI:10.1002/ana.20377] [PMID]

Pakdaman, H., Harandi, A. A., Abbasi, M., Karimi, M., Arami, M. A., & Mosavi, S. A., et al. (2016). Vagus nerve stimulation in drug-resistant epilepsy: The efficacy and adverse effects in a 5-year follow-up study in Iran. *Neurological Sciences, 37*(11), 1773-1778. [DOI:10.1007/s10072-016-2661-3] [PMID]

Pantoja-Jiménez, C., Magdaleno-Madrigal, V., Almazán-Alvarado, S., & Fernández-Mas, R. (2014). Anti-epileptogenic effect of high-frequency stimulation in the thalamic reticular nucleus on PTZ- induced seizures. *Deep Brain Stimulation, 7*(4), 587-594. [DOI:10.1016/j.brs.2014.03.012] [PMID]

Parker, A. P., Polkey, C. E., Binnie, C. D., Madigan, C., Ferrie, C. D., & Robinson, R. O. (1999). Vagal nerve stimulation in epileptic encephalopathies. *Pediatrics, 103*(4), 778-782. [DOI:10.1542/peds.103.4.778] [PMID]

Penfield, W. (1936). Epilepsy and surgical therapy. *Archives of Neurology & Psychiatry, 36*(3), 449-484. [DOI:10.1001/archneurpsyc.1936.02260090002001]

Perez-Malagon, C. D., & Lopez-Gonzalez, M. A. (2021). Epilepsy and deep brain stimulation of anteriorthalamic nucleus. *Cureus, 13*(9), e18199. [DOI:10.7759/cureus.18199]

Pi, H. J., & Lisman, J. E. (2008). Coupled phosphatase and kinase switches produce the tristability required for long-term potentiation and long-term depression. *The Journal of Neuroscience: The Official Journal of The Society for Neuroscience, 28*(49), 13132-13138. [DOI:10.1523/JNEUROSCI.2348-08.2008] [PMID] [PMCID]

Pool, J. L. (1954). Psychosurgery in older people. *Journal of the American Geriatrics Society, 2*(7), 456- 466. [DOI:10.1111/j.1532-5415.1954.tb02138.x] [PMID]

Pop, J., Murray, D., Markovic, D., & DeGiorgio, C. M. (2011). Acute and long-term safety of external trigeminal nerve stimulation for drug-resistant epilepsy. *Epilepsy & Behavior, 22*(3), 574-576. [DOI:10.1016/j.yebeh.2011.06.024] [PMID]

Rabenstein, M., Agbo, D. B., Wolf, E., Dams, J., Nicolai, M., & Roeder, A., et al. (2019). Effect of naturally occurring α-synuclein-antibodies on toxic α-synuclein-fragments. *Neuroscience Letters, 704,* 181-188. [DOI:10.1016/j.neulet.2019.04.004] [PMID]

Rakhade, S. N., & Loeb, J. A. (2008). Focal reduction of neuronal glutamate transporters in human neocortical epilepsy. *Epilepsia, 49*(2), 226-236. [DOI:10.1111/j.1528-1167.2007.01310.x] [PMID]

Reeves, R. E. (2007). Anatomy: A regional atlas of the human body. *Clinical Anatomy, 40*(2), 222. [DOI:10.1002/ca.20437]

Rezaei, M., Ahmadirad, N., Ghasemi, Z., Shojaei, A., Raoufy, M. R., & Barkley, V., et al. (2021). Alpha adrenergic receptors have role in the inhibitory effect of electrical low frequency stimulation on epileptiform activity in rats. *International Journal of Neuroscience,* 1-9. [DOI:10.1080/00207454.2021.1929211]

Rogawski, M. A., & Löscher, W. (2004). The neurobiology of antiepileptic drugs. *Nature Reviews Neuroscience, 5*(7), 553-564. [DOI:10.1038/nrn1430] [PMID]

Ruffoli, R., Giorgi, F. S., Pizzanelli, C., Murri, L., Paparelli, A., & Fornai, F. (2011). The chemical neuroanatomy of vagus nerve stimulation. *Journal of Chemical Neuroanatomy, 42*(4), 288-296. [DOI:10.1016/j.jchemneu.2010.12.002]

Russo, A., Hyslop, A., Gentile, V., Chiarello, D., Messana, T., & Miller, I., et al. (2021). Early implantation as a main predictor of response to vagus nerve stimulation in childhood-onset refractory epilepsy. *Journal of Child Neurology, 36*(5), 365-370. [DOI:10.1177/0883073820974855] [PMID]

Ryvlin, P., Gilliam, F. G., Nguyen, D. K., Colicchio, G., Iudice, A., & Tinuper, P., et al. (2014). The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: The PuLsE (Open P rospective Randomized Long-term E ffectiveness) trial. *Epilepsia, 55*(6), 893-900. [DOI:10.1111/epi.12611] [PMID] [PMCID]

Ryvlin, P., Rheims, S., Hirsch, L. J., Sokolov, A., & Jehi, L. (2021). Neuromodulation in epilepsy: State-of- the-art approved therapies. *The Lancet Neurology, 20*(12), 1038-1047. [DOI:10.1016/S1474-4422(21)00300-8]

Sadegh, M., Mirnajafi-Zadeh, J., Javan, M., Fathollahi, Y., Mohammad-Zadeh, M., & Jahanshahi, A., et al. (2007). The role of galanin receptors in anticonvulsant effects of low- frequency stimulation in perforant path-kindled rats. *Neuroscience, 150*(2), 396-403. [DOI:10.1016/j.neuroscience.2007.09.068]

Sadeghian, A., Salari, Z., Azizi, H., Raoufy, M. R., Shojaei, A., & Kosarmadar, N., et al. (2020). The role of dopamine D(2)-like receptors in a "depotentiation-like effect" of deep brain stimulation in kindled rats. *Brain Research, 1738,* 146820. [DOI:10.1016/j.brainres.2020.146820]

Salam, M. T., Sawan, M., & Nguyen, D. K. (2010). Low-power implantable device for onset detection and subsequent treatment of epileptic seizures: A review. *Journal of Healthcare Engineering, 1*(2), 169-184. [DOI:10.1260/2040-2295.1.2.169]

Schachter, S. C., & Saper, C. B. (1998). Vagus nerve stimulation. *Epilepsia, 39*(7), 677-686. [DOI:10.1111/j.1528-1157.1998.tb01151.x]

Scherrmann, J., Hoppe, C., Kral, T., Schramm, J., & Elger, C. E. (2001). Vagus nerve stimulation: clinical experience in a large patient series. *Journal of Clinical Neurophysiology, 18*(5), 408-414. [DOI:10.1097/00004691-200109000-00004]

Schiller, Y., & Bankirer, Y. (2007). Cellular mechanisms underlying antiepileptic effects of low- and high- frequency electrical stimulation in acute epilepsy in neocortical brain slices in vitro. *Journal of Neurophysiology, 97*(3), 1887-1902. [DOI:10.1152/jn.00514.2006]

Schneggenburger, R., Sakaba, T., & Neher, E. (2002). Vesicle pools and short-term synaptic depression: lessons from a large synapse. *Trends in Neurosciences, 25*(4), 206-212. [DOI:10.1016/S0166-2236(02)02139-2]

Sills, G. J., & Brodie, M. J. (2002). Update on the mechanisms of action of antiepileptic drugs. *Epileptic Disorders, 3*(4), 165-172.

Silva, R. C., Montenegro, M. A., Guerreiro, C. A., & Guerreiro, M. M. (2006). Clobazam as add-on therapy in children with epileptic encephalopathy. *Canadian Journal of Neurological Sciences, 33*(2), 209- 213. [DOI:10.1017/S0317167100004996]

Sirven, J. I. (2015). Epilepsy: A spectrum disorder. *Cold Spring Harbor Perspectives in Medicine, 5*(9), a022848. [DOI:10.1101/cshperspect.a022848] [PMID] [PMCID]

Soss, J., Heck, C., Murray, D., Markovic, D., Oviedo, S., & Corrale-Leyva, G., et al. (2015). A prospective long-term study of external trigeminal nerve stimulation for drug-resistant epilepsy. *Epilepsy & Behavior, 42,* 44-47. [DOI:10.1016/j.yebeh.2014.10.029] [PMID]

Spiegel, E. A., Wycis, H. T., Marks, M., & Lee, A. J. (1947). Stereotaxic apparatus for operations on the human brain. *Science, 106*(2754), 349-350. [DOI:10.1126/science.106.2754.349]

Sprengers, M., Vonck, K., Carrette, E., Marson, A. G., & Boon, P. (2017). Deep brain and cortical stimulation for epilepsy. Cochrane *Database of Systematic Reviews, 7*(7), CD008497. [DOI:10.1002/14651858.CD008497.pub3] [PMID] [PMCID]

Staba, R. J., Wilson, C. L., Bragin, A., Fried, I., & Engel Jr, J.(2002). Quantitative analysis of high- frequency oscillations (80-500 Hz) recorded in human epileptic hippocampus and entorhinal cortex. *Journal of Neurophysiology, 88*(4), 1743-1752. [DOI:10.1152/jn.2002.88.4.1743]

Stefulj, J., Bordukalo-Niksic, T., Hecimovic, H., Demarin, V., & Jernej, B. (2010). Epilepsy and serotonin (5HT): Variations of 5HT-related genes in temporal lobe epilepsy. *Neuroscience Letters, 478*(1), 29-31. [DOI:10.1016/j.neulet.2010.04.060]

Terasaki, T., & Hosoya, K.I. (1999). The blood-brain barrier efflux transporters as a detoxifying system for the brain. *Advanced Drug Delivery Reviews, 36*(2-3), 195-209. [DOI:10.1016/S0169-409X(98)00088-X]

Theodore, W. H., & Fisher, R. S. (2004). Brain stimulation for epilepsy. *The Lancet Neurology, 3*(2), 111-118. [DOI:10.1016/S1474-4422(03)00664-1]

Traub, R. D., Wong, R. K., Miles, R., & Michelson, H. (1991). A model of a CA3 hippocampal pyramidal neuron incorporating voltage-clamp data on intrinsic conductances. *Journal of Neurophysiology, 66*(2), 635- 650. [DOI:10.1152/jn.1991.66.2.635]

Van Buren, J. M., Wood, J. H., Oakley, J., & Hambrecht, F. (1978). Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. *Journal of Neurosurgery, 48*(3), 407-416. [DOI:10.3171/jns.1978.48.3.0407]

Velasco, A. L., Velasco, M., Velasco, F., Menes, D., Gordon, F., & Rocha, L., et al. (2000). Subacute and chronic electrical stimulation of the hippocampus on intractable temporal lobe seizures: Preliminary report. *Archives of Medical Research, 31*(3), 316-328. [DOI:10.1016/S0188-4409(00)00064-3]

Velasco, F., Velasco, M., Ogarrio, C., & Fanghanel, G. (1987). Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: A preliminary report. *Epilepsia, 28*(4), 421-430. [DOI:10.1111/j.1528-1157.1987.tb03668.x]

Vercueil, L., Benazzouz, A., Deransart, C., Bressand, K., Marescaux, C., & Depaulis, A., et al. (1998). High-frequency stimulation of the subthalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. *Epilepsy Research, 31*(1), 39-46. [DOI:10.1016/S0920-1211(98)00011-4]

Vetkas, A., Fomenko, A., Germann, J., Sarica, C., Iorio-Morin, C., & Samuel, N., et al. (2022). Deep brain stimulation targets in epilepsy: Systematic review and meta-analysis of anterior and centromedian thalamic nuclei and hippocampus. *Epilepsia, 63*(3), 513-524. [DOI:10.1111/epi.17157] [PMID]

von Gersdorff, H., & Borst, J. G. (2002). Short-term plasticity at the calyx of Held. *Nature Reviews. Neuroscience, 3*(1), 53–64. [DOI:10.1038/nrn705] [PMID]

Vonck, K., Thadani, V., Gilbert, K., Dedeurwaerdere, S., De Groote, L., & De Herdt, V., et al. (2004). Vagus nerve stimulation for refractory epilepsy: A transatlantic experience. *Journal of Clinical Neurophysiology, 21*(4), 283-289. [DOI:10.1097/01.WNP.0000139654.32974.4E] [PMID]

Walker, B. R., Easton, A., & Gale, K. (1999). Regulation of limbic motor seizures by GABA and glutamate transmission in nucleus tractus solitarius. *Epilepsia, 40*(8), 1051-1057. [DOI:10.1111/j.1528-1157.1999.tb00818.x] [PMID]

Wang, Q. Q., Zhu, L. J., Wang, X. H., Zuo, J., He, H. Y., & Tian, M. M., et al. (2016). Chronic trigeminal nerve stimulation protects against seizures, cognitive impairments, hippocampal apoptosis, and inflammatory responses in epileptic rats. *Journal of Molecular Neuroscience, 59*(1), 78-89. [DOI:10.1007/s12031-016-0736-5] [PMID]

Weiss, D., Breit, S., Hoppe, J., Hauser, A. K., Freudenstein, D., & Krüger, R., et al. (2012). Subthalamic nucleus stimulation restores the efferent cortical drive to muscle in parallel to functional motor improvement. *European Journal of Neuroscience, 35*(6), 896-908. [DOI:10.1111/j.1460-9568.2012.08014.x] [PMID]

Westover, M. B., Cormier, J., Bianchi, M. T., Shafi, M., Kilbride, R., & Cole, A. J., et al. (2012). Revising the "Rule of Three" for inferring seizure freedom. *Epilepsia, 53*(2), 368-376. [DOI:10.1111/j.1528-1167.2011.03355.x] [PMID] [PMCID]

Windels, F., Bruet, N., Poupard, A., Urbain, N., Chouvet, G., & Feuerstein, C., et al. (2000). Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in substantia nigra and globus pallidus in the normal rat. *The European Journal of Neuroscience, 12*(11), 4141–4146. [DOI:10.1046/j.1460-9568.2000.00296.x] [PMID]

Wright, G. D., McLellan, D. L., & Brice, J. G. (1984). A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. *Journal of Neurology, Neurosurgery & Psychiatry, 47*(8), 769-774. [DOI:10.1136/jnnp.47.8.769] [PMID] [PMCID]

Wyckhuys, T., De Smedt, T., Claeys, P., Raedt, R., Waterschoot, L., & Vonck, K., et al. (2007). High frequency deep brain stimulation in the hippocampus modifies seizure characteristics in kindled rats. *Epilepsia, 48*(8), 1543-1550. [DOI:10.1111/j.1528-1167.2007.01038.x] [PMID]

Wyckhuys, T., Geerts, P. J., Raedt, R., Vonck, K., Wadman, W., & Boon, P. (2009). Deep brain stimulation for epilepsy: Knowledge gained from experimental animal models. *Acta Neurologica Belgica, 109*(2), 63–80. [PMID]

Yang, C. H., Huang, C. C., & Hsu, K. S. (2005). Behavioral stress enhances hippocampal CA1 long-term depression through the blockade of the glutamate uptake. *The Journal of Neuroscience: The Official Journal of The Society for Neuroscience, 25*(17), 4288–4293. [DOI:10.1523/JNEUROSCI.0406-05.2005] [PMID] [PMCID]

Zabara, J. (1992). Inhibition of experimental seizures in canines by repetitive vagal stimulation. *Epilepsia, 33*(6), 1005-1012. [DOI:10.1111/j.1528-1157.1992.tb01751.x] [PMID]

Zagon, A. (2001). Does the vagus nerve mediate the sixth sense? *Trends in Neurosciences, 24*(11), 671- 673. [DOI:10.1016/S0166-2236(00)01929-9] [PMID]

Zare, M., Nazari, M., Shojaei, A., Raoufy, M. R., & Mirnajafi-Zadeh, J. (2020). Online analysis of local field potentials for seizure detection in freely moving rats. *Iranian Journal of Basic Medical Sciences, 23*(2), 173-177. [PMID]

Zhong, K., Wu, D. C., Jin, M. M., Xu, Z. H., Wang, Y., & Hou, W. W., et al. (2012). Wide therapeutic time-window of low-frequency stimulation at the subiculum for temporal lobe epilepsy treatment in rats. *Neurobiology of Disease, 48*(1), 20–26. [DOI:10.1016/j.nbd.2012.05.011] [PMID]

Zhu-Ge, Z. B., Zhu, Y. Y., Wu, D. C., Wang, S., Liu, L. Y., & Hu, W. W., et al. (2007). Unilateral low- frequency stimulation of central piriform cortex inhibits amygdaloid-kindled seizures in Sprague- Dawley rats. *Neuroscience, 146*(3), 901-906. [DOI:10.1016/j.neuroscience.2007.02.014] [PMID]

Zucker, R. S., & Regehr, W. G. (2002). Short-term synaptic plasticity. *Annual Review of Physiology, 64*, 355–405. [DOI:10.1146/annurev.physiol.64.092501.114547] [PMID]