

Review Article

A review on the roles of electrical low-frequency deep brain stimulation and modulatory action of the serotonergic system in seizure

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Abstract

Epilepsy is a common neurological disorder that affects approximately 50 million people and about 30% of them have seizures despite antiepileptic-drug therapy. Even if 50% of these 600,000 or so patients benefit from surgical resection, many would still need new therapeutic approaches. Deep brain stimulation (DBS) has been suggested as an alternative to drug therapy. Low frequency stimulation (LFS) is an effective pattern of DBS that can decrease epileptic seizures. The incidence of epileptic seizures has been described by an imbalance between excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission. This phenomenon may be affected by other neurotransmitter systems, including serotonin (5-hydroxytryptamine, 5-HT). The Serotonergic system undergoes many alterations in the epileptic brain. The link between LFS and serotonin release has been studied and it is documented that 5-HT_{1A} receptor antagonist reduces the anti-convulsant effects of LFS. Thus, considering the effects of the serotonergic system in neuronal activities in the epileptic brain, it may be involved in the anti-convulsant mechanism(s) of LFS. In this review, we introduce the effects of low frequency stimulation on seizure and its possible mechanisms. The role of some neuromodulators in mediating the anti-convulsive effects of LFS and the probable signaling changes will be discussed.

Keywords:

Epilepsy;
Low frequency stimulation;
Neuromodulator

Received: 11 May 2019

Accepted: 1 Aug 2019

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Introduction

Epilepsy as a common neurological disorder characterized by repeated spontaneous neurological or behavioral changes, often associated with cognitive impairment, psychiatric symptoms and social function deficit (Neligan et al., 2012; Sander, 2003; Beghi and Hesdorffer, 2014; Fiest et al., 2017). More than 20% of epileptic people have drug-

resistant epilepsy (Kwan et al., 2011). Drug-resistant epilepsy has been suggested by the International League Against Epilepsy (ILAE) as a failure of an adequate trial of at least 2 anti-epileptic drugs that are appropriately chosen, applied and tolerated (Kwan et al., 2010). People with persistent seizures have a huge burden of disability, poor quality of life and increased mortality and morbidity. Surgery has been known as the first line treatment of drug-resistant epilepsy. Nevertheless, when surgery is

contraindicated or ineffective, deep brain stimulation (DBS) has been suggested as an important therapeutic option. In DBS, deep brain structures are stimulated (according to a predetermined program) by implanting electrodes connected to a pulse generator (Li and Cook, 2018). The anti-epileptic effects of DBS were first studied in the 1970s and the 1980s (Van Buren et al., 1978; Cooper et al., 1976; Upton et al., 1987; Penfield, 1936), even though the first time DBS was used to treat epilepsy by the neurosurgeon Wilder Penfield was forty years before (Penfield, 1936).

Low frequency stimulation (LFS) is an effective pattern for deep brain stimulation that can decrease epileptic seizures. In the first experiments, the decreasing effect of LFS on the kindled seizures was ignored (Gaito, 1980; Gaito et al., 1980). In 2002, Velisek et al. reported that LFS during kindling acquisition delayed the kindling process in immature animals. Induced seizure activity has been decreased by LFS in several *in vitro* studies (Khosravani et al., 2003; Barbarosie and Avoli, 1997; Albensi et al., 2004). Several clinical studies demonstrated that LFS reduced interictal spiking in patients with temporal lobe epilepsy (Albensi et al., 2004; Yamamoto et al., 2002). It has been shown that LFS application targeting amygdala results in a substantial increase in seizure threshold and suppression of behavioral seizures (Gharib et al., 2018; Gharib et al., 2019; Rezaei et al., 2017; Burattini et al., 2014). There are some evidences that LFS evokes serotonin release in the nucleus accumbens and induces long-term depression via generation of endocannabinoid (Burattini et al., 2014). Besides, microinjection of a selective antagonist of serotonin 5-HT_{1A} receptors into the hippocampal CA1 region reduces the anti-convulsant effects of LFS. It means that the anti-convulsant action of LFS depends on the activation of hippocampal 5-HT_{1A} receptors. Therefore, 5-HT_{1A} receptors of the hippocampal CA1 area are involved in mediating the anti-convulsant effects of LFS in fully kindled animals (Gharib et al., 2018; Gharib et al., 2019).

This review focuses on animal and clinical studies that have investigated the effect of LFS in seizure control. The results are organized based on the history of using LFS in seizure treatment. Then we will address the role of some brain neuromodulators in mediating the anti-seizure action of LFS.

Anti-epileptic mechanisms of LFS

Mechanisms involved in the neuromodulation by DBS or in the anti-epileptic effects of LFS have not been completely recognized. Some hypotheses that have been proposed include: 1- depression of excitatory synapses; 2- potassium-mediated depolarization block; 3- glial-neuronal interplay; 4- decreased excitatory/increased inhibitory synaptic neurotransmission and 5- reduction in the excitability of neurons (Durand and Bikson, 2001; Schiller and Bankirer, 2007).

Short-term synaptic depression of excitatory neurotransmission has been reported during the LFS application in cortical hippocampal slices (Lopez-Meraz et al., 2004). It has been suggested that LFS may accomplish its anti-seizure effects through long term deputation (LTD) or depotentiation-like mechanisms. For example, the application of NMDA antagonists during LFS administration remove both LTD and seizure activity (Albensi et al., 2004). However, the role of LTD-like mechanisms in LFS anti-seizure action, has been disputed by Goodman et al. (2005) according to evidences, including: 1) anti-seizure effects of LFS take place even after using a stimulus train at duration which is too short to induce LTD; 2) the anti-seizure effect of LFS occurs immediately following its application, a time-course that is not consistent with an LTD-mediated mechanism and 3) an increase in afterdischarge threshold following LFS may be responsible for its anti-seizure effect (Goodman et al., 2005). Added to above mentioned results, the other reason is that it is very difficult to induce LTD in adult rats. Therefore, the LFS anti-seizure action may be through depotentiation-like mechanisms.

The potassium-mediated axonal block has been observed during high frequency stimulation (HFS) of hippocampal fiber tracts (Jensen and Durand, 2007). However, its role in LFS has not been studied. It has been established that glial cells interact with neurons during ictogenesis (Tian et al., 2005; de Lanerolle et al., 2010). Therefore, it is possible that there is glial-neuronal interplay mediating seizure reduction by LFS as well.

Measuring the cAMP concentration by ELISA technique showed that LFS application prevents the increase of cAMP concentration in kindled animals (Namvar et al., 2017). In order to examine the hypothesis that Gi activity is a general signaling

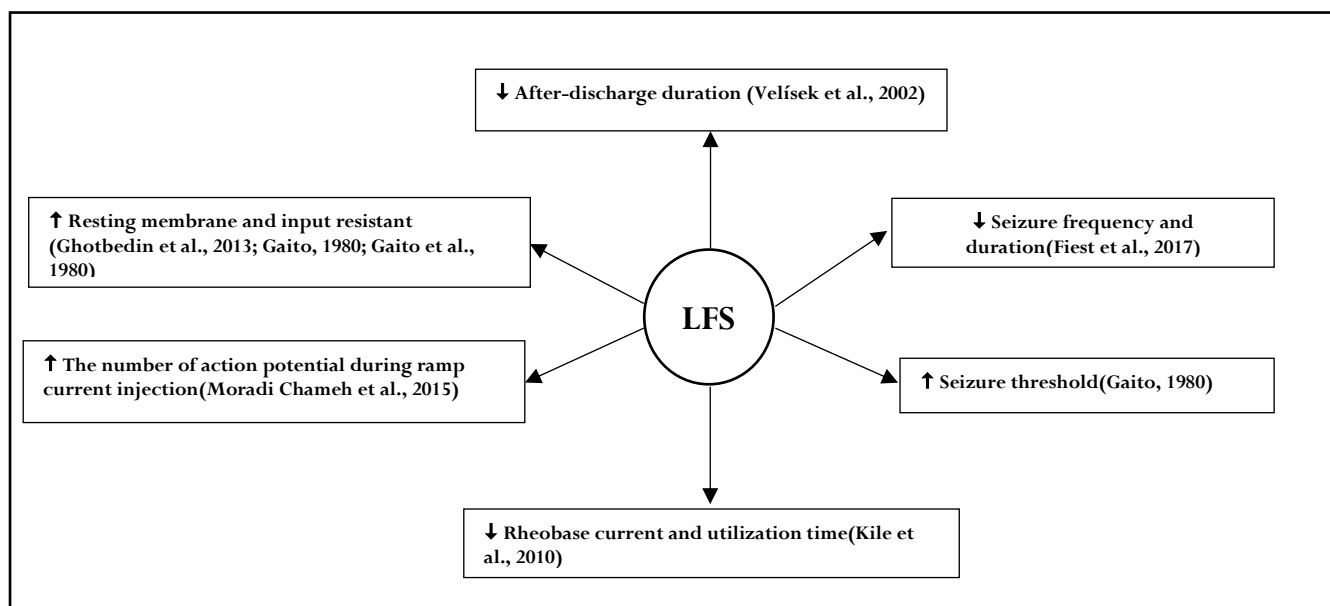


Fig.1. Effects of LFS on electrophysiological properties in seizure.

mechanism for the occurrence of LFS anti-convulsant effects, the expression of α_i and α_s subunits were measured following LFS application. Although there were no significant changes in the ratio of α_i to α_s expression in kindled animals in the presence or absence of LFS, but the expression of regulator of G protein signaling (RGS) proteins was affected by LFS. Administration of LFS decreased the expression of RGS4 and RGS10 which reduce the G_i activity. LFS also prevented the seizure-induced decrease in the expression of RGS2, which reduce the activity of G_s . Therefore, LFS actions change the situation of G protein signaling in a manner that increases G_i activity and reduces G_s activity (Namvar et al., 2017). However, it is necessary to assay the effect of LFS on the enzyme activity of G protein alpha subunits following seizure induction in laboratory animals.

In addition to G_i signaling, the role of the ERK signaling pathway has also been shown to mediate the anti-epileptic effects of LFS (Mardani et al., 2018b). Given the widespread function of the signaling pathways G_i and ERK and the role of many other signaling pathways in controlling them (Mardani et al., 2018b), it can be expected that LFS acts to produce anti-convulsant effects of a wide range of signaling molecules and its determination needs more research.

Studies on the effects of LFS on epilepsy

The first study on LFS was done by Wilder Penfield in the 1930s to treat epilepsy. Different parts of the

cerebral cortex were stimulated with an electrical probe, while the patient was kept awake. The convulsive seizure in particular areas was implicated during stimulating the various regions of the cerebral cortex (Penfield, 1936). Then, Irving Cooper, the famous US neurosurgeon, stimulated the cerebellum and other regions of brain as treatments for cerebral palsy, epilepsy or dystonia in around 200 patients (Cooper and Upton, 1978; Cooper et al., 1980) and up to 200 patients were treated (Rosenow et al., 2002).

In 1980-1981 John Gaito demonstrated that low frequency (1–3 Hz) stimulation in adult rats before and after high-frequency (60 Hz) kindling stimulus interferes with amygdala kindling. This interference increases significantly the seizure threshold and suppresses behavioral seizures (Gaito, 1980; Gaito et al., 1980; Gaito and Gaito, 1981) (Fig. 1). During these years, eight patients with medically refractory focal epilepsies were also treated by low frequency repetitive transcranial magnetic stimulation (rTMS), on 5 consecutive days (Tergau et al., 1999).

In immature rats during the 3rd postnatal week, the magnitude of LTP and LTD is larger than in earlier and later development (Dudek and Bear, 1993; Teyler et al., 1989; Velísek et al., 1993). According to the results of these researches and John Gaito, in 2002, Libor Velísek designed his experiment and concluded that applying LFS in immature rats significantly decreased the afterdischarge duration after amygdala kindling stimulation (Velísek et al.,

Table 1: 5-HT receptor types (Hoyer and Martin, 1997)

Receptors types	Receptor subtypes	Function
5-HT1	1A, 1B, 1D, 1E, and 1F	Negatively coupled to adenylyl cyclase ($G_{i/o}$)
5-HT2	2A, 2B, and 2C	Activating the phospholipase C cascade ($G_{q/l}$)
5-HT3	-	The only ligand-gated channel receptors
5-HT4	-	Positively coupled to adenylyl cyclase (G_s)
5-HT5	5A	Positively coupled to adenylyl cyclase (G_s)
	5B	Unknown
5-HT6	-	Positively coupled to adenylyl cyclase (G_s)
5-HT7	-	Positively coupled to adenylyl cyclase (G_s)

2002).

In 2003, Khosravani and colleagues used an *in vitro* model of recurrent spontaneous seizures in hippocampal slice according to Rafiq et al. model (Rafiq et al., 1993; Rafiq et al., 1995). They applied low frequency stimulation (0.5Hz for 20–50s) via an extracellular stimulating electrode to the mossy fibers. They reported that the transition from the interictal activity to the seizure-like event is aborted (Khosravani et al., 2003). Goodman and colleagues demonstrated that LFS reduced the stage 5 incidence of amygdala-kindled seizures in fully kindled animals and also, LFS strongly has been suggested as an effective therapy for the prevention of seizures in patients with epilepsy (Goodman et al., 2005). In conformity with this results in human studies, Yamamoto and colleagues in 2006 showed that LFS suppressed not only interictal but also ictal activities. They reported that the intensity of stimulation was important to suppress the seizures in epileptic patients, so that the habitual seizures was suppressed by LFS with the intensity of 15mA but not with 0.5mA.

In 2006, Ghorbani Moghadam and colleagues investigated the effective parameters of LFS on kindled seizure. They examined the effect of changes in some LFS parameters on the piriform cortex and reported that the inhibitory effect of LFS on kindled seizures depends on LFS parameters such as pulse duration, intensity, applied duration and time of application. They concluded that in fully kindled animals, application of different patterns of LFS exerted an inhibitory effect when applied during an inter-seizure interval of 7 days. Afterdischarge duration was also significantly decreased when LFS

was delivered daily after each kindling stimulation. Kile and colleagues in 2010 applied LFS on the Q54 model of epilepsy (a genetic model) and reported that 3Hz LFS significantly decreased seizure frequency and duration, but the effect was not immediate, supporting that the underlying mechanisms of action may be complex and long lasting.

The role of serotonin and other neuromodulators in the anticonvulsant effects of LFS

After approving LFS as an anti-convulsant method in animal and human studies, the mechanism of its effects was investigated. In a series of experiments, the role of various neurotransmitters in the mediation of LFS anti-convulsant effects in the kindling model was studied (Ciranna, 2006). In the study conducted by Gharib et al. using microinjection of NAD-299 (a selective 5-HT_{1A} antagonist) in the hippocampal CA1 region, the role of 5-HT_{1A} receptors in mediating LFS' improving effect on spatial learning and memory was investigated in amygdala-kindled rats. LFS was applied after the termination of kindling stimulations. NAD-299 was microinjected into the hippocampal CA1 before LFS application. As in the previous studies (Jalilifar et al., 2017; Esmaeilpour et al., 2013) and our study, application of LFS following daily kindling stimulations reduced the behavioral seizure stages, afterdischarge duration, stage 5 seizure duration and increased the latency to stage 4 seizure. However, microinjection of NAD-299, dose dependently blocked the inhibitory effect of LFS on behavioral and electrophysiological parameters in kindled animals. It could be presumed that 5-HT_{1A} receptors in the CA1 area are involved in mediating the antip-epileptic effects of LFS (Gharib et al., 2018;

Table2: Summary of studies reporting the effect of 5-HT in epilepsy.

Type of Convulsion	Model	Results	Authors
Focal	KA, Acute seizure evocation	Increases in hippocampal 5-HT tissue content and extracellular 5-HT levels	(Alfaro-Rodríguez et al., 2011; Tchekalarova et al., 2015)
	KA, spontaneous recurrent limbic seizures	Decreases in 5-HT	(Tchekalarova et al., 2011)
	post-SE rat model for focal epilepsy using pilocarpine using acute seizure phase	Increase in 5-HT hippocampal content and level	(Cavalheiro et al., 1994; Meurs et al., 2008)
	post-SE rat model for focal epilepsy using pilocarpine using spontaneous recurrent seizure phase	No increase in 5-HT hippocampal content and level	(Cavalheiro et al., 1994; Szyndler et al., 2005)
Generalized	Rat unilateral hypoxia-induced epilepsy	Decrease in the 5-HT _{1A} and 5-HT _{1B} R immunoreactivities	(An and Kim, 2011)
	Pentylenetetrazole (PTZ, a prototypic antagonist of GABAA receptors)	Anticonvulsant effects of 5-HT _{1A} R agonists	(An and Kim, 2011)
	Tonic-clonic seizures evoked by amygdala kindling	Anticonvulsant effects of 5-HT _{1A} R agonists	(López-Meraz et al., 2005)
	picrotoxin (another typically used antagonist of GABAA receptors)	Anticonvulsant effects of 5-HT _{1A} R agonists	(Peričić et al., 2005)
		Anticonvulsant effects of 5-HT _{1B} activation	(Wesołowska et al., 2006)
Generalized Non-convulsive		5-HT _{2B} R had no effect on the threshold	(Upton et al., 1998; Di Giovanni and De Deurwaerdère, 2016; De Deurwaerdère and Di Giovanni, 2017)
	Genetic Absence Epilepsy Rats from Strasbourg (GAERS)	5-HT _{2CR} agonists dose-dependently suppressed absence seizures	(Venzi et al., 2016)
	Wistar Albino Glaxo rats from Rijswijk (WAG/Rij) rats in polygenic rat model of absence epilepsy	mCPP decreased spike-wave discharges (SWDs) cumulative duration via the activation of 5-HT _{2CRs}	(Jakus et al., 2003)
	WAG/Rij rats	SB 242084 had anti-absence effects in GAERS but no effect on SWDs	(Jakus et al., 2003)
	WAG/Rij rats	Antagonism of 5-HT ₇ Rs reduced spontaneous spike-wave discharges	(Graf et al., 2004)

Gharib et al., 2019).

Distribution of serotonin (5-HT) as a neurotransmitter in the central nervous system is documented. In several brain regions, 5-HT behaves as a neuromodulator rather than a neurotransmitter. There are some connections between serotonin and other

neuromodulators actively involved in LFS anti-seizure effects as follows:

Anticonvulsant effects of the neuropeptide galanin have been well established and best described in models of limbic epilepsy, in this process, serotonin concentration has been affected according

Table 3: Studies on epilepsy and LFS application in male Wistar rat animal model.

Author	Target structure	LFS parameter	Drug application	Major outcomes
(Gharib et al., 2018)	Amygdala	0.1 ms pulse duration at 1 Hz, 200 pulses, 50–150 μ A	- NAD (a selective 5-HT _{1A} antagonist) - 2.5 and 5 μ g/1 μ l	- NAD-299 blocked the inhibitory effect of LFS in kindled animals. - 5-HT _{1A} receptors mediate the antiepileptic effects of LFS.
(Ghasemi et al., 2018)	hippocampal CA1 pyramidal neurons	1 Hz, 600 and 900 pulse numbers		- More LFS pulses increased inhibitory effects on epileptiform activity.
(Mardani et al., 2018a)	Perforant path	0.1 ms pulse duration at 1 Hz, 800 pulses	-AM281, a CB1 receptor antagonist - 0.5 and 2 μ g/ μ l	- Role of cannabinoid CB1 receptors in mediating the inhibitory effect of LFS
(Mardani et al., 2018b)	Perforant path	0.1 ms pulse duration at 1 Hz, 800 pulses	- FR180204 (inhibitor of ERK) - 1 μ g/ μ l	- Role of ERK in the antiepileptogenic effect of LFS.
(Esmaeilpour et al., 2018)	Hippocampal CA1 region of the right hemisphere	0.1 ms duration at 1 Hz, 200 pulses		-Impairment of learning by hippocampal kindling and its improvement using LFS.
(Esmaeilpour et al., 2013)	Hippocampal CA1 region	200 monophasic square wave pulses of 0.1ms duration at 1Hz		- Application of LFS overcame the kindling-induced impairment in LTP.
(Namvar et al., 2017)	Adult male Wistar rats	0.1 ms pulse duration at 1 Hz, 200 pulses, 50 – 150 μ A	-Rolipram -0.25 μ M	- LFS to the perforant path retarded the kindling development and prevented the kindling-induced potentiation and rolipram prevented LFS effects.
(Ghafouri et al., 2017)	Pyramidal cells in the hippocampal CA1 area	200 pulses at 1 Hz, 0.1 ms		- LFS prevented increase in spontaneous glutamatergic transmission and the decrease in spontaneous GABAergic transmission.
(Esmaeilpour et al., 2017)	Hippocampal CA1 area	200 monophasic square wave pulses of 0.1 ms duration at 1 Hz		- LFS has a long-term improving effect on spatial learning and memory in kindled animals.
(Ghotbedin et al., 2013)	Neurons in the CA1 area of the hippocampus			- Amygdala kindling increases neuronal excitability and raises conductance of calcium- dependent potassium channels. - LFS after kindling stimulations prevents these changes.
(Ghafouri et al., 2016)	CA1 area of the hippocampus	200 monophasic square wave pulses of 0.1 ms duration at 1 Hz		- LFS reduce the Y-maze performance impairment in kindled rats and increase the calcineurin A- α gene-expression.
(Asgari et al., 2016)	CA1 area of the hippocampus		-Phenobarbital	- Sub-threshold dose of phenobarbital can potentiate GABAergic currents in an ineffective pattern of LFS.

Continue to Table 3:

Author	Target structure	LFS parameter	Drug application	Major outcomes
(Rohani et al., 2014)	CA1 area of the hippocampus	0.5, 1 and 5 Hz		- By preventing ultrastructural changes during kindling, LFS can prevent neuronal hyperexcitability.
(Shojaei et al., 2014)	Dentate gyrus	200 monophasic square wave pulses of 0.1 ms duration at 1 Hz		- LFS as an effective therapeutic method in amygdala kindling seizures
(Ghotbedin et al., 2013)	Pyramidal neurons in hippocampal slice	3 s, 50 Hz monophasic square-wave pulses of 1 ms		- LFS prevents the kindling induced changes in functional electrical properties of CA1 pyramidal neurons.
(Esmailpour et al., 2013)	Amygdala, piriform cortex and substantia nigra	200 monophasic square-wave pulses, 0.1 ms pulse duration at 1 Hz	-	- Stronger inhibitory effect of LFS on kindling development when applied in substantia nigra. Also, LFS had greater inhibitory effects when applied to the amygdala compared to piriform cortex.

(Mazarati et al., 2005). In 2007, Sadegh and colleagues demonstrated that the inhibitory effect of LFS on the perforant path– kindled seizure acquisition was mediated through activation of galanin receptors. Galanin modulates some classical neurotransmitters and thus represents an intriguing tool for restoring the balance between the inhibition and the excitation. Galanin inhibits glutamate release in the hippocampus and has been considered as an endogenous anti-convulsant (Mazarati et al., 2001; Mazarati and Lu, 2005; Lundström et al., 2005). Blockade of galanin receptors by microinfusion of M35 (non-selective galanin receptor antagonist) into the dentate gyrus, decreased the anti-convulsant effects of LFS on perforant path kindling development. This indicates that galanin receptor activation may contribute to the inhibitory effects of LFS on kindling epileptogenesis. RT-PCR studies also confirmed that kindling decreased GalR2 mRNA level, but LFS prevented this effect. LFS application delayed the kindling procedure and delayed the development of different kindled seizure stages (Sadegh et al., 2007). In addition to galanin, adenosine also plays an important role in the anticonvulsant effect of LFS mechanism.

The link between serotonin and adenosine has also been studied and both adenosine and 5-HT seem to be implicated in epileptiform activity. The hippocampal 5-HT release is modulated by endogenous adenosine via A1 receptors (Feuerstein

et al., 1985). In 2009, Mohammad-Zadeh reported that, activation of adenosine A₁ receptors has a role in mediating the anti-convulsant effects of LFS on perforant path kindling acquisition so that microinfusion of an adenosine A₁ receptor antagonist, CPT, suppressed this inhibitory effect of LFS (De Mendonca et al., 1997). In addition, adenosine and its derivatives modulate several forms of short-term and long-term activity dependent synaptic plasticity (De Mendonca et al., 1997). For example, it has been shown that an adenosine receptor agonist, 2-chloroadenosine, decreases LTP at schaffer collateral–CA1 synapses (Arai et al., 1990; Dolphin, 1983). Activation of adenosine receptors also has a role in suppressing the effect of LFS on LTP (depotentiation). Considering the similarities between the kindling phenomenon and LTP (Cain, 1989; Mohammad-Zadeh et al., 2007), similar mechanisms may account for LFS induction of depotentiation and the anti-convulsant mechanisms of LFS on kindled seizures. In addition, LFS prevented the kindling-induced increase in the pEPSP slope and PS amplitude in the dentate gyrus. However, no significant change was observed in cumulative afterdischarge duration after LFS application during the first 7 days of kindling procedure. Field potential recordings confirmed a kindling-induced potentiation in the dentate gyrus. Application of LFS after kindling stimulations completely inhibited this potentiation during the first 7 days of kindling acquisition

(Mohammad-Zadeh et al., 2009).

Other studies have shown that neuronal structures changed by LFS application. Rohani and colleagues in 2014 reported that LFS application could prevent some kindling induced ultrastructural alterations in perforant path-dentate gyrus synapses. Kindling stimulations increased the synaptic strength and for this reason, the postsynaptic membrane expanded, the thickness of the post-synaptic density and the numbers of synaptic vesicles increased and the efficacy of synaptic transmission enhanced (Rohani et al., 2014). Some studies showed a relationship between serotonin and LFS. Gharib et al. (2018) showed that serotonergic receptors (5-HT_{1A} receptors) in the hippocampal CA1 area may be involved in mediating the LFS anticonvulsant effect.

There are two types of synapses: flat or convex and concave. The convex synapses have usually inhibitory actions and the concave synapses are excitatory. In kindled animals that received LFS, most of the synapses were flat or convex, so that the number of concave synapses was also reduced compared with the kindled animals. The observed changes can show a compensatory mechanism through which the LFS may reduce the excitatory effects of kindling stimulations and can partly explain the anti-epileptogenic effect of LFS. Nevertheless, the number of synaptic vesicles did not change in kindled-LFS group compared to the kindled group (Jessell et al., 2013). It has been reported that kindled seizures can result in synaptogenesis (Chang et al., 1993; Suemaru et al., 2000; Saegusa et al., 2004). In kindled animals most of these synapses are excitatory. However, the application of LFS may induce the generation of new inhibitory synapses too. In conclusion, application of LFS after the termination of kindling stimulations can exert its anti-convulsant actions partly through reducing the kindling induced alterations in ultrastructural properties of newly generated synapses. LFS exerted these effects when applied at the frequencies of 0.5, 1 and 5Hz (Jessell et al., 2013).

Another possible mechanism involved in the anti-convulsant effects of LFS is the activation of GABAergic terminals and subsequent GABA release (Windels et al., 2000; Mantovani et al., 2006). Consistent with this idea, in 2004, Cuellar-Herrera suggested that electrical stimulation of parahippocampal cortex is effective in patients with less

severe epilepsy, an effect which was associated with a high GABA tissue content and a low rate of cell loss (Cuellar-Herrera et al., 2004). Modulation of GABA-mediated inhibitory transmission by 5-HT and 5-HT modulation of glutamate- and GABA-mediated effects in nervous structures are mostly deputed to cognitive functions, pain transmission and motor control (Ciranna, 2006).

Autoradiography experiments also revealed an increase in benzodiazepine receptor binding in the basolateral amygdala following application of LFS in amygdala-kindled rats, suggesting that the anti-epileptic effects of LFS may involve activation of GABA-benzodiazepine system (Lopez-Meraz et al., 2004). This anti-convulsant effect was related to the enhancement of the expression level of $\alpha 5$ subunits of extrasynaptic GABA-A receptor (Shen et al., 2013). In addition, it has been shown that the application of LFS may protect against seizures by modulating the expressions of $\alpha 1$ and $\beta 2$ subunits of the GABA-A receptor (Yang et al., 2014). In relation to the role of GABAergic system in LFS mechanism in 2016, Asgari and colleagues indicated that pretreatment of either the seizure focus or hippocampal slices by an ineffective pattern of LFS can increase the responsiveness of GABAergic currents to phenobarbital. On the other hand, co-application of a sub-threshold dose of phenobarbital and an ineffective pattern of LFS can significantly affect the evoked and miniature IPSCs in hippocampal pyramidal neurons.

An electrophysiological study conducted by Ghotbeddin in 2017 showed that both resting membrane potential and input resistance decreased in kindled animals and LFS induction prevented this reduction. Changes in membrane resistance may be because of changes in the size and morphology of cells or may result from direct changes in ionic conductance. Cellular activity is dependent on a combination of intrinsic ionic conductance and interaction with excitatory and inhibitory synaptic inputs. The firing pattern of a neuron is determined by its intrinsic membrane properties and synaptic inputs. Therefore, spontaneous activity of the cells originates from their intrinsic membrane properties and synaptic inputs can modify this activity. Increased frequency of stimulations during current clamp enhances calcium entry and the subsequent activation of calcium-dependent potassium channels (SK) increases inter-

spike intervals and reduces firing frequency, while the final action potentials occur in the form of a train of action potentials (Ghotbedin et al., 2013).

Namvar and colleagues in 2017 reported that there is a negative relationship between phosphodiesterase activity (and therefore cAMP concentration) and anti-epileptogenic action of LFS. The observed increase in early and late paired-pulse indices shows that kindling can potentiate the GABAergic currents as a compensatory mechanism against the neuronal activity. The other factor which reduced the paired pulse indices during kindling may be an increase in the neurotransmitter releasing probability. The inhibitory effects of LFS on kindling-induced potentiation of early and late paired pulse depression, or kindling-induced elevation in neurotransmitter releasing probability, depends on the reduction of cAMP level. (Namvar et al., 2017).

In 2018, Mardani and colleagues concluded that ERK activation was necessary to LFS anti-epileptogenic effect, since the effects of LFS on seizure parameters abolished by FR180204 (an inhibitor of ERK1 and ERK2) application (1µg/µl). In addition, microinfusion of FR180204 prevented the inhibitory effect of LFS on kindling-induced changes in PS amplitude and pEPSP slope. LFS application suppressed the kindling-induced potentiation of early and late paired pulse depression in the dentate gyrus. Inhibition of ERK (FR180204) significantly reduced these effects of LFS. Inhibition of ERK signaling had an anti-epileptogenic effect on kindling procedure when FR180204 was microinjected alone at high dose (2µg/µl). As FR180204 had no significant effect on seizure and field potential parameters at the low dose of 1µg/µl, the preventing effect of FR180204 on LFS anti-epileptogenic effect was not related to its anti-convulsant action. Immunoreactivity of activated ERK (p-ERK) decreased in the dentate gyrus of kindled animals. Paired-pulse stimulations showed a potentiation in late paired-pulse depression, which is related to activation of GABA-B receptors. It means that kindling leads to activation of GABA-B receptors. Application of the LFS on perforant path following kindling stimulations could strongly increase p-ERK immunostaining in the dentate gyrus (Mardani et al., 2018b).

Effect of LFS on seizure-induced impairment in learning and memory

Given that, epileptic patients, especially those with temporal lobe epilepsy, often show cognitive and memory disorders (Mula and Trimble, 2009; Holmes, 1991), in addition to electrophysiology studies, behavioral studies were also conducted. Cognitive deficits also occur following electrical kindling of various limbic sites including the hippocampus. Considerable pieces of evidence have indicated that kindling can cause deficits in a variety of hippocampal-dependent behaviors, including spatial learning in spatial discrimination task and Morris water maze (Beldhuis et al., 1992; Cammisuli et al., 1997), working memory in a radial maze (Leung et al., 1994), reference memory in a radial maze (Lopes da Silva et al., 1986) and spatial memory in Morris water maze (Gilbert et al., 1996; Sutherland et al., 1997; Hannesson et al., 2001; Hannesson and Corcoran, 2000). Kindling-induced impairment in cognitive functions can be observed up to 4 weeks following the last kindled seizure (Leung et al., 1994). In relation to the effect of LFS on behavior, in 2016, Ghafouri and colleagues investigated the spontaneous alternation behavior of kindled rats in the Y-maze test. Application of LFS in CA1 region of the dorsal hippocampus can prevent kindled seizure-induced impairment of spontaneous alternation behavior in the hippocampus of fully kindled animals. Also, administration of LFS in fully kindled animals significantly increased gene expression of calcineurin-A compared to the control group. After that, similar results were obtained by Esmaeilpour and colleagues in Morris water maze and novel objective recognition tasks. They reported that application of LFS can improve kindling-induced impairment in learning and memory. Fully kindled animals that received LFS had an improved performance in Morris water maze and novel objective recognition task. This effect was not permanent (only one week in our study); however, by increasing the number of applied LFS packages its effectiveness remained for a longer duration (Esmaeilpour et al., 2017).

In addition, they reported that hippocampal kindling leads to impairment of learning in the passive avoidance test. However, application of LFS in CA1 region of the dorsal hippocampus could prevent the kindled seizure-induced impairment of emotional learning in fully kindled animals. When memory was assessed in the passive avoidance test, kindling-

impaired acquisition of passive avoidance was demonstrated by a shorter step through latency and longer time spent in the dark compartment. Application of LFS modulates this kindling-induced impairment since LFS induction partially reversed kindling-induced reduction in step through latency and increase in time spent in the dark compartment (Esmailpour et al., 2018).

In 2018, Gharib and colleagues investigated both behavioral and electrophysiological variations in the amygdala of fully-kindled rats. They reported that application of LFS in the amygdala decreased the electrophysiological and behavioral indices of seizure severity in the amygdala of fully-kindled rats. This anti-convulsant action of LFS was dependent on activation of the hippocampal serotonin 5-HT_{1A} receptors, because microinjection of a selective antagonist of these receptors into the hippocampal CA1 region reduced the anti-convulsant effects of LFS. 5-HT_{1A} receptors of the hippocampal CA1 area were involved in mediating the anti-convulsant effects of LFS in fully kindled animals. Then, 5-HT_{1A} receptor selective antagonist was injected into the full-kindled animals (i.e., following at least 3 consecutive stages 5 seizures) with secondarily generalized seizures. A stage 5 seizure initiated in the amygdala had to spread bilaterally to become generalized and eventually reach the motor cortex. They showed that the activity of the hippocampus was necessary for spreading the seizure discharges. In their study, administration of LFS to amygdala significantly decreased both behavioral and electrophysiological parameters of seizures. They showed that amygdala could be a suitable brain region for LFS anticonvulsant action and LFS and 5-HT_{1A} signaling pathways had crosstalk that could be involved in the anticonvulsant actions of LFS mediated by 5-HT_{1A} receptors (Gharib et al., 2018).

In 2019, Gharib et al. in continuing the above mentioned experiment reported that in addition to its anti-convulsant effect, LFS improves learning and memory in kindled animals. They showed that in kindled animals, LFS reduced impairments in spatial learning and memory in the Morris water maze and novel object recognition tests. Microinjection of NAD at doses of 5 µg/µl reduced the effects of LFS on learning and memory. Hippocampal slices revealed that the gene expression level of 5-HT_{1A} receptors increased significantly in the hippocampus of

amygdala-kindled rats. However, LFS applied after kindling stimulations inhibited this effect. It seems that activation of 5-HT_{1A} receptors in the CA1 field is necessary for LFS' improving effects on spatial learning and memory in kindled animals; although surprisingly, LFS application prevented the elevation in gene expression of 5-HT_{1A} receptors in kindled animals.

Conclusion

Many studies supporting the anti-convulsant role of LFS. Considering the fact that LFS as an effective pattern of DBS will be a new therapeutic manner in the treatment of drug-resistive epileptic patients, it is necessary to find its anti-convulsive mechanisms. It seems that neurotransmitters/neuromodulator receptors, which exert anti-convulsant effects, are the main mediators of LFS anti-seizure action. However, finding the main mechanism of LFS action needs more studies.

Acknowledgments

This study was financially supported by Grant # 9511056349, Deputy of Research and Technology, Hamadan University of Medical Sciences, Hamadan, Iran. The authors would like to express their gratitude to the staff of the Neurophysiology Research Center for helping them carry out this study.

Conflict of interest

The authors state that there is no conflict of interest.

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