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Deep brain stimulation, epilepsy and inflammation: a brief review

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ABSTRACT

Epilepsy is among the wide spread neurological disease. Considering that the occurrence of seizures in 20 to 40% of epileptic patients is resistant to drug therapy, many researches are being conducted to reach new methods of epilepsy treatment. The most common epileptic syndrome in adults is temporal lobe epilepsy. In most patients with temporal lobe epilepsy, the structures of the middle temporal lobe, including the hippocampus, are involved in seizure generation and propagation. One of the relatively new therapies for controlling drug-resistant seizures is direct stimulation of the epileptic focus by electrical stimuli. Numerous studies have shown that the application of deep brain electrical stimulation (DBS) has anticonvulsant effect on the epileptic focus, but the mechanism of its anticonvulsant effect is not yet fully understood. Many abnormalities occur following seizures and it can be postulated that DBS may prevent or reduce these abnormalities. One important abnormality is inflammation. Here we briefly reviewed the probable relationships between anticonvulsant action of DBS and inflammation.

Key words: Brain stimulation; Epilepsy; Inflammation; Seizure

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Introduction

Epilepsy is one of the most common neurological disorders. About 1% of the world population have epilepsy and nearly 80% of the cases occur in developing countries. This disease is more common in new-borns and elderly (1). In general, seizure is a sudden abnormal and synchronous neural activity in the brain (2). According to the new definition of epilepsy that has been expressed by the international league against epilepsy (ILAE), "epilepsy includes patients with one unprovoked seizure with a probability of further seizures, similar to the general recurrence risk after two unprovoked seizures, occurring in a 10-year period" (3). Epilepsy involves disturbances in behavior, sensation, perception and motion. These disturbances may be associated with a change in level of consciousness (4).

Among the various epileptic syndromes, temporal lobe epilepsy is the most common

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epileptic disorder in adults, which may be occurred following other brain disorders such as stroke, trauma and neurodegenerative diseases. Studies have shown that in this type of epilepsy, different parts of the limbic system, including amygdala and hippocampus, play an important role in the generalization and propagation of seizures (5).

The hippocampus is a part of the limbic system that plays an important role in stabilizing information, learning and long-term memory. Hippocampal surgery in patients with temporal lobe epilepsy has been associated with a reduction or elimination of epilepsy (6). Due to the great importance of this area in seizure generation and propagation (4), a large amount of research has been focused on this area and many neuromorphological and electrophysiological findings about temporal lobe epilepsy are based on studies performed on the hippocampus.

The hippocampus has four main sections called CA1 to CA4. The CA1 region is the most complex part of the hippocampus and contains principal pyramidal cells and different types of interneurons. An important feature of the hippocampus is that it is highly irritable. Therefore, high frequency and weak electrical stimuli can cause local epileptic seizures in this region. Hippocampus is the most important center for the development of complex partial epilepsy in humans. In order to understand the processes involved in generating or maintaining neurological conditions of epilepsy, due to the immorality of experiments on humans, most studies are performed on laboratory models of epilepsy in animals, one of the most important of which is the kindling model of seizure (7).

Kindling is defined as the progressive development of behavioral and electroencephalographic seizures in response to repeated application of a low-intensity, sub-threshold electrical or chemical stimulations. Accordingly, based on the type of stimuli, this model is divided into two types: electrical and chemical. In electrical kindling, electrodes are implanted surgically in the desired areas of the brain. Then, weak electrical stimuli (below the threshold) with a given intensity, frequency, duration and intervals apply to a relevant area. In chemical kindling, convulsive chemicals inject frequently into the animal at concentrations that are not initially capable of causing a generalized seizure (8). These substances may inject systemically or directly into the animal's brain. These chemical agents increase excitation or decrease inhibition by various mechanisms. Pentylenetetrazole (PTZ) is one of the most important chemicals commonly used in chemical kindling (9).

Considering that the occurrence of seizures in 20 to 30% of epileptic patients is resistant to drug therapy (10), many researches are being conducted to find new methods of epilepsy treatment. Direct stimulation of the epileptic focus by electrical stimuli (deep brain stimulation; DBS) is a new therapy for controlling drug-resistant seizures. Deep brain stimulation is uses for treatment of many neurological disorders including Parkinson's disease, dystonia, and has been considered as an effective manner for Alzheimers' disease and epilepsy. Different patterns of deep brain stimulation are using in laboratory models and clinics. One important parameter in determining the effectiveness of deep brain stimulation is the frequency of stimulation. Although, in most of clinical cases, high frequency stimulation is the common pattern of deep brain stimulation, however, numerous studies have shown that the low frequency electrical stimulation (LFS) has also anticonvulsant effect on the epileptic focus (11–13). The anticonvulsant mechanism of DBS (and therefore, LFS) has not yet been completely understood.

Low Frequency Stimulation (LFS)

Application of LFS following the induction of synaptic long-term potentiation (LTP) leads to elimination of potentiation and returning the synaptic activity to baseline. This phenomenon is called depotentiation. Applying LFS in a pattern that causes depotentiation, has long-term protective effects against epilepsy and increases the subsequent discharge threshold in hippocampal and amygdala kindling (14). In 1995, Weiss et al. reported that electrical stimulation at 1 Hz for 15 min, applied immediately after kindling stimulations, retarded the kindling process. This effect was associated with an increase in the threshold of seizure

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discharges (15). Also, electrical stimulation of the hippocampus or perforated pathway at the frequencies of 1 or 50 Hz reduced inter-ictal events that lasted 30 to 60 minutes, but had no effect on the rate of spontaneous seizures (16). Another study showed that applying LFS at the frequency of 1-3 Hz had an inhibitory effect on epileptic activity and increased the seizure threshold (17). Applying LFS to the Schaffer collaterals also inhibited epileptiform activity in hippocampal slices (18).

The mechanism of LFS anticonvulsant effects has not fully understood yet, but decreased neuronal excitability, increased seizure threshold, enhancement of inhibitory synaptic transmision, and decreased excitatory synaptic activity have been observed following LFS administration (19, 20). The anticonvulsant mechanism of LFS seems to be similar to the mechanisms involved in depotentiation (21). For example, in many synapses, depotentiation depends on activation of NMDA receptors and can be blocked by NMDA receptors' selective antagonist, DL-APV (22). The dependence of depotentiation to NMDA receptors indicates that influx of calcium into the cell is important for this type of synaptic plasticity. Therefore, similar mechanism may also involve in anticonvulsant action of LFS.

In addition, LFS can prevent or reduce another factors involve in seizure generation or maintenance such as inflammation, gliosis and apoptosis. These factors have been briefly reviewed in the next sections.

Inflammation, gliosis and epilepsy

Inflammation is one of the mechanisms involved in seizure generation. Inflammatory responses are involved in seizure development in PTZ kindling model. There are a lot of evidences indicating that inflammation and immune reactions occur in various diseases of the nervous system, including epilepsy (23–25). In fact, inflammation, followed by apoptotic cell death, is highly involved in seizure generation and development. Of course, little is known about the role of inflammation in epilepsy, but it is hypothesized that activation of the innate immune system and its associated inflammatory reactions in the brain cause structural and molecular changes during and after the seizures. The asnwer to the question that whether innate immune responses occurred in epileptic tissue benefit or harm the nervous system still needs further studies. During inflammation in the brain, microglia and astrocytes are the first cells that are activated and secrete proinflammatory cytokines such as TNFα to return the central nervous system conditions to normal (24).

The interaction of glial cells and neurons has a role in the regulation of synaptic transport activity. In fact, the increment in neuronal firing may activate the astrocytes through astrocytic metabotropic glutamate receptors type 3 and 5 (mGluR3 and mGluR5). Activation of these receptors increases cAMP levels and consequently, the intracellular calcium levels in astrocytes leading to the formation of calcium waves in the astrocyte network (26). The increase in the intracellular calcium of astrocytes activates calcium-dependent ion channels, which in turn induces the release of glutamate from these cells (27). Previous studies have shown that gliosis occurs following seizures and there is a relationship between seizure severity and gliosis severity (28, 29). In fact, gliosis is a compromised response of the brain tissue to seizures (30).

The most important inflammatory factors seen in laboratory models during seizures are:

A) Cytokines: Cytokines level increases in the areas of the brain where seizures are generated and propagate. Among the most important proinflammatory cytokines released by microglia are IL-1β, TNF-α, IL-6. While these cytokines are poorly expressed in a normal brain, they show a remarkable increase in expression in an epileptic tissue. (31, 23).

B) Free radicals: Free radicals are produced in inflammatory reactions by mononuclear phagocytic cells and macrophages (32). The most important of them include nitric oxide, superoxide and hydroxyl ions of peroxynitrite. Nitric oxide is generated by pathological conditions by nitric oxide synthase. Experimental studies using animal models of seizures demonstrated that the intracellular calcium concentration increases immediately following the glutamate release and leads to enhanced activation of nitric oxide synthase and production of nitric oxide, which in turn destroys adjacent neurons following an inflammatory reaction (33).

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C) Activation of TNF-α and NF-κB receptors: The release of TNF-α increases during inflammation and seizures. Binding the TNF-α to its receptor in the cell membrane activates a protein complex resulting in inhibition of NF-□B phosphorylation. This process allow the NF-□B to enter to the nucleus and start the transcription of genes involved in apoptotic pathways (34).

D) Chemokines: Chemokines direct the microglia, astrocytes and peripheral immune cells toward the site of inflammation, trauma and infection. All microglia, astrocytes and immune cells entered the affected area are a source of chemokines (32).

Vascular endothelial growth factor and epilepsy

Vascular endothelial growth factor (VEGF) is a homodimer glycoprotein and, as its name implies, it was primarily introduced as an endothelial mitogen that is involved in angiogenesis. It was later shown that VEGF has also neurotrophic function and is involved in neuronal growth and survival (35). VEGF exerts its effect mainly by binding to its membrane tyrosine kinase receptors (VEGF receptors 1, 2, and 3). Following the VEGF binding, the receptors dimerize and are activated by transphosphorylation (36). In the hippocampus, VEGF protects neurons from excitotoxicity due to increased activity of glutamate receptors in epilepsy (37) and prevents neuronal depletion following epilepsy acquisition (38). In previous laboratory studies, it has been shown that the use of VEGF in the hippocampal sections of epileptic rats reduces the epileptiform activity induced by bicuculine (39). The inhibitory effect of VEGF on seizures is exerted through its type 2 receptors (40).

Endogenous VEGF level increases significantly following the pilocarpine epileptic seizures in mice. Injection of VEGF into the hippocampus significantly protects brain tissue against neuronal loss in CA1 area in pilocarpine model (38). Other researches also show that seizures lead to an increase in VEGF, and VEGF decreases neuronal loss in the hippocampus following epilepsy (41). The stimulating factor for increase in VEGF synthesis in nerve tissue following seizure activity is unknown. Hypoxia is the most well-known factor in the expression of VEGF in cells, and hypoxia can also occur during seizures (42).

Factors involved in the anticonvulsant effect of DBS

As mentioned previously, the anticonvulsant mechanisms of DBS have not been completely determined. Potentially, the factors involved in seizure generation and/or propagation may be affected by DBS. For example, synaptic glutamatergic transmission, that are involved in hyperexcitability of neuronal circuitries following seizure induction, are highly affected by DBS and their activity is reduced (21). The same situation can be considered for inflammation and other neural and neuronal elements. In the next part, we review the effect of DBS on some of these agents.

a) DBS and inflammation

During seizures, IL-6 and TNF-α production are significantly increased (43). Enhancement of IL-6 and TNF-α may induce seizure through various mechanisms including exerting a modulatory effect on glutamatergic transport (44), enhancing the function of N-methyl-D-aspartic glutamate receptors (NMDA) through activation of cytoplasmic tyrosine kinases (45) and changes in synaptic transmission through GABAergic neurons (46). In this regards, previous studies have reported that administration of deep brain stimulation in the anterior nucleus of the thalamus at high-frequencies (130 Hz at 400 μA) has anticonvulsant and anti-inflammatory effects (47–49) at the time of stimulation. Our recent experiments showed that applying deep brain stimulation at low-frequencies (LFS; 1 Hz) in hippocampal CA1 area of PTZ kindled animals decreases the seizure-induced increment in IL-6 and TNF-α production one week after LFS (12). Due to the fact that the rate of nerve damage in response to LFS is less than the damage caused by high frequency stimulation (19), LFS may be suggested as a better stimulation pattern in epileptic patients. On the whole, it may be hypothesized that the reduction of inflammatory factors following the application of LFS to some extent is involved in LFS anticonvulsant action.

Interestingly, the application of LFS in intact animals increases the production of IL-6 and TNF-α (12). This is completely opposite to the effect of LFS in kindled animals. It is probably

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due to the fact that the effect of LFS on the nervous system depends on the initial level of activity of the neural circuits. If the excitability of the neural tissue is high (as in kindled animals), the application of LFS will reduce the excitability of the neurons and therefore the amount of inflammatory agents. On the other hand, if the level of neural circuit activity is normal (as in intact animals), LFS increases neuronal activity and excitability and hence increases the producing of inflammatory factors. However, there is also another report showing that DBS did not affect the interleukin -6 levels in the experimental animals (50) and showing the increase of TNF-α following DBS application (51).

b) DBS and gliosis

In the PTZ kindling model, the amount of markers that indicate the activity of astrocytes and microglia (GFAP and Iba-1, respectively) increases (52). Therefore, it is likely that LFS will have therapeutic effects by reducing the rate of gliosis.

GFAP is expressed by astroglia and is an indicator of their activity. Epileptic seizures increase GFAP expression in various areas of the brain, including the hippocampus (53). In addition, astrocyte dysfunction involves in the generation of seizure activity. Accordingly, it is possible that the change in astrocytic activity can be considered as important mechanisms involved in the anticonvulsant effects of LFS and DBS. It has been also suggested that inhibition of astrocytic activity may be considered as a new alternative strategies in treatment of epilepsy (53). We recently showed that applying LFS in full kindled animals restored GFAP expression to its normal valuesat one week following its application (12).

Increased astrocyte activity and therefore overexpression of GFAP is observed in many brain diseases (54). Activation of astrocytes may initially protect the brain through various mechanisms, including repairing the blood-brain barrier, limiting the area of injury, and releasing the neurotrophic factors (55). But after their activation, astrogliosis occurs, which is associated with neurotoxic effects and intensifies the progression of the disease (56). As astrogliosis exacerbates inflammatory reactions through the production of cytokines (57) and increment in glutamate secretion, it can aggravate the severity of epileptic seizures (58). This process may be one of the mechanisms involved in seizure-induced brain injury. Accordingly, decreased biological activity of astrocytes following LFS application may play a role in the long-term protective effects of LFS. However, it should be emphasized further studies are needed to determine the timing of inflammatory responses of brain tissue following deep brain stimulation (59, 60).

Astrocyte activation is regulated by many factors, including IL-6 and TNF-α (54). Therefore, the seizure-induced increase in IL-6 and TNF-α may be considered as the reason of the increase in GFAP expression. In other words, the inhibitory effect of LFS on GFAP may be due to its inhibitory effect on these inflammatory factors, rather than its direct effect on astrocytes themselves.

A study conducted on post-mortem brain tissues obtained from DBS treated patients has reported a glial scar at the DBS lead tip (61). Therefore, more studies need to clear the exact effect of DBS on the glial cells and gliosis of brain after the application of DBS (and LFS) in different brain areas and in different brain disorders.

c) DBS and VEGF

VEGF expression increases in the hippocampus following PTZ kindling (37). We recently observed that applying LFS in the hippocampal area in PTZ kindled animals prevented the increment of VEGF expression. There are various reports on the role of VEGF in epilepsy and seizures. Some studies consider that its role is protective, while another ones suggest that its effects be destructive. The vascular effects of VEGF exacerbate seizures and post-seizure brain damage, while its direct effects on neurons can be neuroprotective. In addition, there is a near relationship between VEGF and inflammatory agents. VEGF activates glial cells, which may potentially affect seizure activity or its side effects (42, 62). On the other hand, inflammatory factors such as IL-1 and TNF-α increase VEGF expression (63, 64). Therefore, it may be suggested that LFS through decreasing the expression of both VEGF and inflammatory

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factors, prevent the brain damage following seizure. Recently, it has also been shown that spinal cord stimulation exerts neuroprotection in rat experimental model of Parkinson's disease, at least partially by upregulation of VEGF (65).

Conclusion

DBS stimulation is potentially a new treatment manner for drug-resistive epileptic seizures. As the epilepsy is a prevalent brain disease, these patients constitutes a considerable population worldwide, and then, It is crucial to find all aspects of the DBS anticonvulsant action. Among different DBS parameters, its frequency seems to have many important role in its effectiveness. Recently, there is an increasing trend in showing the effectiveness of LFS as a effective pattern of DBS for controlling the seizures in epileptic patients. The anti-inflammatory actions of LFS may be considered among its important anticonvulsant mechanism. However, more researches are need to find the precise antiepileptic mechanisms of LFS.

Decleration of interest: none

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