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EXPERIMENTAL AND CLINICAL DATA ABOUT THE ROLE OF PHYSICAL ACTIVITY ON COGNITIVE FUNCTIONS IN EPILEPSY

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ABSTRACT

Epilepsy is a common neurological disorder that affects people of all ages. Many studies have demonstrated that epilepsy can cause impairment of the cognitive functions due to extensive loss of mainly hippocampal neurons. It has been noticed that antiepileptic drugs can also brings about untoward effect on learning and memory. The purpose of our study is to present data from human and animal studies supporting the positive role of physical exercise on cognitive functions in epilepsy and its treatment. The beneficial effects of physical exercise for people with epilepsy, including reduction of seizure susceptibility, reduction of anxiety and depression, and better social integration, have increasingly been reported. In addition, experimental studies have also demonstrated a positive effect of physical exercise in animals with epilepsy. Physical exercise enhances the mood and cognitive functions in humans although the physiological backgrounds of those effects are not fully understood. In recent years there has been a growing interest in research concerning the effect of physical exercise and training on the functioning of the brain, learning and memory. Several studies showed that physical training increases the expression of neurotrophic factors, especially the brain derived neurotrophic factor in the hippocampus and cerebral cortex and in this way it has the capacity to enhance learning and memory under a variety of conditions.

Key words: antiepileptic drugs, physical training, BDNF, learning, memory

INTRODUCTION

Epilepsy is a common neurological disorder that affects approximately 50 million people worldwide and it affects people of all ages (1). Epileptic patients are at risk experiencing cognitive deficits as a result of pharmacotherapy as well as etiology of epilepsy. Antiepileptic drugs (AEDs) increase inhibitory neurotransmission and reduce the responsiveness of neurons, and thereby may have a negative impact on memory. Previous studies have shown that physical activity induce neuronal plasticity in both undamaged and injured central nervous system (CNS), enhance neurogenesis in the dentate gyrus of the hippocampus and up-regulation of neurotrophic factors and in that way improve learning and memory (2).

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PURPOSE

The purpose of our study is to present data from human and animal studies supporting the positive role of exercise on cognitive functions in epilepsy.

EFFECTS OF EPILEPSY AND ANTIEPILEPTIC DRUGS ON COGNITIVE FUNCTIONS

Patients with epilepsy can have impaired cognitive abilities. Epilepsy as well as antiepileptic drugs have deleterious effects on cognition in patients receiving them. Many studies with human patients have demonstrated that acute status epilepticus can cause extensive loss of hippocampal neurons (3,4) and that damage progression occurs in patients who continually experience seizures (5,6). The hippocampus plays a fundamental role in learning, memory, and emotional functioning, and it is therefore reasonable to predict that

loss of neurons after status epilepticus could be associated with functional deficits in these behaviors. Therefore individuals with epilepsy often experience functional impairments such as deficits in intellectual functioning, learning and memory, processing speed, attention and concentration (7,8). These impairments can lead to substantial decreases in quality of life. In epilepsy several factors like: biological (underlying neuropathology, seizure type and aetiology, age of onset, frequency, severity and duration of seizures, structural cerebral damage), psychological problems, treatment with AEDs have been attributed to cause neurocognitive impairment (9) **(Figure 1).**

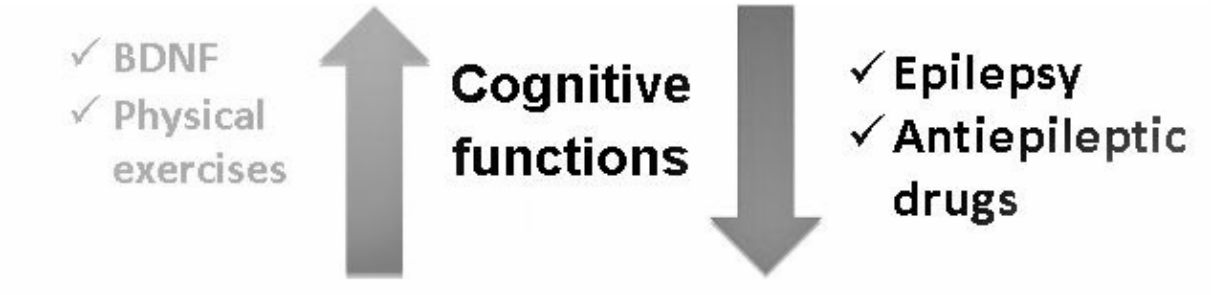

Figure 1. Cognitive functions in epilepsy. The role of physical exercise.

It has been noticed that AEDs can also brings about untoward effect on cognition and behaviour (10-12). At therapeutic doses AED treatment disturbs memory formation, retention and orientation. These adverse effects were especially prominent in patients receiving polytherapy (10-12). Some of the AEDs like phenobarbital has more cognitive and behavioural toxicity as compared to carbamazepine, sodium valproate, clonazepam and phenytoin which cause mild cognitive impairment (13). However, some of the newer antiepileptic drugs have been reported to have favourable cognitive and behavioural profile such as vigabatrine, gabapentin, levetiracetam, tiagabine (13). There are some clinical and preclinical reports available which suggest that topiramate treatment has little negative effect on cognitive functions (14,15). Lamotrigine (LTG) is an AED that appears to be associated with fewer cognitive and behavioral changes than are many other AEDs (16,17). Existing data suggest that the cognitive deficits commonly associated with AED therapy are rarely observed in patients receiving LTG monotherapy (18,19). When LTG is used as an add-on therapy, existing cognitive problems are not exacerbated, and, in some cases, become less severe (17-19). Although many researchers have suggested that lamotrigine is a safe drug (20,21) but there are certain indications which show that it might impair memory (22).

Lacosamide (LCS) is a new AED for the adjunctive treatment of partial – onset seizures in patients with epilepsy. LCS has a novel mode of action. Unlike other sodium channel blocking AEDs, LCS selectively enhances channel slow inactivation without affecting fast inactivation. There is little information about the effects of LCS on cognitive function. Our previous studies in rats showed that LCS significantly decreases the number of avoidances and escapes compared to control group and LTG in Shuttle box (23). Topiramate showed more negative effect on learning and memory compared to LTG.

EFFECT OF TRAINING ON COGNITIVE FUNCTIONS IN EPILEPSY

Physical exercise is also known to enhance the mood and cognitive functions in humans (24-27), although the physiological backgrounds of those effects are not fully understood.

In recent years there has been a growing interest in research concerning the effect of physical exercise and training on the functioning of the brain, with a special focus on its effect on the brain derived neurotrophic factor (BDNF). Several studies showed that exercise induced an up-regulation of the BDNF in the hippocampus and might therefore play an important role in the enhancement of cognitive functions in humans (28).

Physical exercise elicits an increase in the expression of neurotrophic factors, including

brain derived neurotrophic factor (BDNF), nerve growth factor (NGF) and fibroblast growth factor (FGF) in the rat hippocampus and cerebral cortex (29; 30). That way exercise has the capacity to enhance learning and memory under a variety of conditions, from counteracting the mental decline that comes with age (31) to facilitating functional recovery after brain injury and disease (32).

Physical activity can benefit neuronal function and reducing oxidative stress. More specifically, exercise plays an important role in the maintenance of the synaptic structure (33), axonal elongation (34), and neurogenesis in the adult brain (35). Although the above data suggest that the hippocampus becomes activated during aerobic exercise, little attention has been given to the spatial distribution of these neurons after physical exercise in epilepsy.

The beneficial effects of exercise for people with epilepsy, including reduction of seizure susceptibility, improvement of quality of life, reduction of anxiety and depression, and better social integration, have increasingly been reported. Indeed, animal models of epilepsy have revealed seizure-associated impairments in hippocampally-mediated memory tasks as well as a blunting of normal anxiety responses in anxiety tasks (36-38). A number of studies have demonstrated that seizures induced by various experimental manipulations induce plasticity in hippocampal dentate gyrus (39).

Some reports have also shown neuronal plasticity after physical exercise (29).

Some data suggest that AEDs can influence the expression of BDNF. The decreased mRNA levels of BDNF and NT-3 caused by long-term treatment with AEDs may be one cause of cognitive impairment. Xiu –Yu Shi et al., (40) reported that long-term treatment with Topiramate reduces BDNF and NT-3 mRNA expression in the developing brain, while the effect of LTG is dose depended.

The authors also found that LTG increases cell neogenesis. It reduces mRNA levels of BDNF and NT-3 only at high dose level (80 mg/kg). There are not available data for the effects of training on the BDNF in CNS and cognitive impairments observed after AED therapy **(Figure 2).**

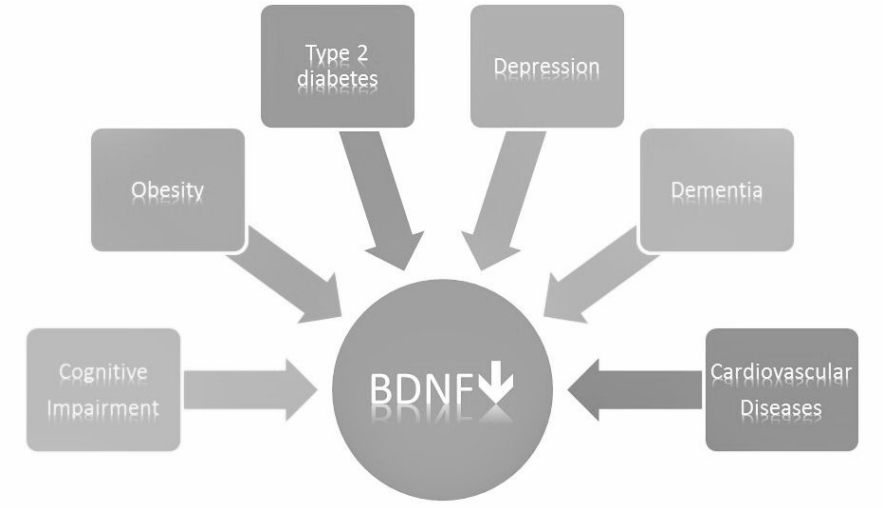

Figure 2. Chronic disorders associated with low circulating levels of brain derived neurotrophic factor (BDNF).

EXERCISE AND EFFECTS ON SEIZURES

Clinical and experimental studies have analyzed the effect of physical exercise on epilepsy. Previous studies have shown positive effects on seizure frequency and severity (41) suggesting that exercise raises seizure threshold and may confer a protective effect on patients with epilepsy (42).

In addition, experimental studies have also demonstrated a positive effect of physical exercise in animals with epilepsy (2). In the kindling model of epilepsy, a model of progressive epileptogenesis, the physical training program retarded the amygdala kindling development (2). Using the pilocarpine model, investigators demonstrated a significant reduction in seizure frequency

during an aerobic training period when compared with controls over 135 days of monitoring (26). In another study, physical training before and during amygdala kind- ling retarded the development of spontaneous seizures (43). Metabolic, electrophysiological, and immunohistochemical studies have also found positive effects of exercise in rat models of epilepsy (44-47).

The risk/ benefit ratio for a person with epilepsy is dependent on the sports activity considered, the type of seizure that might occur, as well as the probability that a seizure will occur during the activity. Some sports activities and their restrictions with respect to people with epilepsy can be found elsewhere. The effects of exercise on mood disorders and stress are of interest. In the general population, regular exercise has been shown to provide mood benefits (48), aid in the treatment of depression (49), and attenuate the impact of stressful life events (50). Studies in persons with epilepsy suggest that they derive similar psychological benefits from physical activity. For instance, Roth et al. (51) examined physical exercise, stressful life experiences, and depression in adults with epilepsy and found that active subjects had significantly lower levels of depression than inactive subjects, as well as better psychosocial adjustment. Similarly, Nakken et al. (52) noted that after a 4-week exercise program, patients with epilepsy had an improved mental state and became more sociable. A study in women with medically refractory epilepsy found that a regular exercise program improved psychosocial functioning and quality of life **(Figure 3).**

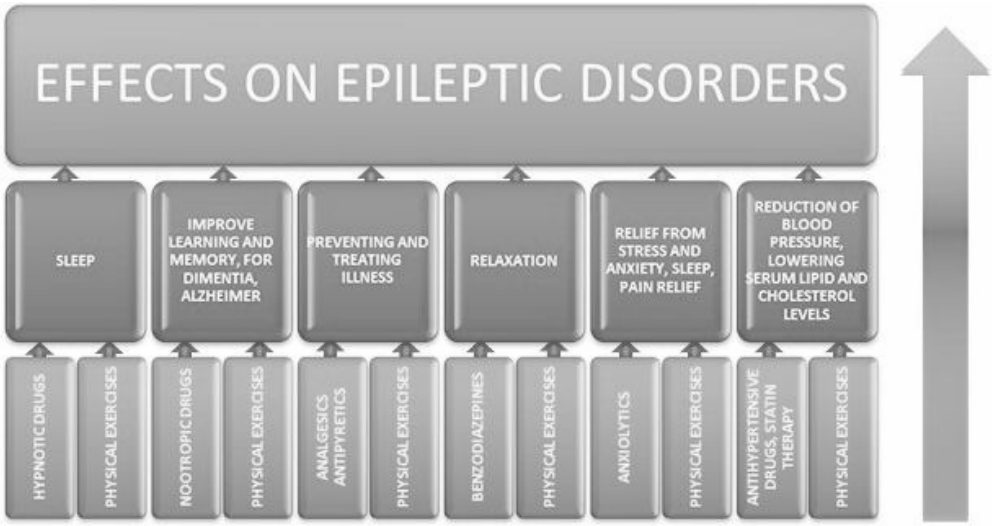

Figure 3. Positive effects of drug therapy and physical training on both seizure and nonseizure conditions in epilepsy.

CONCLUSION

In conclusion, many studies in humans and animal models have demonstrated that epilepsy can cause impairment of the cognitive functions due to extensive loss of mainly hippocampal neurons. On the other hand the antiepileptic therapy also down-regulates the cognitive functions such as learning and memory Recent data report that one of the possible mechanisms underlying these alterations are the changes in neurotrophic factor systems in CNS by epilepsy. Physical training elicits an increase in the expression of neurotrophic factors in the hippocampus and cerebral cortex and in this way it has the capacity to enhance learning and memory under a variety of conditions. Therefore, the adequate exercises could be an appropriate approach to enhance the cognitive functions in epileptic patients, but this needs further investigations.

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