Epilepsy & Behavior 26 (2013) 273–278

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Experimental and clinical findings from physical exercise as complementary therapy for epilepsy

Ricardo Mario Arida [a,*], Antonio-Carlos Guimarães de Almeida [b], Esper Abrão Cavalheiro [c], Fulvio Alexandre Scorza [c]

[a] Departamento de Fisiologia, Universidade Federal de São Paulo/Escola Paulista de Medicina (UNIFESP/EPM), São Paulo, Brazil
[b] Laboratório de Neurociência Experimental e Computacional, Departamento de Engenharia Biomédica, Universidade Federal de São João del-Rei, São João del-Rei, Brazil
[c] Disciplina de Neurologia Experimental, Universidade Federal de São Paulo/Escola Paulista de Medicina (UNIFESP/EPM), São Paulo, Brazil

ARTICLE INFO

Article history:
Accepted 26 July 2012
Available online 23 October 2012

Keywords:
Physical exercise
Epilepsy
Seizure
Complementary therapy for epilepsy
Translational science

ABSTRACT

Complementary therapies for preventing or treating epilepsy have been extensively used. This review focuses on the positive effects of physical exercise programs observed in clinical studies and experimental models of epilepsy and their significance as a complementary therapy for epilepsy. Information about the antiepileptogenic and neuroprotective effects of exercise is highlighted. Considering that exercise can exert beneficial actions such as reduction of seizure susceptibility, reduction of anxiety and depression, and consequently, improvement of quality of life of individuals with epilepsy, exercise can be a potential candidate as non-pharmacological treatment of epilepsy.

This article is part of a Special Issue entitled "The Future of Translational Epilepsy Research".

1. Introduction

Neuroprotective and antiepileptogenic approaches have been extensively explored for preventing and treating epilepsy [1]. Although the most commonly used therapeutic approach to control seizures is pharmacological, non-pharmacological therapies, including complementary and alternative medicine, are often used by people with epilepsy [2–4]. Among them, acupuncture, botanical/herbals, chiropractic care, magnet therapy, prayers, stress management, and yoga are frequently employed [5]. It is interesting to note that neither people with epilepsy nor health care professionals usually include physical exercise programs as a complementary therapy. This reluctance may be due to fear that exercise will cause seizures, stigma, or lack of information. Considering the growing evidence in the literature about the positive effects of exercise for both seizure control and improvement of quality of life of individuals with epilepsy, it seems reasonable to integrate programs of exercise as a complementary non-pharmacological treatment of epilepsy. To this end, our central concern is to propose the potential utilization of a physical exercise strategy for preventing or treating epilepsy.

2. General benefits of exercise for people with epilepsy

It has been proved that regular physical exercise programs provide both physiological and psychological benefits for people with epilepsy [4,6]. People with epilepsy who participate in exercise programs present with fewer seizures than inactive subjects; however, neither the cause nor the effect has been clearly defined [4]. Generally, they can obtain the same benefits from physical training as healthy individuals, i.e., increased maximal aerobic capacity, increased work capacity, reduced heart rate on submaximal standardized work level, weight reduction with reduced body fat [7,8] as well as reduced risk factors for conditions such as diabetes, hypertension, coronary heart disease, obesity, and osteoarthritis [9]. With regard to psychological benefits, studies on this topic have shown that active subjects present better psychosocial adjustment and improvement in mental state [6,10,11]. Brief considerations of these aspects are given in the next topic and are reviewed elsewhere [12].

3. Physical exercise minimizing comorbidities associated with epilepsy

Patients with epilepsy frequently experience psychiatric comorbidities, especially depression and anxiety disorders. These conditions have a negative impact on quality of life [13] and share common pathogenic mechanisms. A broad range of evidence has demonstrated that abnormalities of neurotransmitter systems such as serotonin, noradrenaline, dopamine, glutamate, and GABA are found in mood disorders and epilepsy. Physical exercise can modulate several neurotransmitter systems [14–16] and, therefore, act positively on these conditions. For example, a regular exercise program increases serotonin, noradrenaline, dopamine synthesis and release, up-regulates neurotrophins, reduces stress and, therefore, decreases hypothalamic–pituitary–adrenal activity and adrenal glucocorticoids [17], which consequently, may reduce

* Corresponding author at: Rua Botucatú 862, Ed. Ciências Biomédicas 5º andar, CEP 04023-900 São Paulo, Brazil.
E-mail address: arida.nexp@epm.br (R.M. Arida).

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doi:10.1016/j.yebeh.2012.07.025

seizure susceptibility and epilepsy comorbidities. Accordingly, studies with patients with epilepsy have demonstrated that active subjects have significantly lower levels of depression than inactive subjects [10,11]. Factors such as ability to work, social functioning, family stability, stigma, and adjustment to seizures significantly affect the quality of life of people with epilepsy and are commonly related to depression and anxiety disorders [18,19]. Following this, regular physical exercise has received considerable attention as a mechanism for enhancing resistance to the negative effects of psychosocial stress in a healthy adult population [20]. Indeed, single sessions of moderate aerobic exercise can provide acute mood benefits [21], and exercise programs reduce depression [22]. Therefore, the impact of exercise on the reduction of seizure frequency or seizure susceptibility and neurotransmitter modulation in mood disorders and epilepsy should be considered.

Another comorbidity which has been poorly examined in epilepsy is obesity. During patient management, there is a great risk of weight gain with some antiepileptic medications [23,24]. An elegant study conducted by Daniels and collaborators [25] demonstrated that children with newly diagnosed, untreated epilepsy had a higher body mass index than healthy children. Studies with animal models of epilepsy have also reported significant increase in body weight in the long-term [26–28]. In this regard, obesity not only interferes with body image and self-confidence, but also is associated with other diseases such as dyslipidemia, hypertension, diabetes mellitus, atherosclerosis, and vascular complications [29]. An example of the negative impact of epilepsy and obesity was reported in one study that compared children with epilepsy with those of their siblings without epilepsy. The investigators found more overweight cases in those with epilepsy than in controls (among those 13 to 17 years old), and this statement was consistent with the parental reports of decreased physical activity. In addition, children with a higher seizure frequency had a significantly greater body mass index percentile for age [30].

We also need to bear in mind that some antiepileptic drugs are correlated not only to weight gain but also to reduced bone density [31]. One dominant factor that influences bone health is the limitation of physical exercise in these patients. General recommendations restricting patients' activities may contribute to impaired bone mineralization. Considering that exercise induces positive effects on bone health [32], we may suggest its beneficial influence on bone mineral density regulation in this specific population [33].

4. Antiepileptogenic effects of exercise

Several investigations using physical exercise programs have been undertaken in an attempt to prevent epilepsy. Initial studies indicate that exercise can modulate neuronal vulnerability to epileptic insults. For instance, Arida and collaborators [34] demonstrated that an aerobic training program retarded amygdala kindling development in rats. One of the mechanisms suggested for this effect is the involvement of neurotransmitters. The tonic inhibitory influence of noradrenaline on kindling development [35] is well established. This effect occurs on kindling development but not on kindling state [35]. These findings accord with the observations from Bortolotto and Cavalheiro [36] that indicated that the depletion of noradrenaline induced by DSP4 facilitated the propagation of epileptiform activity and rate of hippocampal kindling. Indeed, in the study by Arida and collaborators [34], trained animals spent shorter after-discharge duration during stage 1 and a longer time in stage 1. Taken into account together, evidence that brain neurotransmission is influenced by exercise [15] and the inhibitory influence of noradrenaline on kindling development [35] suggests that alterations in neurotransmitter systems induced by physical exercise could mediate the inhibitory/excitatory balance to reduce seizure development/frequency. Parallel findings were observed in animals housed in an enriched environment and submitted to the kindling model of epilepsy [37]. Thus, a study that evaluated animals submitted to long-term physical exercise on susceptibility to subsequent seizures induced by pilocarpine showed improvements in behavioral parameters such as latency of the first motor sign, intensity/frequency of seizures, and shorter status epilepticus (SE) than sedentary animals [38]. Other findings with exercise paradigms (swimming training and voluntary wheel running) and convulsant or epilepsy models (penicillin, pentylenetetrazol, and kainic acid) reinforce the above data [39–41].

Evidence indicates that early environmental factors such as physical exercise can result in a "neural reserve" that can be used throughout the life course, i.e., better cognitive performance and a lower likelihood of cognitive impairment in later life [42–44]. Based on these interesting findings, it can be suggested that the practice of physical activities at earlier ages may improve lifelong brain functions and reduce the future risk of brain disorders. In this line, a recent study conducted by Gomes da Silva and collaborators [45] examined whether physical exercise performed during postnatal brain development in rats could modify seizure susceptibility later in life. The exercise program delayed the onset and reduced the intensity of pilocarpine-induced motor symptoms in midlife rats. The above findings show that early physical exercise may interfere positively in the later ictogenesis (i.e., seizure generation process) and epileptogenesis (i.e., epilepsy generation process) and support the hypothesis that the physical activity habits at an early age may shape a neural reserve against brain disorders.

5. Neuroprotective effects of exercise in epilepsy

A potential neural benefit of physical activity is neuroprotection. Animal studies have shown that exercise can reduce brain cell loss or neuronal damage in several animal models of brain insults [46,47]. Although a large body of literature indicates positive effects of exercise for brain recovery in different conditions such as stroke and Alzheimer's and Parkinson's diseases, information about their effects on seizure reduction is not well clarified. To address this, a number of investigations have analyzed the effect of exercise in this context (for a review, see [4]).

The first animal study to investigate the effect of exercise after development of chronic epilepsy showed a reduced frequency of seizures during the physical training period [48]. Subsequent studies using the same exercise protocol and animal model of epilepsy (pilocarpine) reported increased interictal local cerebral metabolic rates for glucose in some brain regions related to attention, vigilance, and alertness (inferior colliculus and auditory cortex) [49], decreased CA1 hyper-responsiveness [50], and positive plastic changes in the hippocampal formation of rats with epilepsy [51].

As mentioned above, information in literature has demonstrated the effect of exercise toward increased resistance to insults and the increased survival of newborn neurons in the hippocampus [46,47,52]. Brain injury resulting from seizures is an active process that embraces multiple factors contributing to neuronal cell death. In this regard, neuronal loss occurs not only with sustained seizures, i.e., SE, but also with repeated brief seizures or a single seizure [53]. Several factors contribute to this phenomenon such as genetic factors, glutamate mediated excitotoxicity, mitochondrial dysfunction, oxidative stress and abnormal concentration of cytokines [54]. At a cellular level, severe seizure activity induces vast influx of calcium via voltage gated and N-methyl-D-aspartate (NMDA)-dependent ion channels [55] which can trigger acute neuronal cell death after SE [56]. As a calcium binding protein superfamily member, parvalbumin (PV) exhibits a great affinity for calcium and may protect cells from calcium overload [57]. Parvalbumin is a marker of inhibitory interneurons since it is mainly co-localized with the neurotransmitter GABA [58]. Considering that a rise in the intracellular calcium levels triggers molecular events associated to neuronal degeneration, decreased expression of PV has been implicated in neuronal death in epilepsy [59,60]. In this respect, a study conducted by Arida and

collaborators [51] demonstrated that physical exercise training increased the number of PV-positive cells and staining intensity of PV-fibers in the hilus of rats with epilepsy. Although the vulnerability of PV interneurons in epilepsy is still an open question, PV might be suggested as one of the candidates for the protective effect of exercise on epilepsy.

Other factors not yet explored in this context need to be considered and are highlighted elsewhere [4]. For instance, stress, neurosteroids, melatonin, and opioids play an important part in this picture. Stress has been considered one of most frequent precipitants of seizures in people with epilepsy [61,62]. Among the use of stress reduction therapies, regular physical activity has been proposed for the treatment of seizures [63]. Based on evidence showing that sensitivity to stress is reduced after long-term exercise, regular physical activity could be a potential candidate for stress reduction in people with epilepsy. The role of neuroactive steroids to reduce hypothalamic–pituitary–adrenal (HPA) axis activation may play an important function in returning to homeostasis following stress. Although increases in neurosteroids in response to stress are adaptive in the short term, lower brain and plasma neurosteroid concentrations are observed in animal models of chronic stress [64,65]. Recently, some researchers have raised the hypothesis that neurosteroids may represent a novel therapeutic target in epilepsy [65,66]. For instance, an elegant study conducted by Lawrence and colleagues [66] demonstrated that inhibition of neurosteroid synthesis can exacerbate seizures, probable due to reduced neurosteroid levels in the brain. Information from literature has suggested that long-term exercise leads to HPA axis adaptation [67]. Although there are no direct associations among neurosteroids and exercise in epilepsy, we could postulate that physical stress (exercise) can induce neurosteroid release and operate as an additional antiepileptic mechanism [68]. Stress also exerts a modulatory effect in the opioid system [69]. For example, β-endorphin is significantly activated depending on the type of stress (intensive exercise). Based on information of opioid system involvement in seizure control [70], exercise might affect seizure susceptibility also via the opioid system.

The efficacy of melatonin as an anticonvulsant has been demonstrated in several animal models as well as in clinical studies [71,72]. Thus, there are favorable reports considering that melatonin is modulated by exercise [73]. To our knowledge, the only study on this topic demonstrated that an exercise program was able to revert the effects of pinealectomy on the amygdala kindling development [74]. From this, the effects of the possible therapeutic use of melatonin associated with regular exercise to ameliorate control of seizures should be considered.

6. From the bench to the clinic

Information concerning the participation of people with epilepsy in physical activities or sport activities has increased considerably in the last decade [4,8,12,30,68,75–84]. Consequently, the effect of exercise on epilepsy has been a less controversial subject, and in this regard, campaigns motivating greater physical activity participation have been launched in the mass media, which have reached control subjects and patients with epilepsy. For this purpose, recently, the ILAE (International League against Epilepsy) has formed a task force to develop new strategies to disseminate information about sport participation in people with epilepsy.

Though people with epilepsy are increasingly involved in physical or sport activities, there is still limited information about the effect of exercise programs or "physical training" in humans. Exercise programs comprise regular exercise, and for effective results, one must have sustained adherence to the training. Factors such as difficulties in arranging transportation, dependence on family, cognitive impairments, low motivation, and fear of having a seizure during exercise contribute to reduced exercise adherence and, therefore, to the difficulties in conducting research on this topic. From the few studies that have evaluated supervised exercise programs for people with epilepsy, encouraging findings were found. Some studies demonstrated no increase in seizure frequency after 4 weeks [7] or 12 weeks of a physical exercise program [85]. Further, in the 12-week study, there was increased quality of life in the exercise group compared to the control group [85]. Women with intractable epilepsy exhibited a decrease in number of seizures during the exercise period. Considering that the investigations cited above include predominantly aerobic exercise, some studies examined whether intensive exercise, i.e., exhaustive effort, alters seizure susceptibility in people with epilepsy. None of the participants with epilepsy had seizures during incremental effort to exhaustion or after physical exertion [83,84,86], supporting observations that, in general, physical exercise is not a seizure-inducing factor [78,79]. In line with this reasoning, no reports of seizure occurrence during exercise to exhaustion have been noted in animal studies [63]. Indeed, early information on this topic has stated that epileptiform activity on the EEG disappears or is reduced in most patients during physical activity [87,88].

Clinical data have indicated that people with epilepsy show a two- to three-fold increase in premature death than those without epilepsy, and the most common epilepsy-related category of death is sudden unexpected death in epilepsy (SUDEP) [89]. The potential risk factors for SUDEP include age, early onset of epilepsy, duration of epilepsy, uncontrolled seizures, seizure frequency, seizure type, quantity of antiepileptic drugs, and winter temperatures [90,91]. Among these factors, studies suggest that seizure frequency is the strongest risk factor for SUDEP [92,93]. We have to bear in mind that preventative measures other than antiepileptic drugs and surgical therapies could be helpful in the prevention of SUDEP [94]. The pathomechanisms for SUDEP are unknown; however, cardiac arrhythmia during and between seizures, arrhythmogenic drugs, or alteration of the autonomic nervous system may play a potential role [95]. In this regard, some beneficial effects of physical exercise against SUDEP can be suggested [80]. It is believed that cardiovascular diseases are often associated with overactivity of the sympathetic nervous system [96], and some of the beneficial effects of physical activity are likely to be related, in part, to reductions in sympathetic activity. To our knowledge, there is only one case report study that evaluated a witnessed case of probable SUDEP in an individual who was performing exercise [97]. Therefore, it is reasonable to believe that regular exercise may attenuate the frequency of seizures and cardiac abnormalities that could predispose patients to SUDEP. This discussion does not apply, however, to patients with exercise-induced cardiac arrhythmias.

7. Conclusions

Translating findings from the laboratory bench is crucial in treating epilepsy. The aim of investigating exercise and epilepsy from a translational science perspective is to transfer knowledge published in the literature to the clinic. This review describes a considerable number of nonclinical studies that could contribute to our knowledge of beneficial effect of exercise on epilepsy. Although the beneficial impact of exercise on epilepsy has been reported in human and animal studies (Fig. 1), our understanding of the mechanisms by which epilepsy is influenced by exercise is still limited. Data arising from laboratory benches can complement the limited information on physical and sport activities in humans. Nevertheless, the neuroprotective and antiepileptogenic actions of exercise illustrated above strengthen the role of exercise intervention as complementary non-pharmacological treatment of epilepsy. In this sense, we should emphasize that people with epilepsy should include exercise as a complementary therapy not only for seizure control but also for non-seizure conditions such as physical health promotion and psychosocial adjustment and improvement in mental state. People with epilepsy should be encouraged to exercise and

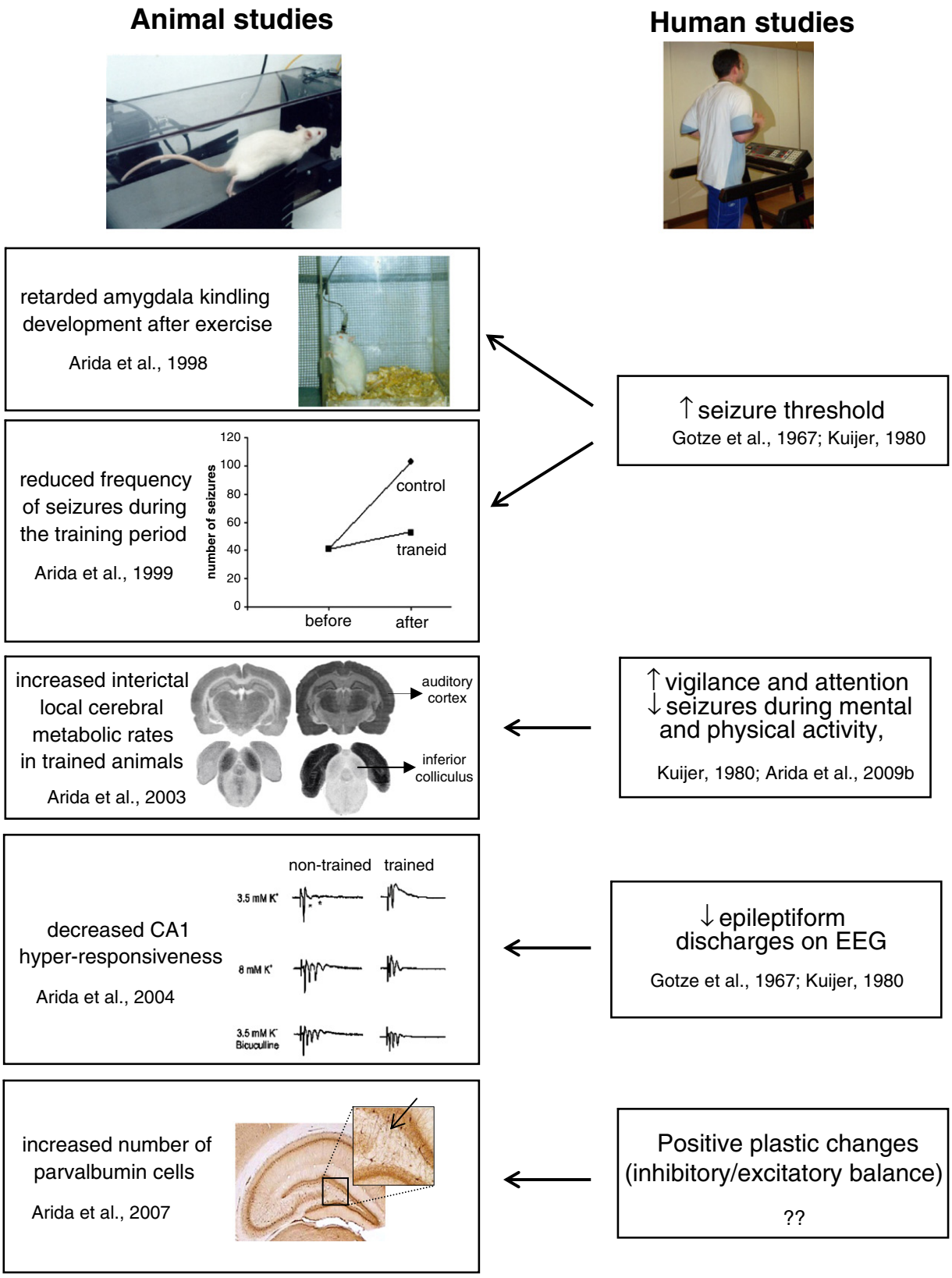

Fig. 1. Comparison between animal and human studies demonstrating the beneficial contribution of exercise to seizure susceptibility/reduction.

efforts should be made to remove any barriers to exercise. To reach these goals, support of health authorities, social workers, sport instructors, and campaigns to inform and stimulate patients to become more active are necessary.

Acknowledgments

This research was supported by CNPq, FAPESP, FAPESP/FAPEMIG, CAPES, INNT, and ClnAPCe (Brazil).

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