1. Introduction

Stress is among the most frequently self-reported precipitants of seizures in people with epilepsy [1–6]. At the same time, seizures, and in particular their unpredictability, are a major source of stress for the person with epilepsy. Not knowing when, where, or if a seizure will occur has been identified by patients with epilepsy as the aspect of the disorder of greatest concern [7]. Patients report that the frequency of their seizures increases if they are exposed to stress, that is, an increase in excitement, tension, sadness, or other emotions caused by change in the patient's internal or external circumstances [8,9]. The majority of subjects believe that some of their seizures are related to stress [10]. In an elegant study conducted by Nakken et al. [4], emotional stress was the precipitant most often reported. The concept that emotional stress lowers seizure threshold is in accordance with psychopharmacological and behavioral studies, in which reductions in stress and anxiety levels resulted in decreased seizure frequency [9,11].

Studies have explored the use of stress reduction therapies, including yoga [12,13], acupuncture [14], meditation [15], and psychotherapy [16], for the treatment of seizures. Although overall positive results are reported, no technique of stress reduction for epilepsy has yet been subjected to a rigorous study design. In view of the evidence indicating that sensitivity to stress is reduced after a physical exercise program [17], physical activity could be a potential candidate for stress reduction in people with epilepsy.

2. Physical exercise and epilepsy

Up to 30% of people with epilepsy may experience stress as a seizure trigger [2], and some report that the stress of participating in sports may exacerbate seizures [18]. Whether exercise is a seizure precipitant or not has received surprisingly little attention in the literature [19,20]. Exercise represents a physical stress that challenges homeostasis. In response to this stressor, the autonomic nervous system and the hypothalamic–pituitary–adrenal axis react to maintain homeostasis. Activation of the hypothalamic–pituitary–adrenal axis by stress affects adrenal steroids and neurosteroids. These changes can alter seizure susceptibility in humans, and in animal models, acute and chronic stress can increase seizure susceptibility [21]. Hence, chronic stress may lead to increased seizure frequency, which may exacerbate the state of chronic stress. Certainly, stress is implicated in increased activity in neural circuits that affect a wide range of brain regions, in regulation of neurotransmitter pathways implicated in epilepsy as well as neuroendocrine changes [22], gene expression, and structural and functional brain changes [23,24].
Whether exercise is helpful, harmful, or simply has no impact on seizure frequency has been debated for years. People with epilepsy have been warned about vigorous exercise for fear that it might precipitate seizures. A significant number of people with epilepsy believe that exercise increases the likelihood of a seizure [25], and many are advised by family, friends, and even their physicians to avoid exercise [26]. However, published reports predominantly contradict this view [27–29]. Lennox [30] wrote: “physical and mental activity seems to be an antagonist of seizures.” Indeed fewer seizures occur during both mental and physical activity compared with periods of rest [31].

Exercise is a complex behavior that not only involves motor function and proprioception, but also engages parts of the brain responsible for attention, vigilance, and motivation. In this regard, it is important to note that temporal lobe structures have been implicated in constructing associations between stimuli and their motivational and emotional components. The increased vigilance and attention involved in exercise could explain the seizure reduction in people with epilepsy [32]. More recent literature indicates a reduced likelihood of seizures during exercise [33–36]. On this point, we discuss possible mechanisms by which physical stress can be beneficial for people with epilepsy.

Before we present information concerning how physical stress can influence epilepsy positively, we have to keep in mind some possible aspects of exercise-induced seizures. With respect to sports activities, when does physical stress activate seizures? Briefly, some factors that could cause seizures during exercise are merely speculative because they occur in adverse situations. Hypoxia, hyperhydration, hypoglycemia, and hyperthermia are some possible events that occur during prolonged exercise, such as in marathons and triathlons, and at high temperatures and under humid conditions. This topic is not the objective of this review and is discussed elsewhere [31,35,37].

3. Mechanism by which physical stress might inhibit seizures

A classic study by Gotze et al. [38] showed that muscular exercise (walking with a heavy pack or deep knee bends) causes a decrease in voltage production and desynchronization of the rhythmic background of spontaneous resting activity. Seizure discharges were present in all 13 patients at rest, but disappeared in most patients during exercise. Similarly, Hordy et al. [39] had 43 patients with epilepsy exercise on a cycle ergometer and found that EEG discharges decreased during exercise. Interictal epileptiform activity has been shown to remain unchanged or to decrease during or immediately after exercise, even in some people with exercise-associated seizures [18]. The specific way by which physical activity provides protection against seizures remains uncertain. In this regard, it is important to have in mind the impact of different types of exercise intensities in epilepsy.

3.1. Exhaustive exercise

With respect to anaerobic exercise, an initial theory is that acidosis serves as a protective mechanism by increasing seizure threshold [38]. Short, intensive physical activity increases serum lactate content and causes metabolic acidosis. It has been known that acidosis reduces the irritability of the cortex [40]. Enzymes controlling brain GABA concentrations appear to be influenced by pH changes. Acidosis increases and alkalosis decreases GABA concentration. The optimum pH of the enzymes GABA transaminase and GABA decarboxylase are such that acidosis increases the GABA concentration in the brain and alkalosis lowers it. For instance, in hippocampal slices in vitro, acidification of the extracellular space to pH 6.7 terminated seizure-like burst firing facilitated by low magnesium levels in artificial cerebrospinal fluid [41]. This suggests that anaerobic, exhaustive exercise may decrease the pH of the blood, leading to changes in the effectiveness of enzymes involved in GABA metabolism, resulting in an increase in GABA concentration in the brain, which has a natural anticonvulsant effect.

There are other propositions not yet explored in this context. During situations of metabolic stress, extracellular adenosine concentrations rise rapidly and are able to activate all types of adenosine receptors [42,43]. Adenosine, a by-product of energy metabolism and ATP utilization, can be effective in preventing seizures. It has been known for more than two decades that extracellular adenosine has an anticonvulsant effect [44]. Adenosine crosses the neuronal membrane by facilitated diffusion between the intra- and extracellular compartments, and extracellular adenosine rises with increased metabolic activity [45]. Studies in humans and animals have demonstrated that seizures increase extracellular adenosine severalfold [46].

Physical exercise is closely linked with neuronal activity [47]. The magnitude of brain activation increases with the intensity of exercise [48], and the brain may become maximally stimulated when exercise is performed at a level near exhaustion [49]. Additionally, whole-brain metabolic activity increases [48,50] because the increased motor command results in elevated metabolic rates in the activated brain structures associated with exercise execution [49]. During intense brain activation, neurons prefer lactate to glucose as their primary energy substrate, which raises the production of ATP [51]. High-intensity exercise increases the ratio of metabolite demand to metabolite availability, accompanied by production of adenosine from AMP. A recent study by Dworak et al. [52] found a significant increase in adenosine concentration after intense exercise, but not after moderate exercise. To our knowledge, the only study that has associated exercise with the epileptic brain metabolism was performed during the interictal phase of the pilocarpine model of epilepsy after a physical exercise program [53]. Brain metabolism during seizures and interictal periods provides an indication of the central nervous system structures responsible for the generation, propagation, and control of the epileptic activity. In this regard, trained rats with epilepsy had higher local cerebral metabolic rates for glucose than control rats with epilepsy only in the inferior colliculus and auditory cortex. Vissing et al. [54] reported higher local cerebral glucose utilization in the auditory and visual cortex during exercise, suggesting that these changes are not related directly to the exercise per se, but to higher mental alertness in exercising than in resting rats. In view of the fact that physical activity does require a certain level of alertness, the increased attention and vigilance observed during physical activity could reduce the number of seizures [31] (Fig. 1). Therefore, the increased metabolic rate in these structures could be another indicator of the smaller number of seizures observed in studies of humans [25,29] and animals [36]. Thus, although no significant changes were observed after physical training, exercise did reverse the low metabolic rates in several structures of animals with epilepsy [53]. As adenosine and other metabolites may accumulate during intense exercise in a spatial and temporal manner, further research is necessary to examine the effects of physical exercise on brain energy metabolites in specific brain structures, such as those involved in epileptic brain.

3.2. Moderate exercise

With respect to aerobic exercise, that is, exercise with a low level of stress, some explanations for the reduction in seizure frequency observed in studies in both humans [22,29,39] and animals [53,55–58] have been proposed. Before we discuss the mechanisms by which moderate exercise interferes in seizures and epilepsy, it is important to clarify that the data on aerobic
exercise discussed in this section are related to moderate physical activity; exercise can be aerobic but also intense. Therefore, we may not refute the data from the literature on intensive aerobic exercise, that is, data from marathon runners or athletes performing endurance activities (2–4 h of aerobic exercise) [28,31] (see Glossary in the Appendix).

During physical activity, the brain receives numerous signals from different sensory organs. This increased sensory input, perhaps proprioceptive impulses, may play a part in the inhibition of seizures [27]. Another hypothesis relates the \( \beta \)-endorphins released during exercise to inhibition of epileptic discharges [59]. Given its status as a “stress hormone,” it is plausible to assume that depending on exercise intensity, the release of circulating \( \beta \)-endorphin will similarly increase. Conversely, studies have shown that light to moderate aerobic exercise does not significantly affect circulating \( \beta \)-endorphin [60,61]. In this regard, there are limited data in the literature demonstrating the influence of exercise on central opioids [62,63]. Sforzo et al. [62] reported enhanced binding of an opioid antagonist in five brain regions following 2 h of warm water swimming. Another investigation has reported that prolonged treadmill running alters opioid peptide content in discrete brain areas [63]. No consensus exists as to the exact nature of the central opioid effect induced by exercise in view of the methodological discrepancies, stress of cool water or treadmill running, and limited number of studies. Although conclusions on this topic must be reserved until more information is available that the opioid system is significantly involved in seizure control [64], we suggest that exercise might affect seizure susceptibility via the opioid system.

Another mechanism by which exercise could reduce seizure susceptibility is related to neurotransmitters. The alterations in neurotransmitter systems provoked by physical exercise could mediate the inhibitory/excitatory balance to reduce seizure frequency. On this point, several lines of evidence show that brain neurotransmission is influenced by exercise. Most studies examining whole-brain noradrenaline levels after physical training show increases in noradrenaline levels in whole brain [65,66] and increases or no significant changes in noradrenaline levels in different brain regions [67,68]. It is well known that among the catecholamines, noradrenaline has a tonic inhibitory effect on kindling development but not on kindling state [69]. Bortolotto and Cavalheiro [70] showed that the depletion of noradrenaline induced by DSP4 facilitated the propagation of epileptiform activity and rate of hippocampal kindling. In this regard, the first study in an animal model strengthened the above findings by showing that an aerobic training program was able to retard amygdala kindling development in rats [55]. Evidence in favor of changes in synthesis and metabolism of catecholamines during exercise and the inhibitory involvement of this neurotransmitter system in amygdala kindling development supports the hypothesis that the effect of aerobic exercise on brain catecholamines can contribute to retard kindling development. Interestingly, in the same study, animals submitted to acute exercise (some bouts of exercise) manifested a tendency toward but no significant alteration in kindling development. These findings reinforce not only the activation of the neurotransmitter systems, but also possible circuitry alterations involved in this inhibitory effect. Subsequently, in the pilocarpine model, a significant reduction in seizure frequency (ca. 50%) was observed during the aerobic training period (45 consecutive days). On the basis of the aforementioned findings in animals (at least in the temporal lobe epilepsy), it seems that physical exercise in general cannot be considered a seizure-inducing factor.

One interesting study evidencing the beneficial influence of physical stress in epilepsy analyzed the effect of physical training on the susceptibility to evoked seizures in the pilocarpine model of epilepsy [71]. Behavioral parameters such as latency to pilocarpine-induced symptoms, seizure intensity and frequency, and status epilepticus duration were significantly ameliorated in trained animals. It seems that physical stress imposed before the brain in-sult induced by status epilepticus can prepare the stress system for new challenges. Despite the positive effect of exercise on seizure reduction, some reports have pointed out a tendency for seizures to occur during the cool down period. For instance, Kuijer [32] noted a tendency toward increased epileptiform activity in the EEGs of patients with epilepsy during the recovery phase after exercise. In laboratory studies, four animals had one seizure 1 min after exercise [55,56].

4. Physical stress and neurosteroids in epilepsy

Stress leads to the activation of two systems, the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis. The main components of these systems are noradrenaline, corticotropin-releasing hormone (CRH), and cortisol (corticosterone in rodents). The degree to which the ANS and HPA axis are activated depends on the severity of the stressor [72]. In general, corticosteroid hormones improve restorative capacity after stress exposure and prepare the organism for future challenges [72]. In this regard, there exists substantial evidence that cortisol plays a role in seizure control [73]. For instance, administration of CRH has been consistently found to induce seizure activity [74,75]. As for corticosterone, more discharge activity, greater convolution susceptibility, and increased seizure rate were reported in rodent models, even after a single corticosteroid administration [76,77].

Exercise represents a physiological challenge that activates the HPA axis [78]. Several lines of evidence suggest that exercise-induced repeated activation of the HPA axis, as occurs in endurance-trained subjects, leads to HPA axis adaptation. Sedentary and trained subjects manifest no difference in HPA axis activity in the resting condition [79,80], but they do differ when the HPA
axis is challenged. These findings suggest that decreased sensitivity to glucocorticoid negative feedback in trained subjects may reflect allostatic modifications of the HPA axis resulting from repeated exercise-induced HPA axis activation [80].

On the basis of the preceding information, does exercise-induced HPA axis adaptation beneficially affect the epileptic brain? Evidence that various stressful conditions downregulate GABAergic transmission and induce anxiety-like states [81] and marked increases in plasma and brain concentrations of neuroactive steroids [82] has led to the view that stress, neurosteroids, and the function of GABAa receptors are intimately related.

4.1. Stress and neurosteroids

Neurosteroids are steroids that are synthesized locally within the brain from either cholesterol or steroid hormone precursors. Such neurosteroids rapidly alter excitability by acting on membrane-bound receptors. Changes in the brain concentrations of neurosteroids may play an important role in the modulation of emotional state as well as in the homeostatic mechanisms that counteract the neuronal overexcitation elicited by acute stress. The ability of neuroactive steroids to reduce HPA axis activation may play an important role in returning to homeostasis following stressful events. This physiological coping response appears to be critical for mental health as it is dysregulated in various mood disorders [83]. For instance, studies in animal models indicate that the neuroactive steroids THP (allopregnanolone) and THDOC (allopregnolone) are stress responsive, serving as homeostatic mechanisms in restoring normal GABAergic and HPA function following stress [84]. Although increases in neurosteroids in response to stress are adaptive in the short term, studies in animal models of chronic stress and depression find lower brain and plasma neurosteroid concentrations and alterations in neurosteroid responses to acute stressors. It has been suggested that disruption in this homeostatic mechanism may play a pathogenic role in some psychiatric disorders related to stress. This is supported, in part, by evidence from animals demonstrating that stressors that produce behavioral depression and anxiety not only alter neurosteroid levels but also regulate GABAa receptor expression and result in insensitivity to benzodiazepines and neurosteroids [85,86]. In humans, neurosteroid depletion is consistently documented in patients with depression and may reflect their greater chronic stress [87,88]. Exercise intervention could make an important contribution in this context. In view of the effectiveness of exercise in reducing depression and anxiety, regular exercise might correct dysregulation of neurosteroid levels induced by stressors.

4.2. Seizures and neurosteroids

Neurosteroids have a variety of central nervous system actions related to their effects on the GABAa receptor, including protective activity in diverse experimental seizure models [89]. For instance, acute swim stress (10 min) increases the seizure threshold in rats. At the time of seizure protection, swim stress is associated with a threefold elevation in plasma THDOC concentrations [90]. The work of Pericic et al. [91] reinforced the anticonvulsant effect of swim stress on convulsions produced by GABAa-related convulsants. The stress-induced seizure protection could be due to circulating neurosteroids synthesized in peripheral tissues or neurosteroids produced locally in the brain (Fig. 2). With respect to this topic, a question must be raised. Can the effects observed with swim stress be extrapolated to other types of stress? It is important to point out that only one type of stress (water exposure) has been explored in these studies, and swim stress is a combination of physical and psychological stress. Stress is known to induce epileptic seizures [2]. However, acute stress has anticonvulsant-like effects in animals [90,92]. On this point, we have two contradictory observations. Although the exact pathophysiology of possible seizure facilitation by stress is unknown, there are neural and endocrine pathways through which stress can alter neuronal excitability and consequently affect seizure susceptibility. The extent of seizure susceptibility during stress might therefore represent a balance between anticonvulsant (e.g., neurosteroids) and proconvulsant (e.g., glucocorticoids and CRH) factors. Stress-induced seizures would therefore occur when the balance is shifted to favor the proconvulsant factors, exceeding the anticonvulsant action of endogenous neurosteroids. On the basis of evidence indicating that sensitivity to stress is reduced after exercise training [17], we can postulate that the reduced seizure frequency after exercise programs observed in studies in humans and animals could be attributed to this adaptation. Whether physical stress can induce neurosteroid release and serve as an additional antiepileptic mechanism remains to be determined. Fig. 3 illustrates possible exercise mechanisms influencing the stress system to reduce seizure susceptibility.

5. Psychological stress of competition in people with epilepsy

It has been demonstrated that the most common factors provoking seizures are excessive mental work, nervous tension, anxiety, and physical fatigue [92]. All of these can occur with competitive exercise. The impression that exercise may prevent seizures is further supported by the reports of professional athletes. Athletic games can induce this type of strain. For example, Bennett [27]
described the case of a 16-year-old high school student who had complex partial seizures in a championship baseball game and during the final minute of a very close basketball game. In an investigation of professional athletes with epilepsy, one baseball player experienced only one seizure, and a basketball player had a single seizure on two separate occasions, either just prior to, during, or immediately after games [27]. In view of the fact that professional athletes experience many hours of intense physical exercise during practice as well as during a season, such a small number of seizures in these athletes lends support to the view that exercise can be antagonistic to seizures. Therefore, in competitive sports, this stress could induce seizures only in stress-sensitive people [31,37].

In summary, it is important to separate two opposing variables. The increased mental activity, concentration, and enjoyment experienced by athletes with epilepsy may play a role in inhibiting seizures. On the other hand, psychological stress, that is, the stress of competition that generates the pressure to win, can sometimes trigger seizures. As people with epilepsy engaged in competitive activities cannot always escape this stressful situation, they cannot be told to “avoid competition” but may be advised to “select competition,” and the selection must take into account other life stresses they face. People with epilepsy can train to cope with the stress of competition and plan competitive series in which the challenge gradually increases. As he or she meets each challenge successfully, the athlete’s confidence grows, until he or she is ready for the highest level. This is a good way to cope with stress.

6. Conclusions

While admitting the deficiencies in our current knowledge, an increasing number of important observations have given us some insight into the beneficial effects of exercise in epilepsy. Several mechanisms by which physical stress can be beneficial for people with epilepsy may act in combination, for example, an adapted brain stress system (HPA) leading to modulation of neurotransmitter systems. Activation of several seizure-inhibitory components (NA, adenosine, neurosteroids, GABA_A receptor, sensory inputs) is a possible contributor to reducing seizure susceptibility. In addition, regular physical exercise also prepares the individual to deal with the psychological stress of competition or daily life. We believe that having seizures is psychologically very stressful, as their occurrence is unpredictable and out of the control of the patient. However, these people also have competitive tendencies, ambitious goals, and the talent to become successful in individual or team sports. Exclusion of their dreams and goals can damage their self-esteem and identity, which will drastically affect their lives.

Acknowledgments

Research was supported by CNPq, FAPESP, CAPES, INNT, and ClnAPCe (Brazil).
Appendix. Glossary

Physical activity and exercise are not interchangeable terms, although, with certain frequency, they are employed without distinction, and physical exercise and sports are even used as synonyms. Physical activity is defined as any bodily movement produced by contraction of skeletal muscle that substantially increases energy expenditure. Physical exercise is a different concept, as it is a type of physical activity that is planned, structured, and repetitive, and is performed for the purpose of maintaining or improving one or more fitness components. Sports involve organized matches, requiring physical exertion, that abide by an established structure and are coordinated within a context of formal and explicit rules and regulations with respect to behaviors and procedures [93].

Aerobic exercise involves large muscle groups in dynamic activities that result in substantial increases in heart rate and energy expenditure. Aerobic exercise does require oxygen for energy. This is observed during exercise that is less intense but of longer duration. This energy system is used primarily during events lasting longer than several minutes. Anaerobic exercise is done at very high intensities such that a large portion of the energy is provided by glycolysis and stored phosphocreatine. Anaerobic exercise does not require oxygen for energy. This is due to the intensity and duration of anaerobic events, which typically are high intensity and last only a few seconds to some minutes [94]. Moderate exercise is defined as activity in the range of 40 to 60 VO2 max. Exhaustive exercise is a physiological response to work defined as the inability to continue exercise and occurs with heavy exertion. It is a form of exercise involving highly intense activities that triggers anaerobic metabolism, especially when the aerobic pathways become insufficient in supplying energy at the required rate [95].

References


Albrecht H. Endorphins, sport, and epilepsy: getting fit or having one. NZ Med J 1986;99:915.


Uzunova V, Sampson L, Uzunov DP. Relevance of endogenous 3α-reduced neurosteroids to depression and antidepressant action. Psychopharmacology 2006;186:351–61.


