Article

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PHYSICAL EXERCISE IN RATS WITH EPILEPSY IS PROTECTIVE AGAINST SEIZURES

Evidence of animal studies

Ricardo Mario Arida[1], Fulvio Alexandre Scorza[2], Vera Cristina Terra[3], Roberta Monterazzo Cysneiros[4], Esper Abrão Cavalheiro[2]

Abstract – People with epilepsy have been discouraged from participating in physical activity due to the fear that it will exacerbate seizures. Clinical and animal studies indicate a reduction of seizure frequency as well as decrease susceptibility to subsequently evoked seizures after an exercise program. Analyses from experimental studies of animals with epilepsy submitted to physical training programs were performed. In all studies the physical training was able to reduce the number of spontaneous seizures in rats with epilepsy. Seizure occurrence during exercise was relatively absent in the majority of studies. No death was found in animals with epilepsy during 1680 h of exercise. Based on these results it is plausible encouraging persons with epilepsy to non-pharmacological treatments and preventative measures such as physical exercise.

KEY WORDS: exercise, physical training, epilepsy, seizure, rat.

Exercício físico em ratos com epilepsia como fator protetor contra crises epilépticas: evidencias de estudos em animais

Resumo – Pessoas com epilepsia têm sido desencorajadas da prática de atividade física por receio do exercício físico exacerbar as crises epilépticas. Estudos clínicos e em animais mostram uma redução da frequência de crises, assim como diminuição da susceptibilidade a crises subseqüentes após programa de exercício físico. Neste estudo realizamos uma análise de estudos experimentais de animais com epilepsia submetidos a programas de exercício físico. Em todos os estudos, o treinamento físico foi capaz de reduzir o número de crises espontâneas em ratos com epilepsia. A ocorrência de crises durante o exercício físico foi relativamente ausente na maioria dos estudos. Nenhuma morte foi encontrada em animais com epilepsia durante 1680 h de exercício físico. Baseados nestes resultados parece aceitável encorajar as pessoas com epilepsia a tratamentos não farmacológicos e medidas preventivas como o exercício físico.

PALAVRAS-CHAVE: exercício,treinamento físico, epilepsia, crises, rato.

Whether people with epilepsy can engage in physical fitness programmes, recreational or competitive sports, has been debated for years. To this point, substantial evidence indicates positive effects of physical exercise on epilepsy. The literature demonstrates that epileptiform discharges on EEG decrease during exercise[1-3]. Physical activity reduces seizure frequency, as well as lead to improved cardiovascular and psychological health in persons with epilepsy[4]. It has been also observed that fewer seizures occur during both mental and physical activity compared with periods of rest[5]. Other studies have suggested that exercise raises seizure threshold and may confer a protective effect on epileptic patients[3,6]. Seizures during exercise are rare, but there are a few reports of exercise-

[1]Departamento de Fisiologia, Universidade Federal de São Paulo/Escola Paulista de Medicina (UNIFESP/EPM), São Paulo SP, Brazil; [2]Disciplina de Neurologia Experimental, Universidade Federal de São Paulo/Escola Paulista de Medicina (UNIFESP/EPM), São Paulo SP, Brazil; [3]Centro de Cirurgia de Epilepsia (CIREP), Departamento de Neurologia, Psiquiatria e Psicologia Médica. Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto SP, Brazil; [4]Programa de Pós-Graduação em Distúrbios do Desenvolvimento do Centro de Ciências Biológicas e da Saúde da Universidade Presbiteriana Mackenzie, São Paulo SP, Brazil.

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Dr. Ricardo Mario Arida – Rua Botucatu 862 / 5º andar - 04023-900 São Paulo SP - Brasil. E-mail: arida.nexp@epm.br

induced ictal events[7,8]. However, the existing clinical data on the impact of exercise on patient outcomes have limitations. There is a lack of prospective studies, studies examining behavioral aspects and studies using appropriate controls. Due to limitations of existing data, several animal studies have been performed to evaluate the effects of a physical exercise program on seizure frequency.

Experimental studies have demonstrated a positive effect of physical exercise in animals with epilepsy[9-13]. Reduction of seizure frequency[10-13] as well as decrease susceptibility to subsequently evoked seizures after an aerobic training program has been observed[14].

Based on the animal studies mentioned above, we aimed to analyze data from all studies of animals with epilepsy submitted to physical training programs. The purpose of this data review as to emphasize and clarify the positive information concerning physical exercise impact on epilepsy. Due to several methodological variations, we excluded studies performed in enriched environment, with adolescent animals, and animal submitted to acute protocols of exercise (few bouts of exercise). Because of limited studies with animal with epilepsy, results are concentrated on the pilocarpine model of epilepsy, an experimental model that mimics the human temporal lobe epilepsy.

METHOD

We analyzed data of 70 adult animals with epilepsy submitted to physical training program colleted from previous studies[10-13]. Briefly, adult Wistar rats weighing 200–280 g at the moment of the initial physical training protocol were used. They were housed under environmentally controlled conditions (7:00–19:00 hr light/dark cycle; 22–24°C) and permitted free access to food and water throughout the experiment. Sustained seizures were induced by a single i.p. administration of pilocarpine hydrochloride (350 mg/kg; Sigma, St. Louis, MO). Scopolamine methylnitrate (Sigma, St. Luis, MO) was injected (1 mg/kg, s.c.) 30 min before pilocarpine in order to reduce peripheral cholinergic effects[15]. The same procedure to induce epilepsy was used in all studies. Following the *status epilepticus* period, the surviving animals were continuously monitored during 24 h for detection of spontaneous seizures, using a video system. Infrared emitting lights were used during the dark periods to allow for video recording of animal activity during this time. After a first spontaneous recurrent seizure (SRS) had been detected animals were continuously monitored to assess seizure frequency. The behavioral observation was monitored before, during and after the physical training program. To determine the number of seizures during these periods, two observers were recruited for all this behavioral analysis.

Rats with epilepsy were also submitted to a voluntary and forced exercise. Animals submitted to the voluntary exercise[13] were placed in a voluntary wheel running. Animals submitted to the forced exercise[10-13] were placed in a motor driven treadmill.

Physiologic tests

Maximum O_2 uptake – ($VO_{2\,max}$) was measured to determine an exercise protocol of adequate intensity (60% VO_{2max}). $VO_{2\text{-}ma}$ was measured with an open-circuit system (Columbus Instruments Oxymax System). The testing protocol for determination of VO_{2max} was as follows. After a warm-up at 12 m/min on a 0% grade for 5 min, treadmill speed was increased by 3 m/min every 3 min until animals refused to run. The VO_2 measurements were realized before and at the end of the physical training program.

Training procedure

The animals of the training group were familiarized with the apparatus for three days by placing them on a treadmill (Columbus instruments) for 10 min/day at a speed of 12 meters/min at 0% degree incline. To provide a measure of trainability, we rated each animal's treadmill performance on a scale of 1–5 according to the following anchors [1=refused to run, 2=below average runner (sporadic, stop and go, wrong direction), 3=average runner, 4=above average runner (consistent runner occasionally fell back on the treadmill), 5=good runner (consistently stayed at the front of the treadmill)][16]. Animals with a mean rating of 3 or higher were included to the exercise groups. This procedure was used to exclude possible different levels of stress between animals. Subsequently they were submitted to an aerobic exercise program of 45 sessions on a treadmill, 7 days per week. The intensity of exercise (60% VO_{2max}) was determined for each animal after the maximum O_2 uptake test. Each training session started with a 5 min warm-up at 12–15 m/min. Running time and speed gradually increased from 30 min at 18 m/min during the first 3 days to 60 min at 18–22 m/min during the subsequent days. Exercise intensity was similar for all animals. For one study the duration of training for one group of animals was of 10 day. The animals submitted to the voluntary exercise were placed in a voluntary wheel running with free access a food and water.

RESULTS

Behavioral features of pilocarpine-induced seizures during the acute period were similar to those reported previously[15]. The behavioral pattern of SRS showed the same characteristics described by Cavalheiro et al.[17]. Briefly, SRS consisted by facial automatisms, forelimb clonus, rearing, loss of postural control, and generalized clonic seizures. In all studies[10-13] the physical training program was able to reduce the number of spontaneous seizures in rats with epilepsy. Detailed data of seizure frequency can be reviewed in previous studies[10-13].

Concerning the analysis of seizure occurrence during exercise we noted a total of 7 seizures in all studies. Three out 70 animals had seizures in the treadmill; two animals presented 3 seizures each during exercise in the first study[10] and one animal presented 1 seizure during exercise in the following study[11]. Interestingly, 4 animals presented 1 seizure, 1 min post-exercise[10,11]. No seizures were

observed during the maximum oxygen uptake test before and after the training period. In the voluntary wheel running, no seizure was observed in the study that utilized this device. In addition to seizure frequency, no death was found in animals with epilepsy during 1680 h of exercise and between exercise periods, i.e., the following 23 h before and after the episode of exercise.

DISCUSSION

Whether exercise is helpful, harmful, or simply has no impact on seizure frequency has been debated for years. The reduction of seizure frequency was clearly noted in all animal studies that analyzed the effect of exercise on epilepsy[10-13]. From 70 animals that underwent to physical exercise only three presented seizures. To this point, these data represent a very low probability of exercise-induced seizures. This limited number of seizures during long period of exercise (1680 h), strengthen this fact. Indeed, seizures exacerbated by physical exercise are uncommon in humans[7,9,18]. One study[19] found that only 2% of patients with epilepsy had exercise-induced seizures (defined as seizures in >50% of training sessions). We also might suggest that in refractory epilepsy, the possibility of exercise to provoke seizure could be increase. To reinforce the findings cited above, a study evaluating physical exercise in woman with intractable epilepsy showed a decreased the number of seizures during the aerobic physical training period[20].

An interesting observation in our study was related to sudden death during exercise. Although it is not the focus of our study, we have to point out that epilepsy is associated with a two- to three-fold increase in mortality compared to the general population and sudden unexpected death in epilepsy (SUDEP) is the most important direct epilepsy-related cause of death[21]. The examination from all studies of animals with epilepsy submitted to physical training did not show any sudden death while exercising at aerobic exercise, at maximal effort (anaerobic) or during the training program period, that is, the remarkable 1680 h hours of exercise without any death occurrence indicate that physical activity may not be considered a risk factor for sudden unexpected death in epilepsy (SUDEP).

Information concerning risk factors for SUDEP is conflicting, but potential risk factors include: seizure frequency, age, early onset of epilepsy, duration of epilepsy, uncontrolled seizures, mainly in the TLE, seizure type, AED number[22] and winter temperatures[23]. Potential pathomechanisms for SUDEP is unknown, but it is very probable that cardiac arrhythmia during and between seizures, electrolyte disturbances, arrhythmogenic drugs or transmission of epileptic activity via the autonomic nervous system to the heart play a potential role[21]. Physical activity reduces seizure frequency as well as lead to improved cardiovascular and psychological health in persons with epilepsy[19]. To our knowledge, there is only a case report study that evaluated a witnessed case of probable SUDEP in an individual who was performing exercise[24]. However, this case report could not be considered a classical SUDEP case, since he died two days later. Although there are some factors in exercise programs that could affect the epileptic disorder, such as, fatigue, hypoxia, hyperthermia[25], hypoglycaemia[25], dehydration and hyperventilation[26], any links at this point are largely speculative; these events occur in extreme conditions. A long term prospective study of exercise in patients with medically refractory seizures is required to answer this question.

Another interesting point to be considered is the exercise-induced stress. Physical and especially psychic stress is generally accepted as factors that precipitate seizures[27]. Stress is among the most frequently self-reported precipitants of seizures in patients with epilepsy[28,29]. Emotional stress was the precipitant most often reported in Nakken et al. study[29]. This is not an unexpected finding, given clinical experience and the results of studies that have suggested a strong association between stressful life events and/or tension states and seizures[27,30]. Temkin and Davis[27] state that daily difficulties increase the risk of seizure occurrence, while pleasant experiences seldom do. It has been also observed that fewer seizures occur during both mental and physical activity compared with periods of rest[30]. The increased vigilance and attention involved in exercise could explain the reduction in the number of seizures[30].

During exercise, not only aerobic but intensive (anaerobic) physical activity increases serum lactate content and causes metabolic acidosis. A study conducted by Gotze et al.[3] suggested that reduced epileptogenic EEG activity during exercise may be caused by an increase in GABA concentration as a consequence of metabolic acidosis. Additionally, contracting muscles produces lactic acid when anaerobic metabolism participates in the production of energy, and this leads to a reduction of the plasma pH value (metabolic acidosis).

On the basis of the available data presented and from clinical studies, seizures occurring during exercise are infrequent and reinforce the beneficial contribution of exercise to seizure reduction. Combinations of neuroprotective and anti-epileptogenic strategies have been effective for combating the disease progression[31]. In this line, we should have in mind that exercise could be a candidate to this intervention.

REFERENCES

1. Nakken KO, Loyning A, Loyning T, Gløersen G, Larsson PG. Does physical exercise influence the occurrence of epileptiform EEG discharges in children? Epilepsia 1997;38:279-284.

2. Horyd W, Gryziak J, Niedzielska K, Zieliński JJ. Effect of physical exertion on seizure discharges in the EEG of epilepsy patients. Neurol Neurochir Pol 1981;15:545-552.
3. Gotze W, Kubicki S, Munter M, Teichmann J. Effect of physical exercise on seizure threshold (investigated by electroencephalographic telemetry). Dis Nerv Syst 1967;28:664-667.
4. Nakken KO, Bjorholt PG, Johannessen SI, Loyning T, Lind E. Effect of physical training on aerobic capacity, seizure occurrence, and serum level of antiepileptic drugs in adults with epilepsy. Epilepsia 1990;31: 88-94.
5. Cordova F. Epilepsy and sport. Aust Fam Physician 1993;22:558-562.
6. Livingston S. Epilepsy and sports. J Amer Med Assocn 1978;224:39.
7. Ogunyemi AO, Gomez MR, Klass DW. Seizures induced by exercise. Neurology 1988;38:633-664.
8. Schimtt B, Thun-Hohenstein L, Vontobel H, Boltshauser E. Seizures induced by physical exercise: report of two cases. Neuropediatrics 1994; 25:51-53.
9. Arida RM, Vieira AJ, Cavalheiro E.A. Effect of physical exercise on kindling development. Epilepsy Res 1998;30:127-132.
10. Arida RM, Scorza FA, Santos NF, Peres CA, Cavalheiro EA. Effect of physical exercise on seizure occurrence in a model of temporal lobe epilepsy in rats. Epilepsy Res 1999;37:45-52.
11. Arida RM, Fernandes MJS, Scorza FA, Preti SC, Cavalheiro EA. Physical training does not influence intericatal $LCMR_{glc}$ in pilocarpine-treated rats with epilepsy. Physiol Behav 2003;79:789-794.
12. Arida RM, Sanabria ERG, Silva AC, Faria LC, Scorza FA, Cavalheiro EA. Physical training reverts hippocampal electrophysiological changes in rats submitted to the pilocarpine model of epilepsy. Physiol Behav 2004;83:165-171.
13. Arida RM, Scorza CA, Scorza FA, Silva SG, Naffah-Mazzacoratti MG, Cavalheiro EA. Effects of different types of physical exercise on the staining of parvalbumin-positive neurons in the hippocampal formation of rats with epilepsy. Prog Neuro-Psychopharmacol Biol Psychiatry 2007;31:814-822.
14. Setkowicz Z, Mazur A. Physical training decreases susceptibility to subsequent pilocarpine-induced seizures in the rat. Epilepsy Res 2006; 71: 142-148.
15. Turski WA, Czuczwar SJ, Cavalheiro EA Turski L, Kleinrok Z. Acute and long-term effects of systemic pilocarpine in rats: spontaneous recurrent seizures as a possible model of temporal lobe epilepsy. Naunyn Schmiedebergs Arch Pharmacol 1983;324:5R.
16. Dishman RK, Armstrong RB, Delp MD, Graham RE, Dunn AL. Open-field behavior is not related to treadmill performance in exercising rats. Physiol Behav 1988;43:541-546.
17. Cavalheiro EA, Leite JP, Bortolotto ZA, Turski WA, Ikonomidou C, Turski L. Long-term effects of pilocarpine in rats: Structural damage of the brain triggers kindling and spontaneous recurrent seizures. Epilepsia 1991;32:778-782.
18. Werz MA. Idiopathic generalized tonic-clonic seizures limited to exercise in a young adult. Epilepsy Behav 2005;6:98-101.
19. Nakken KO. Physical exercise in outpatients with epilepsy. Epilepsia 1999;40:643-665.
20. Eriksen HR, Ellertsen B, Gronningsaeter H, Nakken KO, Loyning Y, Ursin H. Physical exercise in women with intractable epilepsy. Epilepsia 1994;35:1256-1264.
21. Tomson T, Walczak T, Sillanpaa M, Sander JW. Sudden unexpected death in epilepsy: a review of incidence and risk factors. Epilepsia 2005; 46:54-61.
22. Walczak TS, Leppik IE, D'Amelio M, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology 2001;56:519-525.
23. Scorza FA, de Albuquerque M, Arida RM, Cavalheiro EA. Sudden unexpected death in epilepsy: Are winter temperatures a new potential risk factor? Epilepsy Behav 2007;10:509-510.
24. Harrison BK, Asplund C. Sudden unexplained death in epilepsy during physical activity. Curr Sports Med Rep. 2007;6:13-15.
25. Gates JR, Spiegel RH. Epilepsy, sports and exercise. Sports Med 1993; 15:1-5.
26. Esquivel E, Chaussain M, Plouin P, Ponsot G, Arthuis M. Physical exercise and voluntary hyperventilation in childhood absence epilepsy. Electroenceph Clin Neurophysiol 1991;79:127-132.
27. Temkin NR, Davis GR. Stress as risk factors for seizures among adults with epilepsy. Epilepsia 1984;25:450-456.
28. Burdette DE, Feldman RG. Factors that can exacerbate seizures. In: Resor SR, Kutt H (Eds). The medical treatment of epilepsy. New York: Marcel Dekker 1992:79-89.
29. Nakken KO, Solaas MH, Kjeldsen MJ, Friis ML, Pellock JM, Corey LA. Which seizure-precipitating factors do patients with epilepsy most frequently report? Epilepsy Behav 2005;6:85-89.
30. Cordova F. Epilepsy and sport. Australian Family Physician 1993;22: 558-562.
31. Arida RM, Scorza FA, Scorza CA, Cavalheiro EA. Is physical activity beneficial for recovery in temporal lobe epilepsy? Evidences from animal studies. Neurosci Biobehav Rev 2009;33:422-431.