PHYSICAL EXERCISE IN RATS WITH EPILEPSY IS PROTECTIVE AGAINST SEIZURES

Evidence of animal studies

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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 suscetibilidade a crises subsequentes 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 exercise1³. Physical activity reduces seizure frequency, as well as lead to improved cardiovascular and psychological health in persons with epilepsy⁴. It has been also observed that fewer seizures occur during both mental and physical activity compared with periods of rest⁵. Other studies have suggested that exercise raises seizure threshold and may confer a protective effect on epileptic patients¹⁶. Seizures during exercise are rare, but there are a few reports of exercise-
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induced ictal events. 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. Reduction of seizure frequency as well as decrease susceptibility to subsequently evoked seizures after an aerobic training program has been observed. 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 collected from previous studies. 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 methyl nitrate (Sigma, St. Louis, MO) was injected (1 mg/kg, s.c.) 30 min before pilocarpine in order to reduce peripheral cholinergic effects. 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 were placed in a voluntary wheel running. Animals submitted to the forced exercise were placed in a motor driven treadmill.

Physiologic tests

Maximum O\textsubscript{2} uptake – (VO\textsubscript{2max}) was measured to determine an exercise protocol of adequate intensity (60% VO\textsubscript{2max}). VO\textsubscript{2}

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). 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\textsubscript{2max}) was determined for each animal after the maximum O\textsubscript{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. The behavioral pattern of SRS showed the same characteristics described by Cavalheiro et al. Briefly, SRS consisted by facial automatisms, forelimb clonus, rearing, loss of postural control, and generalized clonic seizures. In all studies 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.

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 and one animal presented 1 seizure during exercise in the following study. Interestingly, 4 animals presented 1 seizure, 1 min post-exercise. No seizures were
observed during the maximum oxygen uptake test before
and after the training period. In the voluntary wheel run-
novation, 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 be-
fore 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\textsuperscript{10–12}. From 70 animals that underwent to ph,

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. In-
deed, seizures exacerbated by physical exercise are un-
common in humans\textsuperscript{7,11,18}. One study\textsuperscript{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 rein-
force the findings cited above, a study evaluating physical
exercise in woman with intractable epilepsy showed a de-
creased number of seizures during the aerobic physi-

cal training period\textsuperscript{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 associ-
ated with a two- to three-fold increase in mortality com-
pared to the general population and sudden unexpected
death in epilepsy (SUDEP) is the most important direct
epilepsy-related cause of death\textsuperscript{21,22}. 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 dur-
ing the training program period, that is, the remarkable
1680 h hours of exercise without any death occurrence in-
dicate that physical activity may not be considered a risk
factor for sudden unexpected death in epilepsy (SUDEP).

Information concerning risk factors for SUDEP is con-

cflicting, but potential risk factors include: seizure fre-

cquency, age, early onset of epilepsy, duration of epilep-
sy, uncontrolled seizures, mainly in the TLE, seizure type,
AED number\textsuperscript{21,22} and winter temperatures\textsuperscript{21}. Potential path-

omechanisms for SUDEP is unknown, but it is very proba-
ble that cardiac arrhythmia during and between seizures,
electrolyte disturbances, arrhythmogenic drugs or trans-
mition of epileptic activity via the autonomic nervous
ystem to the heart play a potential role\textsuperscript{23}. Physical activ-
ity reduces seizure frequency as well as lead to improved

REFERENCES

physical exercise influence the occurrence of epileptiform EEG


