Synergic effect of exercises and nutrition on seizure activity and oxidative stress
간질모델에서 운동과 영양의 시너지 효과

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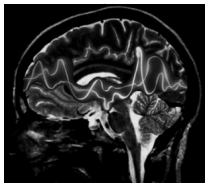
Introduction

What is seizure ?

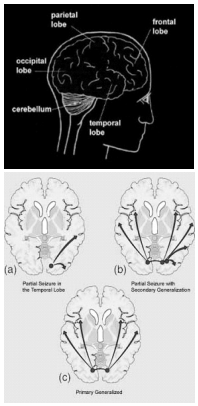
"**Seizure**" is a general term that refers to a sudden malfunction in the brain that causes someone to collapse, convulse, or have another temporary disturbance of normal brain function, often with a loss or change in consciousness.



Introduction

Classification of seizure

1. **Partial seizure** (focal seizure)
   - simple partial seizure
   - complex partial seizure
2. **Generalized seizure**
   - Petit mal seizure
   - Grand mal seizure

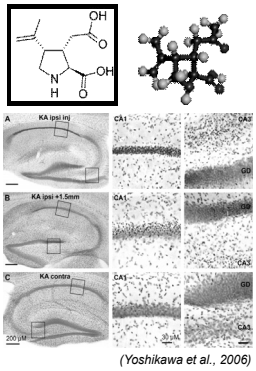


Introduction

Kainic acid (Kainate)

-**Specific agonist** for the kainate receptor which mimics the effect of glutamate

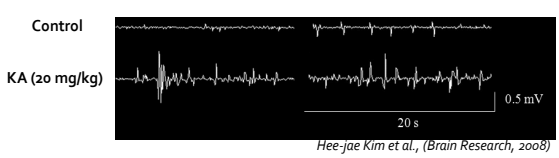
- Used in experiments to distinguish a receptor from the other ionotropic receptors such as **NMDA** and **AMPA**



(Yoshikawa et al., 2006)

Introduction

Kainic acid-induced seizure



Hee-jae Kim et al., (Brain Research, 2008)

Prolonged generalized seizure results in **neuronal injury** and **death** in the brain, and this damage presumably involve the **hippocampus** and **memory** impairments as the major neuronal sequel.

Introduction

Effect of exercise on seizure

In **animal** models, **regular exercise**

- Was found to **retard the development of amygdala kindling** in experimental animal models *(Arida et al., 1998).*

- **Reduced the number of seizure** *(Arida et al., 1999).*

- **Revert electrophysiological changes** in the hippocampus *(Arida et al., 2009).*

- **Induces positive plastic changes** in hippocampal formation of animals with epilepsy *(Arida et al., 1991).*

Introduction

Effect of exercise on seizure

In **human** studies, **regular exercise**

- A positive effect of physical exercise on seizure frequency and severity in people with epilepsy (Nakken, 1999).

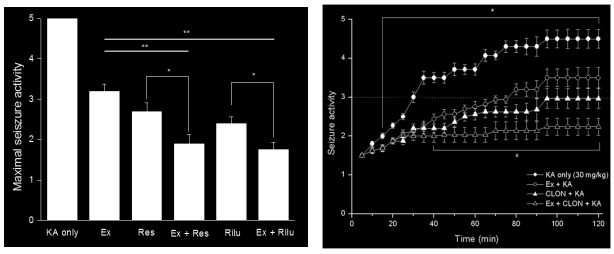
- Electroencephalography (EEG) findings have shown that interictal epileptiform activity remains unchanged or decreases during or immediately after exercise in the majority of patients studied (Esquivel et al., 1991)

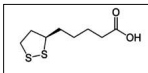
Previous reports (synergic effect)

Potential mechanisms for regulation of seizure activity

Antioxidant

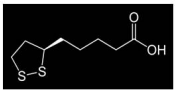
Adrenergic response

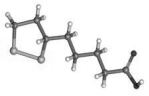




Introduction

Lipoic acid (LA)





Lipoic acid (**LA**), also known as **alpha lipoic acid** (**ALA**) and **thioctic acid.**

LA, as **growth factor**, first isolated in the late 1940s, with **ability to react with ROS**, it was determined to possess antioxidant properties in mitochondrial metabolism.

With current **anticonvulsant evidence** of LA on epilepsy induced by pilocarpine, clinical experiments test LA as a drug for potential treatment for neurological disorders such as depression, Parkinson's disease, and epilepsy.

Purpose

Taken together, previous researchers clearly demonstrated the effect of physical exercise and LA on brain damage or seizure activity by **attenuating oxidative stresses**. However potential synergic effect of physical exercise and LA on preventing seizure development has not been explored yet.

Therefore, in the present study, we investigated

the synergic effect of physical exercise and LA on kainic acid-induced seizure activity caused by oxidative stress?

Materials and Methods

Experimental groups

Experimental group	n
Control	9
KA only	9
Exercise + KA	9
LA + KA	9
LA + Exercise + KA	9

Adult male ICR mice weighing approximately 35 g each (8 week-old)

Materials and Methods

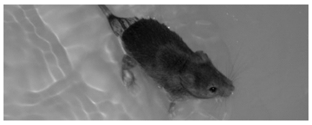
Physical exercise training

8 weeks swimming training (60 min sessions, 5 times per week)

1st week: adaptation to swimming without weights

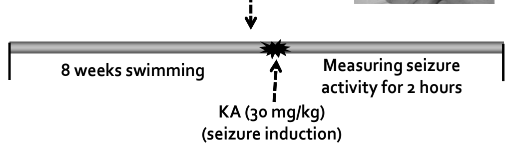
After the water-adaptation period, the mice were made to swim with weights (**5% of body weight**) in order **to improve endurance exercise capacity.**

(Arida et al., 1991).



Materials and Methods

Experimental procedure



Materials and Methods

Measuring of seizure activity

- Monitored for 2 h after the KA injection

Score	Behavior
0	Normal, rare wet dog shakes (WDS), or no convulsion
1	Intermediate number of WDS, rare focal convulsions affecting the head
2	Frequent WDS, frequent focal convulsions, or appearance of generalized convulsions
3	Frequent WDS, focal convulsions, or frequent appearance of generalized convulsions with rearing (but not falling)
4	Frequent WDS, focal convulsions, or frequent generalized convulsions with falling, jumping, and salivation
5	Continuous generalized seizures and death within 2 h

(Kim HJ et al., 2008)

Results

Body weight and endurance capacity

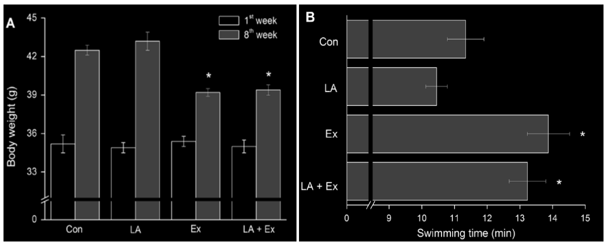
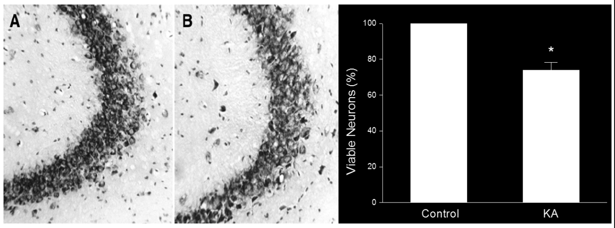


Fig. 1 Effect of 8 weeks of exercise training on body weight (a) and endurance capacity (b). Values are mean ± ME for n = 9 in each group. *p<0.05 compared to control group (independent t test)

Results

Neuronal injury in hippocampus



KA (30 mg/kg, i.p.), Cresyl Violet
Hippocampus CA3 region

Hee-jae Kim et al., (Brain Research, 2008)

Results

Seizure activity and mortality

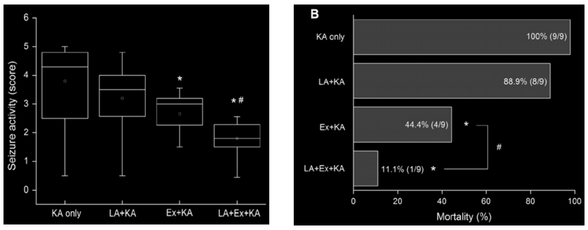
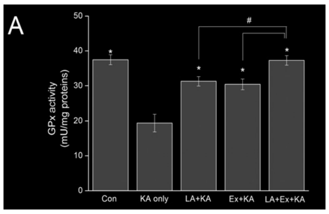
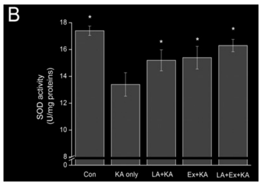


Fig. 2 Effect of exercise training and LA treatment on kainic acid induced seizure activity (a) and mortality (b). Values mean ± ME for n = 9 in each group. *p<0.05 compared to 멫KA only멫group, and #p<0.05 compared to 멫Ex + KA멫or 멫LA + KA멫group. a Kruskal–Wallis test with Dunn멫test and kai square test

Results

Oxidative stress





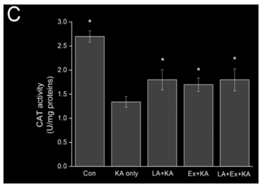


Fig. 3 Effect of exercise training and LA treatment on GPx (a), SOD (b), and CAT (c) activity in cerebral cortex.. *p\0.05 compared to 몇KA only뫷group, and #p<0.05 compared to 몇EX + KA뫷or 몇LA + KA뫷group (independent t test)

Discussion

Side effects of anti-convulsant agents

1) 테그레톨 : 물체가 두개로 보임, 졸림, 어지러움증, 두통, 설사, 항 이뇨호르몬 분비 증가, 백혈구 감소증, 간 기능 이상, 재생 불량성 빈혈, 피부발진, 간도성, 심장박동의 불규칙, 무과립구증
2) 올필, 데파킨 : 졸림, 구역, 구토, 복통, 머리카락 빠짐, 식욕증가, 체중증가, 간기능 이상, 손떨림, 백혈구 감소증, 혈소판 감소증, 간염, 췌장염
3) 루미날 : 졸림, 과운동증, 흥분, 집중력 저하, 피부발진, 발열, 스티븐 존슨 증후군
4) 사브릴 : 졸림, 어지러움증, 두통, 물체가 두개로 보임, 체중 증가, 행동장애, 위장 장애, 시야축소, 피부발진
5) 크로나제팜 : 갈아짐, 비틀거림, 과운동증, 흥분, 집중력 저하, 백혈구 감소증, 혈소판 감소증, 피부발진
6) 라믹탈 : 졸림, 구역, 구토, 비틀거림, 물체가 두개로 보임, 피부발진, 스티븐 존슨 증후군
7) 페니토인(딜라틴) : 안구진탕, 비틀거림, 갈아짐, 잇몸 커짐, 몸에 털이 남. 비타민 D 결핍, 피부발진, 림프절 커짐, 전신성 홍반성 낭창, 스티븐 존슨 증후군
8) 뉴론틴(가바펜틴) : 졸림, 피곤한 느낌, 비틀거림, 어지러움증, 위장장애, 피부발진, 백혈구 감소증
9) 토파맥스(토피라메이트) : 어지러움증, 비틀거림, 두통, 피곤한 느낌, 위장 장애, 신장 결석, 인지장애, 손떨림
10) 자론틴 : 구역, 구토, 비틀거림, 갈아짐, 두통, 식욕부진, 피부발진, 스티븐 존슨 증후군 백혈구 감소증, 혈소판 감소증
11) 조니사마이드 : 졸림, 두통, 구토, 복통, 식욕부진, 간기능 장애

Discussion

Side effects of anti-convulsant agents

Table 1 Drug interaction profiles of the antieplieptic drugs

Elimination	Interaction profile
Carbamazepine	
mostly hepatic (autoinduced)	Decreases levels of calcium channel blockers (dilitiazem, verapamil), its own levels are increased when taken with CCBs; decreases effect of warfarin, antibiotics increase its levels; decreases tricyclic antidepressant levels; interacts with fluoxetine, antibiotics, grapefruit juice
Phenytoin	
mostly hepatic (nonlinear)	Decreases levels of calcium channel blockers (dilitiazem, verapamil); initially increases effect of warfarin then decreases warfarin effect; decreases tricyclic antidepressant levels; interacts with diabetes and arthritis medications
Valproate	
mostly hepatic	Can act as a metabolic inhibitor increasing lamotrigine, phenobarbital, lorazepam levels; concomitant use of it may increase levels of phenytoin, diazepam, warfarin, amitriptyline; clearance of valproate may be increased with phenytoin, phenobarbital, primidone, and carbamazepine
Gabapentin	
mostly renal	Does not reduce or inhibit any CYP-450 or UGT isoenzyme; does not interact with other hepatically metabolized drugs such as AEDs, warfarin, or theophylline; elimination not impaired by other drugs
Lamotrigine	
mostly hepatic	Metabolism significantly induced by phenytoin, carbamazepine, phenobarbital; metabolism significantly inhibited by valproic acid; no interaction with gabapentin, levetiracetam, topiramate, zonisamide

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Conclusion

Our results showed that treatment with LA in trained mice significantly decreased **seizure activity** and **mortality** with increase of **PGx activity.**

These results indicate that physical exercise along with LA could be a **more efficient method for modulating seizure activity.**