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Aerobic exercise promotes the expression of ERCC1 to prolong lifespan: A new possible mechanism

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A B S T R A C T

Aerobic exercise can delay aging and extend lifespan, but its specific mechanism still remains unclear. One popular theory is that with age and the cell division times increasing, DNA damage will inevitably accumulate, leading to dysfunction and failure of various tissues and organs, which will eventually lead to aging. Thus, repairing damaged DNA is a key strategy to extend lifespan. Excision repair cross-complementary gene 1 (ERCC1) is a DNA repair enzyme that recognizes, excises and repairs damaged DNA. Defects or reduced activity of the enzyme can lead to DNA damage accumulation. This study provides that aerobic exercise can significantly extend rats' lifespan and increase the expression of ERCC1 in heart, brain, liver and kidney. Therefore, based on our experiments, we propose the following scientific hypothesis: aerobic exercise can up-regulate the expression of ERCC1 and then may reduce DNA damage accumulation to maintain genomic integrity and stability, thereby delaying aging and prolonging lifespan in humans.

Introduction

Aerobic exercise, aging and life span

The growth, development, aging and death of human follow the laws of nature in an orderly manner. Aging and lifespan are affected by genes, environment, lifestyle, and many other factors. Physical exercise is a simple, cheap and effective health intervention for most individuals [1]. It is widely accepted that exercise can extend lifespan and is beneficial for human health in many different ways. Aerobic exercise can enhance immune function by increasing the T-cells and B-cells number significantly [2–4]. Aerobic exercise also improves cardiovascular function, owing to increases in stroke volume, and cardiac output [5–7]. It was also demonstrated that increased blood flow-induced shear stress through peripheral arteries during exercise improves vascular homeostasis by both decreasing reactive oxygen species and increasing nitric oxide bioavailability in the endothelium [8]. Besides that, aerobic exercise can improve the anti-oxidant capacity of body by reducing the formation of free radicals and increasing superoxide dismutase (SOD) activity and malondialdehyde (MDA) ratio [9]. It can not only promote the elimination of free radicals, but also slow down the reduction of anti-oxidant capacity caused by aging [10]. Thus, aerobic exercise is beneficial for the balance between the oxidation and anti-oxidation systems [11]. Furthermore, it has been demonstrated that aerobic exercise can improve various types of behaviors such as anxiety, depression, and cognition in normal healthy aged C57BL/6 mice over the adult lifespan [12]. Thus, aerobic exercise can delay aging and extend lifespan. However, its specific mechanisms have not been fully clarified.

DNA damage, aging and lifespan

There are several theories on the mechanisms associated with human aging, however, DNA damage appears to be the most widely accepted [13,14]. DNA as the carrier of genetic information is constantly being exposed to various internal and external stressors, including free radicals, ultraviolet light, ionizing radiation and chemical substances, all of which could cause base mutation, deletion, insertion, and even DNA double-strand breaks. It has been suggested that DNA damage will accumulate in mammals with aging [15,16]. Once beyond the DNA repair capacity, DNA damage accumulation would lead to cell cycle arrest and senescence, apoptosis and cellular dysfunction.

ERCC1 and DNA repair

The major DNA repair mechanisms include nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR) and DNA double strand break repair (DSBR). Among them, NER eliminating various structurally unrelated DNA lesions by a multiwise'-cut and patch'-type reaction, is identified as a major mechanism. Excision repair cross-complementary gene 1 (*ERCC1*) belongs to NER family and plays an important role in NER [17,18]. *ERCC1* is located on human

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chromosome at 19q13.32, comprises 10 exons spanning about 15 kilobases, and encode a protein which contains 297 amino acid residues. ERCC1 can form closely heterodimers, ERCC1-XPF, with the DNA repair enzyme deficiency complementary gene F (XPF). ERCC1-XPF heterodimer makes incisions on the damaged DNA strand on the 5′ side of the open "bubble" intermediate formed during NER [19,20]. It was reported that the expression level of ERCC1 and XPF in peripheral blood mononuclear cells (PBMCs) declined in an age-dependent manner [21]. This down-regulation of ERCC1 and XPF were likely lead to genomic instability and ultimately contribute to aging. In general, *ERCC1* is a key gene in NER, and closely related to aging. Therefore, ERCC1 has been considered as a promising target to delay aging and prolong lifespan.

Aerobics can prolong life

In our pilot study, Continuous aerobic exercise (CAE) and Intermittent aerobic exercise (IAE) models were performed to investigate the relationship of aerobic exercise and lifespan. All animal experimental protocols were approved by the Institutional Animals Care and Use Committee at Xi'an Medical University and in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals. CAE group was training as Wang et al. described [22]. In brief, rat treadmill training was set at 5° gradient with speed and duration of 10 m/min (40–50% of V_{O2max}), 60 min per session 5 days a week for 50 weeks. IAE group was establishment according to WISLOFF et al. [23] with the running table slope of 0° gradient. The IAE group warmed up for 10 min at 10 m/min (50–60% of V_{O2max}) before walking for 7 min intervals at 25 m/min (80–90% of V_{O2max}). Each interval was separated by 3 min active pauses, walking at 15 m/min (50–70% of V_{O2max}). Total exercise time was 60 min per session 5 days a week for 50 weeks. The animals were fed by National standard rodent feed ad libitum and allowed euthanasia when they were moribund. The amount and time of death of rat were recorded and then analyzed by using survival curve. The preliminary results showed that the survival rate of CAE group and IAE group significantly increased compared with the control group, while there was no significantly difference between the CAE group and IAE group (Fig. 1A). It was obvious that average lifespan of CAE group and IAE group were much higher than that of control group (Fig. 1B), which indicated that aerobic exercise can extend lifespan.

Aerobic exercise can increase ERCC1 expression

To evaluate whether aerobic exercise can increase the expression of ERCC1, rats were sacrificed, and heart, brain, liver and kidney was taken respectively in different groups (n = 6) after 8, 24 and 50 weeks. ERCC1 mRNA expression was assayed by using Real-time polymerase chain reaction (RT-PCR) in these tissues. As shown in Fig. 2, the expression of ERCC1 mRNA of all these four tissues in CAE and IAE groups were remarkably elevated compared to control group. It was also worth to notice that the ERCC1 mRNA expression was decreasing with aging. These preliminary results indicate that the expression of ERCC1 was highly related with aging and aerobic exercise might delay aging by increasing the expression of ERCC1.

Hypothesis

ERCC1 plays a key role in maintaining DNA synthesis and repair, genome stability and cell homeostasis, whose expression is highly related with aging. Aerobic exercise can up-regulate the expression of ERCC1 mRNA. Thus, increasing the expression and activity of ERCC1 might be a potential mechanism of prolonging lifespan by aerobic exercise.

Hypothesis assessment

ERCC1 is involved in NER pathway by forming an endonuclease required for incising the damaged strand of DNA in NER 5′ to the lesion. It was reported that Ercc1 $^{-/\Delta 7}$ mice were much smaller and median life span was markedly reduced compared to wild-type siblings: 20 and 118 weeks, respectively, which proved that ERCC1 is critical for delaying aging and prolong lifespan by reducing accumulation of DNA damage and genotoxic stress [24,25]. Although life-long spontaneous exercise does not prolong lifespan, aerobic exercise is an intervention that delays age-associated frailty, enhances function [26]. In this study, we found that aerobic exercise extended rats lifespan significantly, and increased the expression of ERCC1 in heart, brain, liver and kidney,

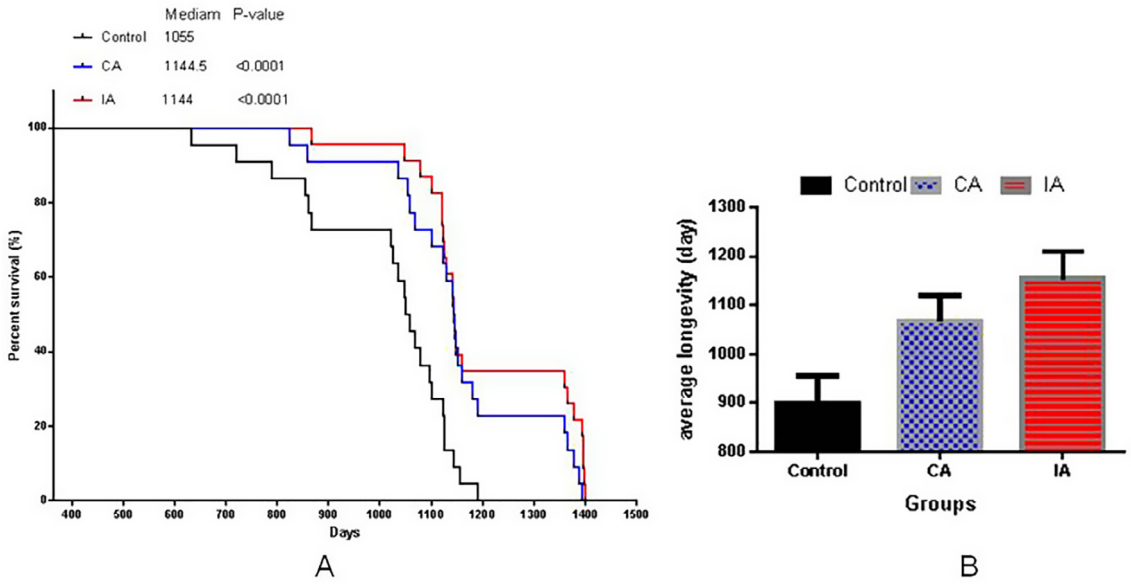

Fig. 1. A: Survival curves of Control group (n = 22), CA group (n = 22) and IA group (n = 23). Compared with the control group, the survival rate of CA group and IA group is increased, while there was no significant difference between CA and IA group. B: average life of Control group (n = 22), CA group (n = 22) and IA group (n = 23). Compared with the control group, the average life expectancy of CA group and IA group is increased, while there was no significant difference between CA and IA group.

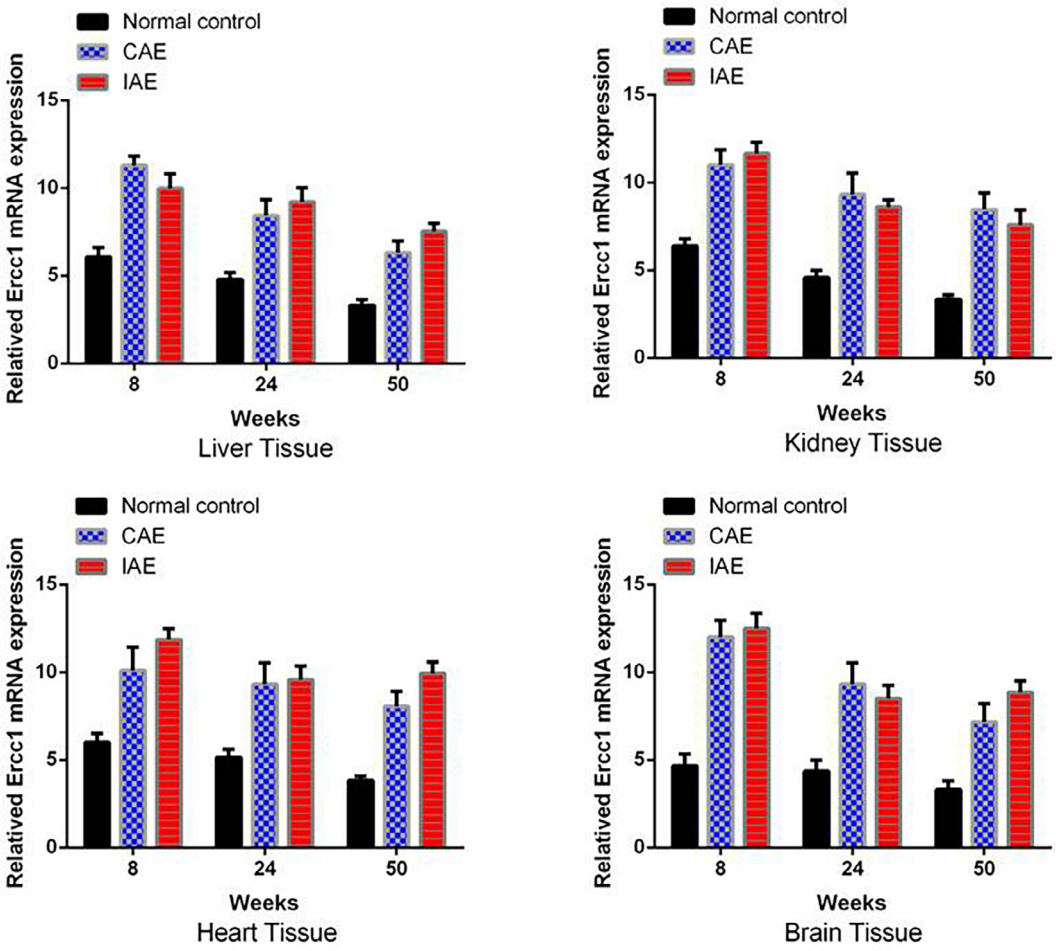

Fig. 2. ERCC1 mRNA expression analyses. After 8, 24 and 50 weeks of aerobic exercise, animals were sacrificed and ERCC1 mRNA expression in brain, heart, kidney and liver were analyzed by qPCR. In each tissue, the expression of ERCC1 was up-regulated in two aerobic exercise groups when compared with control group. There was no significant difference between CA and IA groups.

which suggested that aerobic exercise is beneficial for reducing accumulation of DNA damage and genotoxic stress by elevating the expression of ERCC1.

Summary and conclusion

The dysfunction and failure of various tissues and organs occurred with aging. It is the result of the disruption of balance between DNA damage and repair. The resulting accumulation of DNA damage and genotoxic stress affect DNA replication and transcription function, and eventually lead to the dysfunction and failure tissues and organs. As a key enzyme in DNA repair process, ERCC1 is critical for maintain DNA structural integrity and stability by identify and repair damaged DNA. Our preliminary results demonstrate that aerobic exercise can increase the expression of ERCC1 in rat heart, brain, liver and kidney. Thus, we hypothesize that aerobic exercise would increase the expression of ERCC1 and enhance DNA repair, thereby maintaining the integrity and stability of the ageing genome, which is of great significance for cells to maintain their homeostasis. This evidence may be helpful in guiding people seeking to delay aging-associated physical complications and prolonging their lifespan through aerobic exercise training.

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Conflict of interest

None declared.

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