Aging-related changes of triose phosphate isomerase in hippocampus of senescence accelerated mouse and the intervention of acupuncture

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HIGHLIGHTS

- "Yiqi Tiaoxue, Fuben Peiyuan" acupuncture improved cognitive functions of SAMP8.
- Triose phosphate isomerase activity of SAMP8 decreased with aging.
- Acupuncture could up-regulate TPI activity in hippocampus of 8-month SAMP8.
- The effects of acupuncture might be achieved by regulating TPI activity.

ARTICLE INFO

ABSTRACT

Glycometabolism disorder induced by triose phosphate isomerase (TPI) is closely related to Alzheimer's disease (AD). Senescence accelerated mouse (SAM) is often employed as an AD model characteristic of early cognitive impairment. In order to investigate the variation of TPI with aging, SAM prone 8 (SAMP8) and SAM resistant 1 (SAMR1) were divided into 2-month, 6-month, 8-month and 12-month group. For the analysis of acupuncture intervention, SAMP8 were divided into SAMP8 control group (Pc), SAMP8 acupoint group (Pa), SAMP8 non-acupoint group (Pn) and SAMR1 control group (Rc). Grading score of senescence and Morris water maze results showed that SAMP8 presented aging-related deterioration of learning and memory, and that acupuncture could improve the learning and memory ability of SAMP8. TPI activity and expression were detected by colorimetric method and Western blot analysis, respectively. When compared to SAMR1, TPI activity in 6-, 8- and 12-month SAMP8 decreased significantly. However, acupuncture intervention markedly up-regulated TPI activity in hippocampus of Pa. These findings suggested that the learning and memory deterioration of SAMP8 with aging might be associated with the lower TPI activity and that acupuncture could improve the cognitive impairment by increasing TPI activity, thus correcting the abnormal glycolysis metabolism and maintaining the brain homeostasis and internal environment.

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1. Introduction

Glucose is an important source of energy metabolism in brain nervous activity, and cerebral glucose metabolic rate reflects the brain function. The abnormal glucose metabolism plays an important role in brains of patients with Alzheimer's disease (AD) [19,21]. Triose phosphate isomerase (TPI) is the key enzyme in the glycolysis process. Studies have shown that its deficiency or lower activity might cause the accumulation of dihydroxyacetone phosphate (DHAP), thereby inhibiting the glycolysis processs [18]. Glycometabolism disorder induced by abnormal TPI is closely related to the brain function degeneration, such as learning and memory dysfunction [10]. Senescence accelerated mouse (SAM), firstly cultivated in Kyoto University [20], is mainly characterized by a variety of functional disorders with aging and divided into SAM/prone (SAMP) and SAM/resistant (SAMR). Among those SAM/prone mice, SAMP8 shows deficits in learning and memory, and emotional disorder. It has been reported that amyloid β deposition occurs in SAMP8's brain during the aging process. However, the physiological index of SAMR1 is similar to that in the normal animals. Therefore, SAM is often used as a preferable model to study the mechanism and evaluate the therapeutic effect of aging and AD [13]. Our previous proteomics studies showed that, during the

Table 1
Acupuncture points and manipulation.

Points	Local innervations	Anatomical positions	Manipulation	Twisting angle (°)	Frequency (per min)	Time (s)
Danzhong (CV17)	On the sternal median line, with the anterior cutaneous branch of the 4th intercostal nerve	On the anterior median line on the chest, at the midpoint between the two nipples, at the level of the 4th intercostal space	Twirling reinforcing manipulation	<90	>120	30
Zhongwan (CV12)	On the linea alba abdominus, with T10 spinal nerve subcutaneously	On the anterior median line of the upper abdomen, 10 mm below the xiphisternal synchondroses	Twirling reinforcing manipulation	<90	>120	30
Qihai (CV6)	With anterior cutaneous branch of the 11th intercostal nerve subcutaneously	On the anterior median line of the lower abdomen, 4 mm below the umbilicus	Twirling reinforcing manipulation	<90	>120	30
Xuehai (SP10)	With anterior cutaneous of femoral nerve subcutaneously	When the knee is flexed, on the medial aspect of the thigh, the point is 3 mm above the mediosuperior border of the patella, on the bulge of the medial portion of M quadriceps femoris	Twirling reducing manipulation	>180	<60	30
Zusanli (ST36)	With fibular nerve subcutaneously	1 mm lateral to the anterior tubercle of the tibia, and 3 mm below the capitulum fibulae under knee joint	Twirling reinforcing manipulation	<90	>120	30
Non-acupoints	–	On the bilateral hypochondrium, 3 mm above iliac crest	Moderate reinforcing-reducing twisting manipulation	90–180	60–120	105

process of aging and dementia, a variety of hippocampal glucose metabolic proteins of SAM including TPI appeared abnormal (data not shown). Moreover, "Yiqi Tiaoxue, Fuben Peiyuan" acupuncture has been shown to significantly improve the dementia and vitality of patients with AD [8] and the learning and memory ability of SAMP8 [5]. Based on the preliminary work, we further explored the variation of abnormal TPI in SAM, the relationship between TPI abnormality with aging and dementia degree, as well as the mechanism by which acupuncture improved AD with respect to regulation of glucose metabolism enzyme.

2. Materials and methods

2.1. Animals and groups

Healthy male SAMP8 and SAMR1 were supplied by the Experimental Animal Centre of First Teaching Hospital of Tianjin University of Traditional Chinese Medicine and housed five per cage with free access to diet and water under a 12-h light/dark cycle at $23 \pm 1\,^\circ$C and 45% of humidity.

For the assay of TPI with aging, SAM mice were divided into SAMP8 groups and SAMR1 groups of 2-month, 6-month, 8-month and 12-month. There were 10 mice used for each group.

For the analysis of acupuncture intervention, SAM of 8-month was divided into SAMP8 control group (Pc), SAMP8 acupoint group (Pa), SAMP8 non-acupoint group (Pn) and SAMR1 control group (Rc). There were 10 mice used for each group.

2.2. Acupuncture method

The experimental procedures were carried out according to the National Institute of Health Guide for the Care and Use of Laboratory Animals. The animals were handled while awake, with special care to minimize stress. "Yiqi Tiaoxue, Fuben Peiyuan" acupuncture was applied, and "Danzhong" (CV17), "Zhongwan" (CV12), "Qihai" (CV6), bilateral "Xuehai" (SP10) and bilateral "Zusanli" (ST36) acupoints were selected for Pa (Table 1). The selected points were in accordance with the "Atlas of Animal Points" enacted by the Experimental Acupuncture-Moxibustion Research Association of China. For Pn, two non-acupoints were selected as the control stimulating points (Table 1). Pa and Pn were administrated acupuncture once a day (1 day rest after 6-day treatment) for continuous 21 days. Pc and Rc were given the same time and same level catching-grasping stimulus as the acupuncture groups (Pa and Pn). No mice died in this experiment.

2.3. Grading score of senescence

The grading score of senescence system [20] represents the senescent status according to the animals' appearance and behavior changes of 11 items (reactivity, passive flight reaction, skin glossiness, coarseness, hair loss, ulcer, periophthalmic lesions, corneal opacity, corneal ulcer, cataract, kyphosis). In general, each item has 3–5 grades according to the intensity of changes. For example, grade 0 represents no particular changes and grade 4 represents the most severe changes. Each grade of each item is clearly defined, and the total score represents the senescent degree.

2.4. Morris water maze

The acquired ability of spatial discrimination and learning and memory of animals is reflected by the hidden platform trial [4,14]. After evaluating the senescent grading score, we used hidden platform trial to observe the behavior of SAM. The experiment platform was placed in the middle of the northeast quadrant. Two starting points equidistant from the platform location were defined.