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Investigating the Role of Spatial Learning in Delaying Cognitive Impairment in SAMP Mice via Synaptic Plasticity

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Abstract. Neurodegenerative diseases (NDDs) are a group of debilitating disorders characterized by the progressive loss of neurons and myelin sheaths. A conservative estimate of people suffering from NDDs in 2024 exceeds 50 million. Despite significant advancements in medical technology and the development of various surgical and pharmacological therapies, many NDDs remain incurable, and their molecular mechanisms are poorly understood, which makes early diagnosis and intervention challenging. Therefore, the primary prevention of NDDs requires more attention from people of all ages. To highlight the potential significance of early prevention and cognitive training, this research proposes an experiment to observe the impact of randomized maze training on the learning ability of SAMP8 mice to counteract their accelerated aging-induced memory loss. The experiment will compare trained and untrained mice in their ability to learn a route associated with spatial memory for food within 30 days, indicated by AMPAR/NMDAR ratio, which reflects the level of long-term potentiation. The results are expected to reveal the viability of spatial learning in delaying cognitive impairment.

Keywords: NDDs prevention, SAMP mice, Randomized Maze Training.

1. Introduction

Neurodegenerative diseases (NDDs) are multifactorial, and possible mechanisms include oxidative free radical attacks [1], abnormal protein aggregation [2], neuroinflammation [3], mitochondrial dysfunction [4] and genetic factors [5]. Evidence shows that intellectual and cognitive activities can reduce the risk of NDDs [6]. However, whether these preventive strategies outweigh their inherent adverse consequences remains to be verified.

The senescence-accelerated mouse-prone 8 (SAMP8) model used in this study is characterized by impaired spatial memory retention. Previous studies have demonstrated that moderate exercise can partially offset these deficits in six-week-old SAMP8 mice and significantly increase the level of postsynaptic density protein 95 (PSD-95) and Synaptophysin (SYN) [7]. Other approaches, such as drugs, acupuncture [8] and intermittent fasting [9] have also been applied to ameliorate symptoms of NDDs. However, like exercise, these methods require further investigation to confirm their efficacy and mechanisms of action.

Memory loss and dementia associated with NDDs are partially caused by impairments in synaptic plasticity. Active primary prevention is a strategy to strengthen the synapses and enhance long-term

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potentiation; hence, this research hypothesizes that spatial memory training improves neural flexibility and cognitive resilience. In addition to measuring the time taken by mice to learn the food-associated route and measuring the AMPAR/NMDAR ratio, researchers may also use other techniques to assess the structural changes in the brain.

2. Method

2.1. Animals and apparatus

Twenty male senescence-accelerated mouse-prone 8 (SAMP8) mice, aged six to eight weeks, were housed individually in the institutional animal facility. The experiment lasted for 30 days. On odd-numbered days, all the mice were deprived of food to enhance motivation for spatial learning tasks. The apparatus consists of three parts: a paper box, 60 cm*60 cm paper box, 15 cm in height; a maze base: 59 cm*59 cm PLA white maze base with grooves; partition boards: eighty-one PLA blue partition boards, each measuring 5 cm*1 cm and standing 14 cm high.

2.2. Randomized maze training

2.2.1. Initialization

The maze base was placed inside a paper box. A camera was positioned above the paper box. The mouse was initially at one corner of the maze, and food was placed diagonally at the opposite corner. A randomized maze with difficulty $d = 10$ (size 10* 10) was constructed using the partition boards inserted into the maze base, as shown in Figure 1.

2.2.2. Test, train and evaluation

On Day 2, all the mice were placed in mazes with the partition boards. As soon as a mouse reaches the food, it was returned to its initial place. This process was repeated five times per mouse and recorded for analysis.

On odd-numbered days other than day 2 and day 30, 10 mice that were assigned randomly as the experimental group were in mazes with the partition boards, and the other 10 mice that were in the control group were in mazes without the partition boards. As soon as a mouse reaches the food, it was returned to its initial place. This process was repeated five times and recorded for behavioral analysis.

On Day 30, all the mice were tested in mazes with the partition boards. As soon as a mouse reaches the food, it was returned to its initial place. This process was repeated five times and recorded for behavioral analysis.

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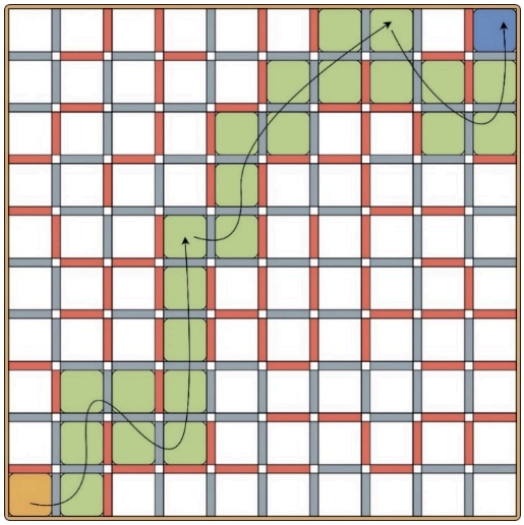

Figure 1. An example of randomized maze training

The maze base is 1 cm high at [$6m$, $6m+5$]* [$6n$, $6n-1$] cm and [$6m$, $6m-1$]* [$6n$, $6n+5$] cm, 2 cm at other places. The orange square represents the starting place of the mouse, and the blue square represents the place where the food is. Red bars represent the places of partition boards, and the arrows represent the route the mouse learns. Source: Figdraw. ID: RTPPW5c66c (Figure 1).

2.3. Test on AMPAR/NMDAR ratio

After the experiment, all the brains of mice were sectioned into acute brain slice samples and stored in artificial cerebrospinal fluid (aCSF) immediately. Then, the electrophysiological recording technique was applied: the electrodes were connected to each sample, and excitatory postsynaptic currents (EPSCs) were recorded under voltages of -60 mV and +40 mV to calculate the AMPAR/NMDAR ratio reflecting synaptic plasticity.

3. Expected results

All slopes were derived using the linear regression model. Denote the natural logarithm of the learning time of a mouse in the n th attempt on Day 2 as $ti(n)$ and on Day 30 as $tf(n)$. IFTD (Initial-Final Time Difference) is defined as $IFTD = ti(1) + tf(5) - tf(1) - ti(5)$; RLTD (Rate of Learning Time Decrease) is defined as the difference of the natural logarithm of the slope of $ti(n)$ and $tf(n)$ decrease. Both IFTD and RLTD were analyzed using two-sample t-test to compare group means, with the alternative hypothesis that the mean value in the control group is greater than that in the experimental group. As shown in Figure 2, the AMPAR/NMDAR ratio was determined based on the amplitude of excitatory postsynaptic currents (EPSCs) [10]. This ratio was also analyzed using a two-sample t-test, but with the alternative hypothesis that the experimental group has a greater mean than the control group.

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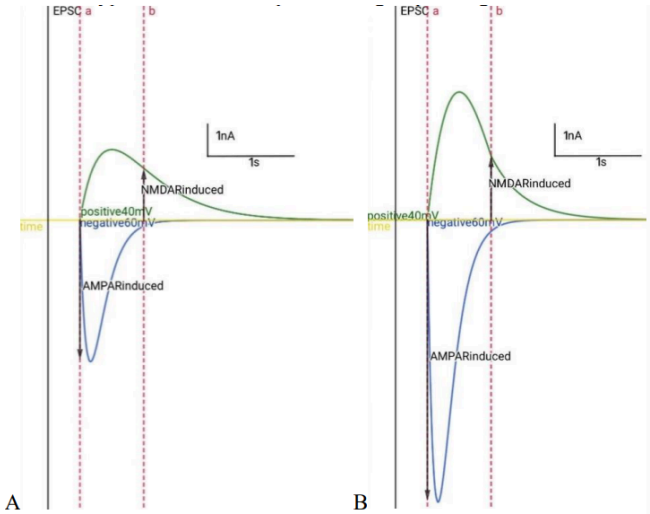

Figure 2. The expected change of EPSC over time in (A) the control group and (B) the experimental group

The red dashed line “a” indicates the time at which the voltage is applied, and the red dashed line “b” represents the time AMPARs are closed. The green curve represents the current change under a voltage of +40 mV, and the blue curve represents the current change under a voltage of -60 mV. The arrows represent the amplitude of the current induced by AMPAR and NMDAR activation. Source: GeoGebra (Figure 2).

4. Discussion

It is expected that despite decreases in IFTD, RLTD and AMPAR/NMDAR ratio for all mice, the experimental group will be less affected, suggesting that randomized maze training might improve the synaptic plasticity and possess a preventive effect in aging mice.

This study proposes an adjustable maze model to train the experimental subjects, aiming to provide opportunities to enhance synaptic plasticity. Compared to traditional paradigms, other alternative models might curtail the variety of routes, for instance: one drawback of the Morris Water Maze is that platform is restricted to four quadrants, so that the mice might be assigned to platforms that are in the same direction or same distance from the center, which reduces the learning time.

Concerning RLTD, IFTD and the ratio of AMPAR to NMDAR might not be significantly different, researchers could attempt to adjust the difficulty level, d, of the maze: ensuring a constant height for all components, the paper box should be $6d$ cm* $6d$ cm, the maze base should be ($6d-1$) cm* ($6d-1$) cm, and the a number of partition boards should be $(d-1)^2$ with the same size. Alternatively, extending the duration of training for the experimental group may help to produce more pronounced effects.

5. Conclusion

Spatial memory training may benefit individuals with genetic predispositions to neurodegenerative diseases. This study reveals how spatial learning activities such as learning a new dance, starting a new drawing of nature or designing a new origami can be utilized to prevent NDDs. This study

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contributes to further research in neuroscience and neurodegeneration; further validation is required using a larger sample size and additional physiological and behavioral indicators.

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