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Stimulating SuM in mice with bad disease

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Abstract. This work is about stimulating SuM in mice with bad disease. It has been widely recognized that patterned opt-ogenetic stimulation on SuM enhances the ABNs. This work try to use Chronic opto-stimulationof SuM and opto-stimulation of SuM on the mice. For the AD patients recover their disease early, who don't have behavioral deficits, Chronic opto-stimulation of SuM may cure them. But, for the AD patients with badly disease, Chronic opto-stimulation of SuM can't effect. The combination of opto-stimulationof SuM and chemogenetic activation of SuM gives a possibility to cure the AD patients in bad situation. This work do the experiment on the mice in 8 month. If the result shows that the combination of opto-stimulationof SuM and chemogenetic activation of SuM have effective affected on AD mice. The method of the combination of opto-stimulationof SuM and chemogenetic activation of SuM may be taken in medical treatment. This work also provide another method, removing a healthy hippocampus. If this is certified to be possible, it can truly reduce the treatment and quickly improve patients' behavioral deficits.

Keywords: Chronic opto-stimulationof SuM, opto-stimulationof SuM, chemogenetic activation of SuM.

1. Introduction

It has been unanimously agreed that stimulating the SuM is necessary to enhance ABNs. But the way of enhance ABN through stimulating is unknowned. In the research[1,2], they suggest that when stimulating SuM, the SuM GABA transmission is improved. Stimulation of SuM neurons enhances the quantity of rNSCs and neural progenitors. SuM neurons provide direct GABAergic inputs to regulate dendritic development of adult-born immature neurons[3,4].

Our experiment is trying to find a better way to cure the AD patients. We want to find the main medicine. We will test whether stimulating SuM still can help the AD patients with behavioral deficits and whether the AD patients behavior recover to normal. If there exist some method which can cure the AD patients obviously. In this work, we stimulate the SuM in AD mice with serious behavioral deficits.

2. Construction and Geometrical Dimensions of Specimens

Studies have proved that the ABNs enhanced when animals are entering into new environment or exercising[5-8,10,11]. The mice that run often have an increase on cognitive performance. It has been found that the increase in the number of ABNs help improve the memory and cognitive performance[9]. As the ABNs increased,the stimulation of SuM is detected. Some experiments moved on to test weather stimulating the SuM affects ABNs[6]. People use patterned optogenetic stimulation to stimulate the hypothalamic supramammillary nucleus. They do experiments on healthy mice and the AD-mice in

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critical window. Though the SuM is stimulated artificially, it still makes a big difference, as figure1 shows[1]. By testing the mice with zero maze, open area, the memory, behavior and emotion improved a lot, nearly reaching the level of wild mice.

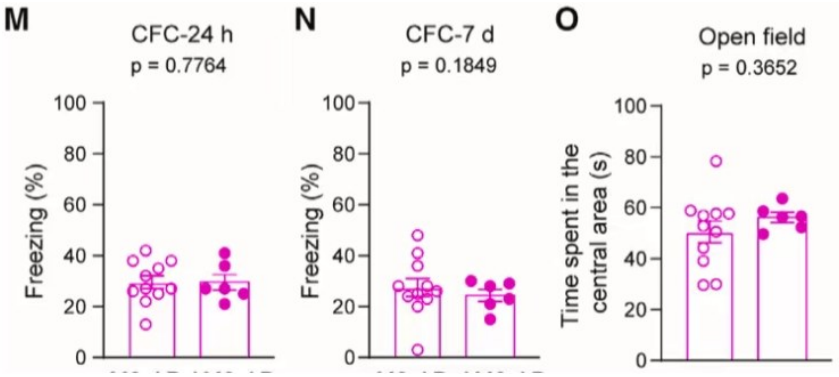


Figure 1. the mice with stimulating the SuM and the wild mice

Another experiment is taken, to figure out whether stimulating SuM is necessary. They only increased the quantity of ABNs, by using triple transgenic mice harboring Ascl1-CreER, floxed hM3Dq, comparing with the AD-mice. Figure 2 [2] shows that there is no difference between the mice with enhanced ABNs and the mice with AD disease, suggesting that stimulating the activity of impaired ABNs in AD brains is not beneficial for hippocampal function. So if we just increase the quantity of ABNs can't help recover the patients memory, emotion and behavior. The stimulation of SuM is necessary.

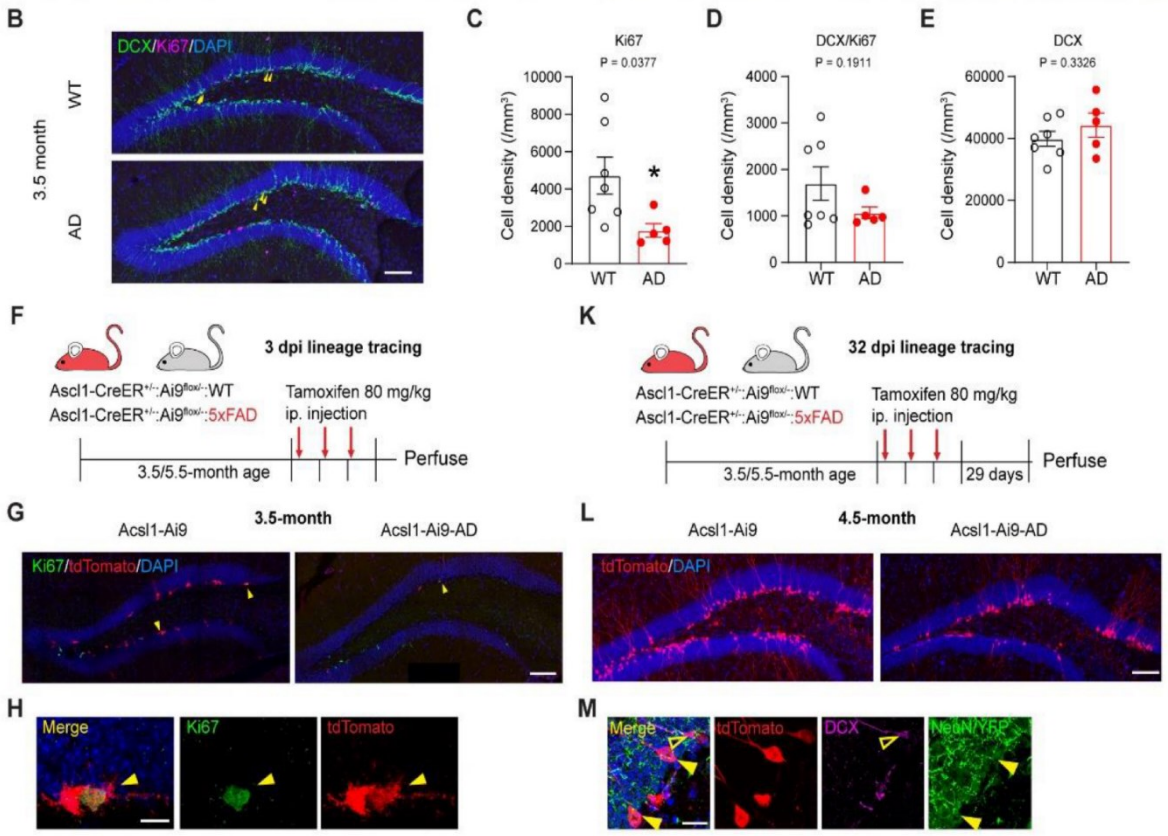
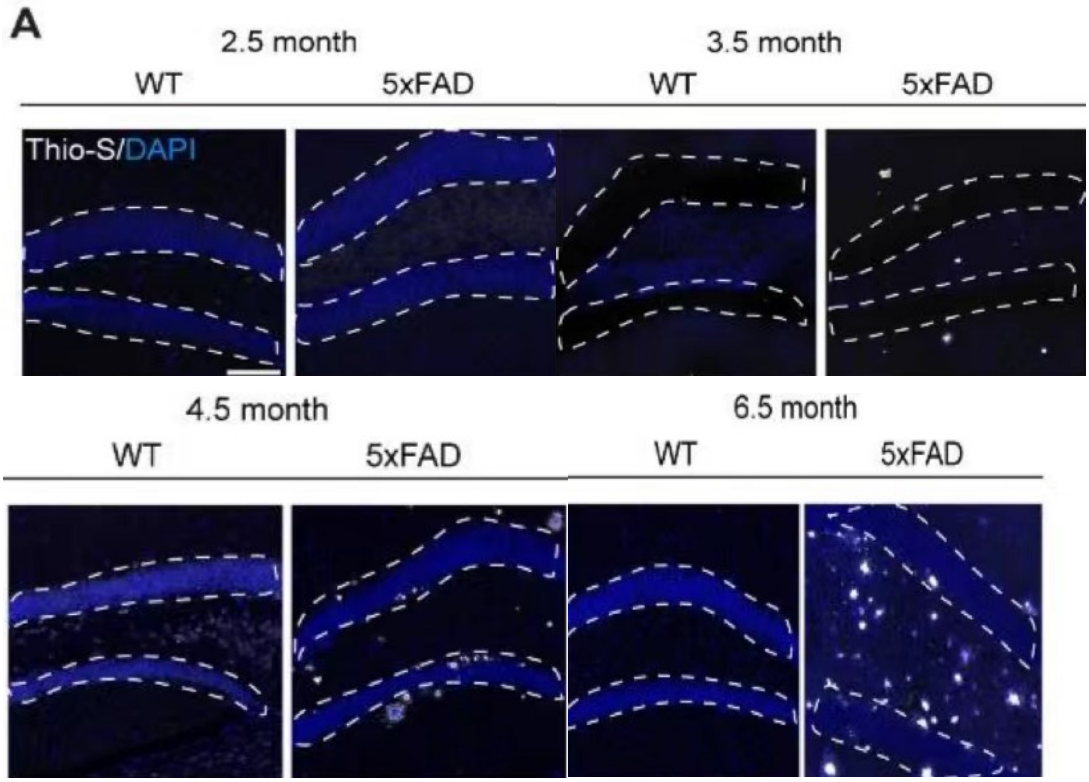


Figure 2. the mice enhanced ABNs without stimulating SuM

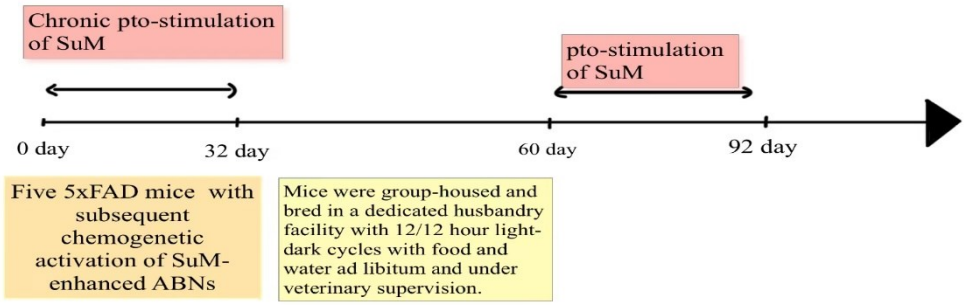
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A research proves that damage of hippocampal neurogensis occurs before behavioral deficits. They test 2.5-month-old mice, 3.5-month-old mice, 4.5-month-old mice and 5.5-month-old mice. They find that there are no Aβplaque deposition in 2.5-month-old mice, little in 3.5-month-old mice and more serious in 4.5-month-old mice and 5.5-month-old mice. Though the novel place recognition and contextual fear conditioning, the behavioral deficits appear about 4.5 month. So it may be a possible period to cure the AD patients.



3. Test Results and Discussions

3.1. Timeline



We use fifteen 5xFAD mice (8 month, males and females) and 10 healthy mice (8 month, males and females) .

3.2. Group division

Group A:Five 5xFAD 8 month-mice
Group B:Five 5xFAD 8 month-mice
Group C:Five 5xFAD 8 month-mice

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Group D:Five healthy 8 month-mice

Group E:Five 5xFAD 8 month-mice

First 32 days, the 5xFAD mice in group A has Chronic pto-stimulation of SuM. The mice in group B has CHronic pto-stimulation of SuM and chemogenetic activation of SuM. On the 34 day, we use Open field (OF) test, Forced swimming (FS) test and Zero-maze (ZM) test to test group A,B,C,D. We need to avoid the acute effect from SuM activation. Then we put all the mice back. The mice were put in dedicated equipment with 12/12 hour light-dark cycles with food and water prepared. On the 60 day, we start pto-stimulation on the SuM of mice in group A. On the 60 day, the mice in group A has pto-stimulation of SuM and the mice in group C has pto-stimulation of SuM and chemogenetic activation of SuM. Then we still use Open field (OF) test, Forced swimming (FS) and Zero-maze (ZM)) to test group A,C,D. On the 95 day, we cut the hippocampus of mice in group D,E. We remove the hippocampus from mice in group D to group E. On 129 day of the experiment, we test the mice in group E'.

3.3. Method

Open field (OF) test

The size of the equipment is a square of 45x45 cm, with white wall and an open roof. We put each mouse on the center of the roof and measure the time the mice stay in the center of the roof(defined as a 25x25 cm square) in 5 minutes.

Forced swimming (FS) test

The FS test equipment is made up of a acrylic cylinder(height of 40 cm, a diameter of 30 cm) and the temperature of the water keeps at 23± 1 degree. Each mouse has 5 minute to swim. We will record the time the mouse remained immobile during the test.

Zero-maze (ZM)test

The ZM test is made up of a 6 cm wide, 45cm outer diameter white ring. It includes four equal walls, and the entire ring was elevated to a height of 40 cm. When the test start, the mice is been put in the closed section. Then we record the time mouse spent in the open section.

3.4. Expect result

On the results of 34 day, there may be no difference between the results of group A and C. But the results of group B ,C may have difference. If the data of group B is higher than group A and near half of group D, it shows that CHronic pto-stimulation of SuM and chemogenetic activation have affect on enhancing ABNs of the AD patients. On the results of 94 day, we can compare the data between group A,C and group D. The data of group C is as similar as Group D, it may shows that the combination of pto-stimulation of SuM and chemogenetic activation of SuM has efficient effect on curing the AD patients. The data of group A,C is much higher than the data of A,B on the 34 day of the experiment. On the results of 129 day, the data of group E' may be as same as the data of group D. If so, it shows the possibility of curing the patients by removing a healthy hippocampus. If the data is as same as the data of group C on the 34 day of the experiment, it may shows that the main factor leading to the AD disease may not mainly in the hippocampus but somewhere else.

4. Conclusion

Through this experiment, it figure out whether the method of the combination of pto-stimulation of SuM and chemogenetic activation of SuM on curing the AD patients. The removing hippocampus may also have obvious effect on curing AD patients with behavioral deficits. The results of the experiment contributes to the AD disease treatment. The method may help the patients with badly behavioral deficits. Peoplw always consider that the low-level neurogenesis happens when humans across aging[12-15]. This work provide the way for people the method to enhance ABNs.

But there are some limitations of this work. The 5xFAD mice is a well-established AD mouse line, which have 5 AD-linked mutations. So this may interfere the results of the experiment. Also, the mice can't represent all the AD disease in human, the method may not affect human.

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