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Reduced Neuroplasticity Decreases Resilience to Depression and Anxiety in a Mouse Model

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Abstract:

It is well studied that adult hippocampal neurogenesis (AHN) increases resilience to depression-like behaviors improving cognitive functions and mood regulation. Also, improving AHN helps with the recovery of stress induced symptoms but the reason remains elusive. We use the mouse model by blocking the NMDA receptors in AHN neurons to evaluate the effect of reducing neuroplasticity on stress induced symtoms.

Keywords: conponent; adult hippocampol neurogenesis; plasticity; depression; NMDA receptorconponent; adult hippocampol neurogenesis; plasticity; depression; NMDA receptor.

1. Introduction

Depression is a kind of mental disorder with high incidence and high recurrence rate, causing changes in thinking abilities, feels, and function in daily activities. Which interferes with ability to work, study, eat, sleep, and enjoy life. The nunber of depression is significantly growing making it a bigger world wide health issue every year. In 2015, disorder caused by depression is estimated to rank the third among all health issues causing diaorder [1]People all around the world suffered from it numbers up to 350 million, according to the World Health Organization which has lasted many years. (When ranked by disability and death combined, depression comes ninth behind prolific killers such as heart disease, stroke and HIV.) Almost half of the world's population lives in a country with only two psychiatrists per 100,000 people.[2]Current antidepressant medications work by increasing the levels of monoamine neurotransmitter molecules at synapses. Although monoamine levels change quickly once treatment with antidepressants starts, the drugs typically take several weeks to exert a clinical effect.[3]. Leading to the idea that their antidepressant effects are not solely due to the direct modulation of monoamines but are also the consequence of long-term downstream changes. Antidepressents work be inducing the AHN.[4]

Adult hippocampal neurogenesis(AHN) is the process which neural stem cells produce new neurons in the hippocampus.[5] This process increases plasticity in the hippocampus. The AHN is crucial in learning, memory and emotion regulation[6]and has

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been linked to memory deficits. It was demonstrated in a previous study in a mouse model that new neurons are mainly derived from neural stem cells in the subgranular region of the hippocampal dentate gyrus. AHN neurons become functionally active and are thought to contribute to learning and memory, especially during their maturation phase, when they have extraordinary plasticity.[7] Also it is proved in an animal model that using tamoxifen to trigger CREer to cut BAX gene inorder to increse AHN promotes resilience to depression reducing depression like symptoms and improving congnite conpetence.[8] Similarly, in an animal model of chronic stress based on chronic corticosterone injections, increasing AHN was able to protect preventively from stress-induced depressive-like behaviors.[9]

We attempt to provide reliable experimental results on the potential link between plasticity of AHN neurons and stress induced behaviors , by blocking the NMDA receptors of AHN neurons decreasing their plasticity, than the mice were put under unpredictable chronic mild stress, the naturalistic model of major depression(MD).[10] Than evaluated the anxiety and depression like behaviors on the forst groupe of mice than tested their congnitive ability through water maze .

2. Method

2.1 . Animals

Male ibax mice at ambryol state is used they were genetically characterized making them resistant to mk801 and the resistant features and bax gene can be deleted by CreER. They were groupe housed and fed in an enrich environmant for 24 weeks, and is then given vehicle treatement or tomoxifen. Than they were held in the same place and treatement for 8 weeks enabling AHN.

2.2 . Experimental Design

Mice were modified to have mk801 resistant synaps as embryol and is kept in rich environment for 24 weeks before reciving 5 times of injection of tomoxifen. They are than held in and enrich enrironment for 8 weeks giving time for AHN and forming new synapses, then half went through 8 weeks of UCMS creating stress and the other half arestill kept in the enrich cages without stress. The mices are split into four groupes based on whether they went through UCMS and whether being injected by tomoxifen. They are then seperated into two groupes based on the kind of tests they are going through, one cohort tested depression like behaviors and the other tested congnition by water maze test.

2.3 . UCMS

We followed the protocol of UCMS from previous essays. The mice are kept in separated cages individually and went through various social and environmental stress of mild intensity everyday and it lasted for eight weeks, to make sure that the positive effect of kept in enrich environment for 24 weeks resisting depression like behaviors will fade during the long UCMS process, and will have same effect on both the dorsal hippocampus and ventral hippocampus. Stress factors include removing and replacing sawdust, pouring water of 20 degrees into the cages, tilting the cages at 45 degrees, affecting their circadian rhythm, and repeating the whole process. Social stress factors is induced by putting mice's in cages that are already occupied by other mice.

2.4 . Nest-Building Test

The mice were kept in larger cages individually and isolated, 10 hours before the following tests. The quality of the nest is judged twice, 5 and 24 hours after a small piece of cotton in put into every isolated cage in the morning, according to previous rating protocal. (Deacon, 2006)

2.5 . Light/Dark Box

Two boxes build up the apparatus, a lightbox and a dark box of the same size and transparent walls. The boxes were connected with a plastic opaque tunnle. Mice were placed in the light box, experiment starts once the mice enters the tunnel and lasts for 5 minutes. The total time spent in the dark box and their times of entry were measured. An entry is counted once the mice has its four paws in the box. This experiment is used as a indicator of anxiety.[11]

2.6 . Novelty-Suppressed Feeding Test (NSF)

The equipment is made out of a open area with red light and litter, food is placed at the center of the open area on a piece of wite paper. This tests the anxiety level of the mouse since they have to face the conflict between eating and avoiding being in an open area. Latency and consumption of food is recorded, starting when mice bites the food.

2.7 . Splash Test

We followed the procedure as previous essay discribed. [12] Mice were being spryed 10 percent of sucrose solution on to their coats in their cages with red light. Grooming behavior is induced and recorded 5 minutes after the spray.

2.8 . Cookie Test

Cookie test is used to test anhedonic behaviors, mice were put in a reward maze test.[13] Three cansecutive chambers that are connected by an opening bulid up the apparatus. Mice are placed in chamber 1 and the butter cookie(reward) is in chamber 3. We measured the latency of eating and the consumption of cookie for 5 minutes atarting from the mice in put into the chamber. On the day for test, common food is removed from the chambers in order to keep mice hungry. In order to prevent phobic to new environment mice were put into the maze 3 times before the test, and cookie is given to the mice twice a day befor the test to prevent phobia. Also the maze is illuminated by red light.

2.9 . Tail Suspension Test

Tail suspension test were used in order to assess stress-coping behaviors. Mice were suspended above the ground with their tails taped for 6 minutes with smooth suroundings eradicating any possibility of escaping. The immobilized time were measured which reflects its degree of depression.[14]

2.1 0. Flexibility/Inhibition Test in the Water Maze

This test evaluates two parts : cognitive flflexibility and inhibitory control. A cross shaped water maze is used, with four arms (N,S,E,W)each each perpendicular to the near by one, water temperature at about 22 degrees. Mice ate trained to find the one hidden plate in one end of the arm. N arm has a small ligt at the end creating a lighter emvironment. At the begining of all experiments mice is put into the water maze at the end of S arm.
For the first four days they had to learn two different strategies based on the environment. To turn right inthe water with lenses (situation A-Task 1) and to go straight to the N end when the water is clear (situation B-Task 2). Four same tasks of same situation is tested everyday, situation A-Task 1for the forst two days, situation B-Task 2 for day 3 and day 4. Than the mice are tested flexibility a week after the first training. On day12 thay were given 6 blocks a day 1 , 3 , 5 of situation A 2 , 4 , 6 of situation B. On day 13 thay will be tested with inhibition 6 blocks a day,with reverse sttustion and task. (eg. situation A-Task2)

3. Expected results

3.1 . Splash Test

The experiment reflects how goal-directed behavior is effected by UCMS by aassessing the duration of grooming after being splashed by sucrose solution on fur.Results show no effect of UCMS on duration.

3.2 . Cookie Test:

Cookie test was used to evaluate anhedonia,the latency ofeating food and total consumption was observed. Tamoxifen groupe has a higher latency and smaller consumption per time compared to vehicle groupe, while UCMS groupe has a generally higher latency and consumption per time.

3.3 . Light/Dark Box Test:

Light/dark box test and NSF test were both used in order to measure anxiety. Tamoxifen groupe enters the dark box more frequently than vehicle groupe. While UCMS groupe also has a higher frequency entering the dark box than NS groupe. However no difference was seen on the duration of time in dark boxes between the four groupes.

3.4 . Novelty-Suppressed Feeding Test(NSF):

NSF test is used to measure anxiety. Tamoxifen groupe has a higher latency and smaller consumption per time compared to vehicle groupe, while UCMS groupe has a generally higher latency and consumption per time.

3.5 . Tail Suspension Test(TST):

TST was used to measure the anxiety level of the mouse. Tamoxifen groupe spend more time immoble than vehicle groupe also UCMS groupe spend more time immoble than NS groupe.

3.6 . Water mase test:

Water mase test is used to test cognitive flflexibility and inhibitory control. Tamoxifen groupe hasan average higher latency to arrive at the platforms and more failures than vehicle groupe. UCMS roupe has a generally higher latency to arrive at the platforms and more failures than NS groupe.

4. Discussion

Many experiments has evalusted the effect of UCMS on AHN and also how AHN effects the symtoms of major depression. However it is poorly studied why the increase in AHN increases resilience to major depression. It is knowen that AHN effects stress induced congnitive deficits but the mechanism is unclear. Also how the changes of neuroplasticity effects AHN is vague. We’ve proved in this experiment that decrease neuroplasticity effects both depression like behaviors and congnitive flexibility, further experiments can be conducted to explore why neu-

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roplasticity would effect depression like behaviors, which may be useful for further developing therapy for major depression.

Also in our experiment the mutant IGluR receptor that doesn't bind with MK-801may efffect the binding with glutimate which will certainlly effect the result of the experiment. The deletion of BAX gene may lead to the change of proportion between glia cell and neurons.

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