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Reducing Synaptic Plasticity Decreases Resilience to Depression and Anxiety in an ASCL1 Mouse Model

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Abstract:

Synaptic plasticity, the ability of synapses to strengthen or weaken over time in response to activity, plays a crucial role in the brain's adaptability and function. This paper examines the impact of synaptic plasticity on resilience to depression and anxiety in an ASCL1 mouse model. By studying the molecular and cellular mechanisms of synaptic changes, how these changes affect behavioral outcomes related to stress and emotional regulation analysis. Through the research and findings of this paper, a deeper understanding of the relationship between the enhancement of synaptic plasticity and mood changes, and provide more treatment ideas for depression and emotion-related diseases.

Keywords: synaptic plasticity, depression, anxiety, stress, neuroplasticity.

1. Introduction

Stress and depression might lead to disruption in neuroplasticity, which is crucial for the brain's ability to adapt and function optimally [1]. Changes in neuroplasticity happen in different parts of the brain, affecting regions responsible for emotion regulation, memory, and cognitive processes [2]. Results include cognitive deficits, affective information processing patterns, and patient-reported symptoms, such as persistent sadness, anxiety, and difficulty concentrating. Anti-depression treatments, including pharmacological and behavioral therapies, have been shown to increase neuroplasticity, thereby enhancing the brain's resilience to stress and mitigating symptoms of depression and anxiety [3].

Therefore, in view of the relationship between stress and depression with neuronal plasticity, as well as the changes in neuroplasticity caused by specific drugs, a hypothesis is designed in this paper that reducing synaptic plasticity decreases resilience to depression and anxiety in an ASCL1 mouse model.

In the experiment design, investigations were conducted to explore the specific mechanisms of synaptic plasticity in brain regions associated with emotion regulation, such as the hippocampus and prefrontal cortex, by conducting multiple tests and experiments on mice starting in the embryo [4]. And the effects of drugs (Tamoxifen and MK-801) that enhance or inhibit synaptic plasticity on depression and anxiety-like behavior in mice were tested by changes in mouse embryos. A variety of tests (such as Novelty-Suppressed, Feeding Test, and Splash Test, among others) were established to assess behavioral changes in mice, including symptoms of depression and anxiety [5].

2. MATERIALS AND METHODS

2.1 Preliminary Experiment

2.1.1 Gene Alteration in Mice Embryos

The simple operation process of gene alteration in mice embryos is shown in Figure 1, the following is the detailed operation process:

(1) Mutant iGluR: The mice were designed to inhibit binding of MK-801 (a pore blocker of the NMDA receptor, a glutamate receptor) and iGluR [6], making iGluR resistant to MK-801 without affecting the binding of glutamate to iGluR. The mutant iGluR gene was inserted between the two loxP sites.

(2) The GFP (green fluorescent protein) gene was added to the position after the second loxP.

(3) Addition of Tamoxifen: Tamoxifen was added because it combines with CREER to form Cre. After they combine, Cre cuts the mutant gene, resulting in a normal iGluR that is not resistant to MK-801, and the cell fluoresces green in AHN.

(4) Based on the previous experiment, synapses are formed in AHN [7].

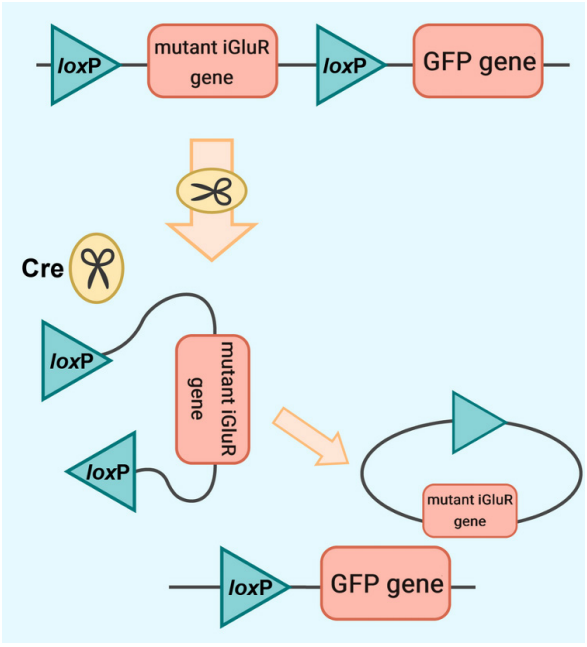

Figure 1 operation process of gene alteration in mice embryos

2.1.2 TUNEL assay

TUNEL is a method for detecting apoptotic DNA fragmentation, widely used to identify and quantify apoptotic cells, or to detect excessive DNA breakage in individual cells [8]. The TUNEL assay will be used to detect apoptotic cells with red fluorescence at week 33 of the experiment.

In the first week of the experiment, the embryos were modified to make them resistant to MK-801, Mice embryos were group-housed and kept under standard laboratory conditions (12/12 h light-dark cycle with lights on at 8:30 p.m. and room temperature around 22 celsius), in enriched cages (46 x 29 x 25 cm, PAULA Ferplast, Castelgomberto. Italy) for 24 weeks. Tamoxifen will be added to the mice at week 24, and they will continue to be kept in the same environment until week 32. MK-801 will be added to the mice at week 32, and they will remain in the same environment for one week. Immunohistochemistry, in the form of a TUNEL assay, will then be performed to detect apoptotic cells, which will fluoresce red.

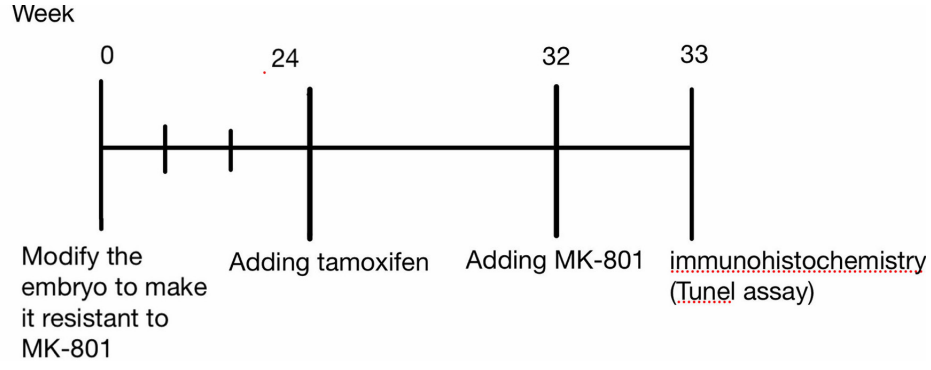

Figure 2 The process of conducting the TUNEL assay

2.1.3 Possible Results

(1) Large number of deaths in AHN: Apoptosis is a natural part of AHN, as not all newly generated cells survive and integrate. Many new neurons undergo apoptosis during development and maturation. The activity of the Bax gene can influence the survival of new neurons in the hippocampus. A higher expression of Bax can lead to increased apoptosis, reducing the number of surviving new neurons. Conversely, reduced Bax activity can decrease apoptosis, potentially increasing the number of surviving new neurons. By preventing Bax-mediated apoptosis, it is possible to increase the number of new neurons that survive and integrate into the hippocampus.

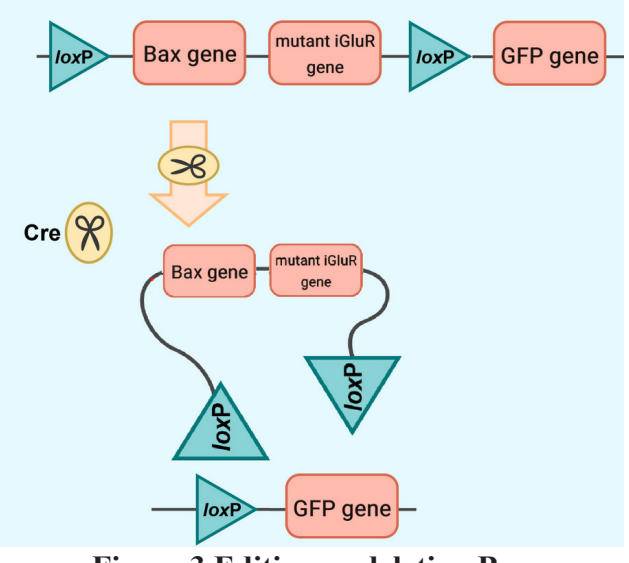

Figure 3 Edition or deletion Bax

(2) No or small number of deaths in AHN: If there's small or no AHN dies at the end of the experiment, then we do not need to increase or decrease the Bax gene in the original cells.

2.2 Research Approach

2.2.1 UCMS (Unpredictable Chronic Mild Stress)

UCMS was applied to some mice, which were isolated in individual cages and subjected to various socio-environmental stressors of mild intensity on a daily basis according to an unpredictable schedule for 8 weeks (from 32 to 40 weeks) [9]. Stressors included removal of sawdust, damping the sawdust, replacing the sawdust with water at 21 celsius, repeated sawdust changes, tilting the cages at 45 celsius, placing a mouse into a cage that been occupied by another mouse, contention in small tubes, and alterations of the light / dark cycle.

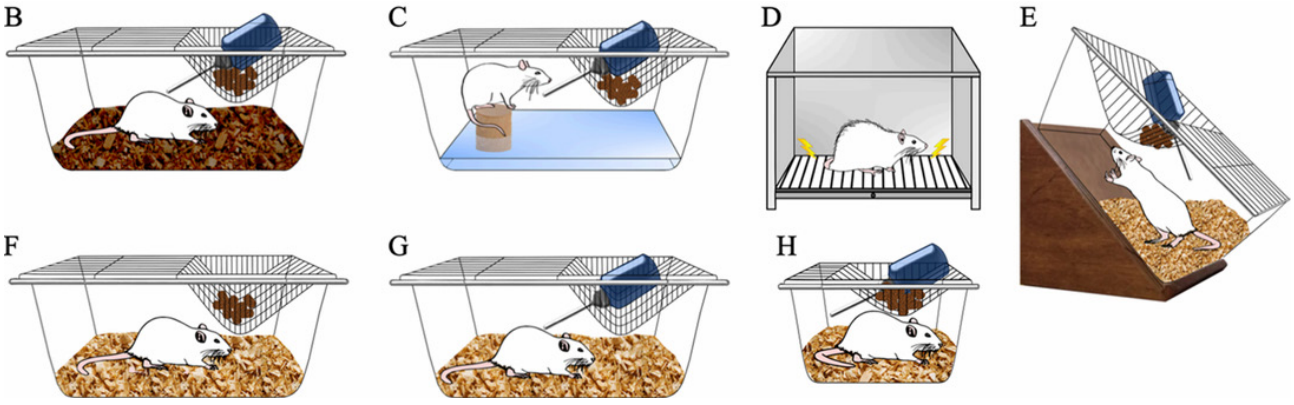

Figure 4 UCMS Mice

2.2.2 Experiments

The variables of this experiment are whether underwent tamoxifen treatment which are tamoxifen (T) or vehicle treatment (V), and whether underwent UCMS which are UCMS or NS (no stress). After week 40, multiple tests were conducted on the mice, including the Nest Building Test, Light / Dark Box Test, Novelty-Suppressed Feeding Test, Splash Test, Cookie Test, Tail Suspension Test, and Flexibility / Inhibition in the Water Maze Test.

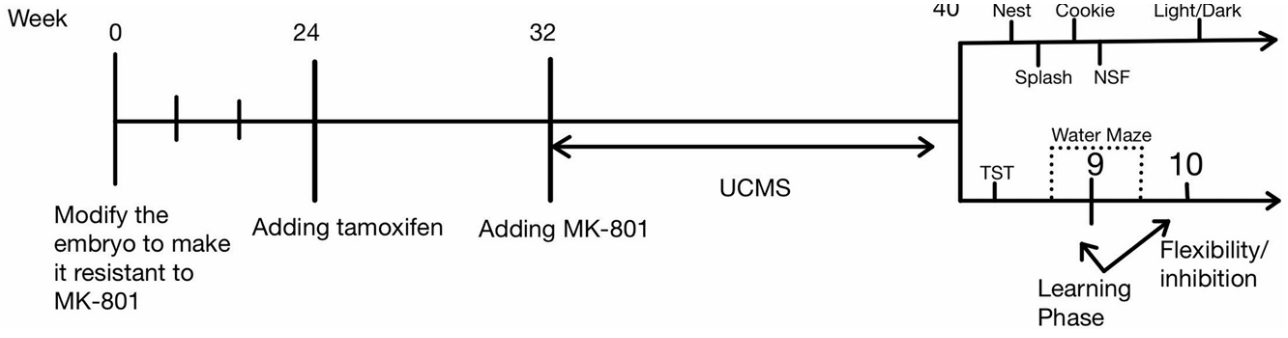

Figure 5 The whole process of the experiment

3. RESULTS

3.1 Experimental Results of Nest Building Test [10]

(1) Tamoxifen vs. vehicle treatment: The group T had a lower score compared to the group V. This suggests that underwent tamoxifen treatment, it resulted in reduced nest building activity or performance compared to vehicle treatment.

(2) UCMS vs. NS: Similarly, the group UCMS had a lower score compared to the group NS. This implies that the UCMS condition negatively affected nest building compared to the NS condition.

3.2 Experimental Results of Light / Dark Box Test [11]

(1) Tamoxifen vs. vehicle treatment: Group T appears more frequently in the dark box than group V. Thus, tamoxifen treatment increased anxiety behavior more than vehicle treatment.

(2) UCMS vs. NS: Similarly, group UCMS appears more frequently in the dark box than group NS. Thus, UCMS conditions increased anxiety behavior more than NS con-

ditions.

3.3 Experimental Results of Novelty-Suppressed Feeding Test [12]

(1) Tamoxifen vs. vehicle treatment: The group T often smelled food for a longer incubation period and consumed less food than group V. This suggests that tamoxifen treatment is associated with more depressive behaviors than vehicle treatment.
(2) UCMS vs. NS: Similarly, the group UCMS often smelled food for a longer incubation period and consumed less food than the group NS. This implies that UCMS condition is associated with more depressive behaviors than NS condition.

3.4 Experimental Results of Splash Test [13]

(1) Tamoxifen vs. vehicle treatment: The grooming duration of group T was longer compared than group V. This suggests that tamoxifen treatment led to an increase in grooming time. Therefore, tamoxifen treatment was associated with more depressive and anxious behavior than vehicle treatment.
(2) UCMS vs. NS: Similarly, the grooming duration of group UCMS was longer compared than group NS. This implies that UCMS conditions led to an increase in grooming time. Therefore, UCMS conditions were associated with more depressive and anxious behavior than NS conditions.

3.5 Experimental Results of Cookie Test

(1) Tamoxifen vs. vehicle treatment: The group T had a longer feeding latency and a lower intake compared to the group V. This showed that receiving tamoxifen treatment increased depressive and anxious behavior compared to receiving vehicle treatment.
(2) UCMS vs. NS: Similarly, group UCMS had a longer feeding latency and a lower intake compared to group NS. This implies that UCMS conditions increased depressive and anxious behavior compared to receiving NS conditions.

3.6 Experimental Results of Tail Suspension Test

(1) Tamoxifen vs. vehicle treatment: The group T spent less time in mobility than group V, mostly immobility. This showed that tamoxifen treatment led to more anxiety and depressive behaviors such as immobility compared to vehicle treatment.
(2) UCMS vs. NS: Similarly, group UCMS spent less time in mobility than group NS, mostly immobility. This implies that UCMS conditions led to more anxiety and depressive behaviors such as immobility compared to NS conditions.

3.7 Experimental Results of Flexibility / Inhibition in the Water Maze Test [14]

(1) Tamoxifen vs. vehicle treatment: The group T takes longer time to reach the platform and has a higher number of failures compared to group V. This suggests that when undergoing tamoxifen treatment, it resulted in impaired cognitive flexibility or greater inhibition compared to vehicle treatment, and therefore a slower learning ability and a slower reach to the platform with a greater error rate.
(2) UCMS vs. NS: Similarly, group UCMS takes longer time to reach the platform and has a higher number of failures than group NS. This implies that UCMS conditions resulted in impaired cognitive flexibility or greater inhibition compared to NS conditions, and therefore a slower learning ability and a slower reach to the platform with a greater error rate.

4. DISCUSSION

The study aimed to test the hypothesis that reducing synaptic plasticity decreases resilience to depression and anxiety in an ASCL1 mouse model. The results of the experiment have the following findings. First, tamoxifen and UCMS use is associated with impaired cognitive flexibility and increased neural inhibition. This suggests that tamoxifen causes rigidity in the brain's response, affecting the brain's perception and understanding of new things. Second, tamoxifen and UCMS increased depressive and anxious behavior. This is consistent with the hypothesis that stress increases anxiety and depression.
Previous experiments have consistently shown that synaptic plasticity is associated with stress, depression, and resilience [15]. This study supports this claim, thus reducing synaptic plasticity and cognitive flexibility through tamoxifen treatment is associated with increased inhibition, which may also lead to increased anxiety and depression. Previous experiments focused more on the benefits of synaptic plasticity, while this study focused more on the hazards of synaptic plasticity. This leads to more about the relationship between neuroplasticity and mental health. UCMS confirmed the previous hypothesis in the ASCL1 mouse model that chronic stress paradigms reliably induced anxious behavior in mice.
The limitations of the experiment are several. First, only one test method, TUNEL assay, was used in this experiment. This results in the possibility that the full range of neurological changes may not be observed. Second, the use of only one chronic stress model (UCMS) limits the generalizability of the findings to other types of stressors. Third, focusing only on tamoxifen treatment also represents insufficient exploration of other possible effects on synaptic plasticity and resilience. Finally, the duration of

the experiment may not be long enough to fully explore the effects on behavior and neuroplasticity.

In the future, more studies should be conducted on the specific effects of synaptic plasticity or long-term potentiation (LTP) on depression. Specific drugs can also be studied to increase synaptic plasticity to reduce depression and anxiety. These studies will give hope to the many people suffering from depression and other mental illnesses.

5. CONCLUSION

In conclusion, this study demonstrates that reducing synaptic plasticity through tamoxifen treatment decreases resilience to depression and anxiety in an ASCL1 mouse model. The results suggest that synaptic plasticity affects cognitive flexibility, anxiety, and depression. Enhancing synaptic plasticity can inhibit anxiety and depression and restore cognitive flexibility. These findings are of great help to people with depression. Future research should further understand the mechanisms of these effects and better develop effective treatments for people with depression.

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