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Effects of Reducing Synaptic Plasticity on Resilience to Depression and Anxiety in ASCL1 Mouse Model

Xin Gao

International Department of Chengdu Shude High School, Chengdu, 610066, China

charlottegao324@outlook.com

Abstract. Major depression is correlated with neuroplasticity, including synaptic plasticity. This research aims to determine the impacts of altering synaptic plasticity in adult-born hippocampal neurons on ASCL1 mice's resilience to depression and anxiety and hypothesizes that reducing synaptic plasticity decreases resilience to major depressive disorder. For this purpose, this ASCL1 mouse model is used to edit genes controlling the formation of long-term potentiation (LTP) by N-Methyl-D-Aspartate Receptor (NMDAR). Relative studies are discussed and analyzed, giving deeper insights into understanding molecular neural circuits and mechanisms of depression and providing support for novel ideas of depression treatment.

Keywords: depression, synaptic plasticity, neuroplasticity, chronic stress, resilience.

1. Introduction

1.1. Major Depressive Disorder

According to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), major depressive disorder (or major depression, depression) is characterized by at least one of the symptoms, depressive mood or loss of interest or pleasure, for a long period of time [1]. Major depressive disorder is a prevalent mental disorder. The prevalence of major depressive episodes among adults in the US is 21.0 million, representing 8.3% of the total US adult population, while the highest prevalence of 18.6% is among individuals aged 18-25 [2]. Globally, 34% of adolescents (aged 10-19) are at risk of developing major depressive disorder [3]. Major depressive disorder is one of the leading contributors to the world disease burden [4]. Disability-adjusted life years attributed to depressive disorder is 31.7-49.2 million, accounting for 40.5% among total disability-adjusted life years attributed to mental and substance disorders [4].

Traditional medication treatment for major depressive disorder includes selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressants (TCAs), and other antidepressant drugs [5]. Other therapies, such as psychotherapies and brain stimulation therapies (electroconvulsive therapy (ECT) & transcranial magnetic stimulation (TMS)), are also used for some situations [5]. SSRI is one of the most widely used medicines to treat major depressive disorder but has problems like delayed effects, low efficacy, and a disabling discontinuation syndrome similar to withdrawal states of other psychotropic drugs [6]. TCA, as a classical antidepressant drug, causes several cardiac side effects and a high drop-out rate [7]. In addition, it does not function well for patients with severe depression [8,9,10]. Brain stimulation therapies, represented by ETC, are recommended and

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efficacious for severely depressed patients. However, negative effects of this therapy, like retrograde amnesia, limit the application [11]. Recent research is increasingly encouraging, but the prevalence of major depressive disorder remains high due to unsolved problems, such as inadequate treatments, delayed effects of drugs, and high rates of partial or no response, severe side effects as aforementioned [12,13]. Further development in this field requires more depth in the knowledge of neurological mechanisms of depression and anxiety.

1.2. Neuroplasticity

Neuroplasticity, defined as the ability of the nervous system to rearrange its structures, functions, and connections according to the stimuli it receives to better adapt to environmental changes [14,15,16], mainly includes 2 types by their different major mechanisms: neural regeneration (e.g., synaptic plasticity, adult neurogenesis) and functional reorganization [14]. Neuroplasticity is strongly correlated with major depressive disorder. Previous research has found that depression decreases neuroplasticity [17,18] and that antidepressant drugs could correct these neuroplasticity dysfunctions and abnormalities [19]. In neuroimaging studies, depression patients' brain circuit structure changes, including loss of glial cells and neurons [20]. These maladaptive neural behaviors could result from the suppression of high levels of cortisol [18]. Treatments, including Transcranial Direct Current Stimulation (tDCS), SSRI, ketamine, and other methods, increase the antidepressant response in the brain and enhance neuroplasticity, which reduces the symptoms of depression [21,22]. More specifically, these changes happen in the hippocampus [20].

One of the important characteristics of neuroplasticity is synaptic plasticity, which is the ability of the brain network to modify and regulate the strength of connection between neurons in response to stimuli and activities [23,24]. Synaptic plasticity can be influenced by several factors. It could be enhanced by repetitive learning [25,26], exercise [27], drugs, and certain hormones [28]. Conversely, other factors such as aging [29] and some neurological diseases, including major depressive disorder [30] impair synaptic plasticity. Synaptic plasticity undergoes significant changes consistent with depression caused by chronic stress [31]. The loss of functions and numbers of both neurons and glutamate synapses caused the symptoms and seriousness of major depression [13,32], which inspired some novel treatments for depression [33]. These changes are connected with N-methyl-D-aspartate receptor (NMDAR) since NMDAR could induce synaptic plasticity in long-term depression and short-term potentiation [34]. Strengthening or weakening synaptic plasticity could be established by inserting or removing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMDAR) [35]. In addition, NMDAR is important in depression neurology since it changes glutamate release and alterations in neural structures and connections [35].

1.3. Research Purpose

As previously discussed, major depressive disorder requires a more effective, safe, and fundamental way with low side effects, and neuroplasticity is connected to major depressive disorder, which indicates that it possibly plays a role in the mechanism of major depressive disorder. However, previous research mostly focuses on the effects of depression on neuroplasticity, although some research has pointed out possible therapies according to the changes in neuroplasticity [13]. As a result, the effects of neuroplasticity on the resilience to depression and anxiety remain unstudied. In an attempt to further understand the potential link between synaptic plasticity and stress resilience and give deeper insights into future research direction of the disease mechanisms and treatment development, this research intends to explore the effects of reducing synaptic plasticity on resilience to major depressive disorder by controlling the function of NMDAR in adult-born hippocampal neurons in an ASCL1 mouse model of unpredictable chronic mild stress (UCMS), which could cause major depression in animals [36,37]. The hypothesis is reducing synaptic plasticity decreases resilience to major depressive disorder. This study changes neuroplasticity before UCMS and places synaptic plasticity alternations in the experiment timeline's upper stream.

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2. Methodology & Research Design

2.1. Experimental Design

Equal numbers of male and female Achaete-Scute Complex-like 1 (ASCL1) mice aged 24 weeks are used at the start of the experiment. Two methods are combined and used to control the changes in neuroplasticity: (1) Cre-loxP system is utilized in this experiment. The mice are genetically modified in advance in embryos to have an additional gene sequence for mutant ionotropic glutamate receptor (iGluR) between two loxP sites and a sequence of the green fluorescent protein (GFP) gene after the loxP site. (2) Mice are given Dizocilpine (MK-801) when needed to reduce synaptic plasticity. As described in previous studies, MK-801 is a non-competitive NMDAR antagonist used in experiments to bind with iGluR on NMDAR [38,39] and therefore inhibit NMDAR forming long-term potentiation (LTP). The additional genes for mutant iGluR are coded for proteins that prevent the binding of MK-801 to iGluR, which enables mutant NMDAR (mNMDAR) to resist MK-801. However, the changes will not affect the normal binding of glutamate to iGluR on mNMDAR. To induce CreER-mediated recombination of genes encoding for NMDAR and GFP, some mice are given tamoxifen. This deletes the genes of the mutant part on mNMDAR and promotes the expression of GFP genes in adult-born hippocampal neurons. As a result, MK-801 can inhibit these neurons' NMDARs and prevent the formation of LTP, which in turn reduces synaptic plasticity.

Mice are divided into 4 groups considering two variables: UCMS/NS (no stress) and tamoxifen/vehicle treatment. Tamoxifen injection is given to some mice from weeks 24 to 32. UCMS/NS treatments are given in weeks 33-40, while MK-801 injections are given to every mouse. Mice are killed to quantify adult-born hippocampal neural apoptosis by coloring apoptotic cells in red using the terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining method. Then, the percentage of apoptotic adult-born hippocampal neurons determines whether to delete the pro-apoptotic gene *Bax* in the following formal experiment to prevent extensive cell deaths: if the percentage is low, *Bax* will not be cut by Cre proteins, while it will be cut otherwise.

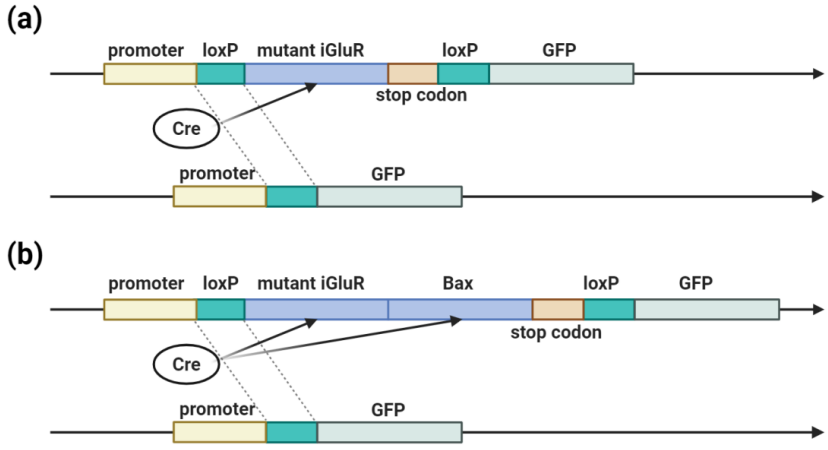

Figure 1. Schematic diagram of part of the gene edition in mice. (a) Gene edition for the preliminary experiment and formal experiment if the results in the preliminary experiment show a small percentile of deaths in adult-born hippocampal neurons. (b) Gene edition for formal experiment if the results in the preliminary experiment show a large percentile of deaths in adult-born hippocampal neurons.

In the formal experiment, if *Bax* is determined to be deleted to protect adult-born hippocampal neurons, mice will be genetically edited on the previous basis: (1) silence the normal positioned *Bax*; (2) add a sequence of *Bax* between the two loxP sites. In the other situation, if *Bax* is decided to remain in the original position, no changes will be made. These mice are continued to be given tamoxifen from weeks 24 to 32 to delete the mutant part of mNMDAR genes (& *Bax*). From weeks 32 to 40, mice are divided into 4 groups: non-stress vehicle (NS-VEH), non-stress tamoxifen (NS-TAM), UCMS vehicle

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(UCMS-VEH), and UCMS tamoxifen (UCMS-TAM). All mice are given MK-801 during this period. After the regimen, mice were tested for their behaviors (anhedonic, goal motivates, stress-coping, & cognition). Tests for cognition levels are included since previous research has shown that depression and anxiety levels might be reflected in cognitive aspects such as learning and memory [40]. All of the learning tests are conducted at last after other examinations for depression and anxiety levels to avoid side-effects of learning-induced reduction of depression level.

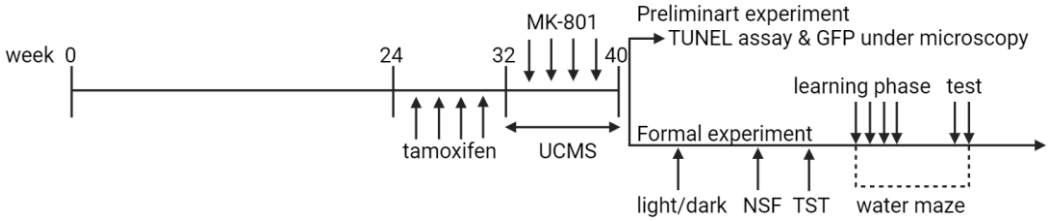

Figure 2. Schematic representation of the experimental design.

2.2. UCMS

Based on previous research [41,42], the standard process of UCMS is conducted from weeks 32 to 40. Mice are separately put into different cages and are subjected to several socio-environmental stressors of a mild intensity and in an unpredictable schedule for 8 weeks: varying sawdust arrangement, changing sawdust into water, playing sounds of natural predators, altering temperature, putting a mouse in a strange cage of another mouse, and changes in the light/dark cycle.

2.3. Analysis of Apoptotic Cells

At the end of the preliminary experiment, mice are sacrificed to quantify apoptosis of adult-born hippocampal after inhibiting NMDARs and LTP formation. The mouse hippocampus is fixed, extracted, and cut into sections. As described in previous research, kits of TUNEL assays color the apoptotic cells fluorescently red by detecting abnormal DNA degradation [43]. By using confocal fluorescence microscopy, cells labeled with the green fluorescent dye and their positions are recorded, representing adult-born hippocampal neurons after injecting tamoxifen. Cell numbers and positions labeled with the red fluorescent dye are also recorded under microscopy, representing apoptotic cells. The two pictures are then integrated to analyze the percentage of apoptotic mutant cells, which are colored in both red and green fluorescent.

2.4. Light/Dark Box

As previously described [44], the apparatus is divided into two rooms. One room is lit with a bright white light while the other room is completely dark with black opaque walls. The two rooms are connected by a small tunnel, allowing mice to move between the rooms. The total time the mice stay in each room is recorded. When a mouse's four paws are in one room, the mouse's entry into that room is recorded. Spending longer time in the dark box implies a higher level of anxiety.

2.5. Novelty-Suppressed Feeding Test (NSF)

The mice are food-deprived for 24 hours to ensure a motivation to eat. They are placed in a novel environment of a big cage with a bright white light, some sawdust, and a small amount of familiar food like cookies. Each mouse is placed into the novel cage separately and is recorded the latency time of eating food and food consumption. A longer time before eating and a smaller amount of food consumption reflect a higher level of anxiety [45].

2.6. Tail Suspension Test (TST)

This is a test of stress-coping behavior. As described in previous studies, a mouse is suspended in the air by an adhesive tape holding its tail to the rope for about 5-6 minutes during which the mouse cannot

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reach any surface [46]. The experimenters will record the immobility time, whose length determines the depression level of the mouse.

2.7. Morris Water Maze (MWM)

The morris water maze is a way of testing the cognitive level of mice. In this experiment, drawing on previous research [42], two contexts are designed for the mice to study. In context 1, the water is filled with gray plastic lenses, whereas in context 2, the water is not. A small amount of food is placed on a platform in different arms of the cross-shaped maze in each context. For day 1-4, mice have 4 trials per day to learn context 1, while during day 5-8, mice have 4 trials per day to learn context 2. On days 8, 10, and 12, mice are tested for the time to find the food in context 1, and they are tested for the time to find food in context 2 on days 9, 11, and 13. The time to find food, failures, and successes are recorded. To prevent mice from seeing the platform and food directly, which hinders the objective of testing mouse memory, the water is evenly mixed with non-toxic white dye in advance.

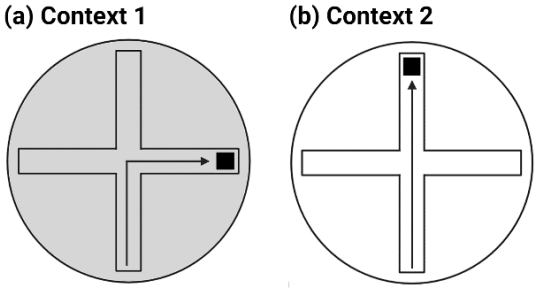

Figure 3. Two contexts in MWM of this experiment. (a) In context 1, gray plastic lenses are placed in the water. Mice are required to turn right in the center to find food. (b) In context 2, no gray lens is in the water. Mice are required to go straight to find food.

2.8. Statistical Method

To analyze data collected in behavioral experiments, two-way ANOVAs, and Fisher post hoc tests are used. For behavioral tests assessing depression or anxiety levels, effects of treatment (tamoxifen/vehicle) and stress (UCMS) are evaluated, which indicates that there are two categorical factors. For MWM, there are treatment effects, stress, and blocks as categorical factors.

3. Expected Results

According to the hypothesis, reducing synaptic plasticity will decrease the resilience to depression and anxiety and increase the vulnerability level. This will be reflected by 3 experiments assessing depression and anxiety behaviors and 1 experiment assessing cognitive level. For the light/dark box, the duration of the UCMS group staying in the dark box will be longer than that of the NS group, while for the vehicle group, the tamoxifen group will have a longer time staying in the dark box. In NSF, the tamoxifen group and UCMS group will have a longer latency time of finding food and a smaller food consumption compared to the vehicle group and NS group respectively. When considering the tail suspension test, the tamoxifen group will have a longer immobility time than the vehicle group, and compared with the NS group, the UCMS group will also have a long immobility time. For MWM, the UCMS group and the tamoxifen group will have more failures and spend more time finding the platform than the NS group and vehicle group respectively.

4. Discussion

This research hypothesizes that reducing synaptic plasticity could reduce the resilience to depression and anxiety in a mouse model. It intends to re-evaluate the correlation between synaptic plasticity and depression and anxiety levels. Since previous research mostly changes neuroplasticity after having depression or anxiety and evaluates the changes in neuroplasticity affected by depression, this research fills up the blank of changing neuroplasticity before having depression or anxiety by putting synaptic

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plasticity upstream in the timeline. The results of this research could be affected by several confounding variables including the sexes of mice and environmental factors. To control these variables, researchers might choose the same number of female and male mice in every group and compare different sexes separately. For environmental factors, mice are fed the same food in the same environment. The strength, duration, types, and frequency of each UCMS are the same. To ensure that adult-born neurons form synapses and connections in the hippocampus, previous studies have done relative research, showing that new and functional neurons born in the hippocampus form synapses and integrate into former networks [47]. More specifically, the first spine of a synapse is 5-10 days, and the peak of spine growth is 3-4 weeks [48].

In the process of neuroplasticity affecting resilience to depression, possible biological and chemical substances might be involved in the neurocircuit of depression at a molecular level. Future research could be conducted in the following aspects: (1) BDNF levels, related to neurogenesis and glial cells, are strongly associated with changes in neuroplasticity and depression according to the meta-analysis of research and clinical trials [49]. Stress could decrease the brain volume, related to a decrease in BDNF, causing symptoms of major depression. Accordingly, antidepressants promote the neurocircuit involving BDNF to increase synaptic plasticity and reduce depression symptoms [50]. In this neurocircuit, the apoptosis of neurons, the speed of adult hippocampal neurogenesis, and the vitality of neurons are also uncertain factors that might finally lead to symptoms of depression and anxiety. (2) The formation of LTP, which is inhibited by the bindings of MK-801 to NMDARs in this experiment, also has some unclear connections to the resilience to depression. In addition, since this is related to learning and cognition functions, other non-spatial cognition tests could be conducted to examine changes in different aspects of cognition levels. (3) Furthermore, structural and functional plasticity, which are also included in the scope of neuroplasticity, could also be explored by similar processes. Similarly, reasons for the difference in vulnerability to depression between different sexes could be explored by comparing hormones and other molecule secretion, as it is shown in research that the disease prevalence in females is twice the prevalence in males [13]. (4) Brain regions other than the hippocampus require more adequate study [31], including their functions and impacts on major depression, which might, in turn, promote the understanding of the hippocampus-pituitary-adrenal (HPA) axis. (5) Aside from researching the mechanisms of depression, other treatments to increase neuroplasticity could be a possible direction in the future.

5. Conclusion

According to analysis of previous research including animal experiments, clinical research, and meta-analysis, major depression is strongly related to neuroplasticity, including synaptic plasticity. This research intends to examine the effects of changing synaptic plasticity in adult hippocampal neurons on resilience to depression and anxiety in the ASCL1 mouse model and hypothesizes that reducing synaptic plasticity could reduce resilience and increase susceptibility to major depressive disorder. ASCL1 mouse model is used to edit genes controlling the formation of LTP by NMDAR so that in the experiments, the time of reducing neuroplasticity could be controlled. Inferred from the conclusions of other related studies, reducing neuroplasticity decreases the resilience to depression. Relative studies are discussed and analyzed, giving deeper insights into understanding molecular neural circuits and mechanisms of depression and providing support for novel ideas of depression treatment.

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