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Application of the Chronic Unpredictable Mild Stress Mouse Model for the Establishment of Depressive Drug Screening Platform

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Abstract

Depression is a common illness worldwide. More than 264 million people are affected. This disease is different from usual mood fluctuations and short-lived emotional responses. Especially when long-lasting and with moderate or severe intensity, depression may become a serious health condition. Seriously, this disease can lead patients to suicide. Many people suffer from depression, but have not been diagnosed or treated correctly. Although many depressive drugs have been used to treat depression, side effects of these drugs were presented in these drug-administrated patients. Therefore, it is necessary to develop a set of drug screening platform for depression, which can screen the target drugs for animal experiments and subsequent human experiments. In this study, ICR mice were used to induce depression via the Chronic Unpredictable Mild Stress (CUMS) for 6 weeks. Level of depression were evaluated by using Tail Suspension Test (TST), Forced Swimming Test (FST), and Open Field Test (OFT). Additionally, the expression of peripheral blood serotonin was also detected after the experimental mice performed with CUMS. According to these results, CUMS-induced depressive mice were seen the significant increase of immobile with FST and TST and the significant decrease of traveled distance with OFT. Moreover, the expression of peripheral blood serotonin was significantly decrease compared to the normal control group and positive control group. According to these results, we have successfully established an animal platform for the depressive drug screening. We also hope it will be applied to verify the efficacy of the depressive drug targets and explore the relevant mechanisms that caused depression.

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Introduction

Use of Anti-Depressive Drugs (ADD) has become progressively more common in the last 20 years. Depression is treatable. According to its managing symptoms, three treatable components can be considered as (1) support therapy; (2) talking therapy; (3) drug therapy. At present, five classes of ADD are involved as (1) Selective Serotonin Reuptake Inhibitors (SSRIs); (2) Monoamine Oxidase Inhibitors (MAOIs); (3) TriCyclic Antidepressants (TCAs); (4) atypical antidepressants as Noradrenaline and Specific Serotoninergic Sntidepressants (NASSAs); (5) Selective serotonin and Norepinephrine Reuptake Inhibitors (SNRIs). Each class acts on a different neurotransmitter/in combination of neurotransmitters for anti-depression [1-5].

Depression is a complex disorder which involved many factors predispose person to the depressive risk. At present, several *in vivo* depressive models are established more than *in vitro* models. These *in vivo* models included (1) the learned helplessness model; (2) the unpredictable chronic mild stress model; (3) the early life stress model; (4) the olfactory bulbectomy model; (5) the social defeat model; (6) the glucocorticoid/corticosterone model; (7) the genetic model; (8) the transgenic model [6-10]. Each animal model has varying degrees of face, construct, and predictive validity for depression and contribute differently to our understanding of antidepressant processes.

In this study, we want to establish a depressive drug screening animal platform (DDSAP) applied with the chronic unpredictable mild stress (CUMS) to suit for the R&D of anti-depressive drugs in the pharmaco-industry. This DDSAP can quickly screen out the targets. In the future, this DDSAP can be also used to provide basic research on anti-depression and therapeutic strategy development.

Materials and methods

Drugs and reagents

Venlafaxine (Effexor) and 0.9% saline were ordered from the clinical Pharmacy. Serotonin ELISA Kit (Cat. No.: ab133053) was ordered from abcam Co. Phosphate buffered saline (No. P3813) was ordered from Sigma-Aldrich Co. Zoletil 50 was ordered from Vibac Laboratories (Carros, France).

Animal care and grouping

All animal experiments were complied with the ARRIVE guidelines and carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978). Animal care in this study were also carried out according to previously described the guidelines of the Institutional Animal Care and Utilization Committee (IACUC) of Agricultural Technology Research Institute (ATRI), Hsinchu, Taiwan (the approval No.: 107118C1). Six to eight-week-old male, specific pathogen free ICR mice (total of No. is 18) were obtained from BioLASCO Taiwan Co., Ltd., Taipei city, Taiwan. These experimental mice were kept on a 12-h light/dark cycle at 23-25°C and 70-75% humidity in the GLP Animal Laboratories, ATRI, Hsinchu, Taiwan. Normal laboratory diet (Panlab, Barcelona, Spain) and fresh water were supplied to mice continuously ad libitum. Eighteen ICR mice were randomly divided into three groups as follows (n = 6/group): the normal control group, the positive control group, and the negative control group. After 7 days adaption, the CUMS procedure was performed (Figure 1). The anti-depressive drug, venlafaxine was dissolved in normal saline, which was administrated to the positive control group (once per day between D21-D41 of depression induction). Additionally, the same volume (200 µL) of normal saline was administrated to the negative control group (once per day between D21-D41 of depression induction).

The chronic unpredictable mild stress

In this study, the chronic unpredictable mild stress (CUMS) was performed. After 1 week of normal feeding, the normal control group (n = 6) continued regular feeding (6 mice/cage) and 12 mice from the other two groups were individually placed in the single cage (one mouse/cage). In this study, the total of CUMS cycles is six. Seven days (D1-D7) of CUMS is an induced cycle such as D1: Closed light, remove food and water, and 20 h cold-wet cage (200 mL water/cage); D2: Change dry cage, restore food and water, 40 min of cage shaking (200 rpm), and continuous light for 24 h; D3: Closed light and remove water, and 24 h of tilted cage (45°); D4: Restore water and stop tilted cage (45°), change to 5 mice/cage, and remove food; D5: Restore food, 40 min of cage shaking (200 rpm), and 20 h hot-wet cage (200 mL water, 45°C/cage); D6: Change dry cage and remove water and 24 h of tilted cage (45°); D7: Stop tilted cage (45°) and continuous light for 20 h (Figure 1).

The tail suspension test

In this experiment, mice were individually suspended by upside down (about 30 cm above the box bottom) in a sound-isolated room. Each mouse was observed the active behavior a period of 10 min to avoid interference and the last 6 min were analyzed. Finally, analyze the mouse mobility and immobility behavior by Depression Suite TailSuspScan software (CleverSys Inc, USA).

The forced swimming test

In this experiment, the mouse was individually placed in a cylinder (45 cm height × 14 cm internal diameter) filled with freshwater (30 cm height, 25 ± 2°C). Each mouse was observed the behavior of swimming, floated motionlessly and escape in 10 min and the last 6 min was analyzed. After the forced swimming test the mouse was warmed. Finally, analyze the mouse mobility and immobility behavior by Depression Suite ForcedSwimScan software (CleverSys Inc, USA).

The open field test

In this experiment, the mouse was individually placed in the open field paradigm. In the beginning, the mouse was placed in the center of the equipment and allowed to freely explore for 15 min. Finally, analyze the walking distance of the mouse by TopScan Lite software (CleverSys Inc, USA).

Detection of the expression of peripheral blood serotonin

The levels of peripheral blood serotonin were determined by using serotonin ELISA kit (abcam; ab133053) according to the manufacturer's instructions. The absorbance values were observed at 405 nm. The results were expressed as nanograms per milliliter.

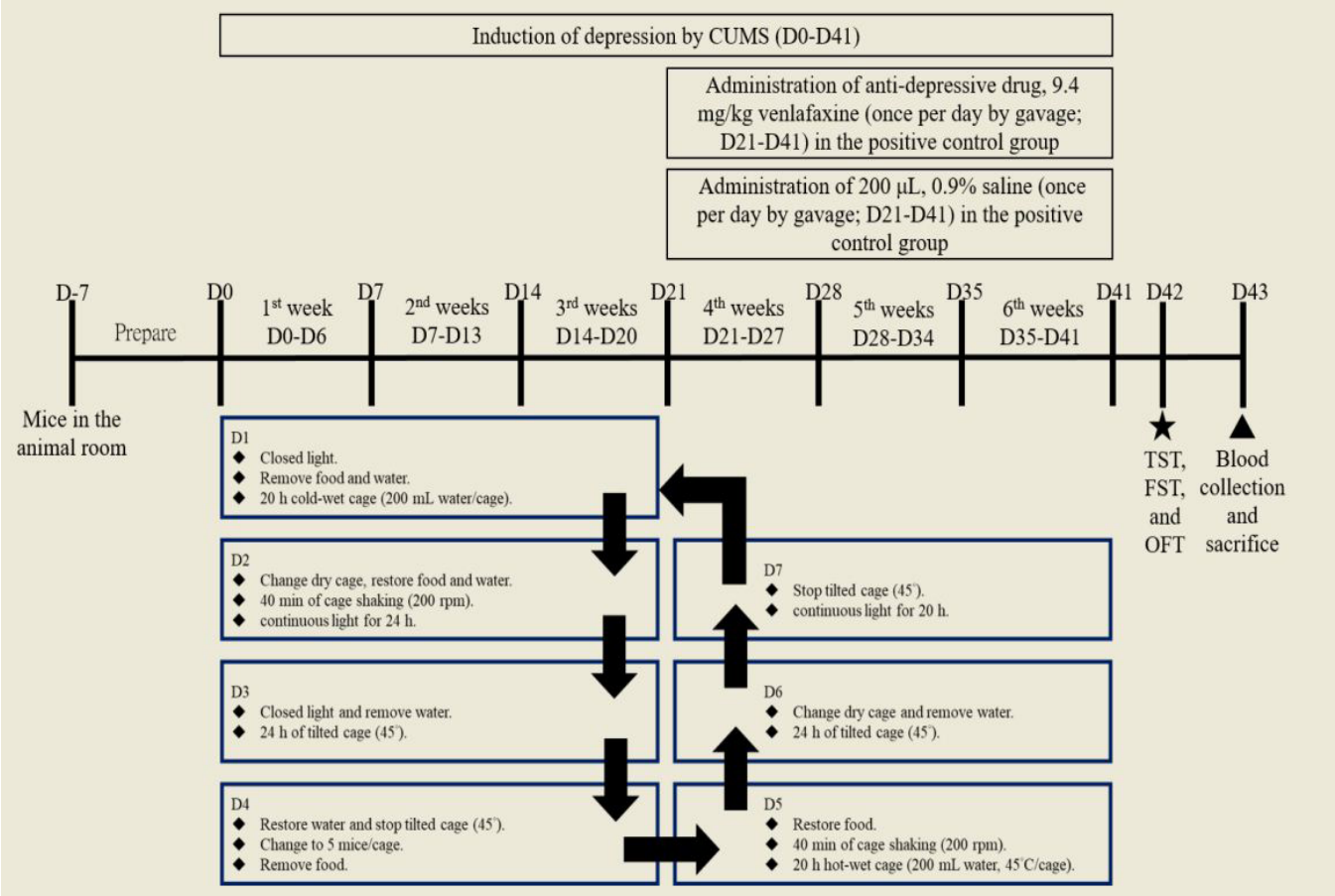

Figure 1: Experimental procedure and the chronic unpredictable mild stress. The tail suspension test (TST); the forced swimming test (FST); the open field test (OFT)

Statistical analysis

The results were expressed as mean ± SEM. All statistical comparisons were made with two-tailed tests. Statistical evaluation was performed using SPSS 10.0 (SPSS Institute). Differences between groups were considered statistically significant at $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

Results

The tail suspension test

It was found that the effects of TST on mice with/without CUMS. The immobile (sec) of mice under TST was significantly increase in the negative control group than in the positive control group and normal control group (Figure 2).

The forced swimming test

The effects of FST on mice with/without CUMS was shown that the immobile (sec) of mice under FST was significantly increase in the negative control group than in the positive control group and normal control group. Additionally, the immobile (sec) of mice under FST was significantly increase in the positive control group than in the normal control group ($p < 0.05$) (Figure 3).

The open field test

It was found that the effects of OFT on mice with/without CUMS. These data were shown that the locomotor activity (distance traveled) is lowest in the negative control group and normal control group. However, there was no significant different between three groups ($p > 0.05$) (Figure 4).

The expression of peripheral blood serotonin

It was found that the effects of the expression of peripheral blood serotonin in mice with/without CUMS. The expression of peripheral blood serotonin of mice under CUMS was significantly decrease in the negative control group than in the positive control group and normal control group (Figure 5).

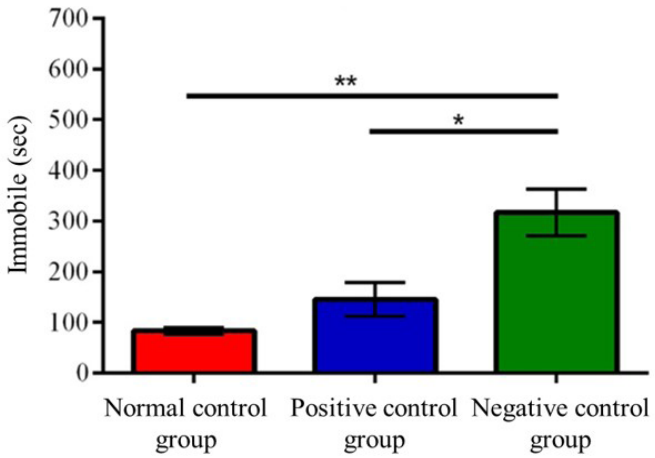

Figure 2: Effects of tail suspension test (TST) on mice with/without chronic unpredictable mild stress (CUMS). Data were expressed as mean ± SEM (n = 6/group). $^{*}p < 0.05$; $^{**}p < 0.01$

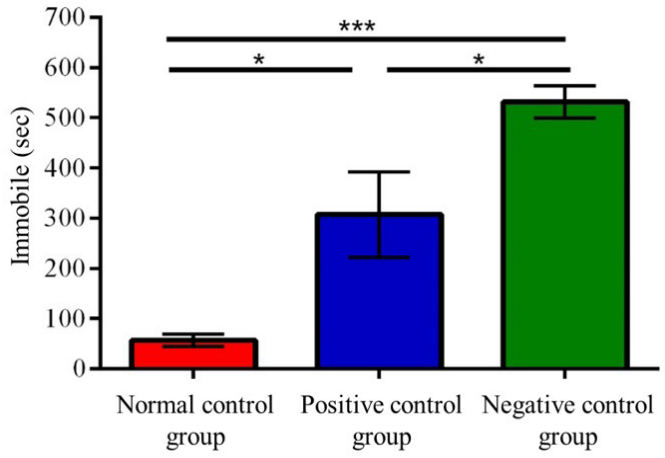

Figure 3: Effects of forced swimming test (FST) on mice with/ without chronic unpredictable mild stress (CUMS). Data were expressed as mean ± SEM (n = 6/group). $^{*}p < 0.05$; $^{***}p < 0.001$

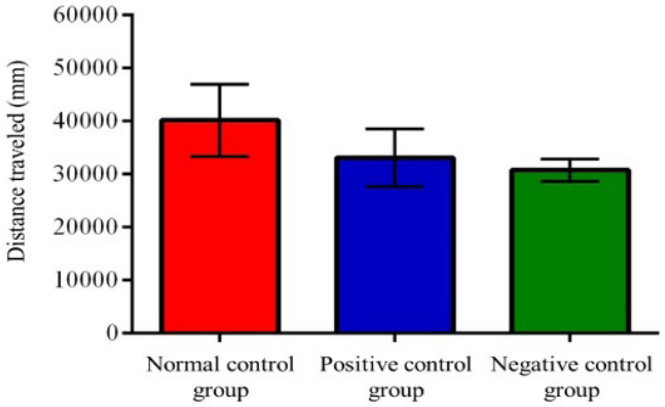

Figure 4: Effects of the open field test (OFT) on mice with/ without chronic unpredictable mild stress (CUMS). Data were expressed as mean ± SEM (n = 6/group)

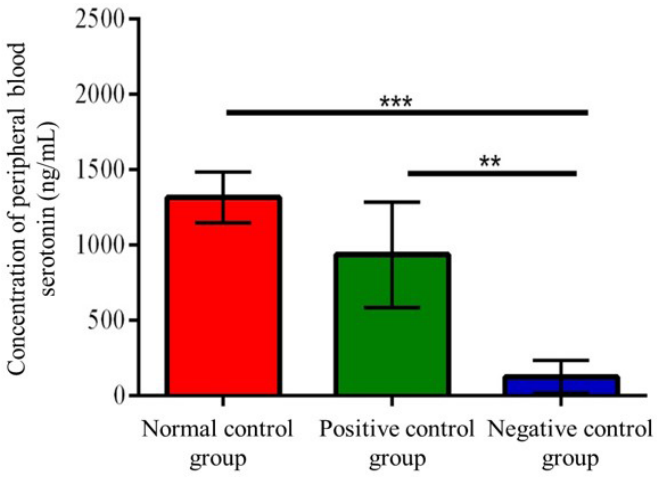

Figure 5: Effects of peripheral blood serotonin with/ without chronic unpredictable mild stress (CUMS). Data were expressed as mean ± SEM (n = 6/group). $^{**}p < 0.01$; $^{***}p < 0.001$

Discussion

Importantly, the current understanding about the pathogenesis in major depression has majorly come from animal models. However, due to the unique and complex features of human depression, the generation of valid and insightful depression models has been less straightforward [11-13]. According to our design for the depression induction via CUMS, twelve ICR mice were successfully induced depression. In this study, the depression model in ICR mice was 100% established, successfully. This animal model with depression will be provide to the researcher for the depression studies.

At present, the reports of World Health Organization (WHO) were presented that depression is the main cause of disability worldwide. All anti-depressive drug are divided five classes such as MAOIs; SSRIs; TCAs; SNRIs; NASSAs. SSRIs are the most commonly prescribed anti-depressive drugs that mainly affect serotonin expression. MAOIs decrease breaking down neurotransmitters as serotonin via inhibiting monoamine oxidase. SNRIs can raise the levels of serotonin and norepinephrine to stabilize mood. TCAs can help keep more serotonin and norepinephrine available into brain. NASSAs enhance adrenergic and serotonergic neurotransmission in the brain. The mechanism of NASSAs is blocking by antagonizing the α2-adrenergic autoreceptors and heteroreceptors and certain serotonin receptors such as 5-HT2A and 5-HT2C, 5-HT3, 5-HT6, and 5-HT7. Clinically, side effects of the treatment for major depressive disorder (also known as major depression, clinical depression, unipolar depression, or MDD) were found depends on the individual and the severity of the illness. Therefore, the research of anti-depressive drugs well be continued in order to R&D of novel anti-depressive drugs with higher efficacy and lower side effects [14,15,16,17].

There are many animal models of depression such as (1) Acute stress models: the forced swimming test (FST) and the tail suspension test (TST) are the most widely used tests of antidepressant action and are also used to infer “depression-like” behavior ; the learned helplessness model is via an uncontrollable and inescapable stress. The experimental animals will develop a state of “helplessness” and will either display increased escape latency or completely fail to escape. (2) Secondary or iatrogenic depression models: Overactive hypothalamic-pituitary-adrenal (HPA) axis models is via the increased production of hypothalamic corticotropin-releasing factor (CRF) and the reduced negative feedback at the level of centrally expressed glucocorticoid receptors; Depression with retinoic acid derivatives induction is via the retinoic acid derivatives as isotretinoin caused an increased risk for depression and suicide; Cytokines and immune system dysregulation models via therapeutic drugs administration to produce clinically significant depression as a side effect. (3) Chronic stress models: Chronic mild stress (CMS) models involved the application of varied intermittent physical stresses applied over a relatively prolonged time period; Psychosocial stress models display their greatest strength since they entirely rely on innate social behavior [18-22]. In this study, we applied a chronic unpredictable mild stress to successfully induced depression-like behavior in ICR mice. Additionally, TST, FST, and OFT were applied to evaluate the degree of depression in these mice. Finally, we collected the peripheral blood from these mice to detect the expression of serotonin. In this study, these results of TST, FST, OFT, and serotonin expression will be the evaluation indexes of depression. Therefore, we have successfully established the Depressive Drug Screening Animal Platform (DDSAP).

Conclusion

Depression is a common illness worldwide. Although many depressive drugs have been used to treat depression, adverse effects of these drugs were presented in these drug-administrated patients. Therefore, it is necessary to develop a set of drug screening animal platform for depression, which can screen the target drugs for the subsequent human experiments. According to these results in this study, we have successfully established an animal platform for the depressive drug screening. We also hope DDSAP will be applied to verify the efficacy of the depressive drug targets and explore the relevant mechanisms that caused depression.

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