

Mice in Aberrant Light/Dark Cycles: A model of Major Depressive Disorder

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Abstract

Major depressive disorder (MDD) is the most prevalent type of mental illness, and is characterized by the presence of such symptoms as depressive mood, diminished interest or pleasure, insomnia, fatigue and diminished ability to think or to concentrate. Patients with MDD are at high risk for suicide, and are among the most common cases of hospitalization in advanced countries. MDD is a complex disease, in which multiple genetic factors are involved in the disease predisposition, and environmental factors cause the onset. Elaborate studies have been conducted to uncover the pathogenesis of MDD. However, lack of knowledge on the physiology and molecular basis of human depression have prevented the understanding of this disease. Establishing animal model of MDD has been highly challenging because of the difficulty to define the common endophenotypes in mice and humans that underlie the depression in humans. We have been studying the

effects of aberrant light/dark cycles on the behavioral phenotypes of laboratory mice. Laboratory mice maintained under normal light/dark cycles show a daily rhythm of activity that is precisely synchronized to the environmental light/dark cycles. When maintained in aberrant light/dark cycles, they show a lengthened rhythm of activity that is governed by the intrinsic circadian timing system, and they lose the ability to adjust to the environmental light/dark cycles. These mice showed an impaired saccharine preference, which is a phenotype associated with anhedonia, one of the diagnostic symptoms of MDD. Mouse under aberrant light/dark cycles will serve as a useful model of MDD and will contribute to the understanding and treatments of MDD.

1 Introduction

Major depressive disorder (MDD) is the most common form of the mood disorder. It is estimated that over 340 million people are af-

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ected by MDD, and nearly 10 % of every human populations suffer from MDD in the lifetime^[1]. Patients with MDD are at high risk of suicide, and cares of MDD patients are heavy burden for their families as well as for the society. According to the “Diagnostic and Statistical Manual of Mental Disorders” by the American psychiatric association (DSM-IV), MDD is classified under the category of depressive disorder. *Table 1* shows the position of MDD in the taxonomic hierarchy of mood disorders^[2]. *Table 2* summarizes the diagnostic criteria for MDD. Patients with depressed mood and/or loss of interest or pleasure for at least 2 weeks, and those with at least five of the nine symptoms listed in *Table 2* are diagnosis as MDD^[2].

2. Pathophysiology of MDD

Patients with mood disorders including MDD have been treated with various types of anti-depressants such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants for nearly 50 years. Current hypothesis of the pathophysiology of MDD is based on the understanding of the possible effects of these antidepressants on the neurotransmitters such as serotonin, noradrenaline and dopamine in the synaptic gap of nerve terminal (*Fig. 1*).

MAOIs such as iproniazid have been known

to inhibit the catabolic process of neurotransmitters in the presynaptic neuron, and were thereby assumed to contribute to the elevated concentrations of neurotransmitters in the synaptic gap^[3, 4]. On the other hand, tricyclic antidepressants such as imipramine were shown to inhibit the function of monoamine transporters which are responsible for uptake of neurotransmitters in the synaptic gap, and have thereby been assumed to contribute to the maintenance of neurotransmitters in the synaptic gap^[5]. Based on these understandings, it was proposed that decreased concentration of neurotransmitters in the synaptic gap of nerve terminal is the major cause of the neuronal defect linked to MDD^[6]. This hypothesis is called the “Monoamine Hypothesis” and has been widely accepted. However recently, accumulating evidences suggested that this hypothesis alone is not adequate to explain the pathophysiology of the disease^[3]. Further studies are needed to understand the cause of MDD and to develop its effective treatments.

3. Pathogenesis of MDD

MDD is thought to be a complex disease, in which multiple genetic factors form the basis of the disease and non-genetic factors such as the experience of mental trauma or stress cause

Table 1. Category of Mood Disorders according to DSM-IV

| |
|--|
| Depressive Disorder |
| Major depressive disorder |
| Dysthymic disorder |
| Depressive disorder not otherwise specified |
| Bipolar Disorders |
| Bipolar I disorder |
| Bipolar II disorder |
| Cyclothymic disorder |
| Bipolar disorder not otherwise specified |
| Other Mood Disorders |
| Mood disorder due to a general medical condition |
| Substance induced mood disorder |
| Mood disorder not otherwise specified |

Table 2. Diagnostic criteria for MDD according to DSM IV

| |
|--|
| (1) depressed or irritable mood |
| (2) decreased interest or loss of pleasure |
| (3) weight gain or loss |
| (4) insomnia or hypersomnia |
| (5) psychomotor retardation or agitation |
| (6) fatigue or loss of energy |
| (7) feelings of worthlessness or inappropriate guilt |
| (8) diminished ability to think or concentrate |
| (9) recurrent thoughts of death and suicide |

Five or more of the 9 symptoms need to be present during the same 2-week period to be diagnosed as MDD. At least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

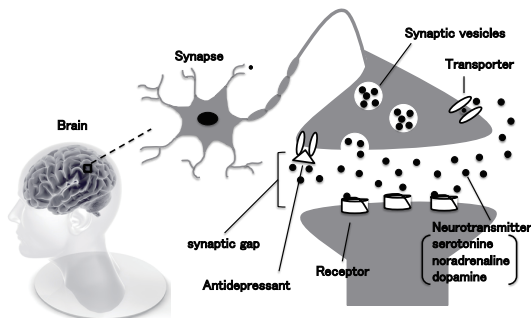


Fig. 1.

“Monoamine hypothesis” of mood disorders supposes that depression is caused by the deficiency of neurotransmitters, which include serotonin, norepinephrine and dopamine. Monoamine oxidase inhibitors (MOI) inhibits the catabolic process of neurotransmitters and contribute to the increased concentration of neurotransmitters. On the other hand, tricyclic antidepressants such as imipramine were known to inhibit the function of monoamine transporters which are responsible for uptake of neurotransmitters in the synaptic gap, and have thereby been assumed to contribute to the maintenance of neurotransmitters in the synaptic gap.

the onset. As to the genes involved in the susceptibility to mood disorders, polymorphism of the promoter region of serotonin-transporter gene was reported to associate with bipolar disorder, suicidal behavior and depression-related personality traits [7]. However, in spite of the international enormous efforts of genome-wide association studies using 1.2 million autosomal and X chromosome single-nucleotide polymorphisms (SNPs), no single locus was identified to be significantly linked to MDD [8] suggesting the extreme complexities of the genes involved in susceptibility to MDD.

4. Mouse models of MDD

For the research of this type of multifactorial disease, animal model is valuable. Establishment of mouse MDD model is highly challenging. As mice do not speak, it is impossible to communicate with mice to know their mood and physiological conditions. However, some behaviors and “endophenotypes” associated with the symptoms of MDD may be measured quantitatively in mice. For example, weight loss is easily measured in mice. Psychomotor retardation, fatigue or loss of energy is also measured as the decreased activity of locomotion of mice in their cages [9]. Anhedonia, which is the loss of the ability to feel the pleasing sense, is associated with MDD and underlies one of the

diagnostic symptoms of MDD. An endophenotype associated with anhedonia is measured in rodents by the saccharine preference test [10].

4.1 Mouse Stress Models

Various stressful conditions have been applied to mice to induce phenotypes associated with depression. In early studies, researchers used the stresses such as forced swimming [11] or tail suspension [12] to induce the depressed states of mice. Chronic social defeat stress [13] is a condition in which a mouse is repeatedly exposed to aggressive dominant animals. Aberrant light/dark cycle stress [14] is a type of mild-stress recently preferred by the researcher due to the awareness of the animal ethics. We are also studying this stress model.

4.2 Aberrant Light/Dark Cycle Stress

Figure 2 compares the actograms of mice placed under normal 12h:12h light-dark cycles (T24 control cycle) and aberrant 3.5h:3.5h light-dark cycles (T7 cycles). Daily activity of mouse in the cage is monitored by infrared sensor. In these actograms, each row shows the day in the experiment beginning from the top. Horizontal axis shows the time in the day. In the normal T24 cycles, mice showed normal rhythms of activity in which their intrinsic circadian rhythms are synchronized with environmental light/dark

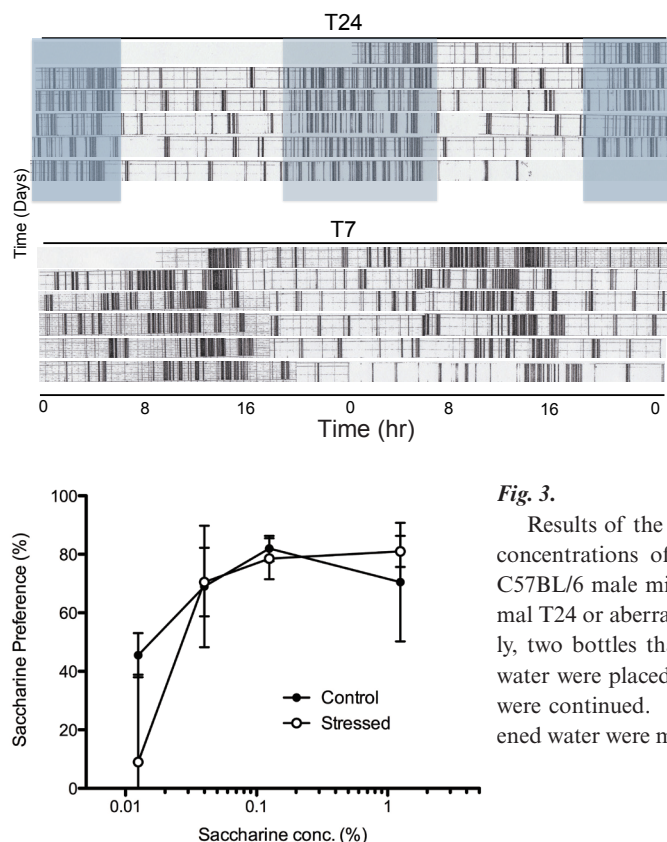


Fig. 2. General activity rhythms of mice under normal (T24) and aberrant (T7) light/dark cycles. Two-months old C57BL/6 male mice are individually housed in a cage where locomotion activity is monitored by infrared sensor. The light intensity during the light period was 800 lx.

Fig. 3.

Results of the saccharine preference tested by various concentrations of sodium saccharine. Two-months old C57BL/6 male mice are individually caged in either normal T24 or aberrant T7 cycle for two weeks. Subsequently, two bottles that supply normal water and sweetened water were placed in the cage, while the light/dark cycles were continued. Consumptions of the water and sweetened water were measured after 24 hrs.

cycles. On the other hand, as was first reported by LeGates and Hatter (2012)^[14], mice under T7 cycles lost their capacity to synchronize their circadian rhythms to environmental light/dark cycles as evidenced by lengthened rhythms governed only by the intrinsic circadian timing system. This results in the gradual shifts of their activity rhythms from the daily cycles.

Figure 3 shows the results of saccharine preference test of mice that were maintained in the aberrant T7 cycles. In this experiment, a mouse can choose either normal water or sweetened water freely to drink from each of the two bottles. Varied concentrations of saccharine solutions were tested. When sweetened waters with saccharine concentrations higher than 0.04% were used, mice both under control T24 and T7 cycles preferred sweetened water. However, when 0.0125% saccharine solution was

used, mice maintained under T7 cycles did not show preference, while mice under control T24 cycles still showed saccharine preference. This is the evidence that mice under T7 cycles had impaired sense for a pleasant signal, a phenotype associated with anhedonia.

Conclusion

Mice maintained under aberrant light/dark cycles (T7 cycles) showed one of the symptoms of the major depressive disorder (MDD), and will serve as a potential model to study the pathophysiology of MDD. We are currently studying the effects of T7 cycles on the rhythmic cycles of *Clock* gene transcriptions in the peripheral tissue. We have preliminary evidence that daily rhythmic cycles of *Clock* gene transcription is disrupted in the peripheral tissue of mice maintained under T7 cycles. Our finding

Table 3. Depression-associated phenotype and endophenotypes that can be modeled in mice*

| DSM-IV symptoms | Possible traits in mice | Appropriate test/analysis |
|--|--|--|
| Depressed or irritable mood | Cannot be modeled | |
| Decreased interest or loss of pleasure | Anhedonia | Sucrose preference test |
| Weight gain or loss | Can easily be measured | Abnormal loss or gain of weight |
| Insomnia or hypersomnia | Abnormal sleep architecture | Electroencephalogram recordings |
| Psychomotor retardation or agitation | Alterations in locomotion | Open field Treadmill running |
| Fatigue or loss of energy | Alterations in locomotion | Treadmill running, Nest building |
| Feelings of worthlessness or inappropriate guilt | Cannot be modeled | |
| Diminished ability to think or concentrate | Deficits in working and spatial memory | Morris water maze, Fear conditioning, Attentional set-shifting |
| Recurrent thoughts of death and suicide | Cannot be modeled | |

* Dedic N. *et al.*, (2011), *Psych. Disord. Trends & Development* (modified)

may be a clue to understand the cause-effect relationship in the pathophysiology of MDD.

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