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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fected by MDD, and nearly 10% of every hu-
man populations suffer from MDD in the life-
time [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 socie-
ty. According to the “Diagnostic and Statisti-
cal Manual of Mental Disorders” by the Ameri-
can psychiatric association (DSM-IV), MDD is 
classified under the category of depressive dis-
order. 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 symp-
toms 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 
antidepressants 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 neurotrans-
mitters in the presynaptic neuron, and were 
thereby assumed to contribute to the elevat-
ed concentrations of neurotransmitters in the 
synaptic gap [3, 4]. On the other hand, tricy-
clic 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 synap-
tic gap [5]. Based on these understandings, it was 
proposed that decreased concentration of neu-
rotransmitters in the synaptic gap of nerve ter-

tinal 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 ev-
edences suggested that this hypothesis alone is 
not adequate to explain the pathophysiology of 
the disease [3]. Further studies are needed to un-
derstand 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.
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. 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 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. 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.

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 or tail suspension to induce the depressed states of mice. Chronic social defeat stress is a condition in which a mouse is repeatedly exposed to aggressive dominant animals. Aberrant light/dark cycle stress 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.
cycles. On the other hand, as was first reported by LeGates and Hatter (2012)\cite{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...
may be a clue to understand the cause-effect relationship in the pathophysiology of MDD.

References


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<th>DSM-IV symptoms</th>
<th>Possible traits in mice</th>
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<td>Depressed or irritable mood</td>
<td>Cannot be modeled</td>
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<tr>
<td>Decreased interest or loss of pleasure</td>
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<td>Fatigue or loss of energy</td>
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<td>Treadmill running, Nest building</td>
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<td>Feelings of worthlessness or inappropriate guilt</td>
<td>Cannot be modeled</td>
<td></td>
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<tr>
<td>Diminished ability to think or concentrate</td>
<td>Deficits in working and spatial memory</td>
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<tr>
<td>Recurrent thoughts of death and suicide</td>
<td>Cannot be modeled</td>
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