INTRODUCTION

In our modern society, which is replete with various stressors, maintaining a calm state of mind is difficult. Puberty, as a time of transition from childhood to adulthood, in both mind and body, includes many stressors but provides little resistance to these stresses, making adolescents prone to mental disorders. Adolescents are susceptible to mental disorders such as affective disorders and schizophrenia [1].

One mood disorder is bipolar disorder (manic depressive disorder), where a person alternates between symptoms of depression (melancholy, loss of motivation, lack of self-confidence, loss of appetite, and sleeplessness) and symptoms of mania (feeling capable of everything, feeling cheerful despite not sleeping, talking non-stop all day, spending money recklessly, gambling, and other forms of elation). Schizophrenia involves symptoms such as hallucination and delusions (a positive symptom), desire to withdraw and not talk to people (negative symptoms), and...
cognitive impairment. In puberty, adolescents who encounter stresses such as social non-conformity, withdrawal, bullying/teasing, bereavement of a close relative, being raised by a stepmother, or addictive drug abuse are prone to development of these mood disorders and schizophrenia. In 2011, the Japanese Ministry of Health, Labour, and Welfare decided to add mental illness to its Four Major Diseases—cancer, stroke, heart disease, and diabetes—that receive special focus in the nation’s medical policies, for creation of "Five Major Diseases." [2].

Among these mental diseases, the lifetime prevalence of depression is high, at 10~15%, and it is expected that by 2020, depression will be ranked second for diseases that cause a loss of life expectancy. Depression is often present in the background of suicide, and, in 2009, the Japanese Ministry of Health, Labour, and Welfare estimated that the societal loss due to suicide and depression is ¥2.7 trillion (USD 27 billion) [3]. Therefore, addressing depression represents an urgent challenge. This article provides a brief overview of the causes of depression and introduces our recent results in an animal model of depression.

CAUSES OF DEPRESSION

Patients suffering from cancer [4, 5], chronic pain [6], diabetes, or other such chronic diseases [7] are increasingly likely to become depressed as disease severity increases. Obsessive, melancholic, and other such personality types have also been associated with susceptibility to depression [8]. Depression may also be caused by drugs that are used in treatment of physical diseases. These therapeutic drugs are diverse and include anti-hypertensive drugs, hormone drugs, anti-ulcer drugs, anti-tuberculosis drugs, anti-Parkinson's disease drugs, immunomodulatory drugs, and psychotropic drugs [9].

MONOAMINE HYPOTHESIS

*Rauwolfia serpentina* (common names include snakeroot) has hypotensive activities and sedative actions. It has been used in Indian folk medicine as a treatment for hypertension and mental illness. One side effect is that some patients present with depression-like symptoms. Reserpine, a component of *Rauwolfia serpentina*, was later found to deplete monoamines, such as serotonin, dopamine, and noradrenaline, which are neurotransmitters, thus causing depression-like symptoms [10, 11]. Patients suffering from incurable disease, tuberculosis often show depression. The anti-tuberculosis drug iproniazid, on the other hand, which is used for the incurable disease tuberculosis, exhibits activity that brightens the mood of patients. This effect is presumably derived from inhibition of the action of monoamine-degrading enzymes and the resultant increase in levels of monoamine [12]. In addition, the tricyclic antidepressant imipramine has also been found to inhibit transporters that capture monoamines from the synaptic cleft, thereby increasing the amount of monoamines in the synaptic cleft [13].

In light of these facts, the monoamine hypothesis posits that depression comprises dysfunction of nerves in which monoamines are neurotransmitters [14].

However, there is also a counterargument which claims that the onset of depression cannot be explained by the monoamine hypothesis: There is no relationship between depression symptoms and changes in the amount of monoamine metabolites in blood and urine. In addition, tricyclic antidepressants immediately cause an increase in levels of monoamines but yield no antidepressant effects unless administered for two weeks or longer [14]. In addition, not all patients who use reserpine develop depression.

RECEPTOR HYPOTHESIS

The following clinical data have given rise to the hypothesis that monoamine receptor hyperactivity is involved in the onset of depression.

Increased numbers of serotonin receptors in brains of suicide victims have been reported [15]. Repeated administration of antidepressant drugs results in a reduction in the number of serotonin receptors and noradrenaline β receptors. These data suggest that neurotransmission via monoamine receptors is enhanced in patients with depression. Antidepressants reduce these receptors, weaken neurotransmission, and moderate monoaminergic nervous system hyperactivity [16]. In contrast, patients with depression have an increased number of autoreceptors, 5-HT1A receptors, which suppress monoamine release. For this reason, it is possible that with a decrease in free monoamine, neurotransmission does not work properly. Antidepressants reduce the number of autoreceptors, increase the amount of free monoamine, and elevate monoaminergic nerve function [16].

In addition, long-term antidepressant-treatment has been found to reduce β-adrenergic sensitivity, while enhancing responses to serotoninergic and α-adrenergic stimulation, suggesting that modulation of receptor sensitivity may be a mechanism of action common to tricyclic antidepressants, atypical antidepressants [17, 18].

BDNF HYPOTHESIS

The brain-derived neurotrophic factor (BDNF) hypothesis of depression postulates that a loss of BDNF is directly involved in the pathophysiology of depression, and that its restoration may
Potential Factors in Depression Onset

underlie the therapeutic efficacy of antidepressant treatment: Decreased BDNF levels are associated with both human depression and a range of rodent models of the disorder. A number of clinically effective antidepressants increase BDNF levels [19, 20]. Further, direct BDNF infusions and genetic overexpression demonstrate antidepressant-like activity [21-23]. While this theory has received considerable experimental support, an increasing number of studies have generated evidence that is not only inconsistent, but also contradicts the hypothesis directly: a number of pharmacological studies have generated negative results and others have described findings that direct contradict the existence of a simple causal relationship between total brain BDNF levels and mood [24, 25]. In addition, the lack of spontaneous depressive phenotype in BDNF knockout mice, negative results from large-scale population studies, and contradictory conclusions regarding gene polymorphisms weaken the BDNF hypothesis of depression [26].

GENETIC FACTORS INVOLVED IN THE ONSET OF DEPRESSION

When an immediate family (parents, children, or siblings) includes a person with depression, the familial incidence is 1.5 to 3 times higher [27, 28]. Research with identical twins has also shown that when one twin develops depression, the probability that the other twin will also develop depression is 25 to 93% [29]. These reports imply that in some cases, genetic factors may play a role in the onset of depression. Studies examining postmortem brains of

Fig. 1. Method for assessment of mental disorder-like behaviors, and behavior of mice with melanoma-associated antigen D1 (MAGE-D1) gene defects. Depression-like behaviors in mice with the MAGE-D1 gene defect were evaluated by circadian and exploratory behavior measurement test, social behavior test, forced swimming test, and sucrose preference test. MAGE-D1 knockout mice showed reduction of circadian behavior, exploratory behavior, social behavior and sucrose consumption and extended duration of immobility, which were behavioral phenotypes of easy fatigability, psychomotor inhibition, decline of socialness, decline in craving, and decrease in motivation, respectively. However, MAGE-D1 knockout mice did not show abnormality in anxiety in the open field test and elevated plus maze test, abnormality in motor function in the rota-rod test and impairment of learning and memory in the water finding test, Y-maze test, novel object recognition test, and fear conditioning learning test.
patients with depression and using animal models of depression have implicated ATP-binding cassette sub-family B member 1 (ABCB1) [30], histone deacetylase (HDAC6) [31], a promoter region related to serotonin transporter gene transcription (5-TT LPR) [32, 33], neurtin [34], and disrupted in schizophrenia 1 (DISC1) [35] as candidate genes. Depression-like behavior can be observed in mice with a gene deficiency in melanoma-associated antigen D1 (MAGE-D1), a member of the family of melanoma-associated antigens, therefore, we have previously proposed that this molecule is also a candidate gene for the onset of depression [36].

**MAGE-D1 gene defect**

Mice with a gene deficiency for MAGE-D1 present with abnormal behavior similar to that observed in patients with depression, such as increased fatigue, restricted psychomotor abilities, diminished socialness, diminished motivation, and diminished cravings (Fig. 1). The release of serotonin is also decreased in the frontal cortex and hippocampus. In the absence of MAGE-D1, serotonin transporters are not ubiquitinated, which targets the transporter for degradation, and, thus, they are not broken down by proteasomes. As a result, there is an overabundance of transporter, and more uptake of serotonin in the synaptic cleft. Accordingly, the amount of free serotonin is reduced. The aforementioned abnormal behaviors were attenuated by sertraline, a serotonin transporter inhibitor. Imipramine also mitigated some of the abnormal behaviors [37] (Fig. 2).

Currently, depression is diagnosed by a psychiatrist based on patient symptoms. However, approximately 80% of new patients seek consultation from a doctor of internal medicine but do not receive a proper diagnosis. If we could provide biomarkers for diagnosis of depression similar to blood glucose for that of diabetes, even a general physician could make a diagnosis. Because patients with intractable depression have diminished amounts of ubiquitinated serotonin transporter in their lymphocytes, we have applied for a patent and propose the possibility that the amount of ubiquitinated serotonin transporter may be a biomarker for depression diagnoses [38].

![Diagram](https://example.com/diagram.png)

**Fig. 2.** Involvement of enhanced abnormal serotonin uptake due to a decrease in ubiquitination of serotonin transporter in depression-like behavior of MAGE-D1 knockout mice. Serotonin levels and release in brain were decreased in MAGE-D1 knockout mice. No decrease of mRNA expression of serotonin synthesis enzyme and no increase of mRNA of serotonin degradation enzyme and mRNA of transporter levels were observed in these mice. Of particular interest, decreased ubiquitination of serotonin transporter was observed in MAGE-D1 knockout mice. These results suggested that enhancement of abnormal serotonin uptake due to a decrease in degradation of serotonin transporter is involved in depression-like behavior of MAGE-D1 knockout mice. In addition, the face, construct, and predictive validities of these mice offer a model for depression. Development of new antidepressants that target the mechanism for regulation of MAGE-D1 and ubiquitinated serotonin transporter could be expected.
In a family in Scotland, five generations include multiple patients with psychiatric disorders, including schizophrenia and mood disorders. The gene Disrupted-in-schizophrenia (DISC1) was shorter in these patients compared to healthy controls. The protein product of the DISC1 gene was later found to be necessary for neural development. We extracted 14-day-old mouse embryos from the mothers’ womb and subjected them to a treatment that would silence the DISC1 gene in the prefrontal cortex using siRNA. The embryos were then returned to the womb to continue gestation and go through natural childbirth in order to investigate the question of whether they would exhibit abnormal behavior eight weeks later. These mice had delayed neural development, undeveloped neural network formation, and diminished function of the prefrontal cortex nerves, for which dopamine is a neurotransmitter. They also had higher responses to stimulant drugs, impairment of memory and learning in visual perception testing, and diminished attention and cognition in pre-pulse inhibition testing. Thus, when a specific gene is prevented from working, mice present with abnormal behavior.

**NEURODEVELOPMENTAL DISORDERS: THE TWO-HIT HYPOTHESIS**

The first “hit” (presented below, such as environmental and genetic factors), when it occurs during the embryonic or perinatal period, appears to cause neural development disorders and create circumstances that are favorable for the onset of psychiatric symptoms, such as affective disorders and schizophrenia.

The first “hit”:
- Environmental factors: Obstetric complications, undernourished birthing, winter birth, birth/growth in a large city, influenza infection during the midgestation period, or relationships with family members (high-risk children).
- Genetic factors (gene mutations): ABCB1, HDAC6, 5-HTT LPR, DISC1, neuritin, dysbindin, neuregulin-1, catechol-O-methyltransferase (COMT), and proline dehydrogenase (PRODH).

The theory is that children who receive the first “hit” are vulnerable to psychiatric disorders, and when they receive the following second “hit” during puberty they may develop affective disorders or schizophrenia.

The second “hit”:
- Environmental factors: Mental stress, social nonconformity, withdrawal and other forms of diminished communication, bullying, bereavement of a close relative, being raised by a stepmother, or addictive drug abuse.

According to epidemiological research, approximately 80% of occurrences of bipolar disorder involve a genetic factor. However, with depression, the genetic factors are 30–40%, and environmental factors play a more important role. Resilience and resistance to stress are common; therefore, although a certain extent of stress might be received during the embryonic or perinatal period, having a genetic predisposition to mental disorders does not imply that a mental disorder will develop.

Environmental enrichment (EE) — the addition of tubes, ladders, and running wheels in an enlarged home environment — enhances motor, sensory, and cognitive function. EE has beneficial physiological and behavioral effects in animal models of neurodegenerative diseases and psychiatric disorders. Of particular importance, EE can ameliorate emotional disturbances induced by psychological stress.

However, having a genetic predisposition to disorders does weaken resistance to stresses received during puberty, and without the ability to recover, a mental disorder is triggered. Knockout of the DISC1 gene resulted in abnormal behaviors observed after growth; therefore, mice were genetically engineered to have a surplus of abnormal DISC1 accumulation in the brain in order to study the question of whether behavior would also be abnormal. However, no substantial behavioral abnormalities were observed. To investigate the interaction between genetic factors and environmental factors, these mice were subjected to stresses in order to determine whether abnormal behaviors would be exhibited.

In one study, when wild-type mice free of genetic abnormalities (C57BL/6) mice) were separated from their mothers and the sibling and reared individually (high stress) at two to seven weeks of age, they exhibited abnormal behavior after reaching adulthood. However, in another study, no abnormal behavior was observed when wild-type mice were separated from the sibling and reared in isolation (low stress) at five to eight weeks of age, equivalent to puberty. The question of what happens when mice that possess an abnormal DISC1 gene (G) are subjected to this low stress (E) was investigated. When mice carrying the G were exposed to the E (combination of genetic factor and environmental stressor, which we designate GXE), despite the fact that the stress was weak, they exhibited abnormal behaviors, including diminished social behavior, depression-like behavior in forced swimming tests, diminished attention and cognitive function in pre-pulse inhibition tests, impairment of learning and memory function in visual perception tests, and increased responses to stimulant drugs (Fig. 3).

Thus, genetic factors and environmental factors are strongly involved in the onset of mental disorders.

The term genetic expression refers to the transcription of
information into RNA on the basis of genetic information in DNA, and the creation of a protein on the basis of the RNA information. In recent years, the existence of a mechanism ("epigenetics") whereby the expression of genetic function is regulated without changing the gene structure has been elucidated. Epigenetic gene function encompasses instances where DNA methylation or demethylation turns the switch on or off with no change in the DNA base sequence, as well as instances where DNA is wrapped around histones, proteins that make up the chromosome, and the switch is turned on or off when the histones are methylated, acetylated, or phosphorylated [49].

Recent breakthroughs in understanding of the mechanisms underlying epigenetic phenomena and their prevalence as contributors to development of human disease have led to a greatly enhanced interest in epigenetic research. The importance of epigenetics in maintaining normal development and biology is reflected by the observation that development of many diseases occurs when the wrong type of epigenetic marks are introduced or are added at the wrong time or in the wrong place. For instance, a clear causality role for DNA methylation in cancer is
suggested by hypermethylation of the same gene as an early event in tumorigenesis, as well as by tumor type-specific methylation landscape [50]. In multicellular organisms, the ability of epigenetic marks to persist during development and potentially be transmitted to offspring may be necessary for generation of a large range of different phenotypes raised from the same genotype [50]. Although high concordance rate of bipolar disorder in monozygotic (MZ) twins supports the contribution of genetic factors in bipolar disorder, importantly, it is not 100%. Since MZ twins have been regarded as having identical genomes, these facts suggest the importance of environmental or epigenetic factors in the onset of mental disorders. In fact, considerable epigenomic differences between MZ twins have been reported by several groups [51].

A study of the DISC1 abnormal gene X isolated rearing stress (GXE) described above showed that gene expression of enzymes that synthesize dopamine was epigenetically suppressed via DNA methylation [47]. Dopamine is a type of neurotransmitter in the frontal cortex; lowering the amount of dopamine compromises neurotransmission, thereby triggering behavioral disorders. After isolated rearing, even when these mice were returned to group rearing for three months, they maintained decreased gene function. This is dependent on glucocorticoids (GC) that are secreted in excess because of stress, and administration of a GC receptor antagonist led to full recovery from neurological and behavioral disorders [47] (Fig. 3).

It is becoming increasingly clear that gene function is subject to epigenetic impact by the environment of rearing, stress, or drugs after birth. Accordingly, as with identical twins, despite being born with identical gene structures, an abnormal gene may or may not work depending on environmental differences after birth. It is possible that these differences determine whether or not a mental disorder will occur.

CONCLUSION

There is much gloomy news, including parental neglect or abuse, bullying/teasing by friends, or overworking of employees in sweatshops. Such environments are truly disadvantaged. Therefore, there have been many patients with depression in recent years, and the number of suicide victims has hovered at approximately 30,000 people per year in Japan. However, it appears that even with a genetic predisposition to mental illness during birth, resistance to mental illness is possible. Resilience is heightened because of a favorable nurturing environment after birth or perhaps due to exercise. People should create enriched environments where they help and support each other, exercise actively, and gain resistance to stress.

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