Challenging bipolar disorder

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Bipolar disorder (manic depression) is a brain disease in which the patient periodically experiences elevated and depressive mood states. It affects about one out of every 100 people. Patients with bipolar disorder often suffer multiple relapses. Some spend almost half of their lives in the depressive state, and a large number commit suicide. Conventional preventive drugs for the disorder, such as lithium, produce strong side effects, and are not completely effective. The mechanism causing bipolar disorder is not yet understood. Tadafumi Kato, Head of the Laboratory for Molecular Dynamics and Mental Disorders at the RIKEN Brain Science Institute, has been progressing research into bipolar disorder, and proposes that it is related to dysfunction in the mitochondria—the energy production centers of cells. In spring this year, Kato's group successfully clarified that a mouse manipulated to develop mitochondrial dysfunction, in the brain only, exhibited abnormal behavior that was very similar to bipolar disorder. As an animal model for bipolar disorder, this mouse is expected to contribute significantly to the analysis of the mechanism triggering bipolar disorder and the development of therapeutic agents.

Mental conditions such as bipolar disorder are brain diseases

Cancer, heart disease, and cerebrovascular disease are the leading causes of death among the Japanese population. However, it is not possible to treat a patient with terminal cancer at the age of, say, 80 years in the same way as a patient who has been unable to work for many years, or is suicidal because they developed a mental disorder at a young age. Thus, an index called the Disability Adjusted Life Year (DALY) was introduced in Japan, so that the effects of age at death are taken into consideration in the mortality rate. Mental disorders such as depression, schizophrenia, and bipolar disorder account for a large proportion of DALYs, along with cancer and lifestyle-related diseases such as cerebral infarction (stroke) and diabetes.

Compared to cancer and lifestyle-related diseases, investigations into the causes of mental disorders, and the development of diagnostic methods and medical treatments, have been significantly delayed.

Kato, who is also a psychiatrist, indicates that social prejudice still remains against mental disorders. "People with functional abnormalities in the brain may suffer from mental disorders in the same way as people with heart problems develop heart disease," he says. "Thus, mental disorders are diseases of a part of the body, the brain, but they are generally considered 'mental problems', or something very special. I think elucidating the causes of mental disorders in detail can contribute to the development of better diagnostic methods and medical treatments, thus leading to the eradication of the prejudice that surrounds mental disorders."

Kato has been investigating the causes of bipolar disorder for many years. Bipolar disorder is a disease in which the patient periodically experiences elevated and depressive states (Fig. 1). According to statistics, about 15% of people contract major depression (unipolar disorder) once in their lifetime, but in many cases the patient does not experience a relapse. In contrast, 0.8% of people develop bipolar I disorder that involves a severe elevated state, and 2–3% of people develop bipolar disorder, including bipolar II, that involves a slightly elevated state. Bipolar

Figure 1: **Symptoms of bipolar disorder.**

Depressive state	Manic state
Feels depressed	Feels elevated
Uninterested and cannot enjoy anything	Has too many ideas to concentrate
Suffers from low self esteem	Full of confidence
Very slow to understand	Chats away for hours
Loses appetite and weight	Continues to be active without eating
Insomnia	Spends large amounts of money
Suicidal idea	Continues to be active all night long without sleeping

disorder requires long-term treatment and places a heavy burden on the lives of the patient and family due to the tendency for multiple relapses.

Bipolar disorder is considered to be caused by an unstable exchange of neurotransmitters such as serotonin, but the mechanism of how this develops is not yet clearly understood. It is certain that bipolar disorder has a profound genetic component. If an identical twin develops bipolar disorder, in 70–80% of cases the other twin also develops the disorder. However, bipolar disorder is not a disease that is simply inherited, because 90% of the children of bipolar patients do not develop the disorder.

"It is certain that more than one gene is related to the development of bipolar disorder, but whether the number is around ten or several dozen is still unclear," says Kato. It may be that everyone has up to five of the genes that lead to the development of bipolar disorder, and it is only when the number of genes reaches 10 that a person develops bipolar disorder, he suggests. Many people have the genes that lead to the development of bipolar disorder because the genes can also benefit us in some way. "For example, some people who have the genes that are considered related to bipolar disorder are said to have a good memory," Kato notes.

Mitochondrial hypothesis

At the end of the 1980s, as a practicing psychiatrist, Kato treated a patient with bipolar disorder, and this triggered his investigation into the causes of bipolar disorder. Reflecting on this turning point, Kato says: "One patient who had been feeling down, and wearing a painful expression on her face up to the previous day, suddenly became open and talkative. She seemed to have become a completely different person overnight. Thus it was clear that bipolar disorder has nothing to do with 'mental problems' and that something is changing in the brain. I felt that we would be able to elucidate such a specific phenomenon with the help of modern scientific technology."

Kato began to explore how material changes take place in the brain of a patient with bipolar disorder using the nuclear magnetic resonance (NMR) method. He successfully determined that one of the body's energy sources called creatine phosphate is reduced in the brain of the patient. From the peer-reviewed literature, Kato and colleagues found that reduced levels of creatine phosphate could also be observed in patients with mitochondrial disease that involves symptoms such as drooping eyelids. "Reminded of similar symptoms exhibited by patients with bipolar disorder, I began to think that mitochondrial dysfunction is related to bipolar disorder," explains Kato.

Mitochondria, which are minute organs in a cell, produce energy and control the calcium concentration that is related to signaling. Separate from the DNA in a cell nucleus, mitochondria have their own DNA composed of about 16,000 base pairs. A cell generally contains a large number of mitochondria, and mitochondrial disease develops when something is wrong with a part of its DNA. "It was also reported that some patients with mitochondrial disease exhibited symptoms that are characteristic of patients with bipolar disorder," Kato notes.

Subsequently, Kato went to the US to conduct research into molecular genetics. There, he investigated

the brains of patients who had died suffering from bipolar disorder, and discovered that some patients had a mitochondrial DNA abnormality in the brain. The abnormality he discovered is called a 'deletion', in which about 5,000 base pairs are grossly lost from among 16,000 base pairs, though this quantity is very small.

This finding led Kato to propose that mitochondrial dysfunction adversely controls the calcium concentration that is related to signaling, and eventually leads to the development of bipolar disorder.

Mouse model for bipolar disorder

Kato, who established the Laboratory for Molecular Dynamics of Mental Disorders in 2001, proceeded with research to verify his mitochondrial hypothesis (Fig. 2). In April 2006, Kato's group succeeded in producing a transgenic mouse with mitochondrial DNA deletion in the brain. By mutating synthetic enzyme genes in the nucleus that produce mitochondrial DNA.

This mouse exhibited abnormal behavior resembling insomnia and periodic changes in activity levels, which are symptoms commonly observed among patients with bipolar disorder.

The administration of lithium, used as a preventive drug for bipolar disorder, to this mouse improved its abnormal behavior (Fig. 3). In contrast, the administration of a tricyclic antidepressant, which is known to aggravate the symptoms of bipolar disorder, made the abnormal behavior more prominent. As such, Kato's group could have produced the first mouse model for bipolar disorder.

"Elucidating the sources of mental disorders should lead to not only the development of better diagnostic methods and medical treatments, but also the eradication of prejudice against those diseases."

Kato thinks that mitochondrial dysfunction is not the only cause of bipolar disorder, but that it will cause some phenomena common to bipolar disorder, such as changes in signaling in the neural circuits. The common phenomena, however, are not yet understood.

Using diabetes as an example, Kato explains: "Type I diabetes is characterized by the death of the insulin-producing beta cells in the pancreas, whereas Type II diabetes is due to reduced insulin sensitivity of cells. Of course, many reasons can be considered attributable to each type, but both types have the terminal pathway of development in common; a relatively small amount of insulin secretion and raised blood sugar levels. Thus, we test for diabetes by measuring blood sugar levels, and treat patients with diabetes by injecting insulin. These days, research has been carried out to probe the molecular mechanism of why the insulin-producing beta cells die, and why the insulin sensitivity is reduced. This is intended for thorough causal treatment. However, as far as bipolar disorder is concerned, we do not know the key factors that correspond to insulin, blood sugar levels, or the common terminal pathway of diabetes. Thus, compared with diabetes, research into bipolar disorder is still at the level it was several decades ago."

At present, diagnostic techniques for bipolar disorder are limited to what patients tell us, and how they behave. However, if the common terminal pathway is understood, an objective diagnostic method that serves to clearly distinguish bipolar disorder from other diseases can be developed. Thus investigation into Kato's mouse model could help elucidate the common terminal pathway. "It is very important to pin down where in the brain of this mouse the mitochondrial DNA abnormalities are accumulated, or what portion of the brain causes abnormal behavior," says Kato. It is known that mitochondrial DNA abnormalities are related to mitochondrial disease and various other diseases. However, the changes that are characteristic of bipolar disorder still elude scientists. "Investigation into the changes should help [researchers] find the changes in the neural circuits that are common to all patients with bipolar disorder," he continues.

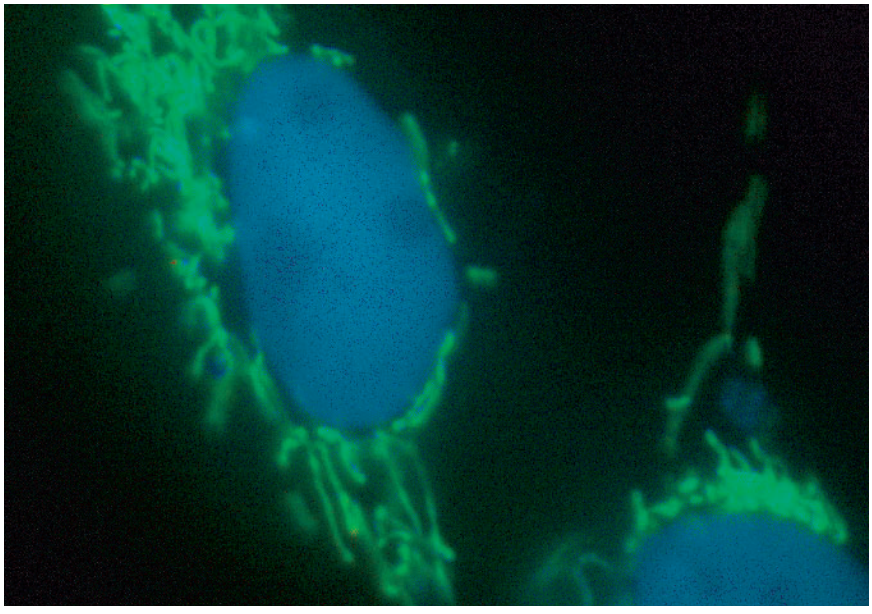

Figure 2: Cell nucleus and mitochondria
Many mitochondria (green) can be observed around the cell nucleus (blue). The Laboratory for Molecular Dynamics of Mental Disorders studied individual differences in the mitochondrial DNA sequences (polymorphism) and has found that the differences between individuals at base positions 8701 and 10398 are related to calcium concentration control. However, the relationship between the two positions and bipolar disorder has not yet been clarified.

This mouse is also expected to contribute significantly to drug discovery research. All current bipolar disorder drugs were used originally for the treatment of other diseases and then found to relieve the symptoms of bipolar disorder. However, as Kato notes, this is a symptomatic rather than a causal treatment. The development of bipolar disorder drugs has been delayed in part due to the lack of animal models with bipolar disorder. According to Kato, lithium worked well in his mouse model, but caused strong side effects. Kato thinks it is possible to develop highly effective drugs with reduced side effects by investigating how lithium improves the abnormal behavior of the mouse.

It is also known that the deletion of mitochondrial DNA causes changes in signaling mediated by intracellular calcium. Thus Kato and his colleagues want to find the molecules playing a key role in these signaling changes, and investigate whether or not drugs that affect those molecules can improve the abnormal behavior.

The mitochondrial hypothesis is beginning to attract attention even in the US, and a pharmaceutical company is conducting clinical trials in which therapeutic agents for mitochondrial disease are administered to patients with bipolar disorder. The results of a small-scale preliminary trial showed that the therapeutic agents were effective. Thus, large-scale trials are under consideration. If the large-scale trials are successful, drugs for bipolar disorder can be developed and commercialized on the basis of the mitochondrial hypothesis in the decade ahead.

Brain science that challenges categorization as 'mental problems'

In the future, advances in research into bipolar disorder may provide us with new treatments such that people with a natural tendency to develop bipolar disorder can receive advice about how to lead their life to prevent the condition from developing. For example, keeping regular sleeping hours makes a difference. Even if a person has already developed bipolar disorder, proper treatment can commence immediately as long as the condition can be diagnosed objectively. When someone is depressed, we can firstly prescribe antidepressant drugs, whereas we need to administer mood stabilizers if the depression is caused by bipolar disorder, Kato says. "I want to reach the day when we can conduct causal treatment immediately after the first development of the disorder …, thus preventing recurrence of the disease."

Recently, in addition to researching bipolar disorder, the Laboratory for Molecular Dynamics of Mental Disorders began researching issues related to child-abuse that have recently become a serious social problem. The group's first task is to investigate why some animals raise their young. "With mice, we are searching for the neural circuits that have something to do with raising young, and we are also studying how the neural circuits develop and why a neural circuit may fail to develop properly," explains Kato. "In the future, we want to expand our research to the study of humans."

Brain scientists are now accepting challenges that have conventionally been considered 'mental problems' thereby contributing to the improvement of our lives and society.

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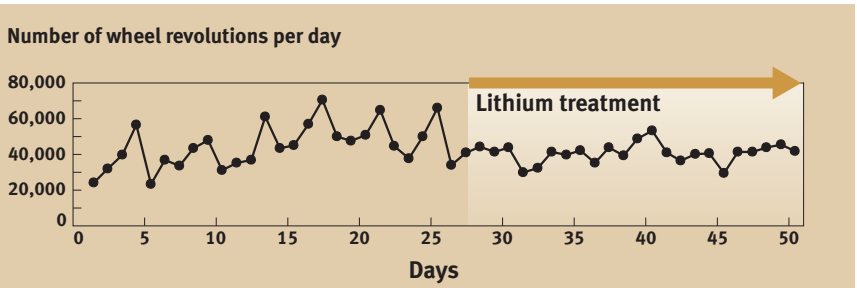
Figure 3: Effect of lithium administered to a mouse model for bipolar disorder.



The fluctuations similar to elevated and depressive states disappear after lithium administration.

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About the researcher

Tadafumi Kato was born in Tokyo in 1963. In 1988, he graduated from the Faculty of Medicine, the University of Tokyo. After serving for one year as a resident at the Department of Neuropsychiatry, the University of Tokyo Hospital, he returned to school and earned his PhD at Shiga University of Medical Science in 1995. From 1995 to 1996, he worked as an international visiting fellow in the US at the Department of Psychiatry, University of Iowa College of Medicine, and then returned to Japan to Shiga University of Medical Science in 1989, where he served as a research associate until 1997. From 1997 to 1999, he was a research associate at the Faculty of Medicine at the University of Tokyo, and then appointed as a lecturer at the same university in 1999. In 2000, Kato became head of the Laboratory for Molecular Dynamics of Mental Disorders at the RIKEN Brain Science Institute (BSI). Since 2004, he has been concurrently serving as the director of the Aging and Psychiatric Research Group at the BSI.