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Mitochondrial dysfunction contribution to bipolar disorder confirmed using model mice

Bipolar disorder, a mood disorder marked by alternating periods of manic and depressive episodes, affects approximately 1% of the global population. While neurotransmitter instability and genetic factors are implicated, the cause of bipolar disorder remains unknown. Drs. Takaoki Kasahara and Tadafumi Kato at RIKEN Brain Science Institute (RIKEN BSI) developed a mouse model that showed behavioral abnormalities which resemble those of bipolar disorder. Using this model system, they successfully demonstrated that mitochondrial dysfunction is involved in bipolar disorder.

Mood stabilizers can effectively treat this disorder, but they also have side effects. Precisely why they are effective, however, remains a mystery. Developing new drugs that directly act on mechanisms in bipolar disorder that lead to its pathology may mitigate those effects and better treat the disorder.

Mitochondrial dysfunction has been seen in patients with bipolar disorder. Moreover, patients with mitochondrial disorders sometimes display mood disorders. Therefore, the researchers began investigating mitochondrial dysfunction's role to bipolar disorder in 2000. They started by creating mouse strains with mitochondrial DNA mutations located specifically in neurons by introducing a gene for the enzyme that produces abnormal mitochondrial DNA. The mice with this genetic alternation would be active earlier and for longer periods than normal, nocturnal mice. While normal mice only moved in the dark (or at night), mutant mice would start moving before dark and be active when the lights were on (or during day), resembling patterns of sleep disturbance seen in patients. In addition, mutant mice showed changes in activity associated with estrous cycle that were not seen in normal mice. These activity changes

resembled the cyclical episodes of manic and depressive periods in bipolar patients. Lithium, a mood stabilizer, improved the abnormal restlessness seen in these animals, while a tricyclic antidepressant exacerbated their behavioral abnormalities. Together with colleagues from Nagoya University, they also showed that these mice had altered levels of serotonin and other neurotransmitters.

Hence, mitochondrial dysfunction appears to be related to bipolar disorder and this mouse model should prove useful in determining the causes of and, hopefully, the development of new mood stabilizers for bipolar disorder. The results will be published in *Molecular Psychiatry* (June 2006 issue).

1. Background

Bipolar disorder is a mental disorder with a serious social burden. Mood stabilizers, like lithium, valproate, carbamazepine, and lamotrigine, are effective treatments for this disorder, but they have side effects. Yet, the lack of a viable animal model for this disorder hampers efforts to developing novel, more effective mood stabilizers.

While there are several theories that attempt to explain the pathology of this disorder (including the monoaminergic hypothesis and inositol hypothesis) there is no definitive explanation.

Dr. Kato, the leader of this research team, first proposed the mitochondrial dysfunction hypothesis of bipolar disorder in 2000. His proposal is based on findings showing that patients with bipolar disorder had abnormal energy metabolism in the brain and abnormal mitochondrial DNA in the postmortem brains. In addition, mood disorders have been reported in patients with mitochondrial diseases.

Other groups around the world are also studying the possible role of mitochondrial dysfunction in bipolar disorder.

2. Methods and Results

(1) Verification of mitochondrial dysfunction hypothesis

The team produced genetically modified mice that accumulate abnormal mitochondrial DNA in the brain by introducing a mutation in the gene that encodes for an enzyme which synthesizes mitochondrial DNA, called *POLG*. *POLG* is a causative gene for chronic progressive external ophthalmoplegia, a mitochondrial disease that sometimes accompanies bipolar disorder or depression.

They then examined the spontaneous activity of these mice. A running wheel

was placed in the cage (Fig 1). The activity of female mice with the mutation would change periodically following the estrous cycle (Fig 2). Mice are nocturnal and typically run only when it is dark, however mutant mice, female and male, would be active even after the lights were turned on and move before the light were turned off. Of course a direct comparison with human sleep patterns is difficult, but this behavior does appear to resemble sleep disturbance in humans with bipolar disorder (Fig 3). Furthermore, the periodic activity change in mutant mice was improved when they were given lithium, a mood stabilizer (Fig 4).

A tricyclic antidepressant can cause manic switch and induce rapid cycling in patients with bipolar disorder. When given to our mice, behavioral abnormalities worsened and manic switch-like behavioral responses were observed in some of the mice (Fig 5). Long-term abnormal behaviors such as reduced activity with disturbed sleep-wave cycle, developed in mutant animals after several weeks.

These behavioral characteristics resemble the symptoms of bipolar disorder and suggest that mitochondrial dysfunction may cause bipolar disorder.

(2) The first likely animal model for bipolar disorder

To date, there is no established animal model for bipolar disorder, but the criteria for animal models of a mental disorder should have:

- 1) Face validity: Behavior of the model animal should resemble symptoms of human patients
- 2) Predictive validity: Drugs that are effective for the disease should also be effective for the model animal
- 3) Construct validity: Abnormalities seen in patients must be introduced into the model animal

While the model does satisfy these criteria, whether this mouse has bipolar disorder is difficult to say.

3. Future directions

Our findings demonstrate that the mitochondrial dysfunction may at least partly explain bipolar disorder, and strongly supports this team's hypothesis (Table). If successfully reproduced by other researchers, the mouse model may assist efforts to develop new

mood stabilizers to treat bipolar disorder.

The mice are available to any academic researcher through RIKEN Bio-Resource Center (<http://www.brc.riken.jp/lab/animal/en/>).

Table. Progression of mitochondrial dysfunction hypothesis of bipolar disorder
(* denotes research from Kato and colleagues.)

1992 Reduction of high energy phosphate in the brain detected by magnetic resonance spectroscopy in depressive patients (*)

1993 Lower brain pH in bipolar disorder (*)

1995 Possible role of maternal inheritance in bipolar disorder (McMahon, Johns Hopkins Univ.)

1996 Increased mitochondrial DNA deletion in the patients' blood (*)
Both of two mood stabilizers, lithium and valproate, increased bcl-2, a mitochondrial protein (Chen et al, NIH)

2000 Mitochondrial dysfunction hypothesis was proposed (*)

2001 April: Started the development of the POLG transgenic mice (*)

July: POLG was found to be a causative gene for a mitochondrial disease (CPEO), comorbid with depression (Van Goethem et al, Antwerp Univ.)

2003 A pedigree in which CPEO and bipolar disorder is linked, was reported (Siciliano et al, Pisa Univ.)

2004 March: Mitochondria-related genes were altered in the postmortem brains of bipolar disorder patients, supporting the mitochondrial dysfunction hypothesis (Konradi et al, Harvard Univ. Medical School)

May: Lactate accumulates in the brains of bipolar patients, supporting the mitochondrial dysfunction hypothesis (Dager et al, Washington

- Univ.)
- June: RepliGen finds that a drug developed for mitochondrial diseases, RG2417, is also effective for bipolar disorder
- December: Mitochondrial DNA 3644 mutation associated with bipolar disorder (*)
- 2005 January: Konradi et al finding was found to be affected by sample pH (*)
- March: Accumulation of mtDNA 3243 mutation in the brains of bipolar patients (*)
- 2006 April: This report. (Mice with mtDNA mutations show bipolar disorder-like behavioral abnormalities)
- May: A symposium titled "Mitochondrial-ER function in Bipolar Disorder" at 61st Annual Meeting of Biological Psychiatry at Tronto.
- June: A symposium titled "Mitochondrial Dysfunction in Psychiatric Disorders" in CINP2006 at Chicago

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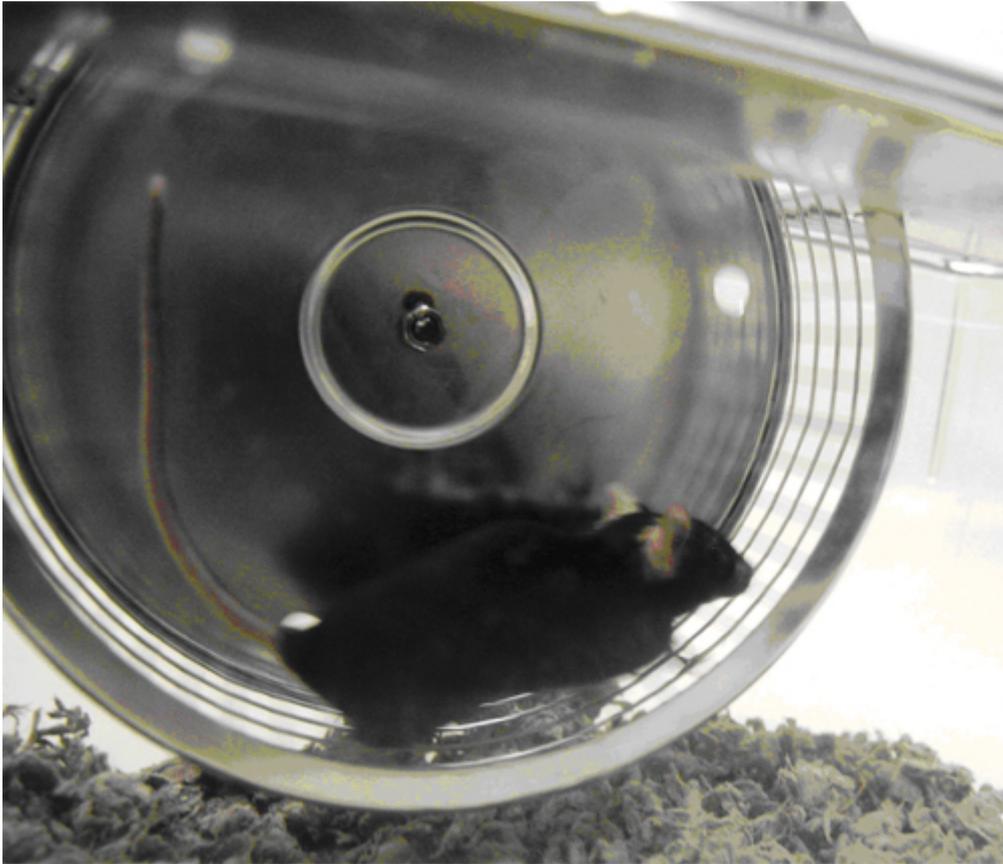


Fig 1. The mouse on running wheel

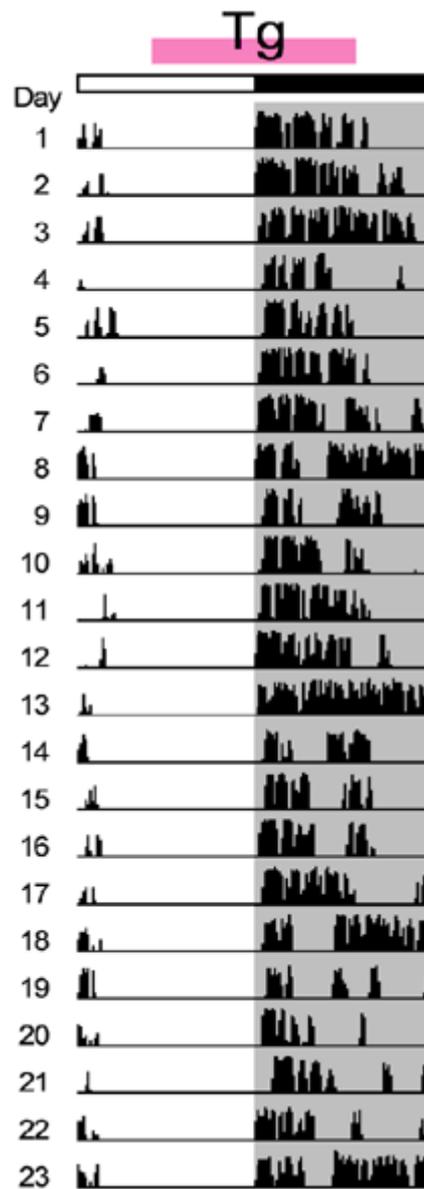
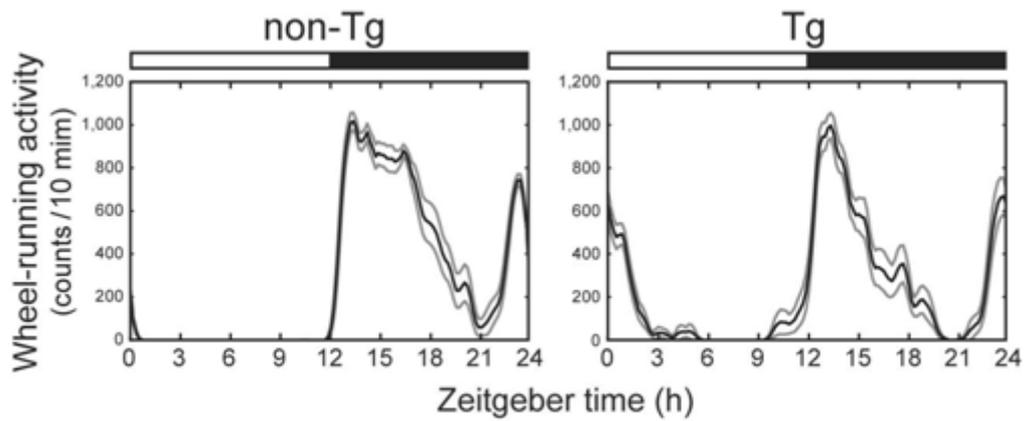


Fig 2. Behavioral pattern in a bipolar disorder model mouse (female)

Horizontal axis, time (24 hours); the vertical axis, wheel running activity
Wheel running activity increased every 5 days.



(Zeitgeber time 0 corresponds to 8:00 am.)

Fig 3. Altered diurnal activity rhythm in a bipolar model mouse (male)

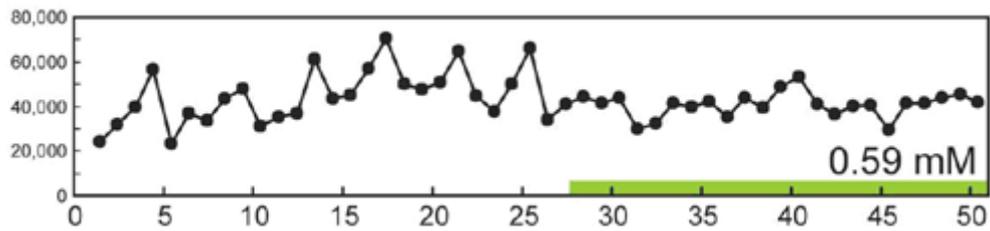


Fig 4. Effect of Lithium

Vertical axis, wheel running activity; horizontal axis, days.

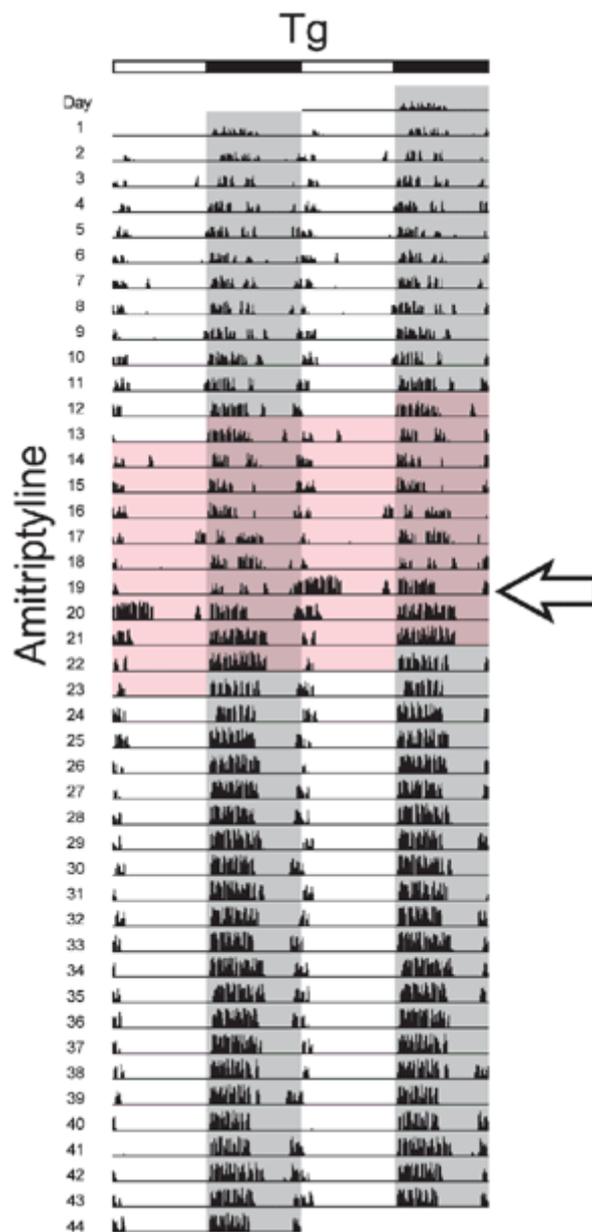


Fig 5. Manic switch like behavior induced by a tricyclic antidepressant in a bipolar model mouse (male)