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Neurobiological basis of bipolar disorder: Mitochondrial dysfunction hypothesis and beyond

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ABSTRACT

Bipolar disorder is one of two major psychotic disorders together with schizophrenia and causes severe psychosocial disturbance. Lack of adequate animal models hampers development of new mood stabilizers. We proposed a mitochondrial dysfunction hypothesis and have been studying the neurobiology of bipolar disorder based on this hypothesis. We showed that deletions of mitochondrial DNA (ΔmtDNA) play a pathophysiological role at least in some patients with bipolar disorder possibly by affecting intracellular calcium regulation. Mutant polymerase γ transgenic mice that accumulate ΔmtDNA in the brain showed recurrent spontaneous depression-like episodes which were prevented by a serotonin-selective reuptake inhibitor and worsened by lithium withdrawal. The animal model would be useful to develop new mood stabilizers.

1. Introduction

Bipolar disorder is a major mental disorder showing manic and depressive episodes, which frequently accompany psychotic symptoms (Goodwin and Jamison, 2007). Because genetic factors are known to contribute to this disorder based on twin studies among others (Kato, 2015), genetics-based animal models would be useful to understand its neurobiology. Because causative genes of bipolar disorder have not been identified yet, animal models of Mendelian diseases that frequently have comorbid bipolar disorder, such as Darier's disease (Nakamura et al., 2016), Wolfram disease (Kato et al., 2008), and mitochondrial disease (Kasahara et al., 2016), would be one strategy. In this review, we summarize our ongoing research project of neurobiological basis of bipolar disorder based on the mitochondrial dysfunction hypothesis.

2. Mitochondrial disease and bipolar disorder

In 1990's, we had studied the brain phosphorous metabolism in patients with bipolar disorder using phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) and found that phosphocreatine was decreased in the frontal lobe of patients with bipolar depression (Kato et al., 1992, 1994), decrease of phosphocreatine in the occipital cortex associated with photic stimulation was enhanced in a subgroup of patients (Murashita et al., 2000), intracellular pH in the frontal lobe (Kato et al., 1993, 1998a) and whole brain (Hamakawa et al., 2004) was decreased in the euthymic state. Decrease of phosphocreatine (Barbiroli et al., 1993) and enhanced response of phosphocreatine to photic stimulation (Kato et al., 1998b) was also reported in patients with mitochondrial diseases, and thus we focused on the possible role of mitochondrial dysfunction in bipolar disorder. Although the results of recent ^{31}P-MRS studies are not always consistent with each other, they also show some abnormalities of energy metabolism in bipolar disorder or improvement by treatment (Dudley et al., 2015, 2016; Jensen et al., 2008; Shi et al., 2012, 2015; Sikoglu et al., 2013; Stork and Renshaw, 2005; Weber et al., 2013).

After the proposal of mitochondrial dysfunction hypothesis of bipolar disorder, three groups performed structured interviews in patients with mitochondrial diseases (Fattal et al., 2007; Inczedy-Farkas et al., 2012; Mancuso et al., 2013) and reported that the prevalence of bipolar disorder in mitochondrial diseases is 16–21%, nearly 20 times higher than general population (Goodwin and Jamison, 2007). This suggests that having mitochondrial disease is a strong risk factor for bipolar disorder.

3. Evidence of mitochondrial DNA (mtDNA) deletion

Among mitochondrial diseases, chronic progressive ophthalmoplegia (CPEO) is an adult onset disease characterized by accumulation of partially deleted mitochondrial DNA (ΔmtDNA). In an autopsied case of CPEO with comorbid recurrent severe retarded depression, more ΔmtDNA was accumulated in the brain than in muscles, suggesting that the phenotype caused by accumulation of ΔmtDNA in the brain includes recurrent depression (Suomalainen et al., 1992). Stimulated by this report, we quantified the levels of ΔmtDNA in the

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postmortem brains of patients with bipolar disorder, and found that it was significantly increased (Kato et al., 1997). Although this finding was later replicated by another group (Sequeira et al., 2012), the finding is not always consistent across samples and brain regions (Mamdani et al., 2014). A report of a family of CPEO with ΔmtDNA, in which all affected members had bipolar disorder, also supported the role of ΔmtDNA in bipolar disorder (Mancuso et al., 2008).

Initially, we also focused on the association of bipolar disorder with mtDNA polymorphisms (Kato et al., 2001) and showed that mtDNA 10398 polymorphism, which was associated with bipolar disorder, is associated with mitochondrial calcium signaling (Kazuno et al., 2006). We also reported a genetic association of a complex I subunit gene with bipolar disorder (Washizuka et al., 2004). However, later it was revealed that genetic association studies in a modest number of samples can show false positive findings (Chanock et al., 2007), and recent genome wide association studies (GWAS) also suggested that the statistical threshold to observe genuine genetic association should be more conservative. To examine whether or not mtDNA polymorphisms are associated with bipolar disorder, tens of thousands of samples should be examined. Most recent GWAS including 9784 bipolar patients, in which mtDNA is not considered, did not show association with mitochondria related genes (Hou et al., 2016). Re-analysis of GWAS data did not show significant association of mtDNA polymorphisms with bipolar disorder (Sequeira et al., 2012). We should await the results of further large scale GWAS to conclude whether or not mtDNA polymorphisms or polymorphisms of other mitochondria-related genes are associated with bipolar disorder.

4. Mitochondrial dysfunction and calcium signaling

Based on the initial findings, we proposed mitochondrial dysfunction hypothesis of bipolar disorder in 2000 (Kato and Kato, 2000). In this hypothesis, we proposed that mtDNA mutations as well as common variations may confer a risk of bipolar disorder by affecting intracellular calcium signaling systems. In spite that calcium levels are maintained low in cells, higher concentration of calcium is accumulated in two organelles, mitochondria and endoplasmic reticulum (De Stefani et al., 2016), where calcium released from endoplasmic reticulum is taken up by mitochondria (Fig. 1). Elevation of intracellular calcium levels has been reported in blood cells (Warsh et al., 2004). Lithium, the most established mood stabilizer, acts on intracellular calcium signaling by inhibiting inositol monophosphatase and upregulating mitochondrial Bcl-2 on the mitochondrial outer membrane (Chen et al., 1999). GWAS showed association of bipolar disorder with *CACNA1C*, encoding α1C subunit of voltage gated calcium channel (Ferreira et al., 2008). Exome or whole genome sequencing also suggested a possible role of genes related to calcium signaling (Ament et al., 2015; Kataoka and Matoba et al., 2016), though they did not show mutations significantly associated with bipolar disorder at the genome wide significance level. These findings altogether suggest a role of intracellular calcium signaling in bipolar disorder. Genetic factors, such as rare transmitted mutations, de novo mutations, and polymorphisms, may contribute to dysfunctional intracellular calcium signaling in bipolar disorder, and mitochondria-related genes affecting mitochondrial calcium signaling would be one of these factors.

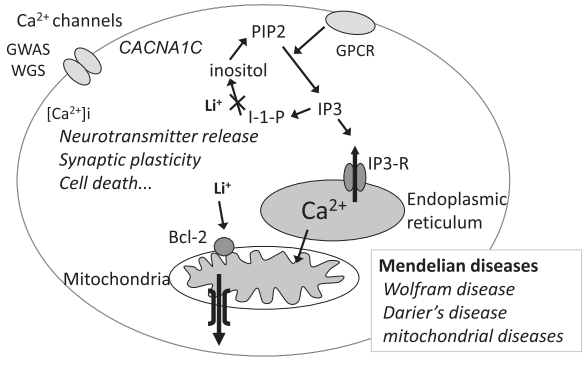

Fig. 1. Role of mitochondria in intracellular calcium signaling. Intracellular calcium level is maintained low, but two organelles, endoplasmic reticulum and mitochondria, have high levels of calcium. Mendelian diseases that accompany bipolar disorder are the diseases of these two organelles. GPCR, G protein coupled receptor; PIP2, Phosphatidylinositol 4,5-bisphosphate; I-1-P, inositol 1-phosphate; IP3. Inositol triphosphate; IP3-R, inositol triphosphate receptor; Bcl-2, B-cell lymphoma 2.

5. Multiple lines of evidence of mitochondrial dysfunction

Since then, numerous studies on mitochondrial dysfunction in bipolar disorder have been published. Downregulation of mitochondria-related genes (Konradi et al., 2004; Sun et al., 2006) and upregulation of a subset of mitochondria-related genes (Iwamoto et al., 2005) in postmortem brains, increase of lactate in the brain (Dager et al., 2004), decrease of complex I in postmortem brains (Andreazza et al., 2010), abnormal mitochondrial structure in cells of bipolar patients (Cataldo et al., 2010), and elevation of isocitrate in cerebrospinal fluid associated with impaired function of isocitrate dehydrogenase (Yoshimi et al., 2016). A recent study showed that neurons derived from induced pluripotent stem cells (iPSCs) of patients with bipolar disorder had hyperexcitability associated with upregulation of mitochondrial genes, increased mitochondrial membrane potential, and smaller size of mitochondria (Mertens et al., 2015). In addition to the landmark studies noted above, numerous studies have been reported in this area, and a PubMed search by "(mitochondria OR mitochondrial) and (bipolar disorder)" returns 325 papers (August 30/2016).

6. An animal model of mitochondrial DNA deletions in neurons

To develop an animal model of bipolar disorder based on mitochondrial dysfunction hypothesis, we focused on the accumulation of ΔmtDNA in the brain, which is observed in patients with bipolar disorder and CPEO. To this end, we introduced a point mutation, D181A, in polymerase γ (*Polg1*), the mtDNA polymerase, to remove exonuclease activity and generate ΔmtDNA (Kasahara et al., 2006). After we finished the generation of mice with neuron-specific mutant *Polg1*, it was discovered that *POLG1* is one of causative genes of CPEO with comorbid depression (Van Goethem et al., 2001). Although knock in mice of D257A mutation of *Polg1* (Kujoth et al., 2005; Trifunovic et al., 2004) were also reported, these mice show muscular impairment and are not suitable for behavioral analysis (Fuke et al., 2014). The neuron specific transgenic mice of D181A mutation of *Polg1* (m*Polg1* Tg mice) showed accumulation of ΔmtDNA specifically in the brain. They did not show gross abnormality in sensorimotor functions and learning and memory. The m*Polg1* Tg mice were found to have intracellular calcium signaling abnormality, shown by attenuation of G-protein-coupled receptor-mediated calcium increase in hippocampal neurons (Kubota et al., 2006).

7. Behavioral phenotypes of mutant *Polg1* transgenic mice

By an extensive behavioral analysis, we found that the m*Polg1* Tg mice show altered intra-day wheel running activity rhythm (Kasahara et al., 2006). This was improved by electroconvulsive stimulation (Kasahara et al., 2008). Furthermore, by observing the wheel running activity for one month, we found that female m*Polg1* Tg mice show fluctuation of wheel running activity associated with estrous cycle. This was flattened by lithium treatment.

We further extended the length of behavioral observation to more than half a year (Kasahara et al., 2016). The female mice showed recurrent spontaneous hypoactivity episodes, lasting approximately 2 weeks. This disappeared after ovariectomy, suggesting a role for female hormones. It is well known that prevalence of depression is twice as high in females than males, and women with bipolar disorder experience

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more depressive episodes than males (Diflorio and Jones, 2010). One of mechanisms proposed to explain the female bias is "limbic system hyperactivity" (Parker and Brotchie, 2010) where emotional dysregulation may be caused by high binding of gonadal steroids in the limbic system (Rainbow et al., 1982). The mechanism of female only depression-like episodes and their potential relationship between hormonal control of depression episodes will require future study.

There is no consensus how we can assess whether or not the observed hypoactivity episode is "depressive episode". Thus, we simply thought that Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (American Psychiatric Association, 2013) is the de-facto standard of depressive episodes. Of course, there are numerous differences in behavior between humans and mice. Furthermore, we cannot communicate with mice by language and thus subjective symptoms such as depressive mood, guilty feeling, and suicidal ideation, can never be assessed in mice. However, other items of DSM-5 criteria of major depression refer to more objective signs such as sleep and appetite. Thus, we assessed 6 out of 9 items of criteria A and criteria B of major depressive episode.

Among criteria A, diminished interest or pleasure was assessed by comparing wheel running activity which is hedonic activity, and home cage activity. The mice showed normal home cage activity but showed reduced wheel running activity, suggesting that the mice had anhedonia. During the episodes, the mice ate more food and showed weight gain. Electroencephalography (EEG) recording suggested that the mice show increased sleep during dark period (active phase) and decreased total sleep. By measuring the speed of wheel running, the mice in the episodes showed slower movement, suggesting psychomotor retardation. A treadmill test showed that the mice showed fatigability during the episode. Thus, 5 of the 9 items of A criteria of major depression were met. On the other hand, the other item, "diminished concentration" was assessed by five-choice serial reaction time test. The mice showed the same performance during the episodes. Thus, the mice in the episode did not have diminished concentration. This also indicates that the mice in the episode did not have consciousness disturbance. The criterion B refers to the impaired social and occupational life. For this item, we performed pup retrieval assay. Whereas majority of wild type mice and the m*Polg1* Tg mice in the euthymic state retrieved all three pups in the home cage, the m*Polg1* Tg mice in the episode retrieved significantly less number of pups. This finding suggests that the m*Polg1* Tg mice in the episode showed impaired social function. Collectively, we concluded that the episode observed in m*Polg1* Tg mice satisfies the DSM-5 criteria of major depressive episode and is equivalent to the depressive episode in humans (Kasahara et al., 2016).

We also found that a selective serotonin reuptake inhibitor, escitalopram, inhibited depressive episodes, and lithium withdrawal induced depressive episodes (Kasahara et al., 2016). We previously showed that administration of amitriptyline, a tricyclic antidepressant, induced manic like behavioral change (Kasahara et al., 2006). We also examined the levels of corticosterone, and found that excretion of corticosterone increased during the episode. By measuring the body temperature, the m*Polg1* Tg mice was found to show diminished intraday fluctuation of body temperature with higher average body temperature, which is similar to the findings in human depression (Tsujimoto et al., 1990).

8. The animal model meets three validity criteria

Collectively, we concluded that the m*Polg1* Tg mice satisfies three validity criteria of animal model; construct validity, that is similarities of the mechanisms between the model and the disease, face validity, commonalties between the behavioral features of the model and those of the human disorder, and predictive validity, the efficacy of human drugs for the phenotype of the model animal. Though the mice did not show any spontaneous manic or hypomanic episodes, tricyclic antidepressant-induced manic like behavioral changes and atypical features such as body weight gain/increase of appetite and hypersomnia suggest that the mice might have "bipolar spectrum".

9. Responsible brain region

Though we initially explained as if "mitochondrial dysfunction hypothesis" is specific to bipolar disorder, it is not at all true. Indeed, mitochondrial dysfunction is a risk factor not only for bipolar disorder but also for other medical diseases such as diabetes mellitus (Kadowaki et al., 1994) and Parkinson's disease (Orth and Schapira, 2002).

People tend to eat too much in the modern food-rich environment. Although there are several hormones to increase blood glucose level, only one, insulin, can decrease it. Thus, pancreatic islet is Achilles' heel of humans in the modern life. If a person has a latent mitochondrial dysfunction, the first symptom might become apparent at the vulnerable point, such as pancreatic islet. In the case of Parkinson's disease, production of dopamine causes oxidative stress, and thus dopamine neurons by its nature should have vulnerability. Associated with elongation of human life span, mitochondrial dysfunction of such vulnerable point might cause a disease in susceptible individuals.

If this speculation is true, which region of the brain is responsible for bipolar disorder associated with mitochondrial dysfunction? In the case of Parkinson's disease, accumulation of ΔmtDNA in substantia nigra was reported (Bender et al., 2006). Vice versa, we may be able to identify the brain region responsible for bipolar disorder, an equivalent of substantia nigra in Parkinson's disease, by searching for the brain region accumulating ΔmtDNA. Thus, we performed comprehensive search for brain region(s) accumulating ΔmtDNA in the brain of m*Polg1* Tg mice. We identified that emotion related neural circuit such as medial prefrontal cortex, nucleus accumbens and amygdala, accumulated relatively high amount of ΔmtDNA. However, highest level of ΔmtDNA was detected in paraventricular thalamic nucleus (PVT).

10. The possible role of paraventricular thalamic nucleus (PVT) in bipolar disorder

PVT receives input from hypothalamic CRH (corticotropin releasing hormone) neurons, suprachiasmatic nucleus, and dorsal raphe serotonergic neurons, and send output to anterior cingulate cortex, nucleus accumbens and amygdala (Hsu et al., 2014; Kirouac, 2015). Although PVT itself has not been a strong candidate region of mood disorders, it has connection to many candidate regions of mood disorders. The role of PVT in regulation of emotion is recently drawing attention, and its role in retrieval of fear memory (Do-Monte et al., 2015) and opiate withdrawal (Zhu et al., 2016) have been reported by optogenetic manipulation of specific circuits involving PVT.

To test whether there is causal relationship between PVT dysfunction and depressive episodes, we functionally knocked down PVT by expressing tetanus toxin that impairs neural transmission in PVT by Cre-loxP system (Kasahara et al., 2016). We found that the mice showed the hypoactivity episodes similar to mPolg Tg mice. This suggest that accumulation of mtDNA in PVT has a pathophysiological role in depression-like behavior in mPolg Tg mice.

However, it is still not known whether PVT dysfunction plays a role in human disease. Thus, we performed immunostaining of the thalamus sections of patients with CPEO and mood symptoms. We found that COX (cytochrome oxidase) negative cells, lacking in COX, a mtDNA-derived protein, are abundant in paraventricular thalamus in those patients.

Collectively, these findings suggest that dysfunction of PVT associated with mitochondrial dysfunction is causative for mood episodes at least in patients with mitochondrial disease. It should be verified whether some of patients with bipolar disorder or recurrent depression without mitochondrial diseases also have dysfunction of PVT.

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If PVT dysfunction, if any, can be detected by brain imaging, it would be useful for diagnosis. However, human PVT may be too small to be visible by current neuroimaging technologies.

11. Conclusion

Starting from magnetic resonance spectroscopic studies, subsequent genetic analysis, postmortem brain studies, and animal model studies altogether supported the role of mitochondrial dysfunction in bipolar disorder. However, because mitochondrial dysfunction is not specific to bipolar disorder, we should next focus on which neural circuit is damaged by mitochondrial dysfunction. Thus, the study of mitochondrial dysfunction of bipolar disorder should proceed to the next step. Our study has already indicated that paraventricular thalamic nucleus is a candidate brain region.

The genetics-based animal model generated in this study would be useful to develop new mood stabilizers. Previously, there has been no animal model to show spontaneous recurrent mood episodes, and thus there was no method to screen candidate mood stabilizer to show prophylactic effect for mood episodes. The *mPolg* Tg mouse is the first animal model showing spontaneous recurrent depressive episodes, which responded to existing anti-depression treatments. Thus, the model mice would be helpful to develop new mood stabilizers or antidepressants. We have already searched for candidate drug targets by gene expression analysis of the model mice and postmortem brains of patients with bipolar disorder (Kubota et al., 2010). Further studies to identify promising lead compounds and search for companion diagnostic methods using the model mice will be needed to improve clinical practice of bipolar disorder based on neurobiology of this disorder.

Disclosure

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