**Lecture 7: Wednesday, July 3**

**Neurobiology of bipolar disorder: From genes to neural circuits**

**Tadafumi Kato**

Laboratory for Molecular Dynamics of Mental Disorders, RIKEN CBS

**Abstract**

Bipolar disorder is characterized by recurrent (hypo)manic and depressive episodes and causes severe psychosocial impairment. Genetic factors are known to play a role in this disorder, and recent genome-wide association studies identified candidate genes. We also performed exome sequencing analysis in trio families and found that de novo mutations play a role in this disorder. A number of Mendelian diseases also show bipolar disorder phenotype, and the causative genes of these diseases will also be a clue to understand its neurobiological basis. These include Darier’s disease, Wolfram disease, and chronic external ophthalmoplegia (CPEO). Using animal models generated based on these genes, we are aiming at elucidating neural circuit basis of bipolar disorder. Neuron specific transgenic mice of mutant *Polg* (polymerase γ), a mitochondrial DNA (mtDNA) polymerase, showed recurrent spontaneous depression-like episodes fulfilling the clinical criteria of major depressive episode. The episodes were affected by lithium, a mood stabilizer, and a selective serotonin reuptake inhibitor (SSRI). A comprehensive anatomical search showed that the highest level of mtDNA mutations were accumulated in the paraventricular thalamic nucleus (PVT). Inhibition of neural transmission of PVT neurons by tetanus toxin expression in mice caused similar hypoactivity episodes, supporting the role of PVT in recurrent depressive episodes. The other mutant mice, neuron specific knock out mice of *Ant1* (adenine nucleotide translocator 1) showed a characteristic behavioral phenotype, diminished delay discounting of reward. An anatomical search showed accumulation of cytochrome c oxidase (Cox) deficient neurons in the dorsal raphe (DR). In the mutant mice, serotonergic turnover was enhanced in nucleus accumbens and DR serotonergic neurons showed hyperexcitability. There is strong innervation from DR to PVT, and thus we are focusing on the DR-PVT circuit as a candidate neural circuit of bipolar disorder.


**BIOGRAPHICAL SKETCH**  (May 8, 2019)

**Education:**

1995  Ph.D. (Shiga University of Medical Science)
1988  Graduated from Faculty of Medicine, University of Tokyo (M.D.)

**Research Experiences:**

2018 – Present: Team Leader, Laboratory for Molecular Dynamics of Mental Disorders, RIKEN Center for Brain Science
2018 – Present: Coordinate Professor, Department of Brain Functional Dynamics, Division of Functional Biology, Graduate School of Medicine, University of Tokyo
2001 –2018: Team Leader, Laboratory for Molecular Dynamics of Mental Disorders, RIKEN Brain Science Institute
1997 - 2000: Assistant Professor, Lecturer (1999–), Department of Neuropsychiatry, Faculty of Medicine, University of Tokyo
1989 - 1997, Assistant Professor, Department of Psychiatry, Shiga University of Medical Science
1995 - 1996: International Visiting Fellow, Department of Psychiatry, University of Iowa College of Medicine (The laboratory of Dr. Raymond R. Crowe)

**Honors and Awards:**

2019  Mogens Schou Award for Research, International Society for Bipolar Disorders
2017  Colvin Prize, Brain and Behavior Foundation
2014  Tsukahara Memorial Award, Brain Science Foundation
2008  NARSAD Independent Investigator’s Award
1998  CINP Rafaelson Fellowship Award
1995  Academic Prize of Japanese Society of Biological Psychiatry

**Editorship:**

*Editor in Chief*  Psychiatry and Clinical Neurosciences