Form 1-5-2

Japan-U.S. Brain Research Cooperation Program
Researchers Dispatched to the U.S. Program FY2017: Report

Field: Neurobiology of Disease

1. Researcher

Name: Ryota Shinohara
Title: Assistant Professor
Affiliation: Division of Pharmacology, Kobe University Graduate School of Medicine (Current title and affiliation: Postdoctoral Fellow, Department of Psychiatry, Yale University School of Medicine)

2. Research Title:
Identifying the molecular and neural circuit mechanisms of the action of rapid-acting antidepressants

3. U.S. Joint Researchers/Institutes
Please give the name, title and affiliation.

Ronald S. Duman, PhD
Professor of Psychiatry and Neuroscience, Yale University School of Medicine

4. Research Period, from/to (mm/dd/yyyy):

09/01/2017 – 03/15/2018

5. Abstract, Results, and Research Significance (300 Words):

Depression is a leading cause of disability throughout the world with more than 300 million of people suffering with major depression. A single, subanesthetic dose of ketamine, a non-competitive NMDA receptor antagonist, produces rapid and sustained antidepressant effects in patients with depression. Ketamine infusions into the mPFC or optogenetic activation of principal neurons in the mPFC are sufficient to produce rapid and long-lasting behavioral changes in rodent models, demonstrating the importance of mPFC in the antidepressant response to ketamine (e.g. Duman et al., Nature Medicine, 2016).

mPFC layer 5 principal neurons can be divided into at least two subtypes, referred to as Type A and B, based on morphological complexity, physiological properties, and projection targets. These subtypes can be targeted by expressing Cre recombinase (Cre) under the control of dopamine D1 (Type B), or D2 (Type A) receptor promotor. We recently found that optogenetic stimulation of Type B cells, but not Type A cells, in the mPFC produces rapid and sustained antidepressant and anxiolytic behavioral responses concomitantly with immediate early gene expression in brain regions implicated in emotional behaviors. However, circuit mechanisms underlying the antidepressant and anxiolytic responses of ketamine and optogenetic stimulation of Type B cells remain to be elucidated. In this study, we aimed to identify primary target regions of mPFC Type B cells in antidepressant and anxiolytic responses. We expressed channelrhodopsin-2 (ChR2) selectively in Type B cells of the mPFC and examined the effects of photostimulation of ChR2-expressing axon terminals in downstream target regions. Photostimulation at a frequency of 10 Hz for 60 minutes in respective brain regions was performed 24 hours before the forced swim test (FST) and novelty suppressed feeding test (NSFT). The results showed that projection-specific optogenetic stimulation of mPFC Type B cells is sufficient to produce antidepressant and anxiolytic responses. Experiments are currently being conducted to test whether the above circuit is necessary for the antidepressant and anxiolytic effects of ketamine.

6. Other (Research concerns, particular points of note):

*Please attach any reference materials as necessary.