The Singapore Bioimaging Consortium (SBIC)
presents a seminar

on

"Neuroligin-3 controls Excitatory Synaptic Transmission onto Hippocampal Parvalbumin Interneurons"

Speaker: **Dr Jai S Polepalli**
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Host : **Dr Han Weiping**
Date : **Friday, 28 August 2015**
Time : **11.00am – 12.00pm**
Venue : **SBIC Seminar Room**
11 Biopolis Way
Level 2, Helios Building, Singapore 138667
(Please enter via Level 1)

Abstract

Neuroligins (NLs) are a family of 4 postsynaptic proteins (NL1-4) that interact with presynaptic neurexins. This trans-synaptic interaction between neurexins and neuroligins has been implicated in the formation, maintenance and activity-dependent strengthening of synapses in various brain regions. Disruption of either the presynaptic neurexins or postsynaptic NLs has been implicated in autism spectrum disorders and schizophrenia. Mouse models carrying human NL autism point mutations have shown abnormal social interaction, learning and memory. The deficits in learning and memory in mice lacking NL1 and NL2 genes, as well as in mice engineered to carry the human mutations in NL3/4 have been correlated with synaptic abnormalities in either ionotropic glutamate or GABA receptors. However, the functional role of NLs at synapses, in particular NL3, requires further elucidation. Parvalbumin (PV) interneurons have been implicated in cognition, learning and memory, as well as in the pathophysiology of various psychiatric disorders including schizophrenia and autism spectrum disorders. However, little is known about the molecular regulation of synaptic transmission onto these cells. To study the putative role of NL3 at synapses onto interneurons, we made a conditional knockout mouse for NL3 ($NL3^{fl/fl}$), and crossed it to a mouse line expressing cre under the parvalbumin (PV-cre) promoter to generate the $NL3^{Pvcre-/-}$ mice. These mice showed reduced reversal learning as assayed by contextual fear extinction, while contextual fear conditioning was unaltered. This reduction in extinction learning was rescued by a region and cell type specific expression of NL3 in the hippocampal PV interneurons.

To identify the synaptic and circuit deficits underlying this behaviour, he made whole cell recordings from genetically identified PV cells in the hippocampal CA1 region from acute slices. In the $NL3^{Pvcre-/-}$ mice, a decrease in the paired pulse facilitation of excitatory inputs onto PV cells was observed suggesting an increase in release probability. This increase in release probability correlated with a specific lack of sensitivity of the EPSC amplitude and paired pulse ratio to agonists or antagonists to Group-III mGluRs, which control release at these synapses in wild type animals. This lack of Group-III mGluR mediated control of release at these synapses renders a low pass filter at these synapses, summating incoming excitatory inputs only at frequencies lower than 10 Hz.

About the Speaker

Over the past 10 years, Dr Jai S Polepalli's research has been focused on understanding the circuit, synaptic and molecular mechanisms underlying learning and memory in mammalian brains. After finishing his undergraduate studies in India with a major in Biophysics and Genetics, and then a Masters of Science at the University of Western Sydney, Dr Polepalli moved to the lab of Prof Pankaj Sah at the University of Queensland. His PhD work in Dr Pankaj Sah's lab addressed how amygdala dependent fear memories are inhibited during fear extinction. For his post-doctoral training, he moved to Prof Robert Malenka's lab at Stanford University. His lab has developed molecular biology tools to understand the mechanisms of plasticity and receptor trafficking specifically by knocking down and subsequently rescuing key synaptic proteins. He learned methods of virus (lenti-, adeno associated- and rabies virus) production that allow me to manipulate synaptic molecules in free behaving animals. Using these tools, he studied the mechanisms underlying AMPA receptor exocytosis during LTP. At the presynaptic terminal, the role of SNAREs and associated proteins in synaptic vesicle exocytosis has been well characterized. Hypothesizing a similar mechanism for AMPA receptor exocytosis at the postsynaptic membrane, he has shown that complexin, a crucial presynaptic protein is also present in the postsynaptic compartment. With specific knockdown of complexin in the postsynaptic terminals at CA3 to CA1 synapses in the hippocampus, he demonstrated that activity dependent insertion of AMPA receptors following LTP was compromised. However, the constitutive, activity independent basal recycling of AMPA receptors was unaffected. Dr Polepalli's current research is on Neuroligin-3 (NL3) - a cell adhesion molecule implicated in both autism and schizophrenia. Deletion of NL3 and various mutations in the gene have been identified in autism patients. Despite the deficits in memory and social cognition, no synaptic pathophysiology has yet been established for this molecule. Conditional NL3 loss-of-function mice have been generated and crossed with a mouse line expressing cre-recombinase in a specific population of interneurons (parvalbumin-cre), the specifics of which he will be talking about in this presentation.

--- Admission is free and all are welcome ---