Speaker 3: Anthony Grace, USA
Title: Imbalance between the amygdala and the hippocampus in down-modulating dopamine system responsivity in animal models of depression

Abstract
Dysregulation of the mesolimbic dopamine (DA) system has garnered increasing attention as a key component of major depressive disorder (MDD). It is thought to be particularly relevant to anhedonia, the reduced interest in pleasurable stimuli, which is considered to be a core symptom of MDD. We have shown that rats exposed to either Chronic Mild Stress (CMS) or Learned Helplessness, two stress-induced animal models of depression, resulted in stress-exposed animals showing a reduction in ventral tegmental area (VTA) DA neuron population activity, i.e. the number of DA neurons active and available to respond to environmentally salient rewarding stimuli. This suggests that in MDD, there is a reduced ability of the DA system to respond to rewarding stimuli, which could therefore represent the neural substrate of clinical anhedonia. Drawing from human neuroimaging research, we identified two candidate regions that were investigated in the present study. The infralimbic prefrontal cortex (ILPFC) is the rodent homologue of human Brodmann Area 25, a region that is established to be key to MDD pathophysiology and is under investigation as a target of deep brain stimulation for treatment resistant depression. We found that activation of the ILPFC or the habenula in normal rats potently suppressed VTA DA neuron population activity (p<0.05), albeit in different patterns. ILPFC activation primarily affected medial VTA DA neurons, whereas LHb activation inhibited more central and lateral VTA DA neurons. In rats that underwent CMS (which impacts primarily medial VTA DA neurons), only ILPFC inactivation restored VTA DA neuron population activity to normal levels, while LHb inactivation had no restorative effect on DA neuron population activity.

We have also examined the impact of the rapid acting antidepressant ketamine. In rats exposed to learned helplessness, the decrease in DA neuron activity was accompanied by long-term depression in the hippocampus-accumbens circuit that normally activates the dopamine system, suggesting that the lack of hippocampal drive fails to offset the ILPFC down-regulation. A single dose of ketamine restores hippocampal-accumbens drive, normalizes dopamine neuron firing, and reverses behavioral despair in the forced swim test. These data suggest that the ILPFC and LHb regulate different subpopulations of DA neurons within the mesolimbic system. This appears to have important relevance to understanding the DA system deficits observed in the CMS model of MDD, as this striking pattern of differential regulation appears to explain the unique restorative capacity of ILPFC inactivation in reversing the abnormal DA system hypoactivity observed in this widely used model. Furthermore, these data highlight the importance of the ILPFC as a critical node in depressive circuitry and a potential link between affective and motivational systems in the rodent brain.

Speaker 4: Alan Frazer, USA
Title: Brain Circuits Involved in the Antidepressant-Like Effects of Ketamine

Abstract
There is great interest in studying ketamine given the rapid and sustained behavioral improvement it causes in patients with treatment resistant depression. Much research has focused on the molecular mechanisms of action of ketamine and there is evidence that NMDA receptor antagonism is a necessary component of its activity. Further, such receptors on GABAergic interneurons in the hippocampus are likely to be a primary target for NMDA receptor antagonists. However, there is a lack of understanding with regard to the contribution of specific brain circuits involved in either its rapid and/or sustained antidepressant-like effects. We used different approaches to examine the role of the ventral hippocampus (vHipp)-medial prefrontal cortex (mPFC) pathway in ketamine’s sustained antidepressant-like response in rats, as measured by the use of the forced swim test (FST). These included (1) inactivating pharmacologically the vHipp to mPFC pathway with lidocaine; (2) determining if activation of the pathway using DREADDs would mimic the effect of ketamine in the FST; and (3) activating the pathway using optogenetics to see if this reproduced the effects of ketamine or inactivating it optogenetically to determine if this prevented the effect of ketamine. All three approaches gave results from which it could be concluded that the vHipp to mPFC pathway is both necessary and sufficient for ketamine’s antidepressant-like effect. Activation or inhibition of other pathways neither reproduced ketamine’s effect nor blocked it. Because of this, we hypothesized that another way to mimic the antidepressant-like effect of ketamine would be to block or reduce GABAergic transmission in the hippocampus. L-655,708 is a negative allosteric modulator of GABAA receptors and as such, would be expected to block GABAergic activity. In addition, it exhibits selectivity for the GABAA receptors localized primarily in the hippocampus. Systemic administration of this drug produced a sustained (7 days) antidepressant-like effect in the FST. To examine possible rewarding effects of ketamine that could contribute to its abuse potential, self-administration experiments were carried out. Ketamine was self-administered by rats. However, L-655,708 was not. It should be possible, then, to develop novel antidepressants that recapitulate the beneficial effects of ketamine without having abuse-liability.


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S2: Local inhibitory cell circuit: basic principles and disregulation in major mental illnesses

Chair: Etienne Sibille, Canada
Co-Chair: Seung-Hwan Lee, Republic of Korea

Speaker 1: Xiao-Jing Wang, China
Title: Computational modeling of GABAergic microcircuitry and cognitive deficits in schizophrenia

Abstract

I will first introduce the concept of “cognitive-type” cortical microcircuit exemplified by the prefrontal cortex. Since mental disorders primarily implicate cognitive-type brain systems such as the prefrontal cortex, rather than early sensory systems, progress in this area holds the promise for a new approach to psychiatric diagnosis and treatment.

I will review experimental and computational research on the generation of brain oscillations during awake, behaving conditions, which depend on various subtypes of interneurons and may serve as endophenotypes for determining abnormality of GABAergic systems associated with schizophrenia.

However, interneurons are important not only for synchronous rhythms, but also other important functions such as stimulus selectivity of neural populations, winner-take-all competition or normalization. In particular, working memory is a cardinal cognitive function impaired in mental disorders. Interestingly, computational circuit modeling of the prefrontal cortex suggested that working memory deficits in Schizophrenia are manifest not so much in terms of working memory storage and pyramidal cells in the prefrontal cortex of freely-moving rats using the juxtacellular recording and labelling technique. We investigated their contribution to network oscillations and a delayed cue-matching-to-place task involving working memory and decision making. The neuronal identity was determined with post-hoc histochemical analysis.

We observed two groups of pyramidal neurons which showed task-related firing patterns: neurons that represented the future goal and neurons that fired preferentially during distinct periods of the task. These firing patterns were modulated by the activity of distinct types of interneuron. For example, we observed that the firing of parvalbumin-expressing basket cells displayed strong modulation according to the task episode. Interestingly,