

decrease in sucrose preference. Moreover, selective NR2B antagonist did not produce rewarding effect. These findings suggest that DAPK1 interaction with NMDA receptor NR2B subunit acts as a critical component in the rapid antidepressant actions.

Inflammation can impact the glutamatergic system enhancing excitotoxicity and decreasing neuroplasticity. Using altered peptide ligand (APL) of myelin basic protein (MBP) to immunize rats, we found that myelin-derived altered peptides produced a prolonged antidepressant-like effect by reducing the immobility in the FST and preventing CUS-induced anhedonia. The behavioral outcome was accompanied by increased c-fos expression and restoration of p11 and BDNF levels in the mPFC and dentate gyrus (DG). Moreover, intra-mPFC infusion of lentiviral vectors containing short-hairpin RNA targeting p11 blunted the antidepressant-like effects. Our findings introduce a novel immune-based therapy for treatment of depression.

NMDA receptor trafficking and function are regulated by the receptor tyrosine kinase EphB2 through dynamic interacting NMDA receptors and Src-mediated tyrosine phosphorylation. We observed decrease in EphB2 level in the mPFC of mice that were susceptible to chronic social defeat stress. Activation of EphB2 receptors in the mPFC produced stress-resistant and antidepressant-like behavioral effects in susceptible mice, while EphB2 receptor knockdown increased the susceptibility to stress and induced depressive-like behaviors in a subthreshold chronic social defeat stress paradigm. These behavioral effects were associated with changes in the phosphorylation of cofilin and expression of some synaptic proteins and stress-induced spine remodeling in the mPFC. These results indicate that EphB2 is a critical regulator of stress vulnerability and might be a potential target for the treatment of depression.

Speaker 3: Maura Furey, USA

Title: Antidepressant Effects of Antimuscarinic

Action: Clinical Efficacy and Biomarkers of Response

Abstract

Background: Conventional antidepressant therapy has remained virtually unchanged for the past 50 years. The discovery of the rapid and potent antidepressant effects of the NMDA receptor antagonist ketamine has kindled interest in pursuing new and novel mechanisms for the treatment of depression. The cholinergic neurotransmitter system is implicated in affective illness, whereby a cholinergic agonist rapidly produces depressive symptoms in currently manic bipolar patients and worsens depressive symptoms in unipolar patients. Here studies evaluating the antidepressant effects of the anticholinergic, scopolamine, and potential biomarkers of response will be discussed.

Methods: Currently unmedicated unipolar and bipolar patients participated in double-blind, placebo-controlled, crossover infusion studies using scopolamine (4mg/kg). Prior to each infusion patients completed the Profile of Mood State (POMS) and Visual Analog Scales (VAS) self-rating scales, and were assessed clinically using the Montgomery-Asberg Depression Rating Scale (MADRS). Following a single-blind placebo lead-in session, patients participated in a functional magnetic resonance imaging (fMRI) study while they performed a face-identity and face-emotion working memory task. Clinical efficacy was assessed by measuring change in MADRS over sessions. Biomarker analyses included: 1) baseline self-ratings were used in a discriminant function analysis to identify linear combinations of individual items that predict clinical response, and 2) whole brain task specific blood oxygen level-dependent (BOLD) signal at baseline was correlated with the magnitude of treatment response to scopolamine.

Results: Clinically, patients showed a rapid and robust antidepressant response following the first administration of scopolamine that exceeded the placebo response. The discriminant analysis based on baseline self-ratings separated responders from non-responders in both the unipolar and bipolar diagnostic subgroups. Baseline BOLD response in the bilateral middle occipital cortex, selectively during the emotion working memory task, correlated with the magnitude of treatment response.

Conclusion: These results indicate that antimuscarinic action by scopolamine produces rapid antidepressant effects, and that both clinical ratings and BOLD signal measured prior to treatment may predict clinical outcome. These findings implicate cholinergic and visual processing dysfunction in the pathophysiology of MDD, and suggest that both patient self-ratings and neural activity in the visual cortex may provide useful biomarkers for the identification of patients who will respond favorably to scopolamine.

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Speaker 4: Shigeyuki Chaki, Japan

Title: Synaptic and neural mechanisms of agents with rapid acting antidepressant effects: Evidences for mGlu2/3 antagonists and ketamine

Abstract

Ketamine has been demonstrated to exert rapid and sustained antidepressant effects for patients with depression including treatment-resistant depression (TRD). However, a number of adverse effects preclude routine use of ketamine, thus, alternatives to ketamine are needed. Metabotropic glutamate (mGlu) 2/3 receptor antagonists have been demonstrated antidepressant effects in animal models, and some of the mechanisms underlying antidepressant effects are shared by ketamine, which raise the possibility that mGlu2/3 receptor antagonists could be an alternative to ketamine. Therefore, synaptic and neural mechanisms of mGlu2/3 receptor antagonists were investigated and compared with those of ketamine.

Systemic administration of mGlu2/3 receptor antagonists and ketamine exhibited rapid and sustained antidepressant effects in animal models, including those refractory to current medications. Antidepressant effects of mGlu2/3 receptor antagonists and ketamine were attenuated by NBQX (an AMPA receptor antagonist), K252a (a TrkB inhibitor) and rapamycin (an mTOR signaling inhibitor), suggesting that mGlu2/3 receptor antagonists and ketamine share synaptic mechanisms that both compounds may increase synaptic formation, which is underpinned by the reports that both compounds increase synaptic protein synthesis. Interestingly, local injection of LY341495 or ketamine into the mPFC exerted antidepressant effects in the