NMDA Modulation in Mental Disorders: Novel Diagnosis and Treatment

Hsien-Yuan Lane, MD, PhD

Distinguished Professor, Director, Graduate Institute of Biomedical Sciences
& Department of Psychiatry, College of Medicine
China Medical University and Hospital, Taichung, Taiwan

Given the limitation of current medications for mental disorders, substantial efforts have been made to identify novel targets, especially NMDA receptors-related ones. Dr. Lane's team is the pioneer in the development of glycine transporter-I (GlyT-1) inhibitor and D-amino acid oxidase (DAAO) inhibitor for the treatment of schizophrenia, instilling new hope into treatment of this severe brain disorder. His team is also the first group to show the efficacy of an NMDA enhancer in the treatment of major depressive disorder. They conducted preclinical and clinical trials which showed that a GlyT-1 inhibitor was more efficacious than citalopram, a commonly used antidepressant which is a selective serotonin reuptake inhibitor (SSRI), in the treatment of major depressive disorder.

DAAO is responsible for degradation of D-serine, a co-agonist of the NMDA receptor, and its inhibition can enhance NMDA neurotransmission and thereby treat mental disorders. His team completed a pivotal clinical trial which demonstrated that benzoate, a DAAO inhibitor, was better than the GlyT-1 inhibitor in improving symptoms of schizophrenia; moreover, benzoate was beneficial for cognitive function, global functioning, and quality of life. Very lately, a multi-center clinical trial, led by Dr. Lane, further showed that benzoate can bring hope for the hardest-to-treat (treatment-resistant to the last-line antipsychotic agent, clozapine) patients with schizophrenia.

Since benzoate can improve cognitive function of patients with schizophrenia, it is also important to study whether it can improve cognitive function of patients with Alzheimer's disease. They are also the first group to demonstrate the efficacy and safety of a DAAO inhibitor in the treatment of early-phase Alzheimer's disease.

To date, there is no peripheral biomarker for mental disorders. G72, functioning as a DAAO activator (DAOA), exists exclusively in humans and the other 3 primates. Dr. Lane and colleagues' study indicated that peripheral G72 protein expression was characteristic of schizophrenia. This novel finding would be beneficial for early diagnosis and thereby early intervention of schizophrenia.

In summary, Dr. Lane team's research is helping revolutionizing treatment and diagnosis for mental disorders.