Small Molecule Potentiators of NMDA Receptors for Treating Neurological Conditions

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Technology description

Market Summary

The NMDA receptor is a complex ligand-gated ion channel that has been viewed as a therapeutic target for multiple diseases and disorders for over 30 years. Reduced NMDA function has been implicated in age-related learning decline and schizophrenia, and the disruption of neuronal networks involved in Parkinson’ s disease may also involve the NMDA receptor. Recent work has shown the NMDA non-competitive inhibitor ketamine could be a treatment for depression and obsessive compulsive disorder (OCD), but adverse side effects have created a need for more selective drugs. The GluN2 subunits of NMDA (GluN2A, GluN2B, GluN2C, and GluN2D) are believed to affect synaptic plasticity, but their specific roles have not been identified due to the lack of subunit specific inhibitors, activators, and potentiators. The ability to selectively target a subtype of NMDA receptor may allow for the development of a therapeutic agent or pharmacological probe that improves numerous conditions reliant on NMDA activation without the deleterious side effects associated with a broad disruption of NMDA neuronal circuits.

Technical Summary

Emory researchers have synthesized several classes of small molecule compound series that selectively potentiate NMDA receptors composed of GluN2B, GluN2C, GluN2B/GluN2C/GluN2D, and GluN2C/GluN2D. These compounds increase the sensitivity of the receptor to glutamate as well as prolong the response to the endogenous activator. Several compounds within the class have shown to be highly brain penetrate in rodent models as well as functional in brain slice recordings. These small molecule potentiators of NMDA receptors may lead to therapeutics for numerous conditions including cognitive disability, Parkinson’ s disease, schizophrenia, and other neurological diseases associated with cognitive disability or decline.

Application area

Multiple series of small molecules that selectivity potentiate NMDA receptors composed of specific subunits including GluN2B, GluN2C, GluN2B/GluN2C/GluN2D, and GluN2C/GluN2D.

Advantages

Small molecule potentiators enhance endogenous signals without exogenous activation.
Subunit selectivity allows targeting of specific subtypes of NMDA receptors.
Class of molecules are highly brain penetrant.

Institution

Emory University

Inventors

Stephen Traynelis
Professor
SOM: Pharmacology: Admin
Lanny Liebeskind
Professor
ECAS: Dean of the College
Ethel Garnier-Amblard
Assistant Professor
SOM: Pharmacology
Dennis Liotta
Professor; Executive Director, EIDD
ECAS: Chemistry

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com