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Small molecule modulators of glutamate transporter for treatment of neurodegenerative diseases

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Glutamate is the main excitatory neurotransmitter in the CNS. The concentration of glutamate in the synaptic cleft is tightly regulated by the interplay between glutamate release and glutamate clearance. Abnormal glutamate release and/or dysfunction of glutamate clearance can cause over-stimulation of glutamate receptors and result in neuronal injury or death known as excitotoxicity. Excitotoxicity contributes to a wide range of neurodegenerative diseases. Blocking glutamate receptors and/or reducing glutamate release have been the therapeutic strategies for the prevention of excitotoxicity. Memantine and riluzole are the current available anti-excitotoxic drugs. However, the beneficial effects of these drugs are limited. There is a need for better therapeutics. The glial glutamate transporter EAAT2 is primarily localized in peri-synaptic processes of astrocytes closely associated with excitatory synaptic contacts and is responsible for maintaining low extracellular glutamate concentrations. Many studies using transgenic mice or pharmacological approaches in animal models of disease indicate that increased EAAT2 expression provides neuronal protection and beneficial effects, suggesting a potential approach to preventing excitotoxicity. EAAT2 can be up-regulated by transcriptional or translational activation. We executed high-throughput screening to search for compounds that increase EAAT2 expression through translational activation. This screen resulted in the discovery of 16 classes of compounds that can activate EAAT2 translation. After intensive preliminary studies with these compounds, three lead series were selected. We performed efficacy studies using a compound from one of the lead series in several animal models of disease including SOD1(G93A) mouse model of ALS, $APP_{Sw/Ind}$ mouse model of Alzheimer's disease, a mouse epilepsy model induced by pilocarpine, and a mouse stroke model induced by occlusion of the middle cerebral artery. Significantly, the results show that this compound has profound protective effects in these disease models. These drug-like compounds have great potential to become therapeutic agents for multiple neurodegenerative diseases. Continued development of these compounds is currently underway.

Biography

C. Glenn Lin completed his doctorate in Molecular Biology and Biochemistry at the Johns Hopkins University in 1995. He performed postdoctoral research in the Department of Neurology at the Johns Hopkins University. Dr. Lin joined the Department of Neuroscience at the Ohio State University in 1999, where he directed his research to molecular mechanisms underlying neurodegenerative diseases including amyotrophic lateral sclerosis (ALS), Alzheimer's disease, and epilepsy. His recent research focuses on the role of glutamate transporters and mRNA oxidative damage in the biology of neurodegenerative diseases. He has published numerous papers in major journals and holds four patents.

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