Technology Offer

Ref.-No. M0715

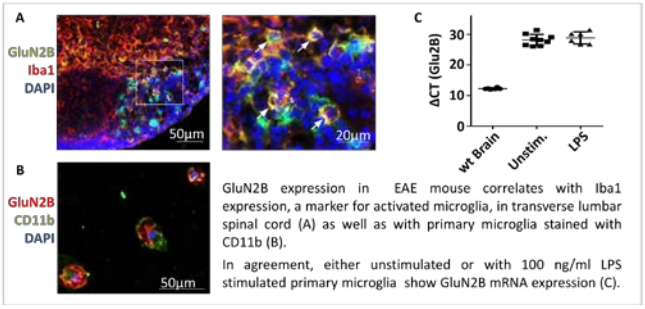
NR2B-selective NMDA-receptor antagonists for the treatment of immune-mediated inflammatory diseases

Introduction

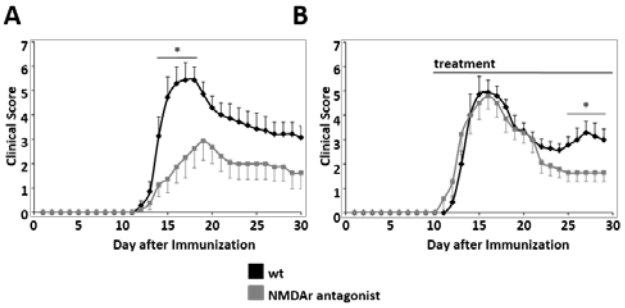
Immune-mediated inflammatory diseases (IMIDs) are a group of chronic and highly disabling diseases that share common inflammatory pathways. Despite an increasing therapeutic armamentarium, there is still an urgent need for novel and improved therapeutic approaches for treating immune-mediated inflammatory diseases, such as multiple sclerosis, preferably exhibiting fewer adverse side effects and an improved clinical efficacy.
NMDA-receptors (NMDAr) are glutamate-gated ion channels reported to be widely expressed in the central nervous system. NMDARs have hence triggered an intense interest as potential therapeutic drug targets. However, their intended use has been classically restricted to treatment of diseases affecting the CNS associated with neuronal dysfunction or glutamate excitotoxicity. Several NMDAR antagonists were developed, including uncompetitive NMDAR antagonists binding to the NMDA ion channel and competitive antagonists acting at the agonist-binding domain on the NR2 subunits. We recently developed novel improved NMDA-receptor antagonists specifically binding to the NR2B subunit of the receptor with high affinity.

Invention

We found that immune cells (microglia and monocytes/dendritic cells), involved in the pathogenesis of IMIDs such as multiple sclerosis, express the NMDA receptor. Specifically, they upregulate the NR2B subunit under inflammatory conditions. Targeting the NR2B subunit of the NMDA receptor on microglia and monocytes resulted in a marked downregulation of activation markers and cytokine expression and/or secretion. The finding was confirmed in an in vivo mouse model of multiple sclerosis (experimental autoimmune encephalomyelitis; EAE), showing a markedly less severe progression of disease after treatment with the novel NR2B-selective compound, even if treatment was begun after symptoms had developed.



GluN2B expression in EAE mouse correlates with Iba1 expression, a marker for activated microglia, in transverse lumbar spinal cord (A) as well as with primary microglia stained with CD11b (B).
In agreement, either unstimulated or with 100 ng/ml LPS stimulated primary microglia show GluN2B mRNA expression (C).



Prophylactic (A) and therapeutic (B) treatment with a selective NR2B-selective NMDAr antagonist significantly ameliorates EAE disease course.

Advantages of the invention

Our newly developed specific NMDAr antagonist binds selectively to the NR2B subunit and shows an increased selectivity and specificity compared to known inhibitors.

New aspects of the invention

Under normal conditions, NR2B is only expressed in specific brain regions. Under autoinflammatory conditions, we found a marked upregulation of NR2B on microglia and myeloid cells. Blockade of NR2B showed a significant anti-inflammatory effect both in vitro and in an animal model of multiple sclerosis.

Patent situation

A PCT patent application has been filed.

For further information please contact:

Clinic Invent
Dr. Elke Benkhart
Landsberger Str. 98
D-80339 München
Tel. +49-(0)89/ 99 88 98 53
Fax +49-(0)89/ 99 88 98 54
E-Mail elke.benkhart@clinic-invent.de