Functions of Metabotropic Glutamate Receptor Subtypes

https://neurodegenerationresearch.eu/survey/functions-of-metabotropic-glutamate-receptor-subtypes/

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Country

USA

Title of project or programme

Functions of Metabotropic Glutamate Receptor Subtypes

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,699,070.64

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01/08/1993

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

positive allosteric modulator, Metabotropic Glutamate Receptors, Antiparkinson Agents, Anti-Anxiety Agents, Antipsychotic Agents

Research Abstract

DESCRIPTION (provided by applicant): Highly selective positive allosteric modulators (PAMs) that increase activity of the mGlu4 subtype of metabotropic glutamate (mGlu) receptor have

robust efficacy in rodent models of Parkinson’s disease (PD) and are now being advanced for clinical testing in PD patients. The antiparkinsonian activity of mGlu4 PAMs is mediated by activity of these agents at a specific synapse in brain called the striato-pallidal synapse. mGlu4 is the only mGlu receptor subtype in presynaptic terminals at striato-pallidal synapses and all mGlu4 PAMs identified to date are capable of increasing activity of these mGlu4 homomeric receptors. More recent studies suggest that, in addition to antiparkinsonian effects, some mGlu4 activators have efficacy in rodent models that predict antipsychotic and antianxiety effects. Interestingly, mGlu4 and mGlu2 are co-localized at synapses in the brain that could be important for these other actions of mGlu4 PAMs. Furthermore, recent studies in cell lines suggest that mGlu4 and mGlu2 have the potential to form mGlu2/4 heterodimers that consist of one subunit of each of these mGlu receptor subtypes. This raises the possibility that mGlu4 and mGlu2 function as mGlu2/4 heterodimers in specific identified brain circuits. While actions of mGlu4 PAMs at these and other synapses are not critical for antiparkinsonian effects, modulation of transmission in these pathways may be critical for efficacy observed in rodent models that predict antipsychotic and anxiolytic activity. We present extensive preliminary studies in which we have identified mGlu4 PAMs that selectively increase activity of mGlu4 when expressed alone but not when mGlu4 is co-expressed with mGlu2. Furthermore, our preliminary data suggest that mGlu4 PAMs that selectively potentiate responses at mGlu4 homomers have different effects on synaptic transmission at specific CNS synapses than do mGlu2/4 PAMs and that compounds belonging to these two groups may have different effects in rodent models of antipsychotic and anxiolytic-like activity. We now propose a series of studies in which we will rigorously test the hypothesis that mGlu4 homomers and mGlu2/4 heterodimers have distinct pharmacological profiles and that modulators that differentially target the homomeric versus heteromeric forms of mGlu4 have fundamental differences in their effects in identified brain circuits and in rodent models used to predict antiparkinsonian, antipsychotic, and anxiolytic efficacy. If homomeric and heteromeric forms of mGlu4 can be selectively targeted by drug-like molecules, this will provide critical new insights that will influence current efforts to develop mGlu4 PAMs as therapeutic agents. In addition to achieving greater specificity by targeting mGlu4 homomers for treatment of PD, these studies raise the exciting possibility that selectively targeting mGlu2/4 heteromeric receptors could provide a novel approach for treatment of schizophrenia and anxiety disorders.

Lay Summary

PUBLIC HEALTH RELEVANCE: We have discovered new drug like molecules that selectively increase activity of a neurotransmitter receptor termed mGlu4 and other drug leads that only increase activity of mGlu4 when it forms a complex with another receptor named mGlu2. Studies are proposed evaluate effects of these compounds in identified brain circuits that express either mGlu4 alone or express both mGlu2 and mGlu4 together. We will then test the hypothesis that selectively targeting mGlu4 provides efficacy in treatment of Parkinson’s disease whereas targeting mGlu2/4 heterocomplexes may be useful for treatment of schizophrenia and anxiety disorders.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

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Parkinson's disease & PD-related disorders

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2016

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