Targeted gene transfer across specific synapse types

https://neurodegenerationresearch.eu/survey/targeted-gene-transfer-across-specific-synapse-types/

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Country

USA

Title of project or programme

Targeted gene transfer across specific synapse types

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,263,532.11

Start date of award

01/04/2014

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Gene Transfer, postsynaptic neurons, presynaptic neurons, Synapses, Neurotransmitter Receptor

Research Abstract
DESCRIPTION (provided by applicant): Developing gene therapies for specific neurological diseases, elucidating the etiology of these diseases, and genetic analyses of neuronal circuits,

behaviors, and learning will all benefit from targeted gene transfer that can deliver different genes into presynaptic neurons and a selected subset of their postsynaptic neurons, based on both projection area and synapse type. Diseases that exhibit deficits in specific circuits include the major neurodegenerative diseases, and other major neurological disorders. Moreover, synaptic plasticity and neural network theories hypothesize that specific behaviors are encoded in specific circuits. Thus, targeted gene transfer across specific synapses will have broad applications to understanding and treating neurological diseases, and to basic neuroscience. To target gene transfer to specific neuron types, we modified a protein on the surface of Herpes Simplex Virus (HSV-1) vector particles; we replaced a panspecific cell binding domain with a neuron type-specific binding domain. In the initial study, we added specific neurotrophic factors to the surface of HSV-1 particles, targeting gene transfer to neurons that contain the cognate receptors. Next, we developed a general method to target gene transfer to specific neuron types, antibody-mediated targeting. We added the Staphylococcus A protein antibody binding domain to a vector particle protein. Complexes of these vector particles and specific antibodies supported targeted gene transfer. We developed targeted gene transfer to deliver different genes into presynaptic neurons and a selected subset of their postsynaptic neurons, based on both projection area and synapse type. The initial study targeted gene transfer across glutamatergic synapses. The first gene transfer, into the presynaptic neurons, uses standard procedures. The vector expresses an artificial peptide neurotransmitter that contains a dense core vesicle sorting domain, a neurotransmitter receptor binding domain (for NMDA NR1 subunits), and the His tag. Upon release, this peptide neurotransmitter binds to the cognate receptors on the postsynaptic neurons. Antibody-mediated targeting to these postsynaptic neurons uses a His tag antibody, as the peptide neurotransmitter contains the His tag. This targeting supported an ~10-fold increase in specificity. The long-term goal of this project is to develop targeted gene transfer across specific synapse types, for elucidating disease etiologies, developing gene therapies, and basic neuroscience. The proposed experiments will optimize targeted gene transfer across synapses, develop targeting across specific synapse types critical in neurology and neuroscience, and apply these advances to a problem in the etiology of Alzheimer’s disease, thereby developing a novel gene therapy. Of note, these targeting strategies and reagents can be used in any gene transfer system.

Lay Summary
PUBLIC HEALTH RELEVANCE: This project will develop targeted gene transfer that can deliver different genes into presynaptic neurons and a selected subset of their postsynaptic neurons, based on both projection area and synapse type. This technology will benefit gene therapies for neurological diseases, elucidating the etiology of these diseases, and analyses of neuronal circuits, behaviors, and learning.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:

2016

Database Categories:
N/A

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N/A