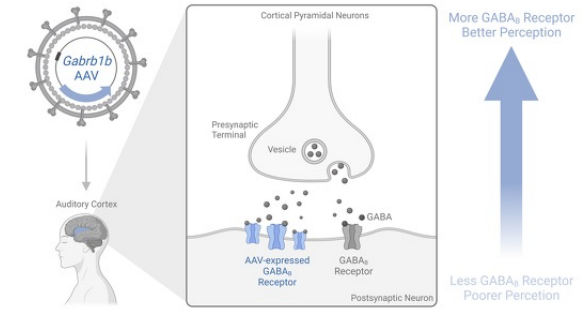
Viral Vector Expression of Gabrb1b for the Treatment of Perceptual Deficits

Innovative and targeted approaches to treat perceptual deficits associated with reduced GABA receptor-mediated inhibitory postsynaptic potentials.



Schematic illustrating the mechanism by which a Gabrb1b-expressing AAV can treat perceptual deficits by restoring postsynaptic GABAB receptor levels.

Technology ID

SAN06-01

Category

Life Sciences/Neuroscience

Life Sciences/Therapeutics/Gene Therapy

Doug Brawley

Authors

Dan Sanes, PhD

View online page

Technology

The Sanes Lab at New York University has developed and characterized a novel approach to therapeutically restore attenuated levels of GABA receptor-mediated inhibitory postsynaptic potentials (IPSPs), which underpin many nervous system disorders. They engineered adeno-associated virus (AAV) vector cassettes with a CaMKII promoter for targeted expression of two different postsynaptic GABA receptor isoforms in specific subset of neurons within the central nervous system: (i) GABAA receptor α1 isoform (Gabra1 gene) and (ii) GABAB receptor 1b isoform (Gabrb1b gene) (see figure on pg. 2). In proof of concept in vivo studies (unpublished), gerbils treated with the expression vector for Gabrb1b showed enhanced functional expression of postsynaptic GABAB receptor localized within neuron subsets of the auditory cortex. In subsequent studies, gerbils were then tested for their ability to perform perceptual tasks following a transient period of developmental hearing loss in order to model perceptual deficits typical of disorders associated with reduced GABA receptor-mediated IPSP capacity. The results showed that animals treated with the Gabrb1b-expressing AAV displayed both amplitude and spectral modulation detection capabilities, two key indicators of perceptual skill, to a level comparable to normal hearing animals.

Background

Perceptual deficits are associated with many nervous system disorders and have been linked to a reduction in synaptic inhibition within the CNS, including the auditory cortex. Such disorders include autism, schizophrenia, and fragile X syndrome, but also less severe and more common

disorders of sustained perceptual deficits that occur following hearing loss from middle ear infections and tinnitus. There is currently a lack of effective therapeutics for perceptual deficits. The Sanes Lab has previously demonstrated in Mowery et al. 2019 that pharmaceutical enhancement of GABA receptor-mediated signaling through the specific inhibition of GAT1 reuptake of GABA partly rescued perceptual deficits caused by transient hearing loss. While these findings help establish the therapeutic potential of targeting GABA signaling for perceptual deficit treatment, such pharmaceutical intervention is likely to have detrimental off-target effects and provide only limited restoration of GABA signaling due to the mechanism by which GABAB receptor-mediated IPSP is reduced in the relevant disorders. In most cases, GABA receptor expression is reduced independent of the production/degradation of the GABA ligand. Consequently, there are is an unmet need for innovative therapeutic strategies to enhance the expression of GABA receptors to overcome the deficient synaptic inhibition associated with numerous nervous system disorders.

Applications

Treatment of perceptual deficits resulting from reduced GABA receptor-mediated IPSP, which includes diseases such as:

- Tinnitus
- Middle ear infections
- Autism
- Schizophrenia
- Fragile X syndrome
- Epilepsy

Advantages

- **Well characterized target:** GABA receptors are integral to perceptual tasks.
- **Targeted therapy:** Treatment with a Gabrb1b-expressing AAV can be specifically targeted to impaired neuron subsets within the auditory cortex.
- **Physiologically appropriate mechanism of action:** A Gabrb1b-expressing AAV restores endogenous GABAB receptor levels in cortical pyramidal neurons.
- **Tailorable modality:** The AAV expression cassette can be easily and quickly modified to fine-tune expression levels and cell type specificity.

Intellectual Property

NYU has filed a PCT application covering composition and method of use.

References

1. Mowery TM, Caras ML, Hassan SI, et al. , Preserving Inhibition during Developmental Hearing Loss Rescues Auditory Learning and Perception