Regulation of glutamate transport in astrocyte subtypes and in ALS

https://neurodegenerationresearch.eu/survey/regulation-of-glutamate-transport-in-astrocyte-subtypes-and-in-als/

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Country

USA

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Regulation of glutamate transport in astrocyte subtypes and in ALS

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4

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Amyotrophic Lateral Sclerosis, Astrocytes, Glutamates, Bacterial Artificial Chromosomes, protein biomarkers

Research Abstract

? DESCRIPTION (provided by applicant): Glutamate (Glu) is the predominant excitatory neurotransmitter in the mammalian central nervous system (CNS). Excessive activation of

glutamate receptors leads to excitotoxicity, which in turn contributes to cell death observed after acute neurologic insults and in chronic neurodegenerative diseases. A family of Na+-dependent transporters controls extracellular Glu and prevents excitotoxic activation of Glu receptors. The GLT1/EAAT2 subtype of transporter mediates the bulk of this activity in the forebrain, and it is almost exclusively expressed in astrocytes. The levels of GLT1 are decreased in several neurologic diseases, including amyotrophic lateral sclerosis (ALS). To study transcriptional regulation of GLT1 we generated a BAC-GLT1-eGFP transgenic mouse that utilizes a large bacterial artificial chromosome (BAC) to express eGFP under the control of the full length GLT1 promoter. To better understand which region of the GLT1 promoter is necessary and/or sufficient for astroglial GLT1 expression, we generated a family of promoter reporter mice that utilize increasing amounts of the 5? non-coding region of the GLT1 gene (2.5, 6.7, 7.9, and 8.3 kilobases) to express tdTomato. When we crossed these mice with the BAC-GLT1-eGFP mice to produce dual reporter mice we made two exciting and unexpected observations. First, the promoter region between 7.9 and 8.3 kb is required for specific expression of tdTomato in astroglia. This region contains a domain that is evolutionarily conserved from rodents to humans, suggesting that this domain is critical for selective in vivo astroglia expression of GLT1. Second, although tdTomato is only found in eGFP-expressing astroglia, not all eGFP-expressing astroglia express tdTomato; the tdTomato/eGFP (double+) astrocytes are enriched in regions where GLT1 selectively decreases in ALS. This suggests that the 8.3 kb portion of the GLT1 promoter is only sufficient to induce expression of GLT1 in a defined subset of astrocytes, providing evidence for the existence of distinct subtypes of astrocytes. Based on these and other preliminary data, we propose two specific aims: 1) We will test the hypothesis that subtypes of astrocytes use different extrinsic stimuli (neurons and endothelia) to activate different intrinsic signals (Pax6 and Notch with associated promoter elements) to control subtype-specific expression of GLT1. We will determine if this differential control of GLT1 generalizes to proteins that are differentially expressed in these subpopulations of astrocytes. We will confirm that these subpopulations of astrocytes are found in humans. 2) We will test the hypothesis that the subtypes of astroglia identified by the 8.3 kb promoter reporter mice are selectively affected in mouse models of ALS. We will confirm pathologic changes using human tissue. Finally, we will test the hypothesis that the subtype of astroglia identified by the 8.3 kb promoter reporter mice selectively contributes to the known non-cell autonomous motor neuron degeneration.

Lay Summary

PUBLIC HEALTH RELEVANCE: We are studying the mechanisms that control expression of the predominant process that limits glutamate signaling and glutamate toxicity. We are determining how these mechanisms contribute to the pathology observed in amyotrophic lateral sclerosis.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

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Motor neurone diseases

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