Environmental Metals, Excitotoxicity and ALS

https://www.neurodegenerationresearch.eu/survey/environmental-metals-excitotoxicity-and-als/

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Country

USA

Title of project or programme

Environmental Metals, Excitotoxicity and ALS

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NIH (NINDS)

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4

The project/programme is most relevant to:

Motor neurone diseases

Keywords

excitotoxicity, Amyotrophic Lateral Sclerosis, Motor Neurons, Metals, Astrocytes

Research Abstract

? DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS), or Lou Gehrig’s disease, is a progressive neurodegenerative disease resulting in motor nerve degeneration and death. Both familial (FALS) and sporadic (SALS) forms exist; the latter greatly predominate. Its cause is unknown. Overstimulation of glutamatergic function – excitotoxicity – with increased Ca2+ and generation of reactive oxygen species (ROS), plays an important, if not integral role,

though other mechanisms likely contribute to ALS pathogenesis. Interaction of motor neurons (MNs) and astrocytes (ASTs) appear to contribute to disease development. Environmental contribution to ALS has been postulated often, but to date not systematically tested. We propose to examine the interaction of the environmental toxicant methylmercury (MeHg) with two genetic mutations found in humans with ALS. Chronic postnatal MeHg exposure of mice with a mutation in superoxide dismutase-1 (SOD1G93A, G93A) hastens the onset of ALS phenotype compared to untreated G93A mice or wt mice exposed to identical MeHg concentrations. We will now test the hypothesis that chronic, low dose, MeHg exposure beginning postnatally enhances development and progression of ALS phenotype in the G93A and G85R SOD1 mutants by increasing [Ca2+]i, generating ROS and inducing mitochondrial toxicity secondary to enhanced release of glutamate (Glu) or actions on AST Glu transporters (EAAT1-2). The two SOD1 mutant strains differ in their time course of development of ALS phenotype and in their primary toxic focus. The G93A mice develop phenotype in ~4 mos and disease is MN-directed. G85R mice develop ALS phenotype over 7-9 months and disease is AST-based. This design will allow us to compare the roles of ASTs and MNs to MeHg induced responses. Specific Aim 1: Examines the development of ALS phenotype and relative role of MNs and ASTs during chronic adult MeHg exposure. Specific Aim 2: Examines oxidative stress as a contributor to MeHg-induced enhancement of ALS phenotype. Specific Aim 3: Examines the cell autonomy of MN function in response to MeHg. Interactions between ASTs and MNs will be examined in chimeric cultures of wt and SOD-1 cells to assess their potential roles in the development of excitotoxicity in MeHg-induced enhancement of ALS phenotype. Early onset effects preceding development of ALS phenotype will be examined using spinal cord slices and co-cultures of MNs and ASTs, from the G93A and G85R strains. Glu-mediated excitatory postsynaptic currents and elevation of [Ca2+] i and levels of ROS will test for MeHg-induced excitotoxicity. Steady- state mRNA expression levels for EAAT1-2 and proteins involved in [Ca2+] i regulation will be measured during development of ALS phenotype to correlate with studies done in cells in culture. MNs in culture derived from SOD1 mice or wt will allow examination of early effects of MeHg on Glu function, [Ca2+] i oxidative stress or mitochondrial damage in isolation. Results of the proposed study should permit assessment of the role of MeHg-induced Glu- mediated excitotoxicity in facilitating development of MN dysfunction and provide verification for the postulate that environmental exposure to metals is a potential risk factor for susceptible populations in development of ALS.

Lay Summary
PUBLIC HEALTH RELEVANCE: Environmental exposure to metals, including various forms of mercury, has been postulated to contribute to the sporadic form of the progressive neurodegenerative disease ALS. The present proposal is designed to test if methylmercury hastens the development of ALS in two mouse models of ALS and determine the role of excitotoxicity in the response.

Further information available at:

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