Protein Aggregation and Inflammasome Signaling in Manganese Neurotoxicity

https://neurodegenerationresearch.eu/survey/protein-aggregation-and-inflammasome-signaling-in-manganese-neurotoxicity/

Principal Investigators

KANTHASAMY, ANUMANTHA GOUNDER

Institution

IOWA STATE UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

Protein Aggregation and Inflammasome Signaling in Manganese Neurotoxicity

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,507,048.62

Start date of award

01/06/2016

Total duration of award in years

5

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Manganese, protein aggregation, alpha synuclein, neurotoxicity, exosome

Research Abstract

DESCRIPTION (provided by applicant): Metal exposure has increasingly been recognized as a potential environmental contributor to chronic neurodegenerative diseases including Parkinson’s

disease (PD) and Alzheimer's disease (AD). Chronic manganese (Mn) exposure has been implicated in Parkinson's-like neurological conditions in humans. Protein aggregation and its prion-like propagation are now considered the central pathophysiological mechanisms of many neurodegenerative diseases collectively known as proteinopathies. However, the role of metals in protein aggregation and the neurotoxicological mechanisms that drive degenerative processes are not well understood. ?-Synuclein (?Syn) protein aggregation has been implicated in PD, and this protein features multiple divalent metal-binding motifs that have been suggested to play a role in ?Syn's fibrillization and neurotoxicity. Since Mn shows affinity to the metal binding sites in ?Syn, we have examined the effect of Mn on ?Syn in neuronal models. Interestingly, we found that ?Syn protected against Mn-induced neurotoxicity during early stages of Mn exposure, but prolonged Mn exposure promoted ?Syn aggregation. In agreement with the emerging concept that aggregated proteins propagate cell-to-cell via exosomal release, we also observed enhanced release of exosomes containing ?Syn into the extracellular environment during Mn exposure. Thus, our exciting finding of Mn-induced ?Syn aggregation and release of exosomes with ?Syn cargo prompts us to further characterize the cellular and molecular mechanisms of neurodegenerative processes in Mn neurotoxicity. Our proposal will test the novel hypothesis that Mn exposure promotes ?Syn misfiling and impairs intracellular ?Syn trafficking, thereby increasing the formation and release of exosomes containing ?Syn protein aggregates, which subsequently trigger microglial activation through the NLRP3 inflammasome pathway in a PKC?-dependent manner. Sustained activation of the PKC?-dependent NLRP3 inflammasome pathway contributes to Mn neurotoxicity. Specific objectives of the proposal are: (i) to characterize the cellular mechanism of Mn-induced impairment in endosomal trafficking, retromer dysfunction and exosome release in cell culture and animal models of Mn neurotoxicity, (ii) to determine NLRP2/3 inflammasome neuroinflammatory signaling in microglia and astrocytes triggered by Mn-induced exosomal ?Syn aggregates and to characterize the proinflammatory regulatory function of PKC? in NLRP2/3 inflammasome activation in Mn neurotoxicity, and (iii), to examine the role of PKC? in mediating the exosomal ?Syn aggregate-induced proinflammatory response in animal models of Mn neurotoxicity and to confirm the presence of ?Syn protein aggregation in Mn-exposed human brain tissues. Our integrated cellular and molecular approach to unraveling the formation and release of exosomal ?Syn aggregates and their functional consequences on neuroinflammatory signaling in manganese metal neurotoxicity will provide novel mechanistic insights into environmentally-linked neurodegenerative disorders.

Lay Summary

PUBLIC HEALTH RELEVANCE: Chronic metal exposure has been implicated in the pathogenesis of major neurological diseases such as Parkinson's and Alzheimer's, but pathological mechanisms underlying metal-induced chronic degenerative processes have yet to be characterized. Our proposal will use cell cultures, animal models and human samples to systematically characterize the protein aggregation mechanisms during manganese neurotoxicity and their consequence in inducing chronic brain inflammation. The outcome of our project will provide new insights into the role of metal exposure in neurodegenerative diseases and will help us to devise better interventional strategies.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

Database Tags:
N/A