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2017 Alzheimer's Association Research Grant (AARG)

Pathomechanisms of TDP-43 in Alzheimer's Disease

Does abnormal accumulation of the protein TDP-43 contribute to nerve cell loss in Alzheimer's disease?

Background

Abnormal accumulation of the protein TAR DNA-binding protein 43 (TDP-43) in the brain is a hallmark of amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease) and frontotemporal dementia (FTD). About half of individuals with Alzheimer's disease also have clumps of TDP-43 in the brain in addition to amyloid plaques and tau tangles. The mechanisms by which the TDP-43 protein promotes brain changes associated with Alzheimer's disease are not yet understood, but initial studies suggest that TDP-43 may build-up in small cellular structures called mitochondria that are needed to produce energy for cells. Abnormal build-up of TDP-43 in mitochondria could impair energy production and contribute to nerve cell loss in the brain.

Research Plan

Xinglong Wang, Ph.D., and colleagues have planned a series of experiments to better understand the role of TDP-43 in Alzheimer's disease. The researchers will use nerve cells growing in laboratory dishes to examine what factors (e.g. beta-amyloid, tau, inflammation) may trigger the accumulation of TDP-43 in nerve cell mitochondria. The research team will also determine if treating Alzheimer's-like mice with a novel molecule that inhibits TDP-43 accumulation in mitochondria can prevent nerve cell loss. In addition, they will test the TDP-43 inhibitor in "induced pluripotent stem cells" (iPSCs) from people with Alzheimer's disease. iPSCs are a special type of stem cell made from skin or blood cells and then "reprogrammed" to become nerve cells. iPSCs allow scientists to rapidly test drug candidates in nerve cells made directly from people with Alzheimer's disease.

Impact

The results of this study could shed new light on the molecular mechanisms underlying abnormal accumulation of the TDP-43 protein in the Alzheimer's brain. These findings could also provide the first steps in testing a novel molecule that specifically inhibits TDP-43 build-up in mitochondria as a potential therapy to prevent nerve cell loss in Alzheimer's and other neurodegenerative diseases.

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Pathophysiologic Link between TDP-43 Pathology and Alzheimer's Disease

Does abnormal build-up of the TDP-43 protein in the brain impact the progression of Alzheimer's disease?

Background

Abnormal accumulation of the protein TAR DNA-binding protein 43 (TDP-43) in the brain is a hallmark of amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease) and frontotemporal dementia (FTD). About half of individuals with Alzheimer's disease also have clumps of TDP-43 in the brain in addition to amyloid plaques and tau tangles. Recent studies have shown that TDP-43 accumulation may be associated with brain shrinkage and cognitive decline in people with Alzheimer's disease, but the mechanisms by which TDP-43 may influence disease progression are not yet known.

Research Plan

Hyan-Sik Yang, M.D., and colleagues have proposed a series of studies to better understand how the abnormal accumulation of TDP-43 affects brain structure and function in older people with and without Alzheimer's disease. They will use large datasets of genetic, brain imaging and cognitive testing measurements collected over several years from participants in the Religious Orders Study (ROS), the Rush Memory and Aging Project (MAP) and the Harvard Aging Brain Study (HABS). They will determine if TDP-43 alone contributes to cognitive decline and changes in the size of the hippocampus, a brain region important for learning and memory. They will also determine if TDP-43 "accelerates" the build-up of plaques and tangles and promotes cognitive decline in people with Alzheimer's disease. The researchers are also interested to see how a genetic variation associated with increased Alzheimer's risk (APOE-ε4) may impact the level of abnormal TDP-43 accumulation in the brain.

Impact

The results of this study could shed new light on how TDP-43 accumulation can affect the progression of Alzheimer's or other dementias. In addition, this work could help determine if TDP-43 could be targeted for the development of new diagnostic and therapeutic strategies for Alzheimer's and other neurodegenerative diseases.

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Longitudinal Cognitive and Biomarker Trajectories of MCI Subtypes

Can improved diagnosis of different types of mild cognitive impairment help predict who is at risk for Alzheimer's disease?

Background

Brain changes associated with Alzheimer's disease begin many years prior to the appearance of clinical symptoms. Mild Cognitive Impairment (MCI) is considered a transitional state between normal aging and dementia. Individuals with MCI demonstrate mild changes in their memory and thinking abilities, but they do not have notable difficulty with everyday activities. MCI is a very diverse diagnosis, as it includes people who have different types and different levels of impairment. More research is needed to determine how different subtypes of MCI may relate to the risk of developing Alzheimer's disease.

Research Plan

For this study, Emily Edmonds, Ph.D., and colleagues will examine data from over 1,000 older adults who have been diagnosed with MCI. These individuals have been divided into specific subtypes of MCI based on their performance on tests of memory and other thinking abilities. For example, some individuals have difficulty with only memory, while others show impairments in language and/or problem solving. The researchers will analyze data collected over several years (up to 10 years) in individuals with different types of MCI to determine who progressed towards Alzheimer's disease and who remained cognitively stable. They will study changes in (1) memory and thinking abilities, (2) the size of different brain regions using brain scans, and (3) the ability to complete everyday activities.

Impact

The results of this study could provide novel information on the long-term brain changes associated with different types of MCI. In addition, this work could improve our ability to diagnose different types of MCI more precisely and better predict who may be at risk for developing Alzheimer's disease.

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2017 Alzheimer's Association Research Fellowship (AARF)

Drug Development of a Novel PDE5 Inhibitor for Alzheimer's Disease

Can a novel compound help preserve nerve cell function and prevent memory loss in Alzheimer's disease?

Background

Nerve cells communicate through specialized structures called synapses that connect one nerve cell to another. Cellular communication is necessary to support memory and other cognitive functions. In Alzheimer's disease, synapses become damaged which may contribute to impaired nerve cell communication and cognitive decline. Recent studies by Jole Fiorito, Ph.D. and others have found that inhibiting a molecule called phosphodiesterase type 5 (PDE5) can help prevent synaptic damage and restore memory function in Alzheimer's-like mice. Drugs that are PDE5 inhibitors (PDE5Is) are currently available to treat certain conditions in humans, but they are not optimized for the long-term treatment of brain disorders such as Alzheimer's.

Research Plan

Dr. Fiorito has recently discovered a novel PDE5I that can effectively cross from the blood into the brain in Alzheimer's-like mice and reduce synapse damage. However, when tested in human liver cells, the drug is broken down (metabolized) too quickly indicating it may not stay in the body long enough to have effects. For their current studies, Dr. Fiorito and team will develop chemical modifications of the candidate PDE5I to help prevent it from being too quickly metabolized in the liver. They also plan to optimize the structure of the candidate PDE5I to increase its ability to enter the brain and ensure it selectively targets pathways involved in nerve cell synaptic function. They will test their novel PDE5I in Alzheimer's-like mice to evaluate its safety when given over long periods of time, and determine if it can help preserve synapses and improve memory function.

Impact

These studies provide the first important steps in the discovery and development of a novel drug molecule that may prevent or reduce brain changes associated with Alzheimer's disease. If successful, the results of this effort could lay the foundation for future human clinical trials to determine if PDE5Is are a therapeutic avenue for slowing or stopping the progression of Alzheimer's disease.

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