Immune regulated amino acid pathways in Alzheimers Disease

https://neurodegenerationresearch.eu/survey/immune-regulated-amino-acid-pathways-in-alzheimers-disease/

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Country

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Immune regulated amino acid pathways in Alzheimers Disease

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1

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Alzheimer's disease & other dementias

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Research Abstract

Current therapies designed to treat Alzheimer’s disease based on a single disease mechanism

have not changed this debilitating disorder in humans. While individual targets are critical to uncover, it is likely that interacting pathways are altered in AD. The immune system of the brain is a network of interdependent pathways whose regulation is not well understood but which is clearly implicated in AD. We know, however, that AD is a chronic disorder and results in slow deterioration of the brain over a number of years. Based on our recently published studies, we propose that loss of neurons in AD is not due to toxic pro-inflammatory mechanisms that rapidly kill cells. Our data suggest a different pathology; one that involves immune-mediated nutrient deprivation caused by prolonged immunosuppression. We propose that prolonged immunosuppression initiated by microglia changes the levels of arginine and methionine in the surrounding microenvironment, disrupting interrelated metabolic pathways either within microglia or other cells that are dependent on a maintained supply of these amino acids for normal function. We hypothesize that a patterned change in levels of the amino acids used during the prolonged immune response will lead to a consistent and definable profile of specific metabolic and functional outcomes within the brain's parenchyma. We further hypothesize these patterns will be different between normal (unaffected) and AD-like conditions and will change with progression of AD-like pathology. In Aim 1 we will use our novel mouse model of AD at early and late stage of disease to define patterns of specific amino acids, tissue metabolites, and gene and protein expression levels that characterize immune regulated arginine and methionine. Entry point into this immune regulated system is through activation of an anti-inflammatory related protein, arginase and through subsequent arginine utilization and its impact on other pathways that require arginine. We will stress the interlocking system by dietary reduction or supplementation of arginine and/or methionine. Aim 2 will measure specific functional outcomes that result from the immune-induced amino acid and metabolite changes in the brains of AD and normal mice including cell proliferation (via polyamines) and methylation and its impact on myelin (via methionine and methyl donors). Aim 3 will block the disrupted and restore normal patterns by blocking arginase to determine if a single target approach is viable at early or late stage disease.

Lay Summary

The exact role of the immune system in the onset and progression of Alzheimer's disease (AD) remains unknown. It is clear however, that AD is a chronic neuroinflammatory process for which there are currently no known therapies. Our data implicate abnormal immune responses in AD that impact multiple metabolic pathways to alter key cellular functions. We will utilize a systems based approach to examine normal and immune-regulated patterns of brain amino acids in a model of AD. These experiments will provide a definable profile of specific metabolic and functional outcomes within the brain's microenvironment that are related to immune regulation of amino acid deprivation from which useful therapies can be discovered.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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