Proceedings of the Nutrition Society (2024), **83 (OCE1)**, E110 doi:10.1017/S0029665124001289

47th Annual Scientific Meeting of the Nutrition Society of Australia and Nutrition Society of New Zealand, 28 November – 1 December 2023, Nutrition & Wellbeing in Oceania

Selenotranscriptome network in Alzheimer's disease

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The interplay between selenoproteins, oxidative stress, and cell death pathways holds promise in unravelling novel therapeutic targets for Alzheimer's disease (AD) in the future. Nonetheless, further comprehensive investigations are warranted to fully comprehend the precise contributions of selenoproteins in the aetiology and potential therapeutic strategies for Alzheimer's disease. Previous work into gene expression networks in AD has included analysis of the entire transcriptome and, as of yet, has not yielded consistent insight into pathological pathways.[1] Despite the comprehensive assessment of the transcriptome enabled by current technologies, one drawback of the whole transcriptome analysis is the risk of overlooking subtle yet significant variations in metabolic pathways.[2] Thus, we aimed to assess gene expression of known selenoprotein and selenium-containing pathways in two different brain regions (dorsolateral prefrontal cortex (DPC) and posterior cingulate cortex (PCC)) across the AD spectrum. We used RNA sequencing data from The Rush University's Religious Orders Study and Memory and Aging Project (ROSMAP) cohort available in the AD Knowledge Portal (https://www.synapse.org/).[3] This study included data available for a total of 889 DPC and 647 PCC samples. Four pathological phenotypes were determined based on pathology (CERAD) and clinical (CDR) status: AD ([(+) pathology, (+) clinical], prodromal disease, corresponding to donors that have not received a clinical diagnosis despite the presence of pathological alterations ([(+) pathology, (−) clinical], controls ([(−) pathology, (−) clinical] and non-AD dementia [(+) pathology, (+) clinical]. This last group was excluded from the analysis as it is assumed they may have been misdiagnosed or presented with non-AD dementia. Six selenium or AD-related pathways were assessed, accounting for 421 unique genes. Group comparisons were performed using linear mixed modelling adjusted for age, sex, *APOE*ε4 status and batch via DESeq2 package with Benjamini-Hochberg adjustment for multiple testing. A total of 18 genes significantly differed between AD and controls in both brain areas (same direction in both brain areas; $P < 0.05$), including eight selenoprotein genes or genes directly associated with selenoprotein synthesis. Fifteen of them were also different (same direction) in PCC (seven selenoprotein/selenoprotein synthesis genes), and four were different in DPC (four selenoprotein/selenoprotein synthesis genes) between AD and prodromal. Only three genes significantly differed between prodromal and control samples (DPC), including the selenoprotein *DIO3* and the transcription factor *SP3*. Our findings indicate a progressive change in gene expression across the different stages of AD. These findings shed light on critical genes involved in selenoprotein synthesis that play a role in AD pathogenesis. Restricting the analysis to a subset of pathways enabled the detection of smaller alterations between groups, which is particularly appropriate in trace element homeostasis, where small alterations may have significant downstream effects.

Keywords: selenium; selenoproteins; selenoproteome; Alzheimer's disease

Ethics Declaration

Yes

Financial Support

This research received no external funding.

References

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