treatment duration and separately enriched preparations of EPA/DHA on seizure frequency and severity.

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PTFS07-03-24 Investigating Specific Molecular and Functional Impacts of Citicoline on Brain Health

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Objectives: Cytidine 5'-diphosphocholine (citicoline) is an endogenously generated nucleotide that serves as an essential intermediate in the synthesis of phosphatidylcholine (PC), the major phospholipid component of human cell membranes. Cognizin®, a citicoline supplement is widely used as a dietary supplement, and supplementation of citicoline has shown beneficial effects on cognitive function and behavior clinically. Despite these encouraging results, the biological mechanisms by which citicoline exerts a neuroprotective effect on brain function and ageing are not completely understood. The objective of this study was to perform an integrative multiomic and predictive modelling analysis to characterize the impacts of citicoline administration on brain health.

Methods: The experiments were performed with a human iPSC-derived tri-culture system consisting of cortical neurons, cortical astrocytes, and microglia cells from BrainXell Inc. Cells were cultivated on MEA plates to have a consistent substrate. The tri-cultures were cultured on 48 well MEAs (Axion Biosystems) for 3-4 weeks until maturation. Maturated cells were treated with citicoline then performed activity recording and RNA Sequencing experiments. The effect of the compounds on the cell activity were assessed using micro-electrode arrays.

Results: Multi-parametric characterization of cell activity after treatment with citicoline or control were recorded. There was a statistically significant dose-dependent response in parameters for cell activity with the treatment of citicoline compared to control. The generation and interrogation of RNA-seq citicoline treatment signatures, accompanied by the investigation of comprehensive network model of neuronal cells revealed the predicted effects of citicoline.

Conclusions: This is the first study to investigate the comprehensive molecular mechanism of citicoline in an in-vitro neuronal tri-culture system with iPSC derived cells. The findings identified the potential impacts and relevance of citicoline supplementation in brain health. However, further analysis is required to decipher the molecular underpinnings of its mechanism of action.

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PTFS07-04-24 Transcriptomic Analyses of Eicosapentaenoic Acid Effects in Adipose Tissue and Cortex From High Fat Diet-Induced Obese Amyloidogenic Alzheimer Disease Mice

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Objectives: Alzheimer's disease (AD) is specified by amyloid-beta (Aβ) plaques and neuroinflammation. Obesity, marked by excessive white adipose tissue (WAT), leads to metabolic dysfunctions, systemic inflammation and enhances risk for AD. We previously reported that eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acids, improved metabolic profiles and reduced serum amyloid β (Aβ40) in diet-induced obese transgenic (TG) amyloidogenic AD mice. Here, we studied the links among obesity, WAT inflammation and neuroinflammation in this AD model.

Methods: To gain mechanistic insights into the metabolic and anti-inflammatory effects of EPA in obese AD mice, male and female APPswePS1E9 TG and non-TG wild-type (WT) littermates were fed HF diets without or with 36g EPA/kg diet (EPA). Metabolic phenotypes were assessed during a 32-week intervention, then blood, WAT (gonadal) and brain (cortex) were collected for further analyses, including fatty acid profiling, and gene expression analyses using RNA-sequencing (RNA Seq) and qRT-PCR. Ingenuity pathway analysis (IPA®) was used to analyze differentially expressed pathways and genes. Data were statistically analyzed by t-test and three-way ANOVA, using GraphPad Prism version 9.

Results: As expected, EPA groups had higher EPA in red blood cells than HF groups ($p < 0.001$). Compared to HF group, EPA reduced NLRP3 gene expression in TG male and female cortex ($p = 0.0205$ and < 0.0001) and in WAT of TG female mice ($p = 0.02$), as assessed by qPCR. RNA Seq analyses using IPA® showed that EPA inhibited oxidative stress ($p < 0.05$) and TNF-a pathways ($p < 0.05$) compared to HF in TG and WT female mice cortex, respectively. Similar analyses in WAT showed that EPA inhibited melatonin degradation 1 ($z = -3.35$, $-\log p = 5.66$) and netrin1($z = -2.82$, $-\log p = 3.84$) pathways in TG males and females, respectively, compared to HF. Moreover, EPA inhibited amyloid fiber formation ($z = -2$, $-\log p = 1.40$) and leukocyte extravasation pathways ($z = -2.64$, $-\log p = 1.56$) in WT males, compared to HF.

Conclusions: EPA protective effects in obese AD mice maybe mediated by inhibition of inflammation/neuroinflammation pathways. Further analyses are required to identify regulatory genes/pathways influencing the links between obesity-induced inflammation and neuroinflammation in AD.

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