LOW DOSE BRAIN RADIATION REDUCES ELEVATED PLASMA BRANCH CHAIN AMINO ACID LEVELS IN APP/PS1 MICE

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Branch Chain Amino Acids (BCAA) have recently been implicated in Alzheimer's Disease (AD). We previously showed that low dose brain radiation (RT) [5 fractions of 2 Gy] reduces amyloid-beta plaque burden and results in improved cognition in the APP/PS1 model of AD. In this study we investigated whether this schedule of radiation altered the metabolomic profile of serum. 10 month old male (M) and female (F) APP/PS1 mice were either treated with whole brain radiotherapy (5 x 2 Gy) or received sham irradiation. Eight weeks later the animals were euthanized and blood, urine and brain tissue collected. 1H NMR spectra were acquired. 256 transients were acquired for each sample and chemical shifts (δ) are reported in parts per million (ppm). Analysis included: 3 F and 5 M with no transgene (as a background controls), 5 F who received no RT, 7 F who received RT, 12 M who received RT and 12 M who received no RT. A total of 46 metabolites were analyzed. The most significantly changed metabolites were the BCAAs leucine, isoleucine and valine.. The effect was most pronounced in female mice where levels were reduced to those found in non-transgenic mice. APP/PS1 mice spontaneously display increased plasma BCAA, suggesting that AD pathology potentiates defects in BCAA metabolism, putting patients with AD at a higher risk of BCAA-induced brain damage. Reduction of these levels by low dose radiation may be beneficial.

NEUROFILAMENT LIGHT CHAIN AND COGNITIVE PERFORMANCE IN SELECTED SIBLINGS FROM THE CATSLIFE STUDY

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Markers of neurodegeneration such as neurofilament light chain (NfL) may be elevated with neurological diseases such as multiple sclerosis (MS) as well as Alzheimer's disease. NfL is a marker of axonal integrity where higher values positively relate to the degree of damage. NfL shows variations in early adulthood among healthy individuals and may relate to executive function performance in otherwise healthy individuals aged 19-32 years. In the ongoing CATSLife (Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging) Quanterix Simoa assays of NfL were measured in 34 individuals selected based on self-reported neuroinflammatory conditions (N = 5) or by APOE genotype (N_nonE4 = 18, N_E4 = 16). The distribution of NfL was consistent with other studies of early-mid adulthood (range = 1.3 - 22.3 pg/ml). Based on partial regression weights predicting log-transformed NfL, NfL was higher in cases (exp(b)=1.08 pg/ml), in males (exp(b)=1.25 pg/ml), by age (exp(b)=1.03 pg/ml per year) and in APOE E4 carriers (exp(b)=1.11 p/mg). Moreover, correlations partialed for age, sex, APOE e4 and case status suggest higher NfL may be associated with lower Full Scale IQ and general cognitive ability (r's = -.18 and -. 28) overall and may be more evident among APOE E4 carriers (r's = -.42 - .44, partialed for age, sex, case status). In this pilot study, the observed NfL associations with general cognitive ability, particularly among APOE E4 carriers, suggests NfL may be a salient biomarker of cognitive functioning by early- to mid-adulthood.

NMN RESCUES ENDOTHELIAL FUNCTION AND NEUROVASCULAR COUPLING, IMPROVING COGNITIVE FUNCTION IN AGED MICE

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Adjustment of cerebral blood flow (CBF) to neuronal activity via neurovascular coupling (NVC) has an essential role in maintenance of healthy cognitive function. In aging increased oxidative stress and cerebromicrovascular endothelial dysfunction impair NVC, contributing to cognitive decline. There is increasing evidence showing that a decrease in NAD+ availability with age plays a critical role in a range of age-related cellular impairments but its role in impaired NVC responses remains unexplored. The present study was designed to test the hypothesis that restoring NAD+ concentration may exert beneficial effects on NVC responses in aging. To test this hypothesis 24-month-old C57BL/6 mice were treated with nicotinamide mononucleotide (NMN), a key NAD+ intermediate, for 2 weeks. NVC was assessed by measuring CBF responses (laser Doppler flowmetry) evoked by contralateral whisker stimulation. We found that NVC responses were significantly impaired in aged mice. NMN supplementation rescued NVC responses by increasing endothelial NO-mediated vasodilation, which was associated with significantly improved spatial working memory and gait coordination. These findings are paralleled by the sirtuin-dependent protective effects of NMN on mitochondrial production of reactive oxygen species and mitochondrial bioenergetics in cultured cerebromicrovascular endothelial cells derived from aged animals. Thus, a decrease in NAD+ availability contributes to age-related cerebromicrovascular dysfunction, exacerbating cognitive decline. The cerebromicrovascular protective effects of NMN highlight the preventive and therapeutic potential of NAD+ intermediates as effective interventions in patients at risk for vascular cognitive impairment (VCI).

ODOR SENSITIVITY AS A BIOMARKER OF AGING

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Recent studies support the deterioration of the sense of smell as an important biomarker for cognitive impairment diseases, including Alzheimer's disease. The model