FUSOGENIC LIPOSOMES DELIVER RESVERATROL TO BRAIN MICROCIRCULATION AND IMPROVE NEUROVASCULAR COUPLING IN AGED MICE

Adam Nyul Toth,[1] Tabea Wiedenhoeft,[2] Stefano Tarantini,[1] Tamas Csipo,[3] Priya Balasubramanian,[3] Anna Csiszar,[1] Agnes Csiszar,[2] and Zoltan Ungvari,[4] *1. University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States, 2. Institute of Complex Systems, Jülich, Germany, 3. OUHSC, Oklahoma City, Oklahoma, United States, 4. University of Oklahoma Health Sciences Center, Oklahoma City, United States*

Adjustment of cerebral blood flow (CBF) to the increased oxygen and nutrient demands of active brain regions via neurovascular coupling (NVC) has an essential role in maintenance of healthy cognitive function. In advanced age, cerebromicrovascular oxidative stress and endothelial dysfunction impair neurovascular coupling, contributing to age-related cognitive decline. Recently we developed a resveratrol (3,4′,5- trihydroxystilbene)-containing fusogenic liposome (FL-RSV)-based molecular delivery system that can effectively target cultured cerebromicrovascular endothelial cells, attenuating age-related oxidative stress. To assess the cerebromicrovascular protective effects of FL-RSV in vivo, aged (24-monthold) C57BL/6 mice were treated with FL-RSV for four days. To demonstrate effective cellular uptake of FL-RSV, accumulation of the lipophilic tracer dyes in cells of the neurovascular unit was confirmed using two-photon imaging (through a chronic cranial window). NVC was assessed by measuring CBF responses (laser speckle contrast imaging) evoked by contralateral whisker stimulation. We found that NVC responses were significantly impaired in aged mice. Treatment with FL-RSV significantly improved NVC responses by increasing NO-mediated vasodilation. These findings are paralleled by the protective effects of FL-RSV on endothelium-dependent relaxation in the aorta. Thus, treatment with FL-RSV rescues endothelial function and NVC responses in aged mice. We propose that resveratrol containing fusogenic liposomes could also be used for combined delivery of various anti-geronic factors, including proteins, small molecules, DNA vectors and mRNAs targeting key pathways involved in microvascular aging and neurovascular dysfunction for the prevention/treatment of age-related cerebromicrovascular pathologies and development of vascular cognitive impairment (VCI) in aging.

IMPAIRED MITOCHONDRIAL AND GLYCOLYTIC FUNCTIONS IN PERIPHERAL BLOOD LEUKOCYTES OF ALZHEIMER'S DISEASE

Ravindra Bharadwaj,[1] Hayley Gibler,[2] Sanjay Srivastava,[3] and Hena Tewari,[4] *1. Texas Tech University Health Sciences Center, Amarillo, Texas, United States, 2. Tecas Tech HSC AMA, Amarillo, United States, 3. Texas Tech HSC, Amarillo, United States, 4. Texas Tech HSC - AMA, Amarillo, Texas, United States*

Recent failures of the trials targeting amyloid to treat Alzheimer's disease (AD) are prompting scientists to explore other pathological pathways. Brains of AD patients have been noted to have impaired mitochondrial function. It has not yet been determined if AD is caused by a systemic defect in cellular bioenergetics. To determine the cellular bioenergetics, we compared the Oxygen Consumption Rate (OCR – indicating oxygen dependent respiration) and Extra Cellular Acidification Rate (ECAR – indicating glycolytic function) in leukocytes of collected blood samples of Alzheimer's and non-dementia patients. Methods: After IRB approval and consents, blood samples from each clinically diagnosed Alzheimer's and age matched normal subjects were collected. Immediately after collection the blood samples were analyzed using Agilent Seahorse XFe/XF Analyzer as per protocol by manufacturer. Results: Impaired mitochondrial and glycolytic functions were noted in Alzheimer's patients as compared to normal subjects. OCR was significantly lower in Alzheimer's patients. A lower rate of respiration was noted both at basal as well as maximal respiration. Reduced spare respiration capacity was also noted in response to the stressors. Similarly reduced ECAR and reduced glycolytic reserve was also noted in Alzheimer's patients, indicating impaired oxygen independent mitochondrial respiration. Discussion: This pilot study demonstrates that there is an impaired mitochondrial and glycolytic function in the peripheral blood cells. This indicates towards a systemic nature of the disease and a potential future bio-marker. Further studies should be planned in this direction.

INCREASED SERUM IL 6 ASSOCIATED WITH MORTALITY AND COGNITIVE IMPAIRMENT IN ELDERLY BRAZILIANS

Marcelo Caldeira,[1] Milena Brunialti,[2] Reinaldo Salomão,[2] Clineu Almada Filho,[3] and Maysa Cendoroglo,[3] *1. Universidade federal de São Paulo, SAO PAULO, Sao Paulo, Brazil, 2. UNIVERSIDADE FEDERAL DE SÃO PAULO, SAO PAULO, Brazil, 3. UNIVERSIDADE FEDERAL DE SÃO PAULO, SAO PAULO, Sao Paulo, Brazil*

Immunological and inflammatory changes are gaining importance in aging as they are associated with functional limitations and mortality. Chronic inflammation associated with aging (Inflammaging) is a systemic and subclinical condition, characterized by changes in the levels of interleukins such as IL1, IL4, IL6, IL8, IL10 and TNF alpha, associated with genetic, physiological and environmental factors, whose importance is to be directly associated with morbidity and mortality in the elderly. Objective: To evaluate, through a longitudinal study, the relationship between chronic inflammation associated with aging and possible outcomes, such as cognitive changes and mortality in independent oldest old adults. Methods: were evaluated 201 elderly, aged 80 years or older, community residents, with preserved cognition, without acute diseases and with controlled chronic diseases. In a 02 years of interval, laboratory collections of inflammatory markers (IL 1, IL 4, IL6, IL10, TNF alpha and CRP) were performed and outcomes such as cognitive impairment and deaths were evaluated. Results: There was a correlation between increased serum IL6 and cognitive impairment, in the group of women (p-value = 0.008) and in the group All (p-value = 0.022). In the group of men, there was a significant difference between the increase in IL6 values (p-value = 0.028) and CRP (p-value = 0.016) in relation to deaths. Conclusion: The results of this longitudinal study showed and confirmed the positive association between changes in inflammatory markers such as IL6 and outcomes such as cognitive impairment and mortality also in elderly Brazilians.