

7th Global Experts Meeting on

NEUROPHARMACOLOGY

July 31-August 02, 2017 | Milan, Italy



Gjumrakch Aliev ^{a,b}

^a*Institute of Physiologically Active Compounds, Russian Academy of Sciences, Russia*^b*GALLY International Biomedical Research Institute Inc., USA*

Mitochondrial lesions as an earlier hallmark for liver and brain neuronal damage during the chronic ethanol self-administration in *Cynomolgus* monkeys: New challenge for treatment strategy

Introduction: Alcoholism is the third leading cause of preventable death in the United States and caused several neurological diseases. Aside from promoting cardiomyopathies, chronic alcohol consumption is associated with an increased risk of dementia, the development of liver or pancreas failure, and cancers of the oral cavity and pharynx. Although a J-shaped curve for all cause mortality has been identified for average alcohol consumption, irregular heavy drinking also carries significantly greater risks for cardiovascular and neurological disease. Alcohol induced cardiovascular and neurological diseases has a complex multigenic etiology. Significant variations in the response to chronic alcohol consumption may be related to unique genotypes that modify the metabolic response to ethanol. Future studies to further characterize the role of different genotypes will help identify those genotypes are more susceptible to chronic alcohol consumption. Mitochondria are important for providing cellular energy ATP through the oxidative phosphorylation pathway. They are also critical in regulating many cellular functions including the fatty acid oxidation, the metabolism of glutamate and urea, the antioxidant defense, and the apoptosis pathway. Mitochondria are an important source of reactive oxygen species (ROS) leaked from the electron transport chain while they are susceptible to oxidative damage, leading to mitochondrial dysfunction and tissue injury. Several studies suggested that alcoholism causes impaired mitochondrial function leads to many types of neurodegenerative diseases. Alcoholism may result in severe neurological deficits and cognitive impairments. Neuropathy and neurocognitive deficits are common among chronic alcohol users, which are believed to be associated with mitochondrial dysfunction in the brain especially cerebellum, cortex as well as liver. The specific type of brain mitochondrial ultrastructural lesions that are adversely affected by alcohol abuse has not been studied. Increasing evidence indicates that chronic alcoholism appears to be linked to oxidative damage and aging. However, the precise connection between chronic alcoholism and oxidative damage is unclear and is under investigation. Our recent gene expression analysis revealed that genes related to oxidative phosphorylation and longevity were down-regulated in the ethanol-fed monkeys, suggesting that alcohol may accelerate aging in monkeys by damaging their mitochondria.

Aim and objective: The main aim and objective of this study was to determine the effect of chronic alcohol self-administration on the mitochondrial structural changes in the livers and brains of adult female *Cynomolgus* monkeys.

Methods: Thus, we determined the alterations of mitochondrial ultrastructure in freshly fixed mitochondria from monkey brain and liver. Two groups of adult female *Cynomolgus* monkeys were trained to self-administer ethanol (4% w/v in water; n=12) or given matched maltose-dextrose (n=4) and given 12 months of 22 hr/day access to alcohol (average daily intakes ranged from 1.9-4.0 g/kg day). At the end of this period, the monkeys were sacrificed and tissues from the liver, frontal cortex and cerebellum were fixed in 4% paraformaldehyde, and then selected tissues were post-fixed with 1.25% glutaraldehyde. These tissues were processed for routine transmission electron microscopy (TEM). The neuronal and liver mitochondrial ultrastructural changes were analyzed using qualitative and quantitative electron microscopy techniques. Two independent morphologists blinded to sample identity examined and scored all electron micrographs. Mitochondria were examined in each micrograph, and each structure was scored according to the degree of injury.

Results: The ultrathin sections of liver, frontal cortex, and cerebellum from the control monkeys did not show any visible changes in mitochondria morphology upon TEM. Most notably, the mitochondria showed intact morphology and an absence

NEUROPHARMACOLOGY

July 31-August 02, 2017 | Milan, Italy

of any edema in the mitochondrial matrix. In some cases controls samples displayed presence of an age-associated decrease in the number of intact mitochondria, as well as an increase in mitochondria with broken cristae in the frontal cortex cerebellum and liver as demonstrated by electron microscopic observations compared to young monkey. In contrast, monkey's chronically self-administering ethanol showed significantly damaged mitochondria in hepatocytes and the frontal cortex, and lesser-damaged mitochondria in the cerebellum. Further, TEM of tissue from the ethanol monkeys revealed liver mitochondria to be more severely damaged than mitochondria in the frontal cortex and cerebellum. Most of the liver tissue contained fibroblasts, the liver parenchyma became a mixture of collagen and fibers. Neurons in the frontal cortex of the ethanol monkeys exhibited severely damaged mitochondria, with the damage mostly localized in the cell body. In addition, the brain tissues from throughout the frontal cortex of the ethanol monkeys showed the presence of generalized edema. Severely damaged neurons, astrocytes, and oligodendrocytes were also seen in the cerebellum of the ethanol monkeys, but degree of lesions significantly lesser than that compared to the frontal cortex. Quantitative study showed that the neuronal and liver mitochondrial damage was associated with damage in vessel wall cells, especially vascular endothelial cells.

Conclusion: Our study first time found that mitochondria are a primary target of chronic ethanol expositions in livers, frontal cortex and cerebellum in ethanol-fed monkeys that most likely initiates alcohol abused dementia and behavior.

Future Prospective: These results are useful for understanding the molecular, biochemical, and signaling mechanisms of the CNS (perhaps liver as well) mitochondrial structural lesions such as edema, cristae alteration can mitigate alcohol-related neurological disorders. We theorize that the future studies comparing the spectrum of mitochondrial pathophysiology and depending of these abnormalities from the oxidative stress-induced hypoperfusion effected cellular compartment during the aging or, more importantly, during the development of alcoholism and/or AD related pathology are warranted which can be used as new and more effective treatment strategies. We are confident that future expanding research using specific mitochondrial antioxidants such as Acetyl-L-Carnitine and alpha Lipoic Acid that already showed benefits Alzheimer's dementia, depression in the elderly, HIV infection, diabetic neuropathies, ischemia and reperfusion of the brain may be also of benefit in treating, and preventing of cognitive impairment, and liver damage caused by alcohol abuses.

Biography

Gjumrakch Aliev, MD, PhD, President "GALLY" International Biomedical Research Institute Inc., San Antonio, Texas, USA. He also hold appointment with the University of Atlanta, Atlanta, Georgia, USA as a Professor of Cardiovascular, Neuropathology, Gerontology, Health Science and Healthcare Administration. He authored and coauthored more than 500 publications in the fields of neurodegenerative diseases research (Alzheimer disease), as well as cardio- and cerebrovascular disease, cancer, and electron microscopy. He is nationally and internationally reputed in his area. Dr. Aliev's accomplishments in the area of biochemistry and cellular biology have tremendous implications for drug design towards CNS Neurological Disorders, AD, cancer, and cerebrovascular and neurodegeneration related pathologies. He is world-renowned expert in electron microscopy. His work has been published in numerous prestigious journals such as Nature Clinical Cardiology, J. Neuroscience, Circulation Research, New England journal of Medicine, Blood, J. Cellular and Molecular Medicine, Atherosclerosis, CNS Neurological Disorders & Drug Targets, International J. Biochemistry and Cell Biology, and many others which reflect his leading role in his research areas. He is currently the Editor in Chiefs for "Central Nervous System Agents in Medicinal Chemistry", "Applied Cell Biology", "World Journal of Neuroscience", "Open Journal of Psychiatry" and "Journal of Aging Science", Cardiovascular & Hematological Agents in Medicinal Chemistry as well as which by itself shows the voluminous and outstanding work he has accomplished in the area of cellular and molecular biology as well as aged associated clinical sciences. He is one of most cited authors in his fields with high impact factors.

aliev03@gmail.com

Notes: