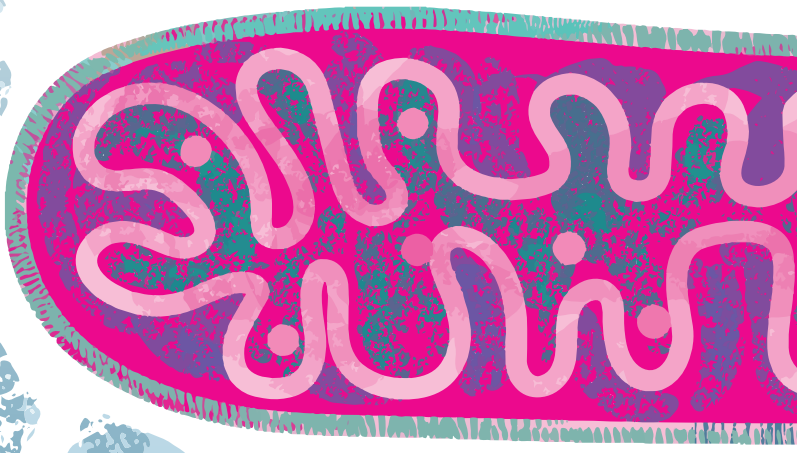
14th Conference on Mitochondrial Physiology

Mitochondrial function: changes during life cycle and in noncommunicable diseases

COST MitoEAGLE perspectives and MitoEAGLE WG and MC Meeting

MiP2019/MitoEAGLE

Belgrade, Serbia, 13-16 October 2019



PROGRAMME ABSTRACT BOOK

MiP2019/MitoEAGLE Organization

Organizing institutions and societies

Faculty of Medicine, University of Belgrade

COST Action CA15203 MitoEAGLE

The Mitochondrial Physiology Society

Organizer

The Mitochondrial Physiology Society

The MiPsociety is an international organization, based in Europe and operating world-wide and has become a legal body in 2011 continuing a tradition of rigorous mitochondrial bioenergetics, integrating molecular, cellular and organismic physiology and pathology. Membership is open to all researchers.

Committee members

Erich Gnaiger, Innsbruck, Austria; Chair since 2003

András Mészáros, Innsbruck, Austria; Co-Chair since 2018

Steven C Hand, Baton Rouge, USA; Treasurer since 2010

Petr Pecina, Prague, Czech Republic

Beata Čižmárová , Kosice, Slowakia

Carlos Palmeira, Coimbra, Portugal

Nina Krako Jakovljević, Belgrade, Republic of Serbia

General secretary: Verena Laner, Innsbruck, Austria;
General secretary since 2013

COST Action CA15203 MitoEAGLE

The MitoEAGLE network aims to improve our knowledge on mitochondrial function in health and disease related to Evolution, Age, Gender, Lifestyle and Environment. Every study of mitochondrial function and disease is faced with EAGLE as the essential background conditions characterizing the individual patient, subject, study group, species, tissue or even cell line. Membership in the MitoEAGLE network is open to all researchers sharing an interest in mitochondrial research and medicine.

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D. Swarovski Research Laboratory

Vice Chair: Elisa Calabria, University of Verona

Grant holder: Medical University Innsbruck, AT

Grant holder legal representative: Rektor Univ.-Prof. Dr. W. Wolfgang Fleischhacker

Grant holder financial representative: Ms Anita Malik

Grant Holder science representative: Ms Schartner Melanie

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Faculty of Medicine, University of Belgrade

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SMART TRAVEL PCO

A2-05

Dual role of mitochondrial damage in anticancer and antipsychotic treatment

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We analyzed the impact of mitochondrial damage in anticancer action of combining lysosomal membrane permeabilization (LMP)-inducing agent *N*- dodecylimidazole (NDI)[1] with glycolytic inhibitor 2-deoxy-D-glucose (2DG) and in antipsychotic action of atypical antipsychotic olanzapine.

NDI-triggered LMP and 2DG-mediated glycolysis block synergized in inducing ATP depletion, mitochondrial damage and reactive oxygen species production, eventually leading to necrotic death of U251 glioma cells but not primary astrocytes. NDI/2DG-induced death of glioma cells was partly prevented by lysosomal cathepsin inhibitor E64 and antioxidant tocopherol, suggesting the involvement of LMP and oxidative stress in the observed cytotoxicity. Moreover, the combined oral administration of NDI and 2DG reduced *in vivo* melanoma growth in C57BL/6 mice by inducing necrotic death of tumor cells.

Based on these results, we propose that NDI-triggered LMPcauses initial mitochondrial damage that is further increased by 2DG due to the lack of glycolytic ATP required to maintain mitochondrial health. This leads to a positive feedback cycle of mitochondrial dysfunction, ATP loss, and reactive oxygen species production, culminating in necrotic cell death.

We also investigated the role of autophagy, a controlled cellular self-digestion process, in regulating survival of neurons exposed to olanzapine. Olanzapine induced autophagy in human SH-SY5Y neuronal cell line, as confirmed by the increase in autophagic flux and presence of autophagic vesicles, fusion of autophagosomes with lysosomes, and increase in the expression of autophagy-related (ATG) genes ATG4B, ATG5, andATG7. The production of reactive oxygen species, but not modulation of the main autophagy repressor mTOR or its upstream regulators AMP-activated protein kinase and AKT1, was responsible for olanzapine-triggered autophagy. Olanzapine-mediated oxidative stress also induced mitochondrial depolarization and damage, and the autophagic clearance of dysfunctional mitochondria [2] was confirmed by electron microscopy, colocalization of autophagosome associated MAP1LC3B (LC3B) and mitochondria, and mitochondrial association with the autophagic cargo receptor p62. While olanzapine-triggered mitochondrial damage was not visibly toxic to SH-SY5Ycells, their death was readily initiated upon the inhibition of autophagy with pharmacological inhibitors, RNA interference knockdown of BECN1 and LC3B. The treatment of mice with olanzapine increased the brain levels of LC3B-II and mRNA encoding Atg4b,Atg5, Atg7, Atg12, Gabarap, and Becn1.

These data indicate that olanzapine-triggered autophagy protects neurons from otherwise fatal mitochondrial damage, and that inhibition of autophagy might unmask the neurotoxic action of the drug.

References;

1. Repnik U, Turk B (2010) Lysosomal-mitochondrial cross-talk during cell death. Mitochondrion10: 662-669.
2. Wang K, Klionsky DJ(2011) Mitochondrial removal by autophagy. Autophagy 7:297-300.