REDOXBA **2023**

Workshop on Redox Nutrition and Toxicology

School of Pharmacy and Biochemistry,
University of Buenos Aires.
Buenos Aires, Argentina

November **12-14, 2023**

Organizing Committe

Silvia Alvarez

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Program at a glance

Workshop on Redox Nutrition and Toxicology

Sunday, November 12th	
14:00-15:00	Registration
Session I	Redox biochemistry: hot topics in 2023
15:00-16:30	Lectures by Invited Speakers
16:30-17:00	Coffee break
17:00-18:30	Lectures by Invited Speakers
18:30-19:00	Talks selected from abstracts
Monday, November 13th	
Session II	Redox nutrition
09:30-10:30	Lectures by Invited Speakers
10:30-11:00	Talks selected from abstracts
11:00-11:30	Coffee break
11:30-13:00	Lectures by Invited Speakers
13:00-14:15	Lunch break
Session III	Redox Toxicology
14:15-15:45	Lectures by Invited Speakers
15:45-16:15	Talks selected from abstracts
16:15-16:45	Coffee break
Session IV	Redox chemistry in biology
16:45-17:45	Lectures by Invited Speakers
17:45-18:30	Talks selected from abstracts
Tuesday, November 14th	
Session V	Redox biochemistry by young investigators
09:30-13:00	Oral presentations (5 min each)
13:00-13:10	Closing ceremony

WORKSHOP ON REDOX NUTRITION AND TOXICOLOGY

BUENOS AIRES, NOVEMBER 12-14, 2023

Program

Day 1 – Sunday, November 12, 2023

14:45-15:00 Opening

Session I – **Redox biochemistry: hot topics 2023**

Chairpersons**: Patricia I. Oteiza,** University of California, Davis, USA
Fernando Dominici, University of Buenos Aires, Argentina

15:00-15:30 **Kelvin J. A. Davies,** University of Southern California, USA
The role of proteases in adaptive homeostasis

15:30-16:00 **Henry Forman,** University of Southern California, USA
Biochemical and physiological limitations of antioxidant therapy

16:00-16:30 **Juan Sastre,** University of Valencia, Spain
Redox signaling in necroptosis

16:30-17:00 Coffee break

Chairpersons**: Silvia Alvarez,** University of Buenos Aires
Verónica D'annunzio, University of Buenos Aires

17:00-17:30 **Francisco Laurindo,** University of Sao Paulo, Brazil
Breaking the protein disulfide isomerase code for redox signaling and homeostasis

17:30-18:00 **Gabriela Salvador,** National University of Bahia Blanca, Argentina
Lipid reprogramming in neuronal ferroptosis

18:00-18:30 **Darío C. Ramirez.** National University of San Luis, Argentina
Mechanism-based and potential therapeutic applications of the nitrone spin trap DMPO for the treatment of inflammatory diseases

18:30-18:45 **Ailén Hvozda Arana**, University of Buenos Aires, Argentina.
Experimental glaucoma induces alterations in mitochondrial dynamics in the primary visual cortex

18:45-19:00 **Mariana Holubiec**, IBCN-CONICET, Argentina
Tau and mitochondria: Can mutations in tau lead to abnormal mitochondrial function?

Day 2 – Monday, November 13, 2023

Session II – **Redox Nutrition**

Chairpersons**: César G. Fraga,** University of Buenos Aires, Argentina
Gabriela Berg, University of Buenos Aires, Argentina

9:30-10:00 **Patricia I. Oteiza,** University of California-Davis, USA
The regulation of NOX1 by plant bioactives: relevance for intestinal physiology and pathology

10:00-10:30 **Andrés Trostchansky,** University of the Republic, Uruguay
Natural polyphenols modulate platelet aggregation and activation by redox mechanisms involving thiol isomerases and mitochondrial function

10:30-10:45 **Analía Karadayian**, University of Buenos Aires, Argentina
Understanding the mechanism of alcohol hangover: the role of acetaldehyde

10:45-11:00 **Luciana Erjavec,** University of Buenos Aires, Argentina
Resveratrol exerts different effects on renal epithelial cells depending on media osmolality

11:00-11:30 Coffee break

Chairpersons**: Mónica Galleano,** University of Buenos Aires, Argentina
Ana Adamo, University of Buenos Aires, Argentina

11:30-12:00 **Angela Mastaloudis,** Brassica Protection Products, USA
Sulforaphane protect intestinal cell monolayers from inflammation/oxidative stress-induced permeabilization

12:00-12:30 **José Viña**, University of Valencia, Spain
Nutritionally-based successful therapies to delay progression to Alzheimer's disease

12:30-13:00 **Marzia Perluigi,** Sapienza University of Rome, Italy
Targeting brain energy metabolism to prevent cognitive decline

13:00-14:15 Lunch break

Session III – **Redox Toxicology**

Chairpersons**: Natalia Magnani,** University of Buenos Aires, Argentina
María C. Fernandez, University of Buenos Aires, Argentina

14:15-14:45 **Florian Gruber,** Medical University of Vienna-CDL SKINMAGINE, Austria
Multimodal imaging of ultraviolet light effects on the epidermal lipidome and metabolic activity

14:45-15:15 **Valerie Schini-Kerth,** University of Strasbourg, France
Fine dust and nano- plastics-induced premature endothelial senescence and dysfunction

15:15-15:45 **Pablo Evelson**, University of Buenos Aires, Argentina
Underlying mechanisms of the effects of particulate matter in primary and distant organs

15:45-16:00 **Pablo E. Tapia**, Nacional University of Tucumán, Argentina
Lemon wastes as a resource of antioxidant agents and their toxicological profiles in multiple models

16:00-16:15 **Mariana Garcés,** University of Buenos Aires, Argentina
In vitro protective role of ibuprofen-curcumin micelles against oxidative stress and inflammasome activation mediated by indoor pollution exposure

16:15-16:45 Coffee break

Session IV – **Redox chemistry in biology**

Chairpersons**: Karina Alleva,** University of Buenos Aires, Argentina
Alejandra Erlejman, University of Buenos Aires, Argentina

16:45-17:15 **Camilo López-Alarcón**, University of Chile, Chile
Key enzymes of the pentose phosphate pathway as targets of peroxyl radicals: consequences for NADPH production

17:15-17:45 **Darío Estrín**, University of Buenos Aires, Argentina
Computer simulation of the interaction of reactive sulphur- and nitrogen-species with heme-proteins

17:45-18:00 **Carolina Lorente,** National University of La Plata, Argentina
Avoiding one-electron oxidation of tyrosine by DOPA

18:00-18:15 **Sandra E. Gomez Mejiba**, National University of San Luis, Argentina
Inmunospin trapping of DNA-centered radicals in a mouse model of Acute lung Distress Respiratory Syndrome (ADRS)

18:15-18:30 **Ana Sofía Valles**, National University of the South, Argentina
Maternal metabolic syndrome affects the progeny's redox balance and increases neuroinflammation with neurodevelopmental and metabolic adverse consequences

Day 3 – Tuesday, November 14, 2023

Session V– **Redox biochemistry by young investigators**
Oral presentations (5-min flash presentations from submitted abstracts)

Chairpersons**: Tamara Zaobornyj**, University of Buenos Aires, Argentina
Virginia Vanasco, University of Buenos Aires, Argentina

09:30-09:38 **Agostina Aramburu**, Department of Biological Chemistry/IQUIBICEN-CONICET, Department of Industry/ITAPROQ-CONICET,

Antioxidant activity of natural polyphenols from fibre microparticles of japanese plum (*Prunus salicina)* and sweet cherry (*Prunus avium* L.).

09:38-09:46 **Agustina Camporino**, Universidad de Buenos Aires, Facultad de Ciencias Veterinarias, Instituto de Investigación y Tecnología en Reproducción Animal (INITRA), Buenos Aires, Argentina.
Impact of carbonyl cyanide 3-chlorophenyl hydrazone (CCCP) treatment in ROS production and meiotic progression during the in vitro maturation of porcine oocytes.

09:46-09:54 **Julieta Borello**, Centro de Excelencia en Productos y Procesos, Córdoba; Ministerio de Ciencia y Tecnología de Córdoba, Argentina.
Veterinary drugs in effluents from the dairy region of Córdoba, Argentina, used as fertilizer for horticultural crops. Risk of bacterial resistance in water for human and animal consumption.

09:54-10:02 **Jonathan Chevriau**, Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Departamento de Fisicomatemática, Cátedra de Física, Argentina, QUIFIB, UBA-CONICET, Argentina.
Diversity and Mechanism of Hydrogen Peroxide Transport Across MIP Channels

10:02-10:10 **Florencia de la Rosa**, Instituto de Ciencias Básicas y Experimentales, Universidad de Morón; Consejo Nacional de Investigaciones Científicas y Técnicas de Argentina.
Lipid shifts in the invasive bivalve Limnoperna fortunei grazing on Microcystis aeruginosa during a heatwave simulated conditions.

10:10-10:18 **Heryerli Fernandez**, Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicadas (INIFTA), Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata (UNLP), CCT La Plata-CONICET.
Antioxidant properties of vanillin during photosensitized oxidation of biomolecules.

10:18-10:26 **Tomás A. Gadze**, Universidad de Buenos Aires, Facultad de Ciencias Veterinarias, Instituto de Investigación y Tecnología en Reproducción Animal (INITRA), Buenos Aires, Argentina.
Effect of Trolox on oocyte oxidative status during in vitro maturation of bovine oocytes.

10:26-10:34 **Miriam Virgolini**, Instituto de Farmacología Experimental de Cordoba, CONICET; Departamento de Farmacología Otto Orsingher, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Argentina.
Ferrostatin-1 mitigates cellular damage in a ferroptosis-like environment in Caenorhabditis elegans.

10:34-11:00 **Coffee break**

11:00-11:08 **Agustina Freire,** Universidad de Buenos Aires. Instituto de Bioquímica y Medicina Molecular (IBIMOL UBA-CONICET), Facultad de Farmacia y Bioquímica. Buenos Aires, Argentina.
Urban Air Exposure in Buenos Aires City Induces Neuroinflammation, Oxidative Stress, and Olfactory Bulb Functional Alterations in Mice.

11:08-11:16 **Romina Higa,** Laboratory of Reproduction and Metabolism. CEFYBO-CONICET. School of Medicine, University of Buenos Aires, Argentina.
Advanced maternal age increases lipid oxidative damage of the decidua during early pregnancy in rats.

11:16-11:24 **Agustin Lucini Mas,** Instituto de Ciencia y Tecnología de Alimentos Córdoba. (ICYTAC-CONICET) SeCyT - Universidad Nacional de Córdoba, Córdoba, Argentina.Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba, Argentina.
Sesame Defatted Flour Supplementation: Effects in Carbohydrate Metabolism and Redox State in High-Fructose/High-Saturated Fatty Acids Diet-Fed Mice.

11:24-11:32 **Sofía Reynoso,** Universidad de Buenos Aires, Instituto de Bioquímica y Medicina Molecular Prof. Alberto Boveris (IBIMOL-UBA-CONICET), Buenos Aires, Argentina.
The urban particulate matter exposure induced-oxiinflammatory response impairs lung damage repair mechanisms.

11:32-11:40 **Juan Santiago Adán Areán,** Instituto de Bioquímica y Medicina Molecular "Prof. Alberto Boveris", Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires.
Mitochondrial pathways in endotoxemia: bioenergetics and ROS production in H9c2 cardiomyocytes.

11:40-11:48 **Ezequiel Hid,** Fisicoquímica, Fac. de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina. 2 CONICET- Universidad de Buenos Aires (IBIMOL), Buenos Aires, Argentina.
(-)-Epicatechin administration attenuates NFkappaB activation through NOX modulation in perivascular adipose tissue of high fructose fed rats.

11:48-11:56 **Analía Czerniczyniec**, Instituto de Bioquímica y Medicina Molecular Profesor Alberto Boveris (UBA-CONICET), Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina.
Differences in mitochondrial function between brain and heart of rats exposed to hyperbaric hyperoxia treatment. Role of nitric oxide.

12:00-12:10 **Closing Ceremony**

Experimental glaucoma induces alterations in mitochondrial dynamics in the primary visual cortex

Hvozda Arana AG[1;3], Caltana L[4], Adán Arean JS[2,3], Chao J[1], Reides CG[1,3], Lerner SF[1], Álvarez S[2,3], Lasagni Vitar RM[1,3], Ferreira SM[1,3]

[1]Universidad de Buenos Aires. Facultad de Farmacia y Bioquímica. Departamento de Ciencias Químicas. Cátedra de Química General e Inorgánica. Buenos Aires, Argentina. [2]Universidad de Buenos Aires. Facultad de Farmacia y Bioquímica. Departamento de Ciencias Químicas. Cátedra de Fisicoquímica. Buenos Aires, Argentina. [3]CONICET- Universidad de Buenos Aires. Instituto de Bioquímica y Medicina Molecular (IBIMOL), Buenos Aires, Argentina. [4]CONICET- Universidad de Buenos Aires. Instituto de Biología Celular y Neurociencia "Prof. E. De Robertis", Buenos Aires, Argentina.

Background and aims: Glaucoma is the first irreversible cause of blindness worldwide and affects eye structures and brain areas related to the visual system. It is known that oxidative stress plays an important role in the development and progression of the disease. The aim of this work was to evaluate the mitochondrial dynamics in the primary visual cortex in a glaucoma model.
Methods: Wistar rats, three-month old, were operated by cauterizing two of the episcleral veins in the left eye: glaucoma group (G n=8); whereas the control group (n=8) received a sham procedure. Seven days after surgery rats were euthanized, and the primary visual cortex was dissected. In the G group, both hemispheres were separated, the ipsilateral (GI) and contralateral (GC) (CICUAL FFyB n° 3314). We evaluated OPA-1 expression in mitochondrial fraction, DRP-1 expression in both mitochondrial and cytosolic fractions, and PGC-1α expression in primary visual cortex homogenates. Mitochondrial ultrastructure was studied by transmission electron microscopy (TEM).
Results: GC and GI showed an increase of 47% and 58%, respectively, in OPA-1 expression in the mitochondrial fraction when compared to control ($p<0.01$). Regarding DRP-1 expression, only GI cytosolic fraction showed 22% of increase ($p<0.01$), with no changes in GC and mitochondrial fraction when compared to control group. However, there were no changes in PGC-1α expression in GC and GI compared to control group. Finally, TEM images showed a slight clarification, swelling and disruption of mitochondrial internal structure in GC and GI compared to control group.
Conclusions: These results suggest that glaucoma impairs mitochondrial dynamics, showing an increase in the fusion process, with no changes in fission process and biogenesis. In addition, mitochondrial ultrastructure is altered in the primary visual cortex. Understanding the key drivers of mitochondrial impairment in glaucoma is crucial to identify new therapeutic targets that would halt disease progression.

Tau and mitochondria: Can mutations in tau lead to abnormal mitochondrial function?

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Tau has been described as a modulator of microtubule dynamics and axonal transport. Different mutations in the protein have been associated with the induction of specific phenotypes in different diseases called Tauopathies, characterized by the abnormal accumulation of tau. Since tau hyperphosphorylation and aggregation have been linked to defects in mitochondrial processes, our goal is to understand whether tau can regulate the general redox state of the neuron as well as the biodynamics and redox homeostasis of mitochondria. Experiments performed by our group showed an increased oxidative state and heightened mitochondrial vulnerability in human organoids modelling Alzheimer´s disease that presented increased tau phosphorylation. Elevated levels of mitochondrial hydrogen peroxide and superoxide anion were coupled with increased mitochondrial fragmentation and loss of mitochondrial membrane polarization under oxidative conditions. Therefore, our goal is to investigate whether tau mutations are associated to changes in mitochondrial homeostasis and redox regulation. To this end, we generated human glutamatergic neurons from induced pluripotent stem cells (hiPSCs) from a V337M Tau-mutant donor and an isogenic control. In this model, we will assess the overall redox status using a battery of ratiometric probes (Hyper7 and roGFP), targeted to different intracellular locations. This will be coupled with a comprehensive metabolic analysis performed using the Seahorse apparatus. Furthermore, we will analyse changes in mitochondrial function, morphology and movement along the axon. In conclusion, these approaches will enable us to further determine whether mutations in tau that lead to its aggregation and hyperphosphorylation are responsible for impaired redox regulation and altered mitochondrial homeostasis.

Understanding the Mechanism of Alcohol Hangover: the role of acetaldehyde

Karadayian A[1], Carrere L[1], Czerniczyniec A[1], Guerra JI[1], Lores-Arnaiz S[1]

[1]Instituto de Bioquímica y Medicina Molecular Profesor Alberto Boveris (UBA-CONICET), Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina.

Alcohol hangover (AH) is characterized by physical and mental symptoms experienced after heavy drinking, occurring when blood alcohol concentration (BAC) approaches zero. We investigated the role of acetaldehyde in the deleterious effects of AH on mitochondrial function at brain cortex synapses. Using 4-methylpyrazole (4MP), an alcohol dehydrogenase (ADH) inhibitor, we aimed to elucidate the impact of acetaldehyde on AH-induced mitochondrial dysfunction.
Male Swiss mice were divided into four groups: saline (control), 4MP (10 mg/kg), ethanol (3.8 g/kg, AH group), and 4MP-ethanol. Animals were sacrificed after 6 hours (BAC=0), and brain cortex synaptosomes were isolated. We found that 4MP strongly prevented the impairment of mitochondrial respiration, respiration-driving ATP synthesis, and coupling efficiency induced by AH. Treatment with 4MP prevented the reduction in enzymatic activity of mitochondrial complex I-III and II-III caused by AH, while the activity of complex IV only partially recovered, remaining 50% lower than in the control group. Interestingly, exposure to 4MP alone reduced the activity of respiratory complex I-III, II-III and IV. Together with this, 4MP treatment restored ATP production and mitochondrial membrane potential, which were reduced by 41% and 48% in the AH group, respectively. Notably, decrements in acetaldehyde levels did not exert any effect on nitric oxide (NO) metabolism. Interestingly, exposure to 4MP alone reduced the activity of respiratory complex I-III, II-III and IV. *In vitro* exposure of brain cortex synaptosomes to 4MP attenuated respiratory complex activity and NO content.
Our results suggest the role of acetaldehyde as the main responsible for AH-induced mitochondrial dysfunction at brain cortex synapses. The impairment of NO metabolism, not prevented by 4MP, may be attributed to the presence of residual ethanol after ADH inhibition.
Understanding these mechanisms can provide valuable insights for the development of targeted interventions to alleviate the negative consequences of alcohol abuse.

Resveratrol exerts different effects on renal epithelial cells depending on media osmolality

Erjavec LC[1,2], Parra LG[1,2], Sendyk DE[1,2], Tulino MS[3], Lopez Nigro M[3,4], Carballo M[3,4], Casali, CI[1,2], Fernández MC[12].

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Resveratrol is a natural polyphenol present in several plants. Nowadays it is commonly sold as an over-the-counter nutraceutical supplement mainly due to its antioxidant properties. Paradoxically, it has been shown to also exhibit pro-oxidizing effects depending on concentration, treatment duration, and cell type. Resveratrol effects on renal tissue also remain controversial, with some models suggesting benefits and others noting nephrotoxicity without apparent cause. Renal medullary interstitium presents a high osmolality due to sodium and urea accumulation that can significantly fluctuate depending on the body's hydration status. Initially, cells activate protective mechanisms to survive in this environment, but then hyperosmolality also works as a physiological signal for cell differentiation. In this work we evaluate resveratrol effect both on cells cultured in isosmolality or subjected to physiological hyperosmolarity, particularly on osmoadaptation and differentiation mechanisms. MDCK cells were pretreated with different resveratrol concentrations (1-25 µM) and then cultured in isosmolar (ISO) or hyperosmolar (HYPER) media for 24 and 48 hours. Results showed that resveratrol reduced cell number and viability in a concentration-dependent manner in HYPER but not ISO cells. Cell cycle analysis indicated that resveratrol increased S-phase and sub-G0 populations in HYPER but not ISO cells. Comet assay showed an increase in DNA damage with resveratrol and in PARP protein cleavage in HYPER cells, which can explain the increase in S-phase and sub-G0 populations. RSV-treated HYPER cells did not exhibit typical epithelial morphology and, at high concentrations, displayed a mesenchymal phenotype. Resveratrol also activated NFκB, evidenced by an increased expression of its target mRNAs, translocation to the nucleus, and transcriptional activation through luciferase reporter assay. Our results suggest that resveratrol concentrations exceeding 5 µM had significant toxic effects on renal cells exposed to physiological hyperosmolality, but not on cells in isosmolality. These findings contribute to explain resveratrol controversial effects in renal models.

Lemon wastes as a resource of antioxidant agents and their toxicological profiles in multiple models

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Lemon production in the northwest represents 95.6% of Argentine production. *Citrus limon* wastes consists mainly of peels and pressed pulp (seeds and membranes), which represent ~50% of the fruit weight after industrial processing. From an environmental point of view, it is essential to take advantage of these residues. In this work, we determined the chemical composition of peel (C), liquid effluent (LE) and solid effluent (SE) extracts and their antioxidant, eco-toxic, cytotoxic and acute toxic effects. The extracts were obtained by consecutive extractions with a hydro-alcoholic solution.
Phenolic compounds resulted for SE: 61.11, LE: 40.81 and C: 32.73 mg EAG/g PS (Gallic Acid Equivalent). From HPLC-DAD the following main compounds were identified: Caftaric acid > 4,5-di-O-caffeoylquinic acid > (-)-Epicatechin > Naringin > Vanillic acid in C; Ellagic acid > 4,5-di-O-caffeoylquinic acid > Naringin > (+)-Catechin > Caftaric acid in EL, and finally in ES: Ellagic acid > 4,5-di-O-caffeoylquinic acid > Caftaric acid > Naringin > Kaempferol-3-O-ruthinoside.
SE showed the best antioxidant capacity (71.19 mg EAG/g PS), the free radical scavenging capacity were for: $ABTS^{\cdot+}$ SC_{50} 45.15 µg/ml, nitric oxide SC_{50} 217 µg/ml, superoxide anion SC_{50} 611.14 µg/ml, and hypochlorite SC_{50} 10.30 µg/ml; while the iron chelating, Fe^{3+} ion reducing, and cupric ion reducing capacities resulted CC_{50} 917.98 µg/ml, RC_{50} 44.63 µg/ml, and 56.80 mg EAG/g PS, respectively.
In the toxicity tests, all extracts (1000 µg/ml) did not affect the HT29-MTX and Caco-2 cell viability by the MTT assay, nor the aquatic bioindicator *Lemna minor*. Only C (250 µg/g) reduced the viability of terrestrial isopod *Armadidillium vulgare*, and SE (500 µg/ml) stopped bacterial growth of *Bacillus subtilis*. Extracts had a moderate toxicity against salt-water crustacean *Artemia salina* (LD_{50} 100-500 µg/ml). In conclusion, the biological potential of lemon residue extracts justifies future *in vivo* studies for its sustainable and healthy applications.

In vitro protective role of ibuprofen-curcumin micelles against oxidative stress and inflammasome activation mediated by indoor pollution exposure

Garcés M[1], Pecorelli A[2],Vallese A[2], Moretton M[3], Magnani N[1],, Chiapetta D[2], Alvarez S[1], Evelson E[1], Valacchi G[2,4]

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The exposure to indoor particulate matter (PM) impairs redox metabolism and promotes inflammation, which aggravates respiratory diseases. Lung epithelial cells are suggested to play a central role in this scenario by the release of inflammatory and oxidative stress mediators following PM uptake. Here, we aim to study the pathways leading to redox metabolism alterations and NLRP3 inflammasome activation in A549 cells exposed to indoor dust (ID) up to 24 h using 25 and 100 µg/mL doses. As a therapeutic approach, we develop nanomicelles to co-encapsulate ibuprofen and curcumin. Characterization of ID showed high content of transition metals while particle size distribution corresponds to fine and ultrafine PM. Viability was not significantly affected under the experimental conditions. Intracellular redox status was assessed by DCF intensity and SOD activity, which were increased after exposure to 100 µg/mL ID ($p<0.001$; $p<0.0001$). Moreover, oxidative damage to lipids as 4-HNE protein adducts was observed after 24 h ($p<0.0001$). Additionally, dose-and time-dependent NFkB nuclear translocation and NLRP3-inflammasome activation was evidenced by increased signal of ASC and NLRP3 after 100 µg/mL ID exposure. Moreover, increased expression of ASC and NLRP3 was also observed at 3 and 6 h ($p<0.001$; $p<0.05$). Consistently, increase in IL-1β levels after 3 h of ID 100 µg/mL exposure ($p<0.001$) was found. As a consequence, alteration in wound healing process ($p<0.05$) and necrosis and apoptosis was observed after 24 h. Interestingly, pretreatment with nanomicelles attenuate the alterations observed due to Nrf2 nuclear translocation ($p<0.01$) and further increase in HO-1 expression ($p<0.001$). Our findings contribute to the understanding of the mechanisms by which ID promotes inflammation and oxidative stress. Nanomicelles containing curcumin and ibuprofen could be a promising therapeutic approach.

Avoiding one-electron oxidation of tyrosine by DOPA

Neyra Recky J. R., Serrano M. P., Dántola M. L., **Lorente C.**

INIFTA, Facultad de Ciencias Exactas, Universidad Nacional de La Plata. CCT-La Plata CONICET

Photosensitized oxidation of proteins induced intermolecular and/or intramolecular cross-linking, depending on the protein nature and the environment conditions. Several amino acids participate in cross-linking due to the formation of a covalent bond between two identical or different amino acids. The amino acids involved in crosslinking are mainly tyrosine, histidine, tryptophan, lysine, cysteine. From a biomedical point of view, cross-linking of proteins is involved in pathologies such as cataracts, photoaging, and inactivation of enzymes.
Tyrosine is an amino acid related to crucial physiological events and its oxidation, that produce beneficial or detrimental effects on biological systems, has been extensively studied. Degradation of tyrosine often begins with the loss of an electron in an electron transfer reaction in the presence of a suitable electron acceptor. The reaction is facilitated by excited states of the acceptor in photosensitized processes. Several products of tyrosine oxidation have been described, the main ones being 3,4-dihydroxy-L-phenylalanine (commonly known as DOPA) and tyrosine dimers. The latter are responsible of protein cross-linking.
We have observed that tyrosine is recovered from tyrosyl radical, after one-electron oxidation, in the presence of DOPA. We propose that under high oxidative stress the oxidation of tyrosine may be controlled, in part, by one of its oxidation products. Also, we present strong evidence of antioxidant action of DOPA by preventing tyrosine dimerization, one of the most serious oxidative protein modifications, and the origin of structural modifications leading to the loss of protein functionality.
In consequence, under oxidative stress the formation of DOPA, avoids tyrosine dimer formation between two neighboring tyrosine residues.

Maternal metabolic syndrome affects the progeny's redox balance and increases neuroinflammation with neurodevelopmental and metabolic adverse consequences

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** Both authors contributed equally to this work.*
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Various lifestyle factors, including diet, can impact on redox balance and brain health. Consumption of fructose-sweetened beverages has drastically increased in the last decades and is widely associated with metabolic disease, systemic proinflammatory status and adverse transgenerational effects. To date, the impact of maternal fructose intake in brain redox balance and function of the offspring is less explored. We investigated whether the progeny of mothers with Metabolic Syndrome (MetS), induced by *ad libitum* consumption of a 20% fructose solution, present any redox alteration in the brain as a consequence of being gestated in a metabolic altered intrauterine environment.
Wistar rats were randomly separated into two groups with access to water or fructose (20% w/v in water) for 10 weeks. After MetS was confirmed, dams were mated with control males and continued drinking water or fructose solution during gestation. At postnatal day (PN) 1, a subgroup of offspring of each sex was sacrificed and brains were dissected for oxidative stress and inflammatory status analysis. The developmental milestones and behavioral test were also evaluated (PN3-PN100) in another subgroup of offspring to identify any long-term consequence to being gestated by a dam with MetS.
Maternal MetS affects the redox balance and increases neuroinflammation in female offspring at birth. Sexually dimorphic effects were also found on the progeny's acquisition of neurodevelopmental milestones and in their psychiatric, cognitive and metabolic state.
Although direct extrapolation of our findings cannot be made to humans, the results presented herein reinforce the necessity of considering the potentially negative effects of fructose-induced MetS prior to, and during pregnancy in offspring’s brain and metabolic physiology.

Session V- **Redox biochemistry by young investigators**

Antioxidant activity of natural polyphenols from fibre microparticles of japanese plum (*Prunus salicina)* and sweet cherry (*Prunus avium* L.)

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Japanese plum and sweet cherries discarded during harvesting can be a useful source of bioactive compounds, recovering valuable compounds such as polyphenols. Natural polyphenols were co-extracted in fiber microparticles (MPCs) obtained from plum and sweet cherries discarded at harvest. This work aimed to evaluate the antioxidant capacity and cytotoxicity of polyphenols co-extracted in MPCs obtained from plum and sweet cherries. MPCs obtained after saturated steam blanching of fruit, processing with deionized water and freeze-drying, retained polyphenolic compounds: pentameric proanthocyanidins (200 ± 20 mg/100 g MPCs) from plums and tetrameric proanthocyanidins (631 ± 34 mg/100 g MPCs) from sweet cherries, and smaller amounts of anthocyanins, flavonoids, and hydroxycinnamates in both. Undifferentiated (ND: 3d culture) and differentiated (DIF: 21d) Caco-2 cells were used as a model of the intestinal epithelial cells. The antioxidant activity of polyphenols was evaluated by dichlorofluorescence (DCF) assay. Oxidative stress was induced with tert-butyl-hydroperoxide (t-BOOH) 3mM for 1h. ND cells co-incubated with plum polyphenol extract (0.5-10.0 µg/mL), presented an antioxidant activity with concentration dependence, reaching a 100% of protection with 10 µg/mL, and 20% for DIF cells for the same concentration ($p<0.001$). Whereas, when ND Caco-2 cells were co-incubated with sweet cherries polyphenol extract (0.5-10.0 µg/mL), as well was obtained an antioxidant activity, with concentration-dependent manner, and was achieved 20% and 50% protection, for ND and DIF cells respectively, for 10.0 µg/mL ($p<0.05$). In conclusion, natural polyphenols extracted from fiber MPCs of plums and sweet cherries showed a protective effect against oxidative stress, with low cytotoxicity. This effect was comparable for Caco-2 ND and DIF cells. Therefore, MPCs of plum skin and sweet cherries may constitute a natural source of polyphenols. We propose the upcycling of natural polyphenols, which could be considered as antioxidant and may exert cytoprotective actions in the gastrointestinal tract by decreasing oxidative stress.

Impact of carbonyl cyanide 3-chlorophenyl hydrazone (CCCP) treatment in ROS production and meiotic progression during the *in vitro* maturation of porcine oocytes

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During *in vitro* maturation (IVM) a series of modifications take place in the oocyte, which lead to its developmental competence and imply a variation in reactive oxygen species (ROS) production. The aim of this study was to evaluate meiotic progression and ROS production in porcine oocytes during IVM in the presence or absence of carbonyl cyanide 3-chlorophenyl hydrazone (CCCP) as mitochondrial electron transport chain uncoupler. Cumulus-oocyte complexes (COCs) obtained by aspiration of antral follicles from ovaries of slaughtered gilts were incubated in 199 medium supplemented with 50 µg/ml gentamicin sulfate, 10% (v/v) porcine follicular fluid, 0.57 mM cysteine, 0.5 µg/ml FSH and 0.5 µg/ml of LH at 39ºC, 5% CO_2 in a humidified atmosphere for 44h. At 12h of IVM, COCs were treated with 0 (control), 0.5 or 1 µM CCCP. At 0, 12, 24, 36 and 44h of IVM, cohorts of COCs were recovered and denuded with a glass Pasteur pipette. Using epifluorescence microscopy, meiotic progression was assessed by Hoechst 33342 and ROS production by 2',7'-dichlorodihydrodiacetate (DCH_2FDA). Digital microphotographs were obtained and processed using IMAGE J software to calculate oocyte fluorescence intensity. Results were analysed by an ANOVA followed by a Bonferroni test. Between 0 and 12h a significant decrease in ROS production was observed ($p<0.05$). In untreated oocytes a significant increase in ROS production was observed between 24 and 44h ($p<0.05$). In 0.5 µM and 1 µM CCCP treated samples a significant decrease in ROS production was observed between 24 and 44h ($p<0.05$) and a slower meiotic progression compared to control samples ($p<0.05$). In conclusion, a faster mitochondrial electron transport induced by CCCP would generate a descent in ROS production that could be linked to a slower meiotic progression. Future studies will analyse the ROS participation as mediators of intracellular signal transduction events related to ERK/MAPK pathway.

Veterinary drugs in effluents from the dairy region of Córdoba, Argentina, used as fertilizer for horticultural crops. Risk of bacterial resistance in water for human and animal consumption

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Wastewater and livestock feces (manure) are used as fertilizer for horticultural crops, a common practice around the world. Livestock are usually treated with drugs, and these and their metabolites, are eliminated in feces and urine. After fertilizing the soil with these effluents, drugs, especially antibiotics (AB), enter the aquatic cycle by drift during fertilization, by direct entry, by runoff from treated fields, and by leaching of waste into groundwater with the risk of causing bacterial resistance to AB. This study aimed to investigate antibiotics and other veterinary drugs in manure and wastewater from dairy farms in the Central Argentine Dairy Basin in the Northeast Region of Córdoba. Using LC-MS/MS, Ivermectin, Tetracycline, Oxytetracycline, Tylosin, Spiramycin, Enrofloxacin, Ceftiofur, Flunixin, Ampicillin, Amoxicillin, Penicillin G, and Flunixin were investigated. Fifty-three samples of cow manure, wastewater, and random samples of fresh feces were collected from each establishment. The highest frequency of appearance of the drugs in the effluents was Tylosin < Tetracycline < Spiromycin < Enrofloxacin < Oxytetracycline < Flunixin (13 to 84.9%) and the concentrations were between 0.1-12.1 µg/L. In feces, the frequencies were Ivermectin < Enrofloxacin < Spiromycin < Flunixin < Tetracycline < Oxytetracycline (1.9-26.4%) and concentrations varied between 2-86.4 µg/kg. In both effluents and feces, Oxytetracycline was found in higher concentration and frequency regardless of the type of production (confined or grazed), the size of the dairy (> or < 182 animals), or its productivity (high or low). The anti-inflammatory Flunixin seems with high frequency (84.9%) but low concentration (0.01-11.20 µg/kg) in liquid effluents and its presence in manure is low frequency (18.9%) but high concentration (1.30-124.00 µg/kg). Fertilizing the soil with manure and effluents contaminated with antibiotics carries a risk of generating resistant bacteria and contaminating underground watercourses, a water source for human and animal consumption.

Diversity and Mechanism of Hydrogen Peroxide Transport Across MIP Channels

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Hydrogen peroxide (H_2O_2) is a fundamental second messenger and the study of its difussion through membranes, in and between cells, has received an impulse when it was clarified that it involves channels belonging to the MIP (membrane intrinsic protein) family. Some MIPs channels are known as aquaporins (AQP), due to its capacity to permeate water, but this family also includes channels that permeate H_2O_2, known as peroxiporins. The physicochemical properties of H_2O_2 and H_2O are remarkably similar and have led to the proposition that all AQP should be a peroxiporin. However, experimental evidence doesn't show this dual aspect for all MIPs questioning the idea of mimicry. In this work, we employ sequence similarity networks (SSN) and atomistic molecular dynamics simulations (MD) to understand the diversification of H_2O_2 transport through the MIP family and to unravel the transport mechanics of H_2O_2 and H_2O across some different MIP subfamilies representatives (plant MtPIP2;3, mammalian HsAQP8 and kinetoplastid TcAQPalfa). The SSN of the MIP superfamily was generated using the EFI-EST server with UniProt information. For MD, homotetrameric channel models were created with Swiss-Model or AlphaFold and embedded in a POPC bilayer, H_2O_2 was incorporated to the system and simulations ran for up to 1µs. Preliminary results revealed: i- presence of peroxiporins in different MIP clusters and ii- H_2O_2 crossing the channel pore alongside H_2O molecules with similar dipole rotation within the channel's middle section but distinct interaction patterns for H_2O_2 and H_2O with pore-lining residues. Notably, in plant MIP channels, pH gating mechanisms controlling water permeation also regulate H_2O_2 transport. These findings have implications for the understanding of controlled transport of H_2O_2, ultimately contributing to our comprehension of critical cellular processes.

Lipid shifts in the invasive bivalve *Limnoperna fortunei* grazing on *Microcystis aeruginosa* during a heatwave simulated conditions

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The success of *Limnoperna fortunei* as an invasive freshwater bivalve species hinge on its remarkable physiological adaptability in the face of changing environmental conditions. This study aimed to probe the physiological reactions of *L. fortunei* following its consumption of *Microcystis aeruginosa*, cultivated at two different temperatures: 26°C (control) and 29°C

simulating a heatwave condition. Initially, we assessed biomass, fatty acid (FA) composition and lipid damage in the cyanobacteria cultures grown at both temperatures at varying time intervals. Subsequently, the bivalves were fed with thawed *M. aeruginosa* cells, and their FA profiles were examined after 15 days of feeding. Notably, *M. aeruginosa* exposed to 29°C exhibited the highest content of FAs 18:2ω6 and cis-18:1ω9, as well as a lower lipid peroxidation throughout the experimental time. The FA profile of the consuming species, *L. fortunei*, when fed with *M. aeruginosa* cultures grown at 29°C, diverged significantly from those fed with cultures cultivated at 26°C. This variation was marked by a substantial increase in eicosapentaenoic acid (EPA, 20:5ω3) and arachidonic acid (ARA, 20:4ω6) concentrations. It is worth noting that *L. fortunei* was already known for its physiological adaptation to thrive at 29°C. However, our results revealed a substantial biosynthesis of EPA and ARA, indicating a 70% and 40% increase, respectively, compared to those at 26°C, thus preventing lipid peroxidation of both FAs. This enhanced biosynthesis of EPA and ARA carries significant implications as a potential source of ω3 and ω6 polyunsaturated fatty acids (PUFAs) for higher trophic levels. Pelagic fishes and birds, which primarily prey on these mussels, may benefit from this transfer of the cyanobacterial response to elevated temperatures. Consequently, such transfers may exert a profound influence on the overall ecological dynamics within freshwater ecosystems.

Antioxidant properties of vanillin during photosensitized oxidation of biomolecules

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Vanillin (4-hydroxy-3-methoxybenzaldehyde) is the molecule that gives vanilla (extract from mature pods of the orchid *Vanilla planifolia),* its aromatic properties. It has been reported that vanillin has antioxidant properties.[1] However, not much is known about its antioxidant capacity in radiation mediated processes. For this reason, the main goal of this work is to evaluate if vanillin can prevent the photosensitized oxidation of biomolecules. Biomolecules are oxidized by both direct and indirect absorption of electromagnetic radiation. UV-A radiation (310-400 nm) is about of 95 % of the total UV radiation of the sun reaching the earth surface, and its poorly absorbed by biomolecules. However, UV-A degrades biomolecules through photosensitized mechanisms.[3] Pterins (Ptr) are natural compounds, present in all living systems, that can be accumulated in human skin during pathological conditions. It has been demonstrated that, under UV-A radiation, Ptr are able to oxidize biomolecules (B) such as proteins, DNA, and their components.[4] Photosensitized degradation of B by Ptr is mainly a type I mechanism and is initiated with an electron transfer from B to triplet excited state of Ptr. In this occasion, we report the efficiency of vanillin to reduce the degradation of a nucleotide (2´-deoxyguanosine 5´monophosphate, dGMP) and an amino acid (tryptophan, Trp) during UV-A irradiation in the presence of Ptr. To carry out this study, aqueous solutions of B and Ptr (pH 6, room temperature) were exposed to UV-A radiation (λexc=365 nm) during different times in presence and absence of vanillin. The photochemical reaction was studied by UV-Vis spectrophotometry, HPLC, fluorescence spectroscopy and LFP. Results indicate that the photoinduced damage of B is reduced in the presence of vanillin. The mechanistic study indicates that in our experimental conditions, although vanillin is capable to deactivate ^{3}Ptr*, the inhibition of the photosensitized process is due to the deactivation of nucleotide radicals.

Efect of Trolox on oocyte oxidative status during *in vitro* maturation of bovine oocyyes

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During in vitro maturation (IVM), oocyte oxidative status is an indicator of its ability to carry out nuclear and cytoplasmic maturation. The properties of the antioxidant trolox (T) are being analysed in different biological systems, but there is not enough evidence about the concentrations in which T could exert an effect on oocyte IVM. The aim was to study the effect of de addition of T during IVM on oocyte cytosolic oxidative status, active mitochondria, reactive oxygen species (ROS) levels, redox state, and nuclear and cytoplasmic maturation. Cumulus-oocyte complexes (COCs) recovered from ovarian follicles were matured in 199 medium for 22 hours at 39°C in 5% CO_2 in air (control) or supplemented with T 25 µM (T_1), 50 µM (T_2), or 100 µM (T_3). To determine the cytosolic oxidative status and active mitochondria, denuded oocytes were incubated for 30 minutes with MitoTracker green FM and RedoxSensor red CC-1 and the fluorescence was measured. The redox state of the denuded oocytes was evaluated by the FAD/NAD(P)H ratio by determining the autofluorescence of these compounds. To determine ROS production, denuded oocytes were incubated for 30 minutes with 5 µM 2', 7'-dichlorodihydrodiacetate fluorescein and the fluorescence was quantified. Nuclear maturation was assessed by metaphase II and cytoplasmic maturation by embryo development after in vitro fertilisation. Cytosolic oxidative status (COS) and active mitochondria in oocytes decreased significantly with T_3 respect to the

control ($p<0.05$). ROS levels in oocytes with T_1, T_2 or T_3 decreased significantly compared to the control ($p<0.05$). FAD/NAD(P)H ratio in oocytes gradually decreased with the increase in T concentration, with significant differences being observed in control and T_1 versus T_3 ($p<0.05$). Nuclear maturation rate did not vary between treatments, although a tendency to increase embryo development was observed. We conclude that supplementation of IVM medium with T may modulate oocyte oxidative status, improving oocyte developmental competence.

Ferrostatin-1 mitigates cellular damage in a ferroptosis-like environment in *Caenorhabditis elegans*

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Although iron (Fe) is the most biologically abundant transition metal, it is highly toxic when accumulated as Fe^{2+}, leading to an oxidative scenario and a type of caspase-independent programmed cell death referred to as ferroptosis. On this basis, the present study aims to evaluate the consequences of Fe^{2+} overload on lethality and on parameters involved in the redox balance in *C. elegans*. We also evaluated whether these alterations can be mitigated by compounds such as ferrostatin-1 (Fer-1), a well-known radical trapping agent that acts by reducing peroxidized lipids. On the day of the experiment, synchronized L4 wild-type N2 worms were exposed to a liquid medium (M9) containing 0, 0.5, 1.0, 1.5, or 2.0 mM $FeSO_4$ for 1 h. At the end of the exposure period, they were checked for survival, resulting in the 0.5 mM Fe^{2+} dose being used for all subsequent studies. The activity of the antioxidant enzymes glutathione peroxidase (GPx), glutathione reductase (GRx), catalase (CAT), and superoxide dismutase (SOD) was determined by spectrophotometry. Lipid peroxidation was measured using the thiobarbituric acid (TBA) assay. We demonstrated an increase in lipid peroxidation and a reduction in GPx activity, with no changes in GRx, CAT, and SOD activities. Pharmacological intervention with Fer-1 mitigated the damage and returned biochemical parameters to basal levels. Overall, these results highlight the importance of metallostasis and associated redox balance. They also have implications for developing novel therapies for diseases associated with Fe overload.

Urban Air Exposure in Buenos Aires City Induces Neuroinflammation, Oxidative Stress, and Olfactory Bulb Functional Alterations in Mice

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An increasing number of studies suggest that the brain may be a potential target of the inhalation-induced effects of particulate matter (PM) present in urban air (UA). It is postulated that the primary mechanisms of neurotoxicity induced by PM involve several alterations, involves oxidative stress and neuroinflammation. Here we aim to study the functional alterations, neuroinflammation and redox imbalance triggered by UA pollution on olfactory bulb (OB). BALB/c 8-week-old mice were exposed to filtered air (FA, control) or urban air (UA) inside whole-body chambers, located in a highly polluted area of Buenos Aires city, Argentina, for up to 4 weeks. In order to study the neuroinflammation, iNOS and GFAP expression levels, together with, *Il6* mRNA, *Il1b* mRNA, *tnfa* mRNA IL6 and TNFα levels were evaluated. After 4 weeks of UA exposure, we found an increase in all the parameters mentioned above ($p<0,05$). Additionally, UA-exposed mice showed decreased level of GSH ($p<0.05$), while GR activity and GPx expression were increased after 4 weeks ($p<0.05$). Moreover, SOD1 activity and HO-1 expression were augmented in UA exposed group ($p<0,05$). Regarding the role of reactive oxygen species in the damage mechanisms, an increased in mitochondrial H_2O_2 production together with an augmented expression of NOX2 and NOX4 isoforms were detected after 4 weeks of UA exposure ($p<0.05$). The neuroinflammation and alteration of redox homeostasis observed may explain the oxidative damage to macromolecules observed by increased levels of 4-HNE protein adducts and carbonyl groups content ($p<0,05$). After performing functional test results suggest that UA exposure leads to an alteration in short-medium term memory. Our findings contribute to unravel the mechanisms by which environmental PM promotes neurotoxicity and provide a novel insight into the alterations triggered by PM exposure that is associated with neuroinflammation and central nervous system functional impairments.

Advanced maternal age increases lipid oxidative damage of the decidua during early pregnancy in rats

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Background and Aims: Pregnancy at Advanced Maternal Age (~35 years, AMA) induces obstetric complications and neonatal adverse outcomes. During early pregnancy, an optimal decidual function is essential for a correct placenta and embryo development. FoxO1 is a transcription factor that plays a role in decidualization, placentation and embryo development by modulating genes related to oxidative stress and cell cycle withdrawal. FoxO1 can be inhibited by phosphorylation. Aim: To evaluate reproductive alterations in a rat model of AMA during organogenesis stage. In decidua of AMA rats analyze lipoperoxidation and mRNA levels of proteins of electron transport chain (ETC), FoxO1 activation and the expression of its target gene *p21*. Methods: 3 months old (Control) and 10 months old (AMA) Wistar rats were mated with young males. Decidua were obtained on day 12 of pregnancy to measure FoxO1 phosphorylation status (Western Blot), mRNA levels of *p21* (senescence marker)*, Ndufa6 and Nd1* (ETC) (RT-qPCR), lipoperoxidation (TBARS) and 4-HNE (immunohistochemistry). Results: AMA rats showed an increase in macroscopic uterine anomalies (+41%, p<0.01) and embryo resorption rate (+44%, p<0.001) as well as a decrease in the number of viable embryos (-24%, p<0.01) and crown-rump length (-11%, p<0.001). Decidua from AMA rats shows increased lipoperoxidation (+40%, p<0.05) and 4HNE immunostaining in the mesometrial region, where placenta develops, and increased *Ndufa6* and *Nd1* mRNA levels. P-FoxO1 levels were reduced (-63%, p<0.05) and total FoxO1 was unchanged. Increased mRNA levels of *p21* (+54%, p<0.05) was observed in the decidua of AMA rats. Conclusion: AMA induced alterations in the pregnant uterus and embryo development during organogenesis stage. Decidua from AMA rats showed an increased lipoperoxidation together with an increase in active FoxO1 and its target gene P21, indicating cellular senescence. Reproductive anomalies in AMA may be related to alterations in decidual metabolism.

Sesame Defatted Flour Supplementation: Effects in Carbohydrate Metabolism and Redox State in High-Fructose/High-Saturated Fatty Acids Diet-Fed Mice

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Diet is a crucial factor that strongly impacts human health. The modern diet, has led to an increased consumption of fructose and saturated fatty acids, which has been associated with a higher risk of some chronic diseases, all related to an increase of processes relative to oxidative stress. Thus, polyphenol supplementation appears to be a promising strategy to cope with this situation. Sesame seeds (*Sesamun indicum*) are well known due to their oil, rich in poly-unsaturated fatty acids. However, during the oil extraction, a by-product (named as Sesame Defatted Flour or SDF) is generated, which is rich in polyphenols (mainly lignans). Therefore, the aim of this study was to evaluate the effect of SDF on some components of carbohydrate metabolism and redox state of mice fed with a low nutritional quality diet (High-Fructose/High-Saturated Fatty Acids). To perform this, 24 C57BL/6 male mice were randomly assigned to one of three diets (Control or C, Low Nutritional Quality or LNQ, and LNQ diet supplemented with sesame defatted flour or LNQ+S). After 12 weeks under experimental conditions, animals were euthanized and blood, liver and kidney samples were obtained (only liver results are shown), to evaluate glucose and lactate levels, and oxidative stress markers such as superoxide anion ($O_2^{\cdot-}$), aqueous and lipid hydroperoxides (AHP and LHP), antioxidant enzymes activities (catalase, glutathione peroxidase and glutathione reductase), reduced glutathione (GSH) and protein carbonyl content (PCP). Overall, LNQ increased liver glucose (+20%), lactate (+60%) and PCP (+15%) with respect to C, and modulated the enzymatic and non-enzymatic endogenous antioxidants. However, sesame supplementation restored glucose and lactate levels to those of the control group and modulated the endogenous antioxidant systems, contributing to a reduction in oxidative damage in proteins. In conclusion, supplementation with sesame showed beneficial effects in mice fed a low nutritional quality diet.

THE URBAN PARTICULATE MATTER EXPOSURE INDUCED-OXIINFLAMMATORY RESPONSE IMPAIRS LUNG DAMAGE REPAIR MECHANISMS

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Airborne particulate matter (PM) has emerged as a major public health concern, as it is linked to higher morbidity and mortality rates. Breathing polluted air triggers oxidative stress and inflammation exacerbating respiratory conditions as PM-induced toxicity may affect the alveolar epithelium function. We aimed to study if the PM-induced oxiinflammation mechanisms are associated with a delayed repair of an acute lung injury. BALB/c mice were exposed to filtered air (FA) or urban air (UA) from Buenos Aires City, in whole-body exposure chambers for 8 weeks. Then, an acute lung injury was induced by intratracheal instillation of 0.1 N hydrochloric acid (HCl). Samples were evaluated 5 days after injury. Breathing UA induces mitochondrial dysfunction evidenced by inner mitochondrial membrane depolarization ($p \leq 0.05$) and decreased O_2 consumption ($p \leq 0.01$). The reactive oxygen species (ROS) production was increased by UA exposure after lung injury, as mitochondrial H_2O_2 and $O_2^{\bullet-}$ production and NADPH oxidase activity were augmented ($p \leq 0.05$). Moreover, when redox-sensitive transcription factors were evaluated, we observed that although Nrf2 expression was higher in the UA+HCl group compared to control values ($p \leq 0.05$), the antioxidant system was impaired. Regarding NF-κB, after lung injury, breathing UA presented increased p65 subunit translocation to the nuclei ($p \leq 0.05$). Consistently, an altered inflammatory response was observed as TNF-α and IL-6 levels were increased ($p \leq 0.001$ and $p \leq 0.01$ respectably), together with elevated total cell count and protein concentration in BAL samples from UA-exposed ($p \leq 0.001$ and $p \leq 0.01$ respectably). Furthermore, lung histology showed thicker alveolar wall ($p \leq 0.0001$) after the induced-injury, due to alveolo-capillary barrier damage. Taken together, our results showed that when PM reaches the lung it promotes a shift to a more oxidant redox environment, along with an exacerbated inflammatory response. As a result, mice exposed to UA were not able to properly repair the alveolar epithelium injury, resulting in a barrier disruption that extend the loss of the lung function.

Mitochondrial pathways in endotoxemia: bioenergetics and ROS production in H9c2 cardiomyocytes

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Alterations in energy production, redox balance and active mitochondrial dynamics in cardiac tissue during endotoxemia have been previously demonstrated. The aim was to elucidate the role of mitochondria in energy and ROS production during endotoxemia in a cardiomyocytes cell model. Rat myoblast cell line H9c2 were differentiated into cardiomyocytes with 100 nM retinoic acid and treated for 1, 3, or 6 h with serum from animals with severe endotoxemia (SE, 8 mg kg^{-1} LPS) or low-grade endotoxemia (LE, 0.5 mg kg^{-1} LPS). ATP production was found decreased by 38% at 1 h and 19% at 3 h in LE. Moreover, in SE the decrease was 50% at 1 or 3 h and 84% at 6 h (control: 161±17 nmol ATP min^{-1}mg $protein^{-1}$, $p<0.05$). Mitochondrial inner membrane potential was increased by 43% at 1 h in LE and 93% at 1 h or 50% at 3 h in SE (control: 100±29, $p<0.05$). ROS production and redox state were assessed through different approaches. ROS production was found increased by 55% at 1 or 3 h in SE ($p<0.05$). In particular, O_2^- production was increased by 56% at 1 h in SE ($p<0.05$). An increase of NO production by 37% was found at 6 h in LE while in SE a 40% increment was found at 1 or 3 h ($p<0.05$). Also, H_2O_2 production presented an increase of 76% between 1-6 h for SE (control: 0.153±0.034 nmol H_2O_2 min^{-1}mg $protein^{-1}$, $p<0.01$). These data were complemented with an analysis of mitochondrial dynamics.Our results highlight the role of mitochondria and their pathways in endotoxemia mainly defined by ATP metabolism and mitochondrial structure. These results are dependent on the time and degree of inflammatory insult in this model of endotoxemia.

(-)-Epicatechin administration attenuates NFkappaB activation through NOX modulation in perivascular adipose tissue of high fructose fed rats.

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Background and aims: Perivascular adipose tissue (PVAT) is a particular adipose tissue pad surrounding blood vessels. In obesity, PVAT becomes dysfunctional and exerts detrimental effects on vascular homeostasis. The objective of this work was to study the effect of the dietary administration of (-)-epicatechin (EC) on the activation of NFkappaB in the aorta thoracic PVAT (taPVAT) of high fructose fed rats. Methods: Rats (male Sprague-Dawley) were divided into four groups: C, control diet; CE, EC (20 mg/kg BW/d) in the diet; F: control diet and 10% (w/v) fructose in drinking water, and FEC, EC in the diet and fructose in the water. After 8 w, animals were euthanized to obtain blood and taPVAT. Results: Analyzing the redox sensitive NFkappaB

pathway, phosphorylation levels of IκBα in Ser32 and p65 in Ser536 were 65% and 75% higher in F respect to C, respectively ($p<0.05$). In the presence of EC in the diet both parameters were partially attenuated. NADPH-dependent superoxide anion production, sensitive to superoxide dismutase, was determined by the lucigenin assay in mitochondria-free homogenates of taPVAT as an estimation of NOX activity. F group showed a 4-fold increase in the chemiluminescence respect to C group ($p<0.05$). In association with this, the expression of gp91phox and p47phox (catalytic and regulator subunits of NOX2) were 75% and 30% higher in the F group respect to C group, respectively. In the presence of EC in the diet, NOX activity and NOX2 subunits expression did not show increases in the fructose-fed rats. Similar results were obtained for NOX4 expression. Conclusions: Taken as a whole, results suggest that the beneficial role of EC attenuating the activation of NFkappaB in taPVAT would be mediated by the modulation of the expression of NOX subunits and NOX activity. This fact would be, in part, responsible for the antihypertensive effect of EC and EC-rich foods.

Differences in mitochondrial function between brain and heart of rats exposed to hyperbaric hyperoxia treatment. Role of nitric oxide.

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Hyperbaric oxygen treatment (HBOT) is currently used as an adjunct therapy in many human pathologies, but a methodological understanding of HBOT's cellular mechanisms of actions appears to be lacking. Taking into account that the brain and heart are highly sensitive to oxygen levels and possesses the highest energy demand, we evaluated oxygen consumption, reactive oxygen species (ROS) and nitric oxide (NO) production in mitochondria from cerebral cortex, hippocampus and cardiac left ventricle using an HBOT model. Three month-old male rats were exposed 5 days a week to pure oxygen at 1.4 ATA for 60 min in an hyperbaric chamber (Oxavita), for up to 30 sessions (similar to human treatments). Control rats were placed in the chamber at normoxic- normobaric conditions. Experiments were carried out 24 h after the last HBOT. Mitochondrial oxygen consumption, respiratory efficiency (ADP/O) and nitric oxide (NO) levels were preserved in the cerebral cortex after HBOT. In addition, a 31% increase in superoxide anion production and a decrease in blood supply were observed. Regarding hippocampus, hyperoxic conditions decreased mitochondrial oxygen consumption (16% and 20 % for state 3 and 4, respectively) with the consequent reduction in superoxide anion levels (38%) and the inhibition of NO production (32%), while preserving respiratory efficiency (ADP/O). HBOT was able to increase 22% Complex IV associated- oxygen consumption in cardiac left ventricle mitochondria. Also, we observed a decrease in NO (51%) and ROS (50%) production.

HBOT modifies tissue specific mitochondrial function through variations in respiratory oxygen consumption and ROS levels, without increasing NO production. Cerebral cortex and cardiac left ventricle heart (robust tissues) maintain their respiratory activity associated with an increase in ROS. In contrast, the hippocampus (less irrigated and sensitive tissue) decreased respiratory activity and ROS production to avoid deleterious effects.

Mitochondrial bioenergetics and ROS production in pancreas during endotoxemia

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The molecular mechanisms involved in the development of sepsis and endotoxemia are multifactorial and have not yet been completely elucidated. The pancreas is one of the organs affected early during endotoxemia and sepsis, which could be relevant in the development of the disease at a systemic level. Given the inflammatory nature of this pathology, pancreatic mitochondria could be affected, compromising tissue bioenergetics. The objective of this work was to analyze the state of mitochondrial function, not only in terms of ATP production, but also as a relevant source of active oxygen species. Female Sprague Dawley rats (45 days old) were treated i.p. with: vehicle (control); LPS 0.5 mg/kg (LPS 0.5) and LPS 8 mg/kg (LPS 8). Mitochondrial function was evaluated by O_2 consumption, ATP production and mitochondrial membrane potential. While the LPS 0.5 group showed a decrease in ATP production only 6 hours after LPS injection, the LPS 8 group showed a similar decrease that became more acute at 24 hours. Furthermore, LPS 8 animals also showed a significant drop (35%) in mitochondrial membrane potential (control value: 147 ± 20 mV) and O_2 consumption rate at 24 h (control value: 62 ± 3 ng-at O/min mg protein). On the other hand, NADPH-dependent mitochondrial superoxide anion production increased significantly (5-fold) only in the LPS 8 group at 6 and 24 hours after starting treatment. Taken together, our results show a decrease in pancreatic cellular bioenergetics that depends on the degree of endotoxemia. A greater knowledge of the mitochondrial mechanisms that are activated in the pancreas during endotoxemia could be

of great relevance since their possible modulation could allow the development of new therapeutic strategies.

Identification of a Novel Mechanism Fostering the Alterations of Brain Energy Metabolism: a Link Between AD and T2DM

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Brain insulin resistance (bIR) is associated with mitochondrial stress, failure of energy metabolism, synaptic loss and ultimately neurodegeneration both in Alzheimer's disease (AD) and Type 2-Diabetes Mellitus (T2DM). Our group previously demonstrated that loss of BVR-A is an early event triggering bIR in AD. Hence, we tested the hypothesis that reduced BVR-A levels link bIR and mitochondrial defects resulting in AD-like neuropathology in T2DM. Alterations of insulin signalling, oxidative stress levels and AD hallmarks were analyzed in the hippocampus of wild-type and the goto-kakizaki (GK) model of T2DM rats. Hippocampal mitochondrial function was evaluated by measuring oxygen consumption rate (OCR), mitochondrial complexes, mitochondrial unfolded protein response (UPRmt) and oxidative stress levels. These data were correlated with peripheral metabolic measurements (fasting glucose, insulin and OGTT) and cognitive tasks (spatial memory). To confirm the role of BVR-A, similar analyses were performed in the hippocampus of WT and BVR-A KO mice. Additional mechanistic insights were gained by evaluating mitochondrial function (sea-horse) and the above-mentioned intracellular pathways in response to insulin, in neuronal cells lacking BVR-A. GK rats displayed a diabetic phenotype and impaired spatial memory. Reduced BVR-A levels along with IRS1 hyper-activation and loss of Akt-mediated inhibition of GSK3b were observed in the hippocampus, consistent with the regulatory role for BVR-A. As result, hyperactive GSK3b accumulated in hippocampal mitochondria fostering their impairment characterized by reduced OCR and activation of UPRmt. Similar alterations in BVR-A KO mice and in neuronal cells lacking BVR-A were observed, reinforcing the role for BVR-A in regulating mitochondrial bioenergetics in response to insulin. These results suggest that early BVR-A loss triggers bIR and the hyper-action of GSK3b, that, in turn, drives the development of mitochondrial stress in T2DM brain. These alterations accelerate the impairment of energy metabolism and development of AD-like neuropathology in T2DM

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