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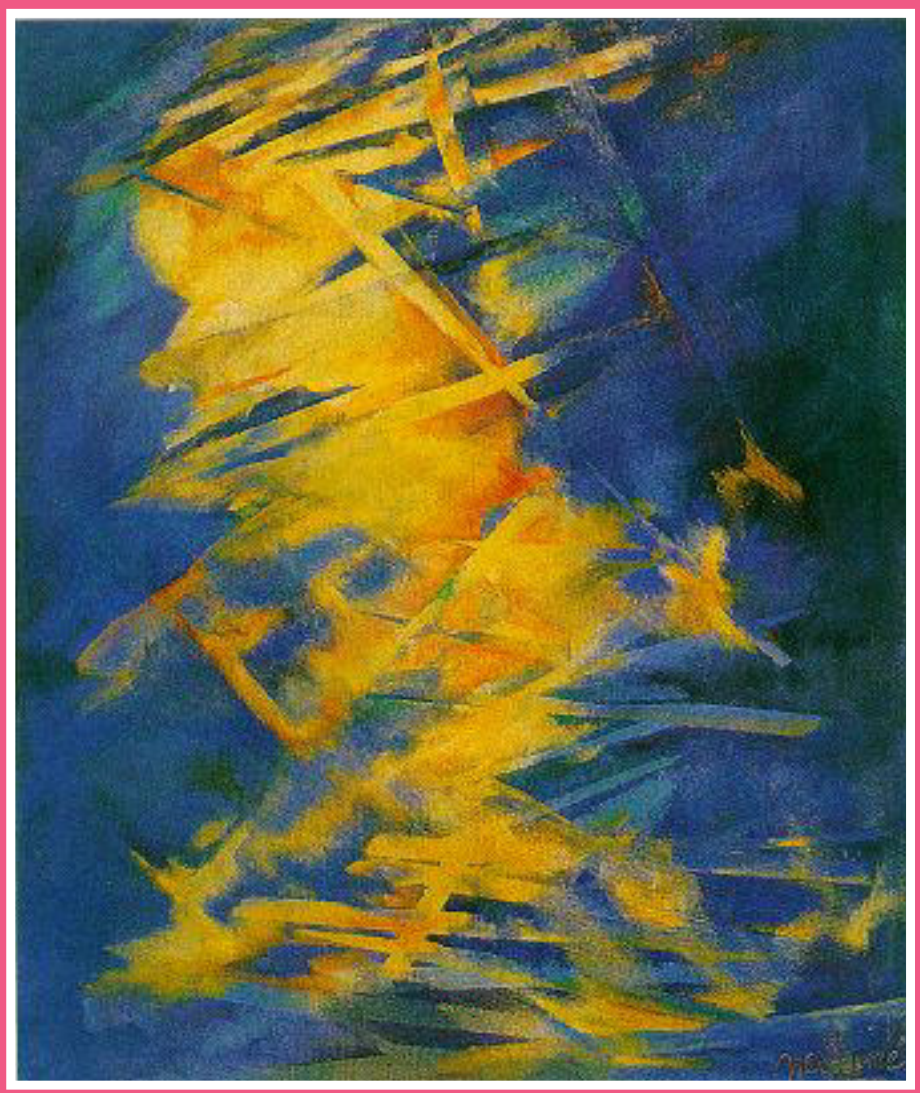

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(1195) **MITOCHONDRIAL RESPIRATORY CHAIN AND KREBS CYCLE ALTERATIONS DUE TO PORPHYRINOGENIC AGENTS IN A MOUSE MODEL OF ACUTE INTERMITTENT PORPHYRIA**

Johanna Romina Zuccoli, Maria Del Carmen Martinez, Silvina Fernanda Ruspini, Alcira Batlle, Ana Maria Buzaleh
CIPYP CONICET

The mitochondria play a vital role in energy metabolism; inside occurs oxidative phosphorylation in the electron transport chain and the generation of reduction equivalents by the tricarboxylic acid (TCA) cycle. Heme deficiency produced by a reduced synthesis or an accelerated catabolism would trigger severe cell damage. Previously we demonstrated that porphyrinogenic agents affected several brain metabolisms included respiratory mitochondrial chain in encephalon *CF1* and Acute intermittent Porphyria (AIP) genetic modelmice. The aims were to study the effects of volatile anesthetics and other xenobiotics on the activity of fumarase and aconitase in a mouse model of AIP; and to analyze if there are protein and lipid damage due to these treatments. For these purposes we use male knockout mice that have 50% reduced the activity of Porphobilinogen deaminase. Animals were treated with Isoflurane (2 ml/kg), Sevoflurane (1,5ml/kg), ethanol (30%), allylisopropylacetamide (AIA, 350 mg/kg), Veronal (167 mg/kg) or starved (24 hs). The enzymes activities were measured in mitochondria of encephalon. Fumarase activity decreased due to Isoflurane (30%; $p<0.05$), AIA (39%, $p<0.05$), Veronal (87%, $p<0.01$); and in fasted animals (50%, $p<0.01$); while it was augmented due to Sevoflurane (42%, $p<0.05$). Aconitase activity increased due to Isoflurane (93%; $p<0.01$), Sevoflurane (86%; $p<0.01$) and Veronal (170%; $p<0.01$); and it was diminished by AIA (40%; $p<0.05$) and starvation (60%; $p<0.01$). Protein and lipid damage were observed as a consequence of all the xenobiotics studied. The changes observed in the activities of TCA cycle would result in a deficiency of the donor reduction equivalents, NADH and $FADH_2$, and could justify the alterations in the activities of respiratory chain complexes previously reported. Results support our hypothesis that there would be more than one factor to explain the pathogenesis of acute attacks.

Keywords: Cadena_respiratoria, Ciclo_de_krebs, Porfiria_aguda_intermitente

(594) **ACUTE COPPER TOXICITY ASSOCIATED WITH MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE AND MULTIORGANIC FAILURE**

Juan Manuel Acosta (1), Fabiana Lairión (1), Paola Paredes Fleitas (1), Manuel Rodríguez (2), Celina Morales (2), Sofía Bajicoff (1), Alberto Boveris (2), Ricardo Gelpi (2), Marisa Gabriela Repetto (2)
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Cytosolic and mitochondrial oxidative damage (OD) is associated with the dose of Cu(II) administered. Previous results shown that Cu(II) doses of less than 5 mg/kg (intraperitoneal (ip) administration), produced cytosolic OD; nevertheless, at slightly higher and toxic doses (6-6.5 mg/kg), the oxidation of mitochondrial phospholipids affects the functionality of mitochondria, and at doses greater than 7 mg/kg animals die before the hour after acute treatment. The aim of this research is to evaluate if acute toxic effects of Cu(II) are associated to mitochondrial dysfunction, OD and multiorganic failure. Sprague Dawley male rats (200 g) received Cu(II) at dose of 6.5-7.5 mg/kg (ip) and were scarified at 1 h and 6 h after treatment. The livers, brains, hearts, and lungs of the rats were excised and the samples were processed according to routine methods for obtaining histopathological preparations that were stained with hematoxylin-eosin. Phospholipid oxidation was measured as thiobarbituric acid reactive substances (TBARS) and mitochondrial function (oxygen uptake, ΔO_2) was evaluated using a Clark type oxygen electrode. Autopsy of these rats indicated that all organs were affected, mainly the heart, in which foci of necrosis were observed in the cardiac tissue. TBARS increased in all the organs evaluated in a dose depended manner (2 to 4 fold at dose 6.5 and 7.5 mg/kg respectively, $p<0.01$) and mitochondrial ΔO_2 decreased with malate-glutamate as substrate mainly in heart and brain (36 and 35% with 6.5 mg/kg dose, and 42 and 27% at dose 7.5 mg/kg, $p<0.05$, respectively), lung (42%, $p<0.05$, at the lowest dose) and liver (41%, $p<0.001$, at the highest dose). With succinate as substrate, the ΔO_2 decreased 30% ($p<0.01$, 6.5 mg/kg) and 70% ($p<0.001$, 7.5 mg/kg) in liver and 30% ($p<0.05$, 7.5 mg/kg) in brain mitochondria. These results indicate that OD and mitochondrial bioenergetic dysfunction are processes associated to the histological damage and precedes the rat death.

Keywords: oxidative stress, copper, lipid peroxidation, mitochondria

(906) **EFFECT OF OXIDATIVE STRESS ON ADIPOCYTE DIFFERENTIATION**

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Oxidative stress (OS) is a major characteristic of adipose tissue in obese patients and its role in adipose hyperplasia/hypertrophy has not been elucidated. The aim of our study was to analyze the effect of OS during adipogenesis as well on differentiated adipocytes. For this purpose, we worked with preadipocytes 3T3-L1 and menadione, a synthetic form of vitamin K known to generate intracellular oxygen species. Two different models were used: the “chronic”, in which OS (5, 10 y 15 μM menadione) was present during the whole process of 3T3-L1 differentiation, and the “acute”, in which differentiated adipocytes were exposed to OS (20 y 50 μM menadione) for 5 h.

Adipogenesis, evaluated by Oil Red O staining as well as by the expression of adipogenic markers (PPARγ, C/EBPα, FAS, FABP4) by Western blot, was observed to be decreased in the chronic model in a menadione concentration-dependent manner ($p<0.01$). The adipogenic markers were also found to significantly decrease upon acute treatment ($p<0.001$). However, no significant morphological changes were observed in differentiated adipocytes acutely treated with menadione. PI3K/Akt and ERK1/2 showed to be inversely regulated: Akt was found to be inactivated whereas ERK1/2 were found to be activated in both models of menadione-induced OS. Interestingly, experiments in which adipogenesis was evaluated in the presence of LY294002, a pharmacological PI3K inhibitor, but in the absence of menadione showed a significant decreased differentiation. Our results demonstrate that acute menadione-induced OS triggers a gene expression program leading to the decreased expression of transcription factors and enzymes which are crucial for lipogenesis and, on the other hand, chronic menadione-induced OS prevents adipogenesis, presumably in part, in a PI3K-dependent manner.

Keywords: adipogenesis, oxidative stress, lipid metabolism

(797) **INTERPLAY BETWEEN HYPERGLYCEMIA (HG), OXIDATIVE STRESS AND LYMPHOCYTE PROLIFERATION ON PERIPHERAL BLOOD MONONUCLEAR CELLS (PMBC) FROM DIABETIC PATIENTS**

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The association between diabetes and immunosuppression is suggested. HG is the main factor involved in diabetic complications by inducing reactive oxygen species (ROS) and oxidative stress.