

# European Journal of Clinical Investigation

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Volume 48

Supplement 1

May 2018

Abstracts of the 52<sup>nd</sup> Annual Scientific Meeting of the  
European Society for Clinical Investigation

"Precision medicine for healthy ageing"

Barcelona, Spain

30th May – 1st June 2018

*Guest Editor:*

Prof. Lina Badimon

Prof. Gema Frühbeck

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# European Society for Clinical Investigation



Founded 12 February 1967

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### Objectives

The objectives of the Society are the advancement of medical practice through science; the cultivation of clinical research by the methods of the natural sciences; the correlation of science with the art of medical practice; the fostering of high standards of ethical practice and investigation; and the diffusion of a spirit of fraternity and international co-operation among and through its members.

### Membership

Any person who has been actively involved in medical research in Europe, for example by involvement in original investigations in clinical or allied sciences of medicine, can apply for membership of ESCI. Members will receive the *EJCI* monthly.

Young scientists under the age of 30 can apply for junior membership (for a maximum of up to three years) to a reduced membership fee.

Any company, corporation, organisation, or trust can apply for corporate membership in the Society.

### Meetings

The Society holds one Annual Scientific Meeting each year, usually in April/May. Meetings are held in different centres in Europe. Other Society's activities include the sponsorship of Workshops and Postgraduate Courses and the encouragement of the exchange of Scientists between Laboratories.

### Agreement between the European Society for Clinical Investigation and the American Federation for Medical Research

An agreement has been reached between the councils of the ESCI and AFMR as follows:

(i) *ESCI members* can now submit abstracts for presentation at the joint Annual Meetings of the AFMR, AAP and ASCI.

(ii) *ESCI members* can apply for membership of AFMR on the normal terms. Those wishing to apply for membership should download an application form from the *Journal of Investigative Medicine*.

(iii) *AFMR members* can submit abstracts for presentation at the Annual Scientific Meetings of ESCI. Details of ESCI Meetings will appear regularly in the *Journal of Investigative Medicine*, and AFMR members can submit abstracts to ESCI when submission opens.

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Enquiries regarding membership of the Society or any of its activities should be addressed to:

Prof. Jean-Philippe Haymann, MD, PhD

European Society for Clinical Investigation (ESCI),

Central Office, Bolognalaan 34,

3584 CJ Utrecht, the Netherlands.

Tel: +31 88 755 8787; Fax: +31 30 251 5724;

E-mail: [esci@umcutrecht.nl](mailto:esci@umcutrecht.nl); [www.esci.eu.com](http://www.esci.eu.com)

can cause various cutaneous diseases, such skin carcinoma, dermatitis, and sunburn. ROS play an important role in the initial step of these diseases; therefore, IDH2 deficient mice (KO) could be a useful model to investigate UV-mediated skin damage. When we exposed the dorsal skin of KO mice to UVB, pyrimidine dimers and (6-4) photoproducts (6-4PPs), marker of photoproducts generated by UVB, were found in the dermis of the knockout mice. Increased collagen degradation, apoptosis, inflammation, and ROS levels in the dermis were also observed. These results indicated that UVB could reach the dermis by penetrating the epidermis. We then attempted to determine how the epidermis was breached, and observed a decrease in the expression level of deltaNp63, a major protein required for epidermis generation, in the KO mice. The mito-TEMPO supplement significantly ameliorates UVB-induced damage in the skin of KO mice. In the present study, we provided a role for IDH2 in protection against UVB-induced skin damage and a new connection between IDH2 and deltaNp63.

**P051-T | Effects of the caffeine on the snails training through the regulation of  $Ca^{2+}$  concentration through ryanodine receptors of the endoplasmic reticulum and mitochondria**

T. Bogodvid<sup>\*†</sup>; D. Silantieva<sup>\*</sup>; V. Andrianov<sup>\*</sup>; L. Muranova<sup>\*</sup>; I. Deryabina<sup>\*</sup>; K. Gainutdinov<sup>\*</sup>

<sup>\*</sup>Kazan Federal University, Institute of Fundamental Medicine and Biology, Kazan, Russian Federation; <sup>†</sup>Volga Region State Academy of Physical Culture, Sport and Tourism, Kazan, Russian Federation

Calcium ions play a critical role in the regulating of a great variety of neuronal processes due to their specific physico-chemical characteristics. They are the most versatile intracellular mediator linking the processes, developing in the surface membrane of the cell, and reactions occurring within the cell. It is generally accepted that intracellular calcium, which is ionized, has the function of universal secondary mediator involved in the regulation of many intracellular reactions, down to gene expression. One of the agents that cause the increasing of intracellular concentration of  $Ca^{2+}$  is caffeine, which acts on the ryanodine receptors in the endoplasmic reticulum and mitochondria. That is, the regulation of intracellular concentration of  $Ca^{2+}$  ions occurs through these receptors. In this regard, the aim of our study was investigate the effects of chronic administration of caffeine on the formation of conditioned defensive reflex in snails.

It was used 5 groups of animals: intact ( $n = 18$ ), snails, received a saline injection 30 minutes before training

(active control,  $n = 11$ ), snails, injected with caffeine 30 minutes before training ( $n = 18$ ), snails injected with caffeine immediately after the training ( $n = 18$ ), snails, which were injected daily with caffeine during the study period ( $n = 8$ ). Our experiments showed that the chronic injection of caffeine increases elaboration of defensive conditioned reflex in snail. The injection of caffeine immediately after the training procedure was produced learning faster than when caffeine applied before training. Thus, changes in intracellular  $Ca^{2+}$  ions concentration by caffeine, which occurs by activation of the ryanodine receptors of the endoplasmic reticulum and mitochondria serves as regulator of plastic processes during learning.

The work is performed according to the Russian Government Program of Competitive Growth of Kazan Federal University (No. 17.9783.2017/8.9) and supported by RFBR (grant No. 18-015-00274).

**P052-T | Dynamics of nitric oxide production in the rat hippocampus as one of the mechanisms of inflammation during ischemic and hemorrhagic insult**

T. Bogodvid<sup>\*†</sup>; V. Andrianov<sup>\*†</sup>; G. Yafarova<sup>\*†</sup>; V. Iyudin<sup>†</sup>; S. Pashkevich<sup>‡</sup>; M. Dosina<sup>‡</sup>; T. Baltina<sup>\*</sup>; V. Kulchitsky<sup>‡</sup>; K. Gainutdinov<sup>\*†</sup>

<sup>\*</sup>Kazan Federal University, Institute of Fundamental Medicine and Biology, Kazan, Russian Federation; <sup>†</sup>Zavoisky Physical-Technical Institute of RAS, Kazan, Russian Federation; <sup>‡</sup>Institute of Physiology of NAS Belarus, Minsk, Belarus

It is known that nitric oxide (NO) and peroxynitrite are involvement in the pathophysiology of well-characterized acute and chronic inflammatory diseases and play an important role in the development of organ damage and inflammation triggered by various drugs and chemical agents (Patcher et al., 2007). Those processes characterized the hypoxia that occurs including the development of tissue ischemia. According to this the study of the pathogenesis, the methods of correction and the mechanisms of stroke is important both from the theoretical and practical points of view. The main purpose of our investigation was to study the dynamics of NO production in the hippocampus of rats after modeling both ischemic and haemorrhagic stroke. Electron paramagnetic resonance (EPR) was used as a method to record NO production in the tissues of the brain of healthy rats and rats after modeling of ischemic and haemorrhagic stroke. Direct measurement of the dynamics of NO production by EPR spectroscopy in our experiments showed that after the emergence of signs of ischemic stroke, 5 hours after the start of ischemia, the content of

NO in the hippocampus decreased 2–3 times and this decrease is maintained at 24 and 72 hours.

The work is performed according to the Russian Government Program of Competitive Growth of Kazan Federal University (No 17.9783.2017/8.9) and supported by RFBR (grant No. 16-04-00098).

### P053-T | Effects of inhibition of tryptophan hydroxylase synthesis on context memory

T. Bogodvid\*<sup>†</sup>; I. Deryabina\*; V. Andrianov\*; L. Muranova\*; D. Silantieva\*; K. Gainutdinov\*

\*Kazan Federal University, Institute of Fundamental Medicine and Biology, Kazan, Russian Federation; <sup>†</sup>Volga Region State Academy of Physical Culture, Sport and Tourism, Kazan, Russian Federation

It is established that serotonin (5-HT) is a basic neurotransmitter for defensive behavior in mollusks and learning on the basis of defensive reflexes. In behavioral experiments it was shown that the disruption of serotonergic system by the neurotoxin 5-7-DHT did not change the original memory, however, led to a memory impairment after repeated reactivation. An unavailability of reactivation under the action of the antagonist of serotonin receptors methiothepin was also shown. These results demonstrated the relevance of analysis of long-term memory after inhibition of 5-HT synthesis. Tryptophan hydroxylase (TPH) is the first and presumably rate-limiting enzyme in 5-HT biosynthesis. P-chlorophenylalanine (p-CPA) is one of the various drugs that depresses TPH, it causes long and deep depletion of brain 5-HT-depots.

Here, we investigated the possible changes of the reconsolidation under the conditions of 5-HT deficit, caused by injection of inhibitor of TPH synthesis (intermediate stage of the synthesis of 5-HT) p-CPA. It was shown that the forgetting process for conditioned situational reflex after reminder and inhibition of protein synthesis did not occur if the 5-HT transmission in nervous system was impaired. This effect was significantly different from the direct action of inhibitor of protein syntheses anisomycin, which completely blocked the reconsolidation of context memory. We concluded that the 5-HT system was included to the process of memory reconsolidation (in our system of situational memory).

The work is performed according to the Russian Government Program of Competitive Growth of Kazan Federal University (No. 17.9783.2017/8.9) and supported by RFBR (grant No. 18-015-00274).

### P056-T | Cytotoxicity of doxorubicin-loaded PLGA and PLGA-PEI nanoparticles: relevance for anti-tumor effects and cardiotoxicity

C. Candido\*; L. Ferreira<sup>†</sup>; E. Silva<sup>‡</sup>; A. Júnior<sup>‡</sup>; R. Peccinini\*; P. Oliveira<sup>†</sup>

\*Department of Natural Active Principles and Toxicology, São Paulo State University (Unesp), School of Pharmaceutical Sciences, Araraquara, Brazil; <sup>†</sup>CNC, Center for Neuroscience and Cell Biology, University of Coimbra, UC-Biotech-Biocant Park, Cantanhede, Portugal; <sup>‡</sup>Laboratory of Pharmaceutical Technology and Biotechnology, Department of Pharmaceutical Sciences, Faculty of Pharmacy, Federal University of Rio Grande do Norte, Natal, Brazil

**Background:** Doxorubicin (Dox) is an antineoplastic antibiotic widely used in therapeutics, although its high cardiotoxicity limits its use. Our objective was to use pharmaceutical technology to improve Dox biodistribution and consequently reduce toxicity, without sacrificing the antitumoral efficacy. We developed two Dox delivery nanoparticle systems of poly (D,L-lactide-co-glycolide)-based nanoparticles (PLGA-NPs) and PLGA-NPS bearing surface polyethyleneimine (PEI/PLGA-NPs) and tested cytotoxicity on human breast tumor cells (MDA-MB-231 and MCF-7), normal human breast cells (MCF-12A) and rat cardiomyoblasts (H9c2).

**Material and methods:** Tumor and normal cell lines were incubated with free Dox, Dox-PLGA-NPs and Dox-PEI/PLGA-NPs for 24 hours (0–1–2–0 μM Dox). Cytotoxicity analysis was performed by resazurin, sulforhodamine B assay, and determination of ATP levels. p53 levels were detected by immunoblotting.

**Results:** Cytotoxicity assays demonstrated that all Dox formulations induced dose-dependent cell death in the tested cell lines (with exceptions for MDA-MB-231). No differences in cell death were observed between free Dox and the NP systems in the normal cell lines. However, for the MCF-7 cell line the Dox-PEI/PLGA-NPs showed higher reduction of cell mass vs observed in free Dox or Dox-PLGA-NPs treatments. Although no statistically differences were observed between the different treatments on H9c2 cells, with the NPs systems p53 levels were decreased by ap. 30% when compared with free Dox.

**Conclusion:** Dox chemotherapy efficiency is compromised by the cardiac side effects and drug delivery systems have been explored in an attempt to overcome off-target toxicity. We tested the cytotoxicity of two NPs systems for drug encapsulation and observed increased toxicity of Dox-PEI/PLGA-NPs in the breast tumor cell line MCF-7, while both NPs formulation seem to lower the activation of p53 in the cardiomyoblast cell line.

The study was supported by CAPES (ref.88881.132300/2016-01); FCT (PTDC/DTP-FTO/1180/2012, SFRH/BD/52

