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CONCLUSION: Clarification of observations A-D leading to better therapy of cardiovascular/hypertension, etc & urogenital/incontinency,etc diseases could support better health in all countries acc to UNO-Agenda21. Reports about long-term research projects not only in journals eg *Physiol Rev*, but also to scientific congresses for physiology,etc initiating discussions about future research strategy are necessary.

Dedicated to moral & scientific support 2014-1980 of Nobel Laureates: Australia-Sir J.Eccles, France-J.-M.Lehn, Germany-M.Eigen/K.von Klitzing/H.Michel/E.Neher, GB-Sir J.Kendrew/Lord A.Todd, USA-J.Deisenhofer-FRG/H.B.Khorana-India/B.Richter/R.Wilson

P2

Molecular and Cell Physiology

P2.1

Regulation of a human stem cell specific microRNA cluster C19MC

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MicroRNAs are small regulatory RNAs of 21-24 nucleotides in length. Their function is fine tuning the post-transcriptional regulation of genes by targeting mRNA molecules via

sequence complementarity with their 3'-untranslated region for mRNA decay and/or translation inhibition. During their maturation process, they are transcribed either from their own microRNA locus or as an intronic sequence of a protein coding gene. This primary transcript (pri-miRNA) can encode a single microRNA or a cluster of microRNAs which, in the canonical pathway, undergo further subsequent nucleolytic cleavages by the Drosha/DGCR8 complex and Dicer to form mature microRNA molecules. Our subject of interest is C19MC, which is the biggest human microRNA cluster containing 54 separate miRNA hairpin structures. These microRNAs are currently believed to be expressed simultaneously and in terms of expression pattern, exclusively in stem cells and placenta. Based on these, we would expect similar expression levels for all microRNAs of the cluster. However, our data from TaqMan Low Density Array measurements suggests that the expression of different parts of C19MC regulated differently. Examining a human embryonic stem cell line (HUES9), we found that certain neighboring miRNAs show similar expression patterns, representing a wide range from high expression to total absence, suggesting the presence of differently regulated sub-clusters inside the cluster. Chip-seq data from Encode project strengthens this idea which seems to be further supported by the presence of certain transcription factor binding sites found inside the cluster. Our goal is to prove the concept of sub-cluster regulation with quantitative measurements of the primary transcripts of the microRNA cluster.

Furthermore, we will examine this phenomenon with functional studies of the putative regulatory regions inside of C19MC.

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P2.2

Beneficial effects of hydrogen sulphide treatment of human adipose derived stem cells in a cell-based model of cell therapy

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Purpose: The potential of cell-based therapies in diseases involving ischemia-reperfusion is greatly hampered by the excessive loss of the administered cells in the harsh, oxidative environment. Our earlier studies indicated that preconditioning of human adipose derived stem cells (ASC) with the hydrogen sulfide donor sodium sulfide (NaHS) increased their survival and efficacy in an in vitro model of cell-based therapy for myocardial infarct. Thus we aimed to better understand the underlying mechanism of action.

Methods: ASCs were treated with 0.3 μ M (ASC 0.3), 3 μ M (ASC-3) or 30 μ M (ASC-30) NaHS 4 times with 3 days between treatments whereas a control group (ASC) received vehicle. The effect of endogenous hydrogen sulphide was investigated using the cystathionine- γ -lyase inhibitor

propargylglycine (PAG, 10 mM). Proliferation was followed by microscopical evaluation. Mitochondrial activity was measured at the beginning of the treatments and on the 9th day. Changes are expressed as percentages of the initial value. The antioxidant effect of NaHS pretreatment (3 and 30 μ M) was examined after H₂O₂ treatments (2 hours, 2 mM) by lactate dehydrogenase (LDH) release.

Results: By the 9th day NaHS dose-dependently increased the proliferation of cells (ASC: $234 \pm 25\%$; ASC 0. 3: $331 \pm 67\%$ *; ASC-3: $405 \pm 61\%$ ****; ASC-30: $471 \pm 33\%$ ** **, vs control, * $p < 0.05$, **** $p < 0.0001$). There was no change in the overall mitochondrial activity as measured with resazurin test. PAG treatment decreased the proliferation from the 3rd day (control: $156.2 \pm 10.3\%$; 10 mM PAG: $81.7 \pm 4.7\%$ ****). LDH-release was reduced when cells were pretreated with 3 μ M NaHS (control: $90.3 \pm 7.9\%$; 3 μ M NaHS: $67.0 \pm 5.7\%$ **; 30 μ M NaHS: $89.5 \pm 10.2\%$, $p < 0.01$).

Conclusions: Hydrogen sulfide can dose-dependently increase the proliferation of human adipose derived stem cells. The unchanged overall mitochondrial activity of increased amount of cells indicates a decreased cellular metabolism that may lead to reduced release of reactive oxygen species from the mitochondria. Antioxidant defenses are more efficient after treatment with 3 μ M NaHS.

P2.3

Endometrial oestrogen and progesterone receptors localization in the fat sand rat, *Psammomys obesus*, a diurnal gerbil

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The aim of this work is to characterize the reproductive function of a diurnal rodent, the fat sand rat, considered such as a model for studying several metabolism diseases. In the female, histological, histochemical and cytological aspects of uterus were studied. Preliminary immunohistological results are presented. Paraffin embedded uterine from isolated females were selected throughout the reproductive cycle. After antigen retrieval, indirect immunohistochemistry method with streptavidin-biotin complex was applied. The uterus was the target of both estrogens and progesterone acting by specific receptors ERs (estrogen receptors) and PRs (progesterone receptors). At estrus and diestrus, labeling of ERs was in the cytoplasm of all epithelial cells; in metestrus, labeling became both in the nuclear and the cytoplasm, few unlabeled cells were observed, the stroma was slightly labeled; at proestrus label for both ERs and PRs was localized in the nuclear fraction. During estrus, PRs, were localized in the nuclear fraction of epithelial and stroma cells; in the lining epithelium, predominate cells were labeled while glandular cells remained immunonegative; in the stroma, labeled cells predominated. In metestrus, labeled PRs were nuclear and cytoplasmic in epithelial cells and only nuclear in the stroma. At diestrus, lining and glandular epithelial cells were completely immunonegative; labeled PRs persisted in the stroma. At proestrus, two cases were observed: negative staining of

epithelial tissue and positive in the nuclear fraction of stroma cells in some female and nuclear positive staining of the epithelial and stroma cells in other females. The localization of ERs and PRs varied during the cycle, therefore estradiol and progesterone acting in different uterine compartment during the estrous phases deserve to be studied.

P2.4

The effects of angiotensin II on autophagy pathways in H9c2 cells

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He hypertension induced cardiac hypertrophy is one of the most common cause of heart failure and predictor of cardiovascular morbidity and mortality. Several studies show that autophagy plays an important role in the cardiac hypertrophy. It is unclear this self-digest process serve as a survival (remodelling) process or contribute to cell death. We investigated the autophagic and apoptotic processes in H9c2 cell line in response to different concentrations of ATII (angiotensin II) treatment. H9c2 cardiomyoblast cells were treated with low (10⁻⁷ M) and high (10⁻⁶ M) concentrations, respectively, of ATII to induce hypertrophy. After rhodamine conjugated phalloidin and DAPI staining we examined the alteration of cell size by fluorescence microscopy. Expression levels of autophagic and apoptotic proteins by Western blots were analyzed. To visualize autophagic vacuoles, MDC treatment and tagging LC3B protein immunocytochemistry were carried out and studied with fluorescence microscope. Based on microscopy studies, the cell size was significantly greater in the treated groups indicating the development of hypertrophy. Enhanced LC3BII/LC3BI ratio and an increased level of Beclin-1, Atg 12, and Bcl-2 were found in response to the lower dose of ATII; the levels of these proteins were not significantly altered in the higher ATII treated group. In the higher ATII treated group, enhanced levels of apoptotic proteins were detected. Furthermore, in the higher ATII treated group we observed reduced MDC signal. Taken together, our results suggest an increased autophagic activity, which may help to reduce damaged protein organelles in response to lower dose ATII treatment. However, in higher dose of ATII treatment, the apoptotic activity is enhanced in H9c2 cell line.

P2.5

Arrestin binding of the beta2-adrenergic receptor is regulated via heterodimerization with the angiotensin type 1A receptor

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Increasing number of evidence shows that the signaling originating from G-protein coupled receptors (GPCR) is