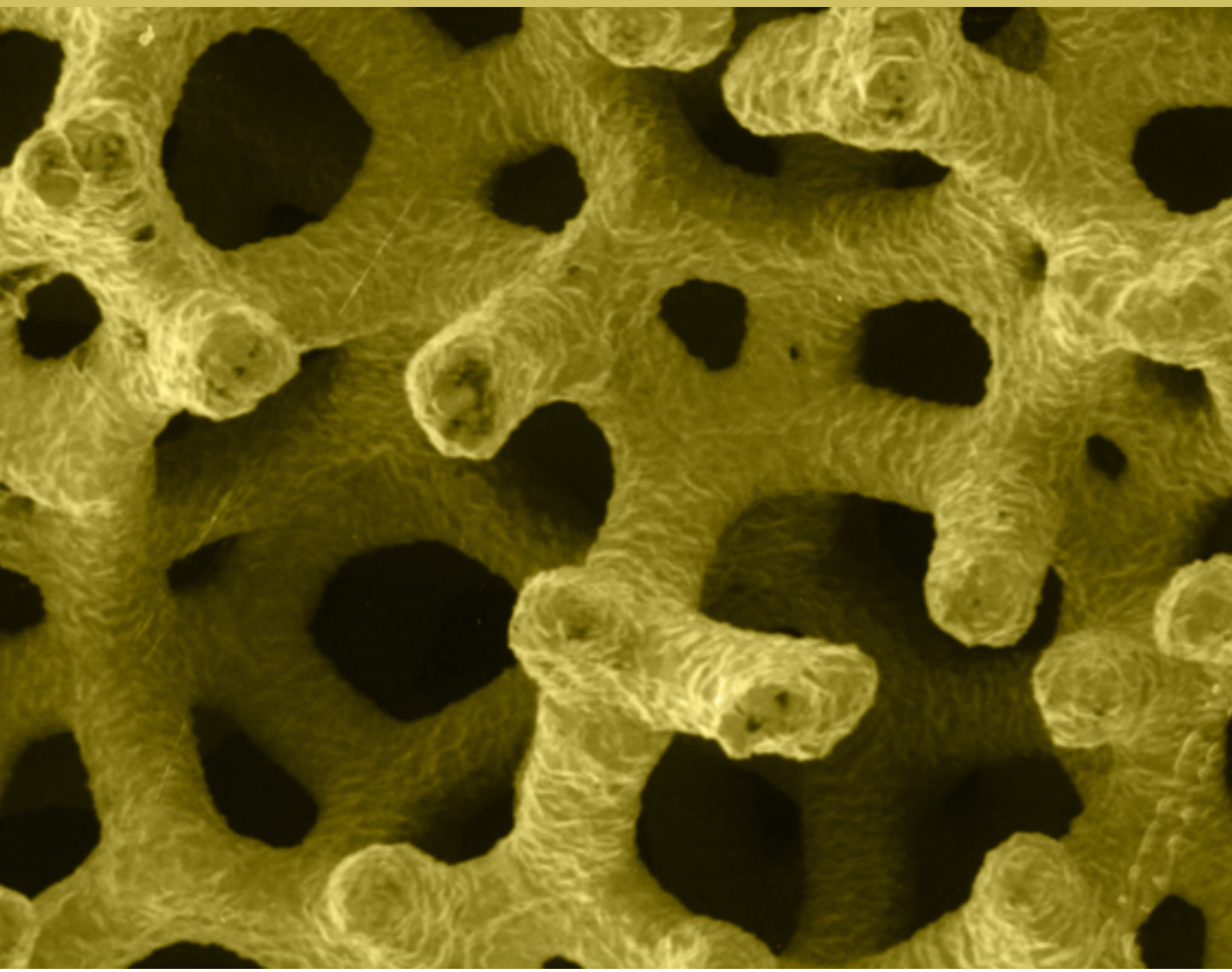
Physiological Mini Reviews

Special Issue
STRATEGIC WORKSHOP RHYTHMS OF LIFE: PERSPECTIVES FOR PHYSIOLOGICAL SCIENCES IN THE 21ST CENTURY.
Brazilian Society of Physiology

9 Volume



Vol. 9 #4, August, 2016
ISSN 1669-5410 (Online)
pmr.safisiol.org.ar

Physiological Mini Reviews

SAFIS
Sociedad Argentina de Fisiología

Vol.9, # 4, August 2016

Especial Issue

STRATEGIC WORKSHOP RHYTHMS OF LIFE: PERSPECTIVES FOR PHYSIOLOGICAL SCIENCES IN THE 21ST CENTURY.

Brazilian Society of Physiology

Physiological Mini-Reviews

[ISSN 1669-5410 (Online)]
Edited by **the Argentinean Physiological Society**

Journal address: Centro de Investigaciones Cardiovasculares y Cátedra de Fisiología y Física Biológica.
Facultad de Ciencias Médicas; Universidad Nacional de La Plata;
La Plata, Buenos Aires, Argentina. Tel.-Fax: +54-211-4834833
http://pmr.safisiol.org.ar

Physiological Mini-Reviews is a scientific journal, publishing brief reviews on "hot" topics in Physiology. The scope is quite broad, going from "Molecular Physiology" to "Integrated Physiological Systems". As indicated by our title it is not our intention to publish exhaustive and complete reviews. We ask to the authors concise and updated descriptions of the "state of the art" in a specific topic. Innovative and thought-provoking ideas are welcome.

Preparation and Submission of manuscripts:
"Physiological Mini-Reviews" will have a maximum of 3000 words, 50 references and 3 figures. Material will be addressed to scientific people in general but not restricted to specialist of the field. For citations in the text please refer to Instructions in our webpage. Final format will be given at the Editorial Office. Most contributions will be invited ones, but spontaneous presentations are welcome. Send your manuscript in Word format (.doc or .docx) to: pmr@safisiol.org.ar

The “Sociedad Argentina de Fisiología” is a registered non-profit organization in Argentina. (Resol. IGJ 763-04)

It is the intention of the Editorial Committee of PMR to add to our publications, special issues with the abstracts of the Congresses of the physiological societies of the Latin American countries who agree to collaborate with our journal, with the main goal of increasing the scientific and academic interaction among our countries.

Physiological Mini Reviews

SAFIS
Sociedad Argentina de Fisiología

PROGRAM AND ABSTRACTS FROM THE STRATEGIC WORKSHOP RHYTHMS OF LIFE: PERSPECTIVES FOR PHYSIOLOGICAL SCIENCES IN THE 21ST CENTURY

Organized by the Sociedad Brasileira de Fisiologia

August 25, 2016

STRATEGIC WORKSHOP PROGRAM

THURSDAY - AUGUST 25TH, 2016
Brasiliana Library - Auditorium István Jancsó University of São Paulo

8:30-8:40

Opening ceremony
by Vagner R. Antunes and Thiago S. Moreira (Brazil)

8:40-9:00

Meritocracy in the physiological science
Gehard Malnic (Brazil)

9:00-9:20

The landscape of physiology in the 21st century
Denis Noble (Oxford University - UK)

9:20-9:40

How to conduct an Original Research in Physiological Science that leads the world!
Katshuhiko Mikoshiba (Japan).

9:40-10:00

Age-related dysregulation of calcium signaling
Cecilia Hidalgo (Chile)

10:00-10:20

Coffee Break

10:20-10:40

Role of the kidney in the pathogenesis of hypertension: time for a neo-Guytonian paradigm or a paradigm shift?
Peter Bie (Denmark)

10:40-11:00

Physiological CO_2 exchange can depend on membrane channels
Walter Boron (USA)

11:00-11:20

Step stones towards the molecular understanding of renal magnesium handling. René Bindels (Netherlands)

11:20-11:40

Role of Calcium sequestration by the sarcoplasmic reticulum in CaMKII -induced arrhythmias and cardiac damage.
Alicia Mattiazzi (Argentina)

11:40-12:00

Gastroprotective role of glucocorticoids during NSAID-induced gastropathy.
Ludmila Filaretova (Russia)

12:00-2:00

Lunch

2:00-2:20

The Perspective of Physiology is better than ever.
Eduardo M. Krieger (Brazil)

2:20-2:40

Physiology, Integrity and Ethics.
Penny Moody-Corbett (Canada)

2:40-3:00

Preparing all students to be "professionals".
Robert Carrol (USA)

3:00-3:20

Darwinian Medicine: a new role of comparative physiology in the 21st century.
Tobias Wang (Danmark)

3:20-3:40

- **Coffee Break**

3:40-4:00

Molecular versus Integrative Physiology: which one is better?
Jens Rettig (Germany)

4:00-4:20

Physiology: from a translational team science perspective.
Patrícia Molina (USA)

4:20-4:40

The health of physiology - a perspective.
Ken O'Halloran (UK)

4:40-5:20

Panel about the perspectives for the physiology in Brazil on the 21st century.
Vagner R. Antunes (USP), Lisete Michelini (USP), Maria José Campagnole-Santos (UFMG) and Aldo Lucion (UFRGS) (Brazil).

5:20-5:50

New Challenges for the physiologists: Presentation and approval of a document (Letter of São Paulo).
Coordinated by Benedito H. Machado (USP) and Thiago S. Moreira (USP), which will be sent to all members of the Brazilian Society of Physiology (SBFis) and also to academic and scientific institutions in Brazil.

5:50-6:00

- **Closing remarks**

ABSTRACTS INDEX

RHYTHMS OF LIFE:
PERSPECTIVES FOR PHYSIOLOGICAL SCIENCES IN THE 21ST CENTURY

Participants in the Workshop

ABSTRACTS OF PRESENTATIONS

Meritocracy in the physiological sciences

Gerhard Malnic. *Departmento of Physiology and Biophysics, Institute of Biomedical Science, University of São Paulo. Brasil*

I am going to present some aspects of the evaluation of Merit, not only in Physiological Sciences, but also of a more general point of view. In several areas, there is a tendency of attributing Merit by the amount of time dedicated to a certain activity, be it Scientific or not. There are promotions for periods of five years or ten years, without a more specific evaluation of what was achieved in such periods. In most Universities, such evaluations imply a more detailed evaluation of the curriculum involved. I am going to analyse a few examples of such evaluations and their criticism at several levels of the evolutions, from basic School systems to the University.

The landscape of physiology in the 21st century

Denis Noble. *University of Oxford, UK.*

The central theory of biology in the 20th century, i.e. the neo-Darwinist interpreta tion of evolution, had concluded that physiological adaptation to environmental challenges could not directly influence the germline or inheritance. I came to doubt this view through experiments and computational models on the cardiac pacemaker, showing that knock-out experiments could not accurately reveal gene function without reverse engineering the physiological mechanisms (Noble 2010). Coincidentally, both genome sequencing and the growth of epigenetics were revealing that the germline is not isolated in the way supposed by neo-Darwinism, and that various forms of inheritance of acquired characteristics exist. By 2010, evolutionary biologists were already proposing replacement of neo-Darwinism by a more inclusive theory (Pigliucci & Müller, 2010). The full extent of the implications were explored in a Special Issue of the Journal of Physiology (Noble et al, 2014), and even further in Noble (2015). The consequence is that the physiological study of function becomes relevant to the processes by which inheritable changes occur. Physiology therefore returns to centre stage.

References

•Noble, D., Jablonka, E., Joyner, M., Müller, G.B., Omholt, S. 2014. Evolution evolves: physiology returns to centre stage. Journal of Physiology, 592, 2237-2244.
•Noble, D. 2010. Differential and integral views of genetics in computational systems biology. Interface Focus, DOI: 10.1098/rsfs.2010.0444
•Noble, D. 2015 Evolution beyond neo-Darwinism: a new conceptual framework. Journal of Experimental Biology. 218, 7-13.
•Pigliucci, M. & Müller, G.B. (eds) 2010. Evolution. The extended synthesis. MIT Press.

How to conduct an Original Research in Physiological Science that leads the world!

Katsuhiko Mikoshiba. *RIKEN Brain Science Institute, Japan*

Physiology is the scientific study of the normal function in living systems. Physiology focuses in how organisms, organ systems, organs, cells, and biomolecules carry out the chemical or physical functions that exist in a living system. To correlate molecules and behavior at various levels (organ – tissue – cell - subcellular organelle – protein – RNA - DNA) is so important for our deep understanding the life. Development of the technology has made it possible to manipulate the molecules to modify behavior and morphology. I here describe some of the examples of the activity taking the examples of the research performed in my laboratory. I have been interested in brain function and structure. To understand the complex structure of the brain which exerts variety of functions including learning & memory and behavior, it is necessary to introduce variety of strategies such as biochemistry, molecular biology, biophysics, structural biology etc. It is sometimes necessary to introduce the developmental and phylogenic aspects. Comparative analysis of the abnormal diseased brain with the control one is also required. Combination and fusion of different research areas gives us unexpected ideas to solve the unknown mechanism of mysterious brain function and structure. I describe here how I solved 1) the mechanism of neuronal positioning in the cortical layers in the brain taking an example to revealing the molecular mechanism by introducing reeler and yotari mutations Neuron 14 899-912 (1995) Nature 385 70-74(1997) Nature 389 730-733 (1997). 2) the mechanism of myelination taking the example of introducing shiverer and mld mutations Nature: 299 357-359 (1982), Annual Rev. Neurosci. 14 201-17 (1991), 3) the mechanism of IP3 receptor/calcium signaling. We discovered IP3 receptor from the analysis of the P400-protein deficient mice. We compared the protein profile of the control with those of pcd, nervous mutant deficient of Purkinje neurons and also staggerer mutant (synapses are absent) in the cerebellum (Nature 342 32-38 (1989); Science 257 251-255 (1992); Cell 73 555-570 (1993); Science 292 920-923 (2001); Nature 379 168-171 (1996); Cell 120:85-98 (2005); Science 309:2232-2234 (2005)). Thus comparison of “Abnormal” with “Normal” gives us great amount of information which cannot be obtained by only studying the normal function of the brain. All these unexpected way of doing research has given us unexpected results which are so important for opening a new field of research. It helps us revealing the mechanism of the function of the mysterious brain. All these way of research will surely make new trends in physiology and open a glorious future of physiology.

Age-related dysregulation of neuronal calcium signaling

Cecilia Hidalgo *Biomedical Neuroscience Institute, CEMC & Physiology and Biophysics Program, ICBM, Facultad de Medicina, Universidad de Chile, Santiago, Chile.*

The aging process usually entails synaptic transmission and plasticity deficits in diverse animal species; these deficits occur in different brain regions and correlate with learning and memory impairments. At the cellular level aging causes defective calcium signaling and promotes excessive generation of reactive oxygen species (ROS), which in turn impinge on calcium signaling. Neuronal calcium signals, defined as transient increments in free calcium concentration, are essential for synaptic plasticity and the activity-dependent gene expression changes underlying long-lasting synaptic plasticity and memory processes. Several studies have reported that aged rodents exhibit synaptic dysfunctions that correlate with altered calcium signaling, which affects neuronal excitability and learning. Given that anomalous calcium signaling during aging leads to significant perturbations of neuronal function, studies aimed at characterizing cellular mechanisms underlying impaired calcium signaling in the aged brain are important to decipher, at least partly, age-related synaptic transmission deficits and cognitive decline. A number of calcium-dependent electrophysiological processes undergo age-dependent changes, which are consistent biomarkers of aging and correlate with cognitive decline. Among them, aging increases L-type calcium channel expression and activity; the ensuing age-related increases in calcium influx are associated with hippocampal electrophysiological alterations and cognitive defects. In addition, neuronal calcium signals arise from calcium release mediated by ryanodine receptor (RyR) and inositol 1,4,5-triphosphate receptor (IP3R) channels present in the endoplasmic reticulum of dendrites and axons. In young rodents, calcium signals produced by activation of calcium release channels have key roles on hippocampal-dependent synaptic plasticity and memory. In aged neurons, activation of calcium release through these channels contributes to their defective function. The increased oxidative tone exhibited by aged neurons affect in particular RyR-mediated calcium-induced calcium release, a process highly sensitive to changes in cellular redox state. Of note, RyR channel inhibition or antioxidant agents significantly decrease the sustained calcium-dependent slow after-hyperpolarization (sAHP) exhibited by aged hippocampal neurons. These findings suggest that oxidation enhances RyR activity and thus contributes to this anomalous sAHP response, which by decreasing neuronal excitability contributes to age-related loss of hippocampal function and memory decline. The expression levels of several genes change during the aging process. We have found that aged rats display increased expression of the RyR2 and RyR3 channel isoforms in the hippocampus but not in the perirhinal cortex; in addition, RyR2 channels from aged rat hippocampus display higher oxidation levels than RyR2 channels from young animals. Based on these combined results, we propose that enhanced RyR-mediated calcium-induced calcium release caused by RyR upregulation and oxidation, in combination with increased L-type calcium channel expression and activity, promote age-related dysregulation of calcium signaling which likely contributes to the synaptic plasticity and memory defects displayed by aged rats.

Role of the kidney in the pathogenesis of hypertension: time for a neo-Guytonian paradigm or a paradigm shift?

Peter Bie, *Department of Cardiovascular and Renal Research, Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark.*

The development of the concepts of blood pressure regulation and of the etiology of essential hy-pertension has been unimpressive for decades. Admittedly, the fraction of hypertensive patients with essential hypertension is decreasing as the knowledge of mechanisms of secondary hypertension in-creases, but the rate of decrease is slow and in most new cases of hypertension the pathophysiology remains unknown.

The 'Guytonian paradigm' places the direct effect of arterial pressure, on renal excretion of salt and water, at the center of long-term control of blood pressure and thus the pathogenesis of hypertension. However, separate neurocentric and renocentric concepts of etiology, driven by clinicians and physiologist, respectively, have prevailed without much interaction.

In this context, several questions regarding the relationships between body fluid control and blood pressure regulation seem pertinent. Are all forms of EH associated with sympathetic overdrive or caused by a shift in the pressure natriuresis curve? Is body fluid homeostasis normally driven by the influence of arterial blood pressure directly on the kidney? Does plasma renin activity provide a key to stratification of patients with EH? The answers to all four questions is 'no'.

It seems relevant to discuss that (i) a narrow definition of EH is useful, (ii) in EH, even the best indices of cardiovascular sympathetic activity are elevated in less than 50% of the patients, (iii) in EH, as in normal conditions, mediators other than renal arterial blood pressure are the major determinants of renal sodium excretion, (iv) chronic hypertension irrespective of etiology is always associated with a shift in the pressure natriuresis curve, but this may be an epiphenomenon devoid of causality, (v) plasma renin levels are useful in the analysis of EH only after metabolic standardization and can be optimized by determination of the 'renin function line', and (vi) AngII-mediated hypertension is not a model of EH; moreover, by definition, animal models of hypertension are not models of EH.

Recent studies of baroreceptors and renal nerves as well as sodium intake and renin secretion help bridge the gap between the neurocentric and renocentric concepts, but progress in our understanding of essential hypertension seems to depend on new results on system functions in EH obtained by physicians, but planned and analyzed by physiologists.

Physiological CO_2 exchange can depend on membrane channels

Gordon J. Cooper, Rossana Occhipinti, Walter F. Boron. Department of Physiology and Biophysics, Case Western Reserve University, School of Medicine, Cleveland, OH

A CrossTalk proposal with the above title recently appeared in J Physiol. The gas-channel field got its accidental when the Boron Lab (B) observed that adding NH_3 or CO_2 to the lumen of gastric glands has no effect on intracellular pH (pHi, leading them to conclude that the apical membranes have negligible NH_3 and CO_2 permeability. In CrossTalk Comments, Peter Pohl argued that this conclusion was unwarranted because a possible lack of carbonic anhydrase (CA) at the apical surface limited CO_2 availability for diffusion into cells. However, PP did not recognize that, even when B perfused glands with 100% (>20 mM) CO_2—here there is no question of CO_2 availability—pHi failed to decrease anywhere in the gland, even in cells nearest the perfusion pipette. Thus PP's argument is unwarranted. Of course, it is unlikely that the lipid phases of all biological membranes have negligible “background” CO_2

permeabilities, but in membranes with a sufficiently low background CO2 permeability, channels could make an important contribution to overall CO2 traffic.
In their CrossTalk opposing view, Hulikova et al argued that all evidence for CO2 channels—except perhaps that in erythrocytes (RBCs)—reflects a failure to account for the effects of unconvected fluid layers (ULs) or the high CO2 permeability of the lipid phase of the cell membrane. However, even if we would grant that the expression of an aquaporin (AQP1) or Rh protein in a Xenopus oocyte somehow alters lipid composition to increase CO2 permeability, it is difficult to explain how the sudden addition of an inhibitor like pCMBS ro DIDS (which reduce CO2 permeability of certain channels) can somehow re-alter lipid composition or increase ULs. It is more difficult to explain—on the basis of ULs or lipid composition—how a single amino-acid mutation to an AQP can render a channel immune to the inhibitory effects of pCMBS or sensitive to Zn2+ or Ni2+. It is likewise difficult to explain, without invoking channels, why some AQPs are permeable to CO2 and others are not.
In their work on tumor spheroids, Hulikova et al conclude that channels do not make an important contribution to CO2 traffic. That may be true. But one should recognize that theirs is an extraordinarily complex (>20,000 cells) and artificial system. Moreover, their conclusions rest heavily on an overly simplistic mathematical model that relies on unknown parameter values.
New preliminary work indicates that, in renal proximal tubules, AQP1 is critical for normal CO2 permeability and thus HCO_3^- reabsorption. AQP1–/– mice also have a markedly reduced ability to stabilize arterial pH in the face of chronic metabolic acidosis. In the only mammalian single cells that have been studied in detail—RBCs—inhibitor and knockout studies strongly argue that nearly all CO2 moves through either AQP1 or the Rh complex. We do not argue that channels are important for CO2 traffic in all cells, but it appears that in the two systems studied to date that handle large amounts of CO2 traffic, channels are critically important.

Step stones towards the molecular understanding of renal magnesium handling

René J.M. Bindels. *Department of Physiology. Radboud University Medical Center, Nijmegen, Netherlands.*

Mg^{2+} is of great physiological importance in their function in neural excitability, muscle contraction, bone formation, and hormone secretion. The human body is equipped with an efficient negative feedback system counteracting variations of the Mg^{2+} balance. Mg^{2+} balance is maintained predominantly by the kidney which increases their fractional reabsorption under conditions of deprivation. Rapid progress has recently been made in identification and characterization of the Mg^{2+} transport proteins contributing to the delicate balance of this cation. Expression cloning approaches in combination with knockout mice models and genetic studies in families with a disturbed Mg^{2+} balance revealed novel gatekeeper proteins including members of the transient receptor potential (TRP) channels. These epithelial Mg^{2+} channels (TRPM6 and TRPM7) form prime targets for hormonal control of the active Mg^{2+} flux from the urine space to the blood compartment. The characteristics of newly identified transporters will be discussed and in particular the distinctive molecular regulation of these new Mg^{2+} transport proteins in (patho) physiological situations will be highlighted.

Role of Calcium sequestration by the sarcoplasmic reticulum in CaMKII -induced arrhythmias and cardiac damage.

Mazzocchi, G., Di Carlo M., Valverde CA, Mattiazzi A. *Centro de Investigaciones Cardiovasculares, Facultad de Medicina - CONICET La Plata, Argentina.*

Mice with constitutive phosphorylation of RyR2 at Ser2814 (S2814D mice) exhibit a higher open probability of RyR2 and sarcoplasmic reticulum (SR) Ca^{2+} leak in diastole. This anomaly increases the propensity to arrhythmias and reperfusion damage (infarct). Although abnormal Ca^{2+} release from the SR has been linked to arrhythmogenesis and ischemia/reperfusion-induced cell death, the role played by SR Ca^{2+} uptake remains controversial. We tested the hypothesis that an increase in SR Ca^{2+} uptake is able to rescue from reperfusion arrhythmias and infarction. To test this hypothesis, we generated PLN-deficient S2814D knock-in mice by crossing the two colonies, i.e. PLNKO and S2814D mice. This new colony was named SDKO mice. Mice were submitted to 15min ischemia/30min reperfusion (I/R) to assess both cardiac damage and reperfusion arrhythmias. At baseline, S2814D and SDKO mice had structurally normal hearts without arrhythmias. PLN ablation (SDKO mice), was able to prevent the arrhythmias evoked by I/R in S2814D mice. In contrast, ablation of PLN was unable to prevent cardiac damage (infarct size and KDH release), but further increase both of them. The mechanisms of these apparent contradictory results were also studied: Ablation of PLN converted Ca^{2+} waves, which are the substrate of ventricular arrhythmias, into non propagated events (Ca^{2+} mini-waves), which are unable to generate arrhythmias. Instead, PLN ablation and the consequent increase in Ca^{2+} sequestration by the SR, was not capable to avoid the reperfusion-induced increase of Ca^{2+} in the mitochondria in SDKO mice, and therefore the infarct and LDH release. Our results demonstrate that increasing SR Ca^{2+} uptake by PLN ablation can prevent the arrhythmic events triggered by CaMKII-dependent phosphorylation of RyR2-induced-SR Ca^{2+} leak and underscore the benefits of increasing SERCA2a activity on SR Ca^{2+} triggered arrhythmias. However, it cannot preclude the cardiac damage produced by CaMKII-dependent phosphorylation of RyR2. Supported by Fondecyt 1140545, BNI P-09-015F.

Gastroprotective role of glucocorticoids during NSAID-induced gastropathy

Ludmila Filaretova. *Pavlov Institute of Physiology, Russia*

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the some of the most commonly prescribed medications worldwide. However, adverse effects complicate their use. NSAID-induced gastropathy is one of the most known serious complications in patients taking these drugs. Although several factors have been postulated as pathogenic elements of the gastric injury induced by NSAIDs, it is, however, believed that prostaglandin (PG) deficiency plays a critical role in the pathogenesis of this injury. A reduction in the biosynthesis of PGs through inhibition of cyclooxygenase is considered as the pharmacological background to both the anti-inflammatory action and the harmful side-effects of NSAIDs. During PG deficiency, other defensive mechanisms might operate to attenuate NSAID-induced gastropathy. According to our results, indomethacin, wide spread NSAID, at ulcerogenic doses, similar to stress, induce an increase in glucocorticoid production that in turn helps the gastric mucosa to resist the harmful actions of these drugs. Gastroprotective effects of

glucocorticoids during treatment with NSAIDs may be mediated by multiple actions, including maintenance of gastric mucosal blood flow, mucus production and repair processes as well as the attenuation of pathogenic elements such as enhanced gastric motility and microvascular permeability. In addition, glucocorticoids released during NSAID-induced activation of the hypothalamic-pituitary-adrenocortical axis may contribute to protection of the gastric mucosa by maintaining general body homeostasis, including glucose levels and systemic blood pressure, which could be a basis for their beneficial influence on gastric mucosal integrity. Glucocorticoid hormones also participate in the healing processes of NSAID-induced gastric injury. Furthermore, glucocorticoids exert a compensatory gastroprotective role in the case of impaired gastroprotective mechanisms provided by PGs. It was demonstrated that there is some cooperative interaction between glucocorticoids and PGs in gastroprotection, in a way that a deficiency of one protective factor can lead to an apparently compensatory increase of the other. The gastric mucosa becomes more susceptible to injury during deficiency of both glucocorticoids and PGs. In conclusion, the results obtained suggest that glucocorticoids may play a role as natural defensive factors in maintaining the integrity of the gastric mucosa during NSAID therapy and might operate to attenuate NSAID-induced gastropathy.
The study is supported by PRAS I.26П.

The Perspective of Physiology is Better than Ever

Eduardo M. Krieger. *InCor/FMUSP, Brasil*

In addition to the central role played by Physiology among the Biological Sciences, Human Physiology in recent years is being considered an essential componente for the implementation of the interdisciplinar activities developed by Translational Medicine and Precision Medicine.
Examples of our group of physiology:
1. Exercise training restores baroreflex sensitivity in hypertension
We have demonstrated in a series of experiments in rats that complete resetting of the baroreceptors in hypertension is accompanied by a decreased sensitivity of the barorreceptor afferent, and consequently also of a decreased sensitivity of the baroreflex (HR and renal sympathetic nerve activity). Exercise training in SHR restores both the barorreceptor sensitivity and the baroreflexes. Based on this evidences, we demonstrated that exercise training restores baroreflex sensitivity in nerver-treated hypertensive patients.
2. We have demonstrated that sino-aortic denervation in rats alter the
behavior of blood pressure during sleep. Later on, we studied the sleep-related changes in hemodynamic and autonomic regulation in human hypertension. We found that the decreased baroreflex sensitivity may explain part of the overactivity of the sympathetic activations during sleep in human hypertension. Therefore, for the implementation of the interdisciplinary activities programmed by the Translational Medicine and the Precision Medicine, the participation of human physiology is required.

Physiology, Integrity and Ethics

Penny Moody-Corbett. *Division of BioMedical Sciences, Memorial University, St John's, Newfoundland and Labrador, Canada.*

The study of physiology dates back centuries and the record of scientific investigation is documented through presentations at scientific meetings and publication of manuscripts in scientific journals, which provide the basis for further discussion and experimentation to advance our understanding of the complexities of physiological systems. However, progress in the field relies upon researchers accurately and honestly presenting the rationale, methods, results and conclusions of their research such that results can be reproduced and further experimentation can build on the past to better understand the world we live in. When the scientific record is tainted by misrepresentation, fabrication or falsification we all lose and the consequences are damaging scientifically and personally and to the reputation of our institutions. Correction of misinformation is difficult, costly and often incomplete. The Physiological Society meetings are an important opportunity for researchers to talk about issues of ethics, integrity and research best practices. It is expected that we address topics that are of concern for the public and we consider how, as physiologists, we should approach these areas of research. Physiology meetings also offer the opportunity to address students, trainees and researchers about the issues surrounding research integrity and the concerns and consequences of research misconduct. The presentation for the Sociedade Brasileira de Fisiologia (Brazilian Society of Physiology) 2016 will consider topics of ethics and integrity throughout the lifecycle of a research project, from conception of an idea to dissemination of results, with a focus on the importance of how we train and communicate the topics of research ethics and integrity to our students and trainees. The presentation will utilize an approach recently developed by the Ethics Office of the Canadian Institutes of Health Research to consider when and how ethics topics arise during the lifecycle of a research project.

Preparing All Students to be Professionals

Robert G Carroll, PhD, Associate Dean for Medical Education. *Brody School of Medicine, East Carolina University, Greenville NC, USA.*

Changes in program assessment have shifted the role and expectations of teaching faculty. This expanded role is clearest when considering our approach to teaching graduate students and our approach to teaching students in the health professions. The terms “Competencies” and “Competency-based Education” form the core of these changing expectation. Competencies are the knowledge, skills and attitudes that enable an individual to learn and perform. When training graduate students, knowledge mastery has to be complimented by critical thinking, experimental design and execution, and professional behavior. The American Physiological Society endorsed this approach in 2003 when it published the APS/ACDP List of Professional Skills for Physiologists and Trainees.
http://www.the-aps.org/mm/Education/Publications/Education-Reports/Higher-Ed/skills
This document begins with core Biomedical Science Knowledge, but also lists Professional Ethics, Laboratory-Related Skills, Research/Analytical Skills, Communication Skills, Teaching and Mentoring skills, Lifelong Learning Skills and Career Development Skills. The

competency based approach for physicians first was established at the graduate medical education, but now guides education at the undergraduate medical level and with the HHMI Scientific Foundations for Future Physicians report in 2009, extends to the undergraduate level. For physiology educators to flourish in the 21st century, we have to acknowledge and embrace our responsibility to guide all of our students in the acquisition of knowledge, but supplement that with the other components of professional behavior.

Molecular versus Integrative Physiology: Which one is better?

Jens Rettig. *Institut für Physiologie und Centrum für Integrative Physiologie und Molekulare Medizin, Universität des Saarlandes, Homburg, Germany.*

Ca^{2+}-dependent exocytosis of signalling substances is one of the most important tasks of any cell in our body. The most heavily studied exocytic event takes place at synapses between neurons where neurotransmitters are released from synaptic vesicles. In order to understand synaptic transmission there are two general approaches: First, one can investigate the molecular mechanism underlying neurotransmitter release in isolated neurons or brain slices with high resolution electrophysiology and imaging. However, information about neuronal networks will not be gained with this approach. Therefore, an alternative approach is to perform integrative physiology in intact brain and animals through fMRI or electrical field stimulation. Here, the temporal and spatial resolution becomes problematic due to technical reasons like synapse number (1014) and speed (< 200 msec). A preparation which unifies the advantages of both approaches are cytotoxic T lymphocytes (CTLs) from the adaptive immune system which kill target cells by formation of an immunological synapse (IS) followed by the directed release of toxic substances from lytic granules. Interestingly, a number of proteins like Munc13, Munc18 or syntaxin, which have been shown to be involved in neurotransmitter release, are instrumental for lytic granule release as well. CTLs function in isolation, also when fighting infections in our body. We have investigated the molecular mechanism of IS formation and function in primary CTLs from mouse and human. Knockout/knockdown approaches have been combined with high-resolution fluorescence microscopy, electron microscopy and functional assays to elucidate the contribution of several key proteins. In addition, molecular states preceding LG fusion could be resolved by total internal reflection fluorescence microscopy (TIRFM) in combination with whole-cell patch-clamp recordings. I will present the latest findings from our lab which identify parts of the molecular machinery that is required for sequential fusion events occuring at the IS.

Literature:

Pattu V, Qu B, Marshall M, Becherer U, Junker C, Matti U, Schwarz EC, Krause E, Hoth M, Rettig J (2011). Syntaxin7 is required for lytic granule release from cytotoxic T lymphocytes. Traffic 12, 890-901.

Qu B, Pattu V, Junker C, Schwarz EC, Bhat, SS, Kummerow C, Marshall M, Matti U, Neumann F, Pfreundschuh M, Becherer U, Rieger H, Rettig J, Hoth M (2011). Docking of lytic granules at the immunological synapse requires Vti1b-dependent pairing with TCR-containing endosomes. J. Immunol. 186, 6894-6904.

Pattu V, Qu B, Schwarz EC, Strauβ B, Weins L, Shruthi S. Bhat SS, Halimani M, Marshall M, Rettig J, Hoth M (2012). SNARE protein expression and localization in human cytotoxic T lymphocytes. Eur. J. Immunol. 42, 470-475.

Matti U, *Pattu V, Halimani M, Schirra C, Krause E, Liu Y, Weins L, Chang HF, Guzman R,

Olausson J, Freichel M, Schmitz F, Pasche M, Becherer U, Bruns D, Rettig J (2013). Synaptobrevin2 is the v-SNARE required for cytotoxic T lymphocyte lytic granule fusion. Nature Comm. 4, 1439.
Dudenhöffer-Pfeifer M, Schirra C, Pattu V, Halimani M, Maier-Peuschel M, Marshall MR, Matti U, Becherer U, Dirks J, Jung M, Lipp P, Hoth M, Sester M, Krause E, Rettig J (2013). Different Munc13 isoforms function as priming factors in lytic granule release from murine cytotoxic T lymphocytes. Traffic 14, 798-809.
Halimani M, Pattu V, Chang HF, Matti U, Marshall MR, Jung M, Becherer U, Krause E, Hoth M, Schwarz EC, Rettig J (2014). Syntaxin11 serves as a t-SNARE for the final fusion step of lytic granules in human cytotoxic T lymphocytes. Eur. J. Immunol. 44, 573-584.
Marshall MR, Pattu V, Halimani M, Maier-Peuschel M, Müller ML, Becherer U, Hong W, Hoth M, Tschernig T, Bryceson YT, Rettig J (2015). VAMP8-dependent recycling endosome fusion with the plasma membrane facilitates T lymphocyte cytotoxicity. J. Cell Biol. 210, 135-151.
Ming M, Schirra C, Becherer U, Stevens DR, Rettig J (2015). Behavior and Properties of Mature Lytic Granules at the Immunological Synapse of Human Cytotoxic T Lymphocytes. PLoS ONE 10, e0135994.
Chang HF, Bzeih H, Schirra C, Chitirala P, Halimani M, Cordat E, Krause E, Rettig J, Pattu V (2016). Endocytosis of cytotoxic granules is essential for multiple killing of target cells by T lymphocytes. J. Immunol. 197, in press.

Physiology; from a translational team science perspective

Patricia E. Molina. *Professor and Head Department of Physiology, Director Alcohol and Drug Abuse Center of Excellence, Louisiana State University Health Sciences Center, New Orleans, LA 70112, USA.*

Chronic risky alcohol consumption is the most common and costly form of drug abuse in the United States. Alcohol permeates to virtually all tissues in the body, resulting in significant multi-systemic pathophysiological consequences. Approximately 3.4% of global non communicable disease-related burden of deaths, 5% of net years of life lost, and 2.4% of net disability-adjusted life years can be attributed to alcohol abuse. The frequent occurrence of alcohol use disorders (AUD) in the adult population, and the significant and widespread detrimental organ system effects highlight the importance of understanding the underlying pathophysiological mechanisms involved in alcohol-induced tissue and organ injury. Alcohol abuse is a major contributing factor to many disease categories, including cardiovascular disease, liver cirrhosis, traumatic injury, diabetes mellitus, pneumonia, and fetal alcohol syndrome. Thus, the study of the biomedical consequences of AUD requires extensive understanding of basic physiological mechanisms perturbed by alcohol directly or indirectly. Studies from our group have used a longitudinal integrated physiological approach to examine how chronic binge alcohol (CBA) consumption affects disease progression; response to antiretroviral therapy (ART), and end organ pathophysiology in simian immunodeficiency virus (SIV) infected macaques. Our team of investigators has conducted studies in multiple organ systems, allowing for maximal utilization of this precious resource and providing a comprehensive understanding of the biomedical consequences of CBA consumption on disease progression. Findings from the macaque studies have provided the foundation for the development and implementation of clinical translational studies in close collaboration with

clinicians, biostatisticians, and behavioral scientists. Through this process, physiology has served as a core science unifying hypothesis development, experimental design, and in time, interpretation of findings from the clinical setting. The goal of our studies is not only to confirm the findings from the pre-clinical studies but to expand our understanding of the clinical and functional implications of the biochemical, molecular, immunological, and epigenetic alterations resulting from CBA in the SIV-infected macaque. Thus, our studies have used alcohol as well as SIV infection as tools to perturb homeostasis, allowing us a unique perspective to understand the impact of behavioral and infectious challenges on basic physiological systems. We propose that physiologists are in a prime position to serve as the lynch pin unifying basic and clinical scientists providing the relevance of understanding fundamental physiological mechanisms as a necessary step in conducting translational science. Success in doing so will require that we open communication with scientists from other disciplines, that we strive to establish the relevance of assigning functional significance to isolated molecular, cell, or organ system alterations in context of both health and disease states. Having a comprehensive approach to the study of a particular organ system or disease state should be an invaluable asset for our clinician partners as we build teams to further our understanding of disease mechanisms. This approach ensures that Physiology as a discipline remains relevant and current to the increasingly complex scientific environment driving our educational and research activities. Physiology has been the center and driving force behind our NIH-funded Comprehensive Alcohol Research Center, bringing together basic, clinical, and social sciences into a team-based scientific approach to understanding the impact of CBA on SIV/HIV-associated comorbid conditions.

The health of Physiology – a perspective

Ken D. O'Halloran. *Department of Physiology, University College Cork, Ireland.*

What does a health check for Physiology in the 21st century reveal? Has it run its course as a research discipline? Will it soon be confined to the lecture halls and libraries of contemporary institutions? Or on the contrary, does it have a bright future, a central role to play in the pursuit of fundamental knowledge for the benefit of human health? Physiology's current predicament is a paradox of sorts: increasingly invisible, and to some in rapid irreversible decline, yet it appears never as popular in terms of Society membership, and global celebrations of the discipline, which demonstrably go from strength to strength. As with any conundrum, there are elegant solutions, and a growing interest within the community to seek them out.

Against the backdrop of significant failings of the modern reductionist approach, Physiology, with its holistic approach to integrative function of complex organisms, has never seemed so relevant and important. Yet there are worrying signs. Morale in many camps is low. Brand Physiology appears in poor shape to those pulling the purse strings; past its heyday, dated, maybe even dead! Many others at the centre and fringes of the discipline are optimistic for Physiology's future, but it is increasingly clear that physiologists must take action, not so as to merely protect Physiology per se, but critically, so as to ensure it is enabled to contribute to the delivery of ambitious expectations set by the wider community, notably funders spending public monies. Physiology is essential to the realisation of plans for better health outcomes. It is pivotal to progress, once one accepts that progress is a slow incremental affair.

It is timely that many conversations have commenced with a view to charting a course for

Physiology through troubled waters. I hope to add constructively to the debate with observations and discussion serving to nudge Physiology ever closer to centre stage, where she belongs, in the theatre of the life sciences. My presentation will focus on: 1) Physiology—a puzzling paradox; 2) Welcome to the Department of Convenient Amalgamations; 3) Blind spots, deaf ears, hard noses: Has Physiology been tight-lipped for too long?; 4) What's wrong with the P word?; 5) More popular than podiatry; 6) Comparatively speaking; 7) Many languages—one voice; 8) Building the brand: leaders and loyalty; 9) Reach out to outreach; 10) Dare to teach; 11) Turning the tide—let's agree on integration; 12) After Fernel: Physiologia for the future