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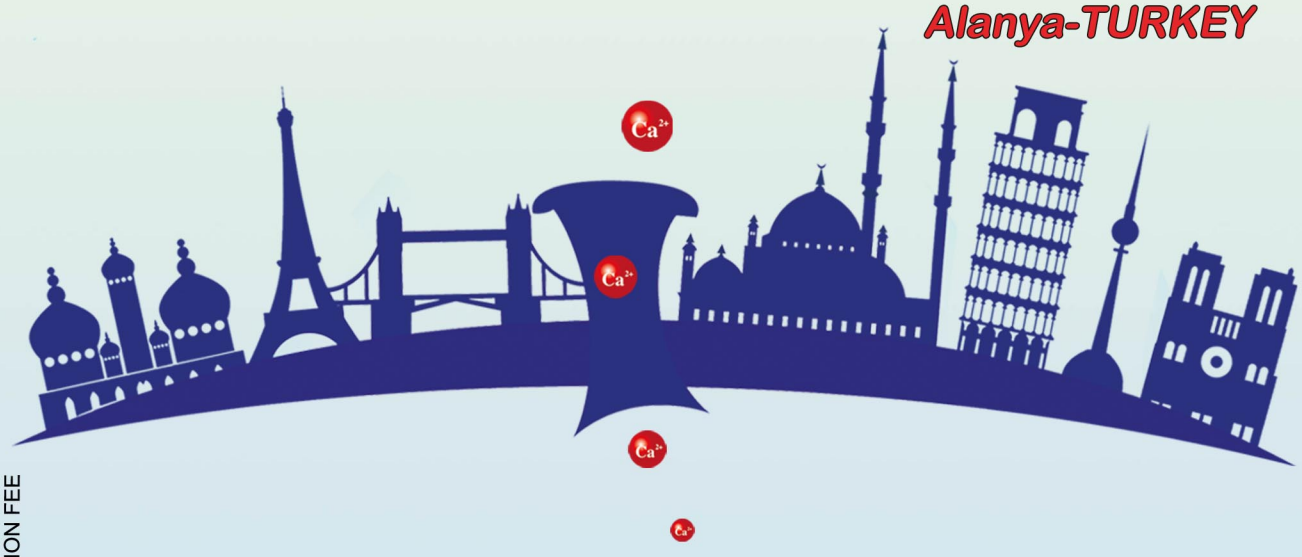

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AIM AND SCOPES
Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

Areas of particular interest are four topics. They are;

A- Ion Channels (Na^+- K^+ Channels, Cl^- channels, Ca^{2+} channels, ADP-Ribose and metabolism of NAD^+, Patch-Clamp applications)

B- Oxidative Stress (Antioxidant vitamins, antioxidant enzymes, metabolism of nitric oxide, oxidative stress, biophysics, biochemistry and physiology of free oxygen radicals)

C- Interaction Between Oxidative Stress and Ion Channels in Neuroscience
(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD^+ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

D- Gene and Oxidative Stress
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7th World Congress of Oxidative Stress, Calcium Signaling and TRP Channels

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7th World Congress of Oxidative Stress, Calcium Signaling and TRP Channels

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7th World Congress of Oxidative Stress, Calcium Signaling and TRP Channels

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Speakers

7th World Congress of Oxidative Stress, Calcium Signaling and TRP Channels

Young Speakers

SPEAKERS

Keynote Speak No. 1

Functions of store-operated calcium channels

James W. PUTNEY
Scientist Emeritus, The Signal Transduction Laboratory, National Institute of Environmental Health Sciences – NIH, Research Triangle Park, NC 27709, USA

In most eukaryotic cells, calcium signaling occurs through an interacting combination of intracellular calcium release and entry of calcium across the plasma membrane. Although various mechanisms can subtend these processes, the most widely encountered mechanisms are intracellular calcium release via the inositol trisphosphate receptor, and entry of calcium through store-operated channels. Storeoperated calcium entry, as the name implies, involves activation of plasma membrane channels in response to a loss of calcium from intracellular endoplasmic (or sarcoplasmic) reticulum stores. The calcium level in the endoplasmic reticulum is sensed by either of two transmembrane calcium-binding proteins, STIM1 or STIM2. When calcium dissociates from the luminal binding site on STIM1 or 2, the protein aggregates and translocates to sites of close apposition of endoplasmic reticulum and plasma membranes. There, STIM recruits and binds hexameric calcium channels composed of Orai1 subunits (or possibly Orai2 or Orai3). This results in activation of the channels and accelerated entry of calcium into the cytoplasm.

The general function of store-operated calcium entry is the activation of downstream signaling mechanisms linked to processes ranging from contraction and secretion to cell growth and differentiation. The development of genetically modified mouse models with global or directed knockout of either STIM or Orai genes has provided significant information on the specific physiological processes that depend on this signaling mechanism. Among these processes are male fertility, neutrophil chemotaxis, and exocrine secretion. These and other aspects of the functions of storeoperated calcium channels will be the focus of this lecture.

Keynote Speak No. 2

Redox lipidomics of programmed cell death signaling

Valerian E. KAGAN
Environmental Sciences, Chemistry, Pharmacology and Chemical Biology, University of Pittsburgh, USA

From the very early stages since the emergence of life on our planet, phospholipids played a very essential role by fulfilling two major functions: 1) as structural building blocks of membranes, and 2) as communication signals. Among many different mechanisms, oxygenation of polyunsaturated lipids played an essential role in coordinating numerous metabolic reactions and pathways, including death programs. Cells overpowered by viruses or bacterial pathogens or overburdened with genotoxic material are destined to die through one of the strictly coordinated death pathways. As several new programs of cell death have been discovered, they turned to be closely interconnected and failure of one of them inevitably triggers another one such the ultimate goal – elimination of the damaged cell representing high risk for the multi-cellular community – is achieved. This paramount role of oxygenated polyunsaturated lipids in regulation is also associated with a risk of their involvement in aberrant injury reactions due to lipid peroxidation and the production of secondary reactive lipid electrophiles. In this talk, we will discuss how redox lipidomics discovered specific predictive oxygenated phospholipid biomarkers acting as signals in two important death programs – apoptosis and ferroptosis. We will present mechanistic data describing the enzymatic machinery that generates highly specific oxygenated phospholipids – cardiolipins and phosphatidylethanolamines in apoptosis and ferroptosis, respectively.

Keynote Speak No. 3

TRP channels in oxygen and thermo biology

Yasuo MORI
Kyoto University, Graduate School of Engineering, Department of Synthetic Chemistry and Biological Chemistry, Kyoto, Japan

Ca^{2+}-permeable cation channels encoded by the transient receptor potential (trp) gene superfamily are characterized by a wide variety of activation triggers that act from outside and inside the cell. Reactive species such as reactive oxygen species (ROS), reactive nitrogen species (RNS) and other electrophiles are known to exert stress on organisms, but are also emerging as molecules that mediate cell signaling responses. Understanding the physiological significance and activation mechanisms of TRP channel regulation by reactive species has lead us to consider TRP channels as viable pharmacological targets; modulators of these channels may offer therapeutic options for previously untreatable diseases. Recent studies have revealed that multiple TRP channels sense reactive species and induce diverse physiological and pathological responses, such as cell death, chemokine production, and pain transduction. TRP channels sense reactive species either indirectly through second messengers or directly via oxidative modification of cysteine residues. In this seminar, I describe the activation mechanisms and biological roles of redox-sensitive TRP channels. Especially, I will focus on TRPA1 channels and discuss its unique and high sensitivity to molecular oxygen. Also, I will extend my discussion on relationships between redox and thermal sensitivities of TRP channels.

Keynote Speak No. 4

ORAI calcium channels in health and disease

Mohamed TREBAK
Pennstate University, Hershey, PA, USA

ORAI (ORAI1, ORAI2, and ORAI3) proteins form a family of highly Ca^{2+}-selective channels at the plasma membrane. ORAIs are activated by stromal-interacting molecules (STIM1 and STIM2), which are Ca^{2+} sensing proteins located in the endoplasmic reticulum. STIM and ORAI proteins are ubiquitously expressed in all mammalian tissues and form store-operated Ca^{2+} entry (SOCE) channels. Mutations or altered expression of STIM and ORAI proteins are associated to a number of diseases, including cardiovascular and airway diseases and cancer. Here we will discuss our current understanding of ORAI channel signaling and regulation and their contribution to several pathologies.

Keynote Speak No. 5

Structure and function of TRPA1

Makoto TOMINAGA
Division of Cell Signaling, Okazaki Institute for Integrative Bioscience, Okazaki, Japan

TRPA1 is a nonselective cation channel with high Ca^{2+} permeability. We found that extracellular Ca^{2+}, but not either divalent cations (Mg^{2+} and Ba^{2+}) or intracellular Ca^{2+}, is involved in heat-evoked activation of green anole lizard TRPA1 (gaTRPA1). Heat-evoked activation of chicken TRPA1 and rat snake TRPA1 did not depend solely on extracellular Ca^{2+}. A comparison of extracellular amino acids in TRPA1 identified three negatively charged amino acid residues (glutamate and aspartate) near the outer pore vestibule that are involved in heat-evoked gaTRPA1 activation in the presence of extracellular Ca^{2+}. These results suggest that neutralization of acidic amino acids by extracellular Ca^{2+} is important for heat-evoked activation of gaTRPA1, chTRPA1, and rsTRPA1. Single channel opening of gaTRPA1 was confirmed in the planner lipid bilayer system.

We found that lysophosphatidic acid (LPA) is an itch mediator, but not a pain mediator by a cheek injection model of mice. Mouse dorsal root ganglion neurons directly responded to LPA depending on TRPA1 and TRPV1. LPA-induced itch-related behaviors were decreased in TRPA1KO, TRPV1KO or TRPA1, TRPV1 double KO mice. TRPA1 and TRPV1 channels were activated by intracellular LPA, but not by extracellular LPA following LPA_5 receptor activation with an activity of Ca^{2+}-independent phospholipase A_2 and phospholipase D. KK672-673 and KR977-978 (K: lysine, R: arginine) of TRPA1 were identified as intracellular LPA interaction sites. Thus, targeting TRPA1, TRPV1 or PLD could be effective for cholestatic itch interventions.

Keynote Speak No. 6

TRPM2 – a critical sensor of warmth and hydrogen peroxide

Peter MCNAUGHTON
King's College, London, UK

We need to be able to make quick judgements about warmth and cold in the external environment, in order to choose a comfortable ambient temperature and to avoid dangerous extremes of heat. When the TRP ion channel family was cloned it seemed that this problem was solved, because a spectrum of thermally activated TRP channels responded to temperatures from extreme cold to painful heat. However, as knockout mice for each of these thermo-TRP channels have been constructed, it has become apparent that many of the supposed thermal detectors actually have little influence on thermal behaviour at the level of the whole organism. In particular, genetic deletion of potential warm-sensitive ion channels TRPV3 and TRPV4 had no effect on behavioural warmth sensation.

With this background we set out to establish the molecular mechanism responsible for warmth sensation. We used calcium imaging to monitor the responses of isolated somatosensory neurons to warm and hot stimuli. We eliminated neurons responding to agonists for known heat-sensitive TRP channels and focussed on a population of neurons that expressed a novel thermal response. We used an RNA sequencing strategy to identify the thermally-sensitive ion channel expressed in these neurons as TRPM2, a TRP channel not previously suspected to be involved in warmth sensation.

The story came together in an interesting way when we looked at thermal sensation in mice in which TRPM2 had been genetically deleted. Wild-type mice are most comfortable at an ambient temperature of 33 degrees Centigrade, and they avoid warmer temperatures such as 38 degrees. The TRPM2 knockout mice, however, were unable to distinguish between 33 degrees and 38 degrees, suggesting that removal of TRPM2 had ablated a "warm" detector. Both mice, however, avoided hot temperatures such as 43 degrees, at which TRPV1 and TRPM3, the known "painful heat" detectors, are activated. This work identifies TRPM2 as a novel thermal detector which is responsible for the detection of non-painful warmth.

Keynote Speak No. 7

Ros signaling via TRPM2 in the mechanism of neutrophil migration

Asrar B. MALIK
Chicago, IL, USA

TRPM2 (transient receptor potential melastatin-2) expressed in endothelial cells (ECs) is a cation channel mediating Ca^{2+} entry in response to intracellular generation of adenosine diphosphoribose—the TRPM2 ligand. Because polymorphonuclear neutrophils (PMN) interaction with ECs generates reactive oxygen species, we addressed the possible role of TRPM2 expressed in ECs in the mechanism of transendothelial migration of PMNs. We observed defective PMN transmigration in response to lipopolysaccharide challenge in adult mice in which the EC expressed TRPM2 is conditionally deleted ($Trpm2^{i\Delta EC}$). PMN interaction with ECs induced the entry of Ca2+ in ECs via the EC-expressed TRPM2. Prevention of generation of adenosine diphosphoribose in ECs significantly reduced Ca^{2+} entry in response to PMN activation of TRPM2 in ECs. PMNs isolated from $gp91phox^{-/-}$ mice significantly reduced Ca^{2+} entry in ECs via TRPM2 as compared with wild-type PMNs and failed to induce PMN transmigration. Overexpression of the adenosine diphosphoribose insensitive TRPM2 mutant channel (C1008→A) in ECs suppressed the Ca^{2+} entry response. Further, the forced expression of TRPM2 mutant channel (C1008→A) or silencing of poly ADP-ribose polymerase in ECs of mice prevented PMN transmigration. Thus, endotoxin-induced transmigration of PMNs was secondary to TRPM2-activated Ca^{2+} signaling and VE-cadherin phosphorylation resulting in the disassembly of adherens junctions and opening of the paracellular pathways. These results show that TRPM2 expressed in EC regulates the transendothelial migration of PMNs, and suggest blocking TRPM2 activation in ECs is a potentially important means of therapeutically modifying PMN-mediated vascular inflammation.

Keynote Speak No. 8

Ca^{2+} signalling and bioenergetics of pancreatic diseases

Alexei V. TEPIKIN
Liverpool, UK

I will discuss functioning of Ca^{2+} signalling mechanisms (including Ca^{2+} release from intracellular stores and store-operated Ca^{2+} entry) in pancreatic acinar cells and pancreatic ductal adenocarcinoma (PDAC) cells. Particular attention will be given to signalling-metabolism coupling and to properties of junctional complexes between the endoplasmic reticulum (ER) and the plasma membrane (PM). I will describe both structure and dynamics (formation and dissolution) of ER-PM junctions. The putative pathophysiological roles of Ca^{2+} signalling in acute pancreatitis and PDAC will be also discussed.

Speak No. 1

Ca^{2+} signals originate from immobile IP_3 receptors at ER-PM junctions

Colin TAYLOR
Department of Pharmacology, University fo Cambridge, Cambridge, UK

Inositol 1,4,5-trisphosphate receptors (IP_3Rs) are ubiquitous intracellular Ca^{2+} channels in the ER. Regulation of IP_3Rs by Ca^{2+} allows regenerative propagation of Ca^{2+} signals, generating a hierarchy of Ca^{2+} release events. The spatial arrangement and dynamics of IP_3Rs are important for producing these regenerative Ca^{2+} signals. To study the distribution and dynamics of IP_3Rs at native expression levels, we used transcription activator-like effector nucleases (TALENs) to tag endogenous IP_3R1 of HeLa cells with EGFP. EGFP-IP_3Rs were functional and formed small clusters within ER membranes. Most IP_3R clusters were mobile, but some were immobile for protracted periods. There was minimal mixing of the mobile and immobile populations of IP_3Rs. Single-particle tracking revealed that IP_3Rs move by diffusion, and along microtubules by both kinesin-1 and dynein motors. Within both mobile and immobile IP3R puncta, some IP_3Rs were tightly packed but others were too far apart for their association to be mediated by direct interactions between IP_3Rs. Simultaneous visualization of EGFP-IP3Rs and Ca^{2+} signals showed that Ca^{2+} signals, whether evoked by photolysis of caged IP3 or activation of endogenous receptors that stimulate IP_3 formation, originate from immobile IP_3Rs at ER-plasma membrane (PM) junctions. These Ca^{2+} release sites closely apposed the ER-PM junctions where stromal-interaction molecule (STIM), the ER Ca^{2+} sensor that stimulates store-operated Ca^{2+} entry (SOCE), accumulated after depletion of ER Ca^{2+} stores. Our results show that IP_3-evoked Ca^{2+} signals are initiated by immobile IP3R clusters tethered near the ER-PM junctions at which SOCE occurs. We suggest that this organization may both optimize delivery of IP_3 to IP_3Rs and allow effective regulation of SOCE by local depletion of Ca^{2+} stores.

Speak No. 2

Radiation links TRPM2, mitochondria, and SOCE to cause loss of salivary gland function

Indu S. AMBUDKAR
Secretory Physiology Section, National Institute of Dental Research, National Institutes of Health, Bethesda MD. 20892, USA

Salivary gland fluid secretion occurs as sequalae to neurotransmitter stimulation of PIP2 hydrolysis, IP_3 generation, and a sustained increase in cytosolic [Ca^{2+}] ([Ca^{2+}]i) that is primarily dependent on Store-Operated Calcium Entry (SOCE). The latter is critically required for regulating sustained fluid secretion and is mediated by the channels Orai1 and TRPC1 that are activated by by the ER-Ca^{2+} sensor protein, STIM1. Radiation treatment of the head and neck region causes irreversible loss of salivary fluid secretion, severely affecting the oral health of patients. There is poor understanding of the mechanisms underlying the loss of salivary gland fluid secretion. Towards identifying this mechanism, we have examined the possible role of Transient Receptor Potential Melastatin-like 2 (TRPM2), a Ca^{2+}-permeable nonselective cation channel that is activated by increase in ROS, in radiation-induced salivary gland dysfunction. Our studies demonstrate that TRPM2 is present in salivary gland cells and is activated in response to radiation treatment. Importantly, deletion of TRPM2, or suppression of activation, converted irreversible loss of salivary gland function to a transient loss of function in a mouse model. We have identified that radiation induces persistent defect in SOCE which underlies the loss of salivary fluid secretion. Our findings show that critical early effects of radiation include TRPM2-mediated Ca^{2+} entry, increase in the mitochondrial [Ca^{2+}] and reactive oxygen species, decrease in mitochondrial membrane potential, and activation of caspase-3. The latter mediates cleavage of stromal interaction molecule 1 (STIM1), inducing loss of SOCE. We suggest that targeting the mechanisms underlying the loss of STIM1 would be a potentially useful approach for preserving salivary gland function.

Speak No. 3

Channel formation by mitochondrial ATP synthases. Regulation by Ca^{2+} and oxidative stress

Paolo BERNARDI
University of Padova, Department of Biomedical Sciences, Via Ugo Bassi 58/B, 35131 Padova, Italy

Mitochondria can undergo an increase of inner membrane permeability (the permeability transition, PT) causing inner membrane depolarization, Ca^{2+} release and cessation of ATP synthesis. Prolonged openings may cause matrix swelling and outer membrane rupture with release of intermembrame proteins. The PT requires matrix Ca^{2+}, is favored by oxidative stress and inhibited by matrix H^+ and Mg^{2+}/ATP(ADP). The PT is mediated by opening of a high-conductance channel, the PT pore (PTP) or mitochondrial megachannel (MMC) [1]. Cyclophilin D (CyPD) is the best characterized protein modulator of the PTP and the receptor for its inhibitor cyclosporin A (CsA). The pursuit of the PTP has taken a new course after the discovery that CyPD interacts with, and modulates, the F_1FO (F)-ATP synthase as well [2]. The subsequent demonstration that bovine, human, yeast and drosophila F-ATP synthases form Ca^{2+}-activated channels set the foundation for the hypothesis that the PTP originates from specific conformations of F-ATP synthase [3]. The debate is open as to whether and how F-ATP synthase can undergo a transition from key energy-conserving enzyme to energydissipating channel that favors or causes cell death. We will discuss recent advances in this rapidly moving field based on site-directed mutagenesis of selected residues of F-ATP synthase.

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Speak No. 4

Redox-control of senescence through TRP modulation

J. Andres MELENDEZ
Colleges of Nanoscale Science & Engineering, SUNY Polytechnic Institute, Albany, NY, USA

Cellular senescence has evolved as a protective mechanism to arrest growth of cells with oncogenic potential. While senescent cells have lost the ability to divide, they remain metabolically active and adapt a deleterious senescence associated secretory phenotype (SASP) central to the progression of several age-associated disease pathologies. The SASP is mechanistically regulated by the pro-inflammatory cytokine interleukin-1 alpha (IL-1α) whose expression and activity is responsive to the senescence associated (SA) oxidant production and the accompanying disruption of calcium (Ca^{2+}) homeostasis. Using primary IMR-90 human fetal lung fibroblasts as a model of replicative senescence, we explored the molecular underpinnings facilitating increased Ca^{2+} entry in senescent cells. We establish that the redox-responsive Transient Receptor Potential TRPC6 channel is compromised due to desensitization owing to SA increases in steady state hydrogen peroxide (H_2O_2) production. SA dysregulation of Ca^{2+} is also accompanied by loss of response to H_2O_2-induced Ca^{2+} influx that can be rescued with catalase pre-treatments. Senescent cells are also insensitive to Ca^{2+} entry induced by hyperforin, a specific activator of TRPC6, that can be restored by catalase pre-treatments, further suggesting redox regulation of TRPC6 in senescence. Inhibition of TRPC6 channel activity restores ability of senescent cells to respond to peroxide-induced Ca^{2+} in addition to suppressing SASP gene expression. Furthermore, mammalian target of rapamycin (mTOR) signaling regulates SASP by means of modulating TRPC6 channel expression. Together, our findings provide compelling evidence that redox and mTOR-mediated regulation of TRPC6 channel modulates SASP gene expression. As TRP channels emerge as targets of pharmacologic intervention for numerous disease pathologies, it is exciting to speculate that effects of

TRP interventions may be attributed in part to inhibition of senescence and the SASP.

Speak No. 5

Blood pressure regulation by vascular TRP channels

Jonathan H. JAGGAR
Department of Physiology, University of Tennessee Health Science Center, Memphis TN, USA

Systemic blood pressure is determined in part by arterial smooth muscle cells (myocytes) that alter resistance vessel tone. In vivo mechanisms that regulate myocyte contractility to control physiological blood pressure and become pathological during hypertension are poorly understood. Several Transient Receptor Potential (TRP) channels are expressed in arterial myocytes, but it is unclear if these proteins control physiological blood pressure and can be targeted to alleviate hypertension. We generated the first inducible, smooth muscle-specific knockout for a TRP channel, namely for PKD2 (also termed TRPP1, $PKD2^{sm-/-}$), to investigate blood pressure regulation by this protein. Data indicate that myocyte PKD2 channel knockout dilates resistance-size systemic arteries and reduces blood pressure. We show that heterogeneous stimuli activate PKD2 channels in arteries of different organs. Regardless of the stimulus or arterial bed, PKD2 current activation in myocytes leads to vasoconstriction. Our data illustrate that hypertension is associated with an increase in the abundance of plasma membrane PKD2 channels in systemic artery myocytes. Inducible, myocyte-specific PKD2 channel knockout causes vasodilation, lowers systemic blood pressure and prevents arterial remodeling during hypertension. Furthermore, I will discuss our evidence that intravascular pressure stimulates post-translational modification of PKD2 channels in myocytes to control arterial contractility. In summary, we show that PKD2 channels are activated by distinct vasoconstrictor stimuli in arterial myocytes of different tissues, control physiological systemic blood pressure, are upregulated during hypertension and knockout reduces high blood pressure. Arterial myocyte PKD2 channels could be targeted to control blood pressure and alleviate cardiovascular diseases.

Speak No. 6

Redox regulation of calcium channel function: From Orai to MCU

Ivan BOGESKI
Molecular Physiology, Institute of Cardiovascular Physiology, University Medical Center, Göttingen, Germany

Store-operated Ca^{2+} entry (SOCE) through the Ca^{2+} release activated Ca^{2+} (CRAC) channels and mitochondrial Ca^{2+} uptake via the mitochondrial Ca^{2+} uniporter (MCU) complex are collective signaling mechanisms responsible for a variety of cellular functions. The CRAC channels are composed of three plasma membrane based proteins, known as Orai1, Orai2 and Orai3 and two Ca^{2+} sensor proteins STIM1 and STIM2 in the endoplasmic reticulum. The mitochondrial Ca^{2+} uniplex comprises MCUa, MCUb, EMRE, MICU1 and MICU2. We aim to understand the role of these proteins in immunity and in cancer and unravel their redox regulation and functional interplay with cellular redox systems. We have shown that Orai1 and Orai2, but not Orai3 channels are inhibited by oxidation. The differential redox sensitivity of the Orai isoforms was attributed to a cysteine residue present in Orai1 and Orai2 but absent in Orai3. Moreover, we found that Orai channels form a feedback loop with the H_2O_2-generating NADPH oxidase 2 (NOX2), thereby affecting monocyte function. In addition, we recently demonstrated that the assembly of the MCU complex is a redox-regulated process. Current studies indicate that redox regulation of Orai, STIM and MCU play a significant role in regulating innate immune responses and cancer pathobiology.

Speak No. 7

Lipid signaling in acute brain injury

Hülya BAYIR
Department of Critical Care Medicine, University of Pittsburgh, PA, USA.

Lipids are central to brain structure and function as brain has a remarkably high lipid content. Among different lipid classes in the brain, phospholipids play essential structural roles and act as important signaling molecules for neuronal health and disease. Acute brain injury has been shown to alter phospholipids primarily by oxidation upon trauma or ischemia/reperfusion. Although initial studies ascribed phospholipid oxidation to random free radical mediated events, recent advancements in liquid chromatography-mass spectrometry based oxidative lipidomics analyses have shown that contribution of enzymatic lipid peroxidation is the major pathogenic mechanism of phospholipid oxidation after acute brain injury. We have shown that cardiolipin (CL), a mitochondria unique phospholipid, is selectively oxidized after trauma or global ischemia of the brain. CL oxidation is a result of transmigration of CL from the inner to the outer mitochondrial membrane with resultant complex formation of CL with cytochrome c. The CL/cytochrome c complex utilizes hydrogen peroxide as the source of oxidizing equvalents to oxidize CL. Hydrolysis of oxidized CL by calcium-independent phospholipase A2 leads to a novel mitochondrial lipid signaling pathway by formation of monolyso-CL and oxidized free fatty acids as signaling lipid mediators after injury. Therapies using mitochondria targeted electron scavengers, hemigramicidin nitroxides, attenuate CL oxidation, neuronal death, and improve histological and neurocognitive outcome after acute brain injury. These data show that CL oxidation and subsequent hydrolysis represent a previously unidentified pathogenic mechanism of acute brain injury and a clinically relevant therapeutic target.

Speak No. 8

Function of ERG (ether-a-go-go) channels in central auditory neurons

Caner YILDIRIM and Ramazan BAL
Department of Physiology, Faculty of Medicine, Gaziantep University, 27310 Gaziantep, Turkey

The cochlear nucleus relay auditory information to the higher auditory centers. There are three different cell types, stellate, octopus and bushy, in the ventral cochlear nucleus (VCN). These cells have different electrophysiological and morphological properties. ERG (ether-a-go-go-related gene) channels, belonging to the voltage-gated potassium channel family, have three subgroups with different biophysical properties, ERG1 (Kv11.1), ERG2 (Kv11.2) and ERG3 (Kv11.3). The aim of the current study was to investigate contribution of ERG channels to the passive and active membrane properties of the VCN stellate neurons.

The electrophysiological whole cell-patch clamp technique was used to study the ERG channels in stellate neurons in coronal slices with a thickness of 175-200 μm. The data presented in the current study are based on the recordings from 128 stellate neurons.

Application of terfenadine (10 μM) and E-4031 (10 μM), which are ERG channel antagonists, resulted in increases of input resistance of stellate cells significantly ($n = 13$; $p < 0.05$). Inactivation of ERG channels by ERG channel antagonists, terfenadine (10 μM) and E-4031 (10 μM), exert excitatory effects upon cell excitability, as indicated by decreased action potential threshold and increased firing rate ($n = 10$; $p<0.01$). ($p<0.05$). Under voltage clamp condition, the E-4031-sensitive tail current first appeared at around -65 mV and the amplitude of the tail current increased gradually with more depolarized membrane potentials. The activation curve for ERG channels was constructed by plotting amplitude of the normalized tail currents as a function of voltage steps. The curve was fitted with a Boltzmann function, which gave a $V_{0.5}$ -51.2 mV with a slope factor of 6.50.

In conclusion, our results show that stellate neurons express ERG channels, which have similar

properties as ERG currents described in other cellular preparations. We think that ERG channels might contribute to setting the threshold, frequency, possibly resting membrane potential, of stellate neurons of the VCN under physiological conditions.

Keywords: ERG channels, patch clamp, electrophysiology, cochlear nucleus, auditory pathway

Speak No. 9

Phototoxicity – light is painfully blue

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The capsaicin and mustard oil receptors TRPV1 and TRPA1, respectively, are highly expressed in polymodal nociceptors, ubiquitous thin nerve fibers that can evoke pain and induce “neurogenic inflammation” by neuropeptide secretion. Reversible oxidation of intracellular cysteine residues of these channel proteins causes activation and sensitization to adequate stimuli. The ion channel activity can be assessed in cultured sensory neurons, transfected cell lines, and in artificial lipid bilayers, using patch-clamp recording, calcium microfluorimetry, and indirectly by single-fiber recording and enzyme immunoassay measurement of stimulated neuropeptide (CGRP) release from isolated organ preparations. Strikingly, we found that ordinary blue light (405 nm) activates human TRPA1 and evokes pain in white human skin. This results from the ubiquitous presence of the heme precursor protoporphyrin IX (Pp IX) that acts as a chromophore to produce singlet oxygen under illumination. The ensuing oxidation of the TRP channels accounts for the pain and skin damage porphyria patients suffer upon sunlight exposure and for the painful side effects of photodynamic therapy of cutaneous cancers. However, another genetic syndrome of extreme and painful photosensitivity, Smith-Lemli-Opitz disease, results from the accumulation of the cholesterol and vitamin D3 precursor 7-dehydrocholesterol (7-DHC) which is neither excited by visible or UVA light nor produces singlet oxygen to oxidize the TRPs. Nonetheless, we could demonstrate that 7-DHC is a particularly sensitive target of light (350-430 nm)-induced oxidation which produces oxysterols known to generate reactive oxygen species and lipid peroxides that activate both TRP channels. The severe abdominal pain attacks of porphyria patients remain to be elucidated.

Keywords: TRPV1; TRPA1; porphyria; photodermatitis; chromophore; singlet oxygen; 7dehydrocholesterol; CGRP.

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Speak No. 10

TPC2-mediated Ca^{2+} release is required for the establishment of the early spinal cord circuitry and the development of slow skeletal muscle cells in zebrafish embryos.

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We recently demonstrated, via the introduction of a translational-blocking morpholino antisense oligonucleotide (MO), a critical role for two-pore channel type 2 (TPC2)-mediated Ca^{2+} release during the differentiation of slow (skeletal) muscle cells (SMCs) in intact zebrafish embryos. Following this initial report, we extended our study and demonstrated that knockdown of TPC2 (with a non-overlapping splice-blocking MO); knockout of TPC2 (via the generation of a $tpcn2^{dhkz1a}$ mutant line of zebrafish using CRISPR/Cas9 gene-editing); or the pharmacological inhibition of TPC2 action (with bafilomycin A1 or trans-ned-19), also led to a significant attenuation of SMC differentiation, characterized by a disruption of SMC myofibrillogenesis and gross morphological changes in the trunk musculature. STED super-resolution microscopy revealed a close physical relationship between clusters of ryanodine receptors (RyR) in the terminal cisternae of the sarcoplasmic reticulum (SR), and TPC2 in lysosomes, with a mean estimated separation of ~52-87 nm. Our data therefore add to the increasing body of evidence, which indicate that localized Ca^{2+} release via TPC2 might trigger the generation of more global Ca^{2+} release from the SR via Ca^{2+}-induced Ca^{2+} release. Furthermore, in zebrafish, one of the first observed behavioral activities is the SMC-mediated spontaneous coiling contractions of the trunk. This behavior begins at ~17 hours post-fertilization (hpf) and coincides with the spontaneous activity of the primary neurons in the spinal cord as well as Ca^{2+} transients generated in the SMCs in the trunk. Here, we report that TPC2-mediated Ca^{2+}-release is also required for the establishment of highly synchronized connectivity within the zebrafish embryonic spinal circuitry. Using the SAIGFF213A;UAS:GCaMP7a double-transgenic line of fish (a kind gift from Prof. Koichi Kawakami), which expresses GCaMP7a in the caudal primary motor neurons (CaPs), Ca^{2+} transients were visualized starting from the early stages of spontaneous activity at ~18 hpf. We report that TPC2 inhibition resulted in a decrease in the frequency and amplitude, as well as the ipsilateral and contralateral correlation, of the CaP Ca^{2+} transients, indicating a significant disruption of the maturing spinal circuitry. Together, our new data suggest a novel function for TPC2-mediated Ca^{2+} signalling in the development, coordination, and maturation of the early neuromuscular activity of zebrafish embryos. This work was supported by: HK RGC-GRF awards 16101714 & 16100115; ANR/RGC award A-HKUST601/13, and HK-ITC (ITCPD/17-9).

Speak No. 11

Redox metabolism in angiogenesis and tumor progression

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Department of Biology, University of Padua, Italy

Endothelial cells (ECs) exhibit a remarkable and unique plasticity in terms of redox biology and metabolism. EC are equipped with a selective and unique repertoire of redox and metabolic mechanisms that play a crucial role to preserve redox balance, and adjust metabolic conditions in both normal and pathological angiogenesis. The identification of such redox signaling and metabolic pathways is crucial to gain of better insights in endothelial biology and dysfunction. We are currently investigating the formation, actions, key molecular interactions, and physiological and pathological relevance of redox signals in ECs using different genetic and molecular approaches. These insights will be useful for establishing innovative therapeutic approaches for the treatment of those conditions where aberrant or excessive angiogenesis is the underlying cause of the disease itself.

Speak No. 12

Exploiting oxidative stress to selectively kill cancer cells via pharmacological targeting of mitochondrial ion channels

Ildiko SZABO
Department of Biology, University of Padova, Italy

Mitochondrial ion channels of the inner membrane play an important role in modulating mitochondrial membrane potential and, as a consequence, the release of reactive oxygen species (ROS) at the level of respiratory chain complexes. ROS in turn can trigger opening of the permeability transition pore and thus lead to the release of cytochrome c and other pro-apoptotic factors from mitochondria, inducing apoptosis. Specific modulation of several mitochondrial potassium channels has been linked to the regulation of apoptosis in vitro. We have recently provided evidence that, by directly acting on a mitochondrial potassium channel, specific channel inhibitors could efficiently kill different types of cancer cells (provided the channel is expressed) that are normally chemoresistant. Mutations of the tumor suppressor p53 and downregulation of pro-apoptotic Bax and/or upregulation of the expression of anti-apoptotic proteins of the Bcl-2 family are known to contribute to chemoresistance. However, these channel modulators, by acting on proteins in the inner mitochondrial membrane, bypass the necessity of upstream pro-apoptotic events such as p53 activation and Bax migration to mitochondria in order to induce release cytochrome c. Since several mitochondrial channels are overexpressed in cancer cells, their specific regulation can lead to substantial ROS release especially in the cancer cells, leading to selective cell death of the pathologic cells versus the healthy ones, according to the ROS rheostat model. In vivo evidence in animal models for melanoma, pancreatic ductal adenocarcinoma and chronic lymphocytic leukemia underlines the usefulness of exploiting mitochondrial ion channels as oncological targets.

Speak No. 13

Cardiovascular complications of sleep apnea: Role of oxidative stress

Ismail LAHER
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Patients with obstructive sleep apnea (OSA) are at increased risk of cardiometabolic diseases. The gold standard treatment for this condition is continuous positive airway pressure (CPAP), which unfortunately does little to mitigate the complications of OSA. Laboratory research in OSA is hampered by the lack of a suitable animal model. We used a mouse model of sleep-disordered breathing that is based on the induction of chronic episodes of intermittent hypoxia (IH), as IH is an important component of clinical OSA. The effect of IH on cardiovascular function was studied in relation to changes in oxidative stress and nitric oxide bioavailability.

Male mice (n=8-10) were placed in customized cages connected to a system that controls the fraction of oxygen inspired (FiO_2) inside the cages. To induce IH, nitrogen gas was flushed inside the cages for 30 seconds bringing FiO_2 to 5% followed by immediate flushing with compressed air for the next 30 seconds. Each cycle brings oxyhemoglobin saturation down to 60%, which is similar to values in apneic episodes in patients with severe OSA. Control mice were housed in the same way but were not exposed to nitrogen (IA group). IH cycles were performed during daytime for 12 hours a day (mice are nocturnal animals). After 8 weeks, plasma was collected to measure oxidative stress and inflammatory markers and aortic blood vessels were isolated for studies of endothelial function using a wire myograph.

There was a loss of endothelial dependent relaxation to acetylcholine (ACh) in aortae from IH groups (Emax: IH 67.2 ± 6.5% vs IA 95.1 ± 3.3%; $p<0.05$). This endothelial dysfunction was related to 1) an increased production of ADMA (IH: 0.63 ± 0.04 vs. IA: 0.46 ± 0.05 μmol/L, $p<0.05$), an endogenous circulating inhibitor of endothelial nitric oxide synthase (eNOS) and 2) augmented eNOS uncoupling caused by oxidative stress whereby eNOS preferentially produced superoxide over nitric oxide. Exposure to IH also increased levels of plasma markers of oxidative stress: 8-isoprostane (IH: 110 ± 20.2 vs. IA: 59.6 ± 5.6 pg/ml, $p<0.05$), and

inflammation: interleukin 6 (IL-6) (IH: 57.4 ± 2.6 vs. IA: 36.5 ± 3.6 pg/ml, $p<0.05$).

Episodes of IH, as might occur in patients with OSA, leads to detrimental regulation of endothelial function that is associated with increases in oxidative stress and inflammation, manifesting as reduced bioavailability of nitric oxide. Endothelial dysfunction is known to precede the clinical diagnosis of cardiovascular disease.

Speak No. 14

The multifaced role of oxidative stress: from apoptosis triggering to activation of cellular defenses

Alberto IZZOTTI
Dept. Health Sciences University of Genoa – IRCCS San Martino Hospital, Genoa, Italy

Since many time oxidative stress has been envisaged as a pathway damaging intracellular structures and contributing to the arising of chronic degenerative diseases. Indeed high levels of oxidative damage can be detected in target organs of cardiovascular diseases (arteries, heart) and ocular disease (cataract, glaucoma). Dealing cancer, oxidative stress is a recognized promoter of cancer development, as demonstrated in experimental animal models of lung and skin carcinogenesis and in human carcinogenesis induced by cigarette smoke. However, recent evidences indicate that oxidative stress has a multi-faced role depending on its level and on the type of targeted tissue. Oxidative stress at low level activates cellular defense against toxic agents as well as against high levels of oxidative stress, a situation referred to as 'hormesis'. Oxidative stress at low level is able to destroy bacteria thus exerting disinfectant activity, especially towards anaerobic and Gram negative bacteria. At the same time, oxidative stress activates wound healing pathways and inhibit macrophage activation thus exerting anti-inflammatory activity. These mechanisms can be used to cure skin wounds and ulcers. Cancer cells, with particular reference to cancer stem cells, are highly vulnerable to oxidative stress as demonstrated by the fact that many anti-cancer drugs are potent intracellular oxidants (e.g., ionizing radiation, anthracyclines). Cancer cells block the main endogenous source of oxidative stress, the mitochondrion, thus blocking the intrinsic pathway of apoptosis activation, a situation referred to as Warburg effect. Based on these premises, oxidative stress as exerted by lipohilic agents could be proposed to kill cancer cells as a complementary tool to standard radio/chemotherapies.

These considerations, indicate that nowadays oxidative stress has a recognized multi-tasking role its biological consequences depending on both dose and cellular target. Oxidative stress cannot be any more considered only a damage-inducing mechanism but, under certain circumstances, as a therapeutic tool.

Speak No. 15

Involvement of TRPM2 and TRPV1 on chemo therapeutic agents-induced peripheral pain

Mustafa NAZIROĞLU
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Neuropathic pain has a tremendous impact on quality of life in diseases such as diabetes and cancer. One of the symptoms of this disorder might be pain and it ultimately progresses to marked degeneration of the peripheral nerves. Abnormal Ca^{2+} channel physiology and expression have been implicated in a number of pain states in cancer treatment with chemotherapeutic drugs. The TRPM2 channel is activated by poly (ADP-ribose) polymerase (PARP) pathways through the production of ADP-ribose and oxidative stress. The TRPV1 is activated by hot chili pepper component (capsaicin) and reactive oxygen species (ROS) (1). The expression levels of TRPM2 and TRPV1 are high in the DRG neuron (2). ROS acts a central role in chemotherapeutic drug-induced dorsal root ganglion (DRG) death and peripheral pain (3).

Selenium is strong antioxidant trace element in cisplatin-induced oxidative stress (3). Recently we observed modulator role of selenium on apoptosis, oxidative stress and calcium entry through TRPM2 and TRPV1 channels in DRG neuron of fibromyalgia-induced rats (3). Recently, I observed similar protective effects of selenium in the oxaliplatin, paclitaxel and cisplatin-induced neuropathic pain of rats and mice, although there was no pain in the TRPM2 knockout mice. In the recent unpublished results, chemotherapeutic agent-based anticancer drugs caused neurotoxicity through excessive apoptosis, mitochondrial oxidative stress and overload Ca^{2+} entry. In this presentation, I will summarize our

and other recent experimental research findings on how these chemotherapeutic drug-induced oxidative stresses, TRPM2 and TRPV1 activations are regulated in peripheral pain by antioxidants such as selenium.

In conclusion, the results indicate that oxaliplatin, cisplatin and paclitaxel-induced TRPM2 and TRPV1 channels activation can result in remarkable peripheral pain induction effects through excessive oxidative stress and overload Ca^{2+} entry in the DRG neurons of rats.

Keywords: Cisplatin; Oxaliplatin; Oxidative stress; Peripheral pain; Selenium; TRP Channel.

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Speak No. 16

Exploring links between oxidative stress, metabolic dysregulation and the onset of cardio-metabolic diseases

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Although frequent sugar-sweetened beverage (SSB) consumption correlates with the development of obesity, diabetes and heart diseases, the underlying molecular mechanisms remain elusive. Moreover, previous laboratory-based studies have employed relatively large SSB dosages that may not reflect real-life consumption patterns, thus potentially skewing the significance of findings generated. For this study, we therefore hypothesized that frequent ‘’moderate’’ SSB consumption triggers oxidative stress and metabolic dysregulation in rats that result in impaired cardiac function.

A model of long-term SSB consumption was established where male Wistar rats (~200 gr) were gavaged with 3-5.1 mL of a local SSB daily for 6 months (~125 mL/day in human terms). In parallel, a control group was gavaged with an iso-volumetric amount of water. Isolated rat liver and heart tissues were subsequently analyzed for oxidative stress markers. As previous research work conducted in our laboratory implicated dysregulation of non-oxidative glucose pathways in the development of cardio-metabolic complications, markers of the polyol pathway, hexosamine biosynthetic pathway (HBP), advanced glycation end-products, and PKC were also assessed. A proteomics analysis was completed for the liver samples, while ex vivo and in vivo heart functional assessments were also performed.

Our data demonstrate that SSB consumption elicited moderate weight gain, while fasting metabolite levels generally remained unchanged vs. controls. Heart function was not significantly altered after 6 months of SSB intake, while myocardial cholesterol and triglyceride levels were not changed. There were early signs of oxidative stress in both liver and heart tissues, but counteracted by compensatory mechanisms. However, SSB intake triggered the activation of the HBP and the PKC pathways in heart and liver tissues, respectively vs. controls. The liver proteomic analysis revealed that the expression level of 140 proteins was significantly altered in the SSB group, with a major finding that SSB consumption induces hepatic endoplasmic reticulum stress. These findings reveal early SSB-induced metabolic changes in liver and heart tissues that may place organisms at risk in the long-term despite an apparently ‘’healthy’’ phenotype.

Keywords: Sugar-sweetened beverages; cardio-metabolic perturbations; oxidative stress

Speak No. 17

A new generation measurement method for ischemia modified albumin*

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N-Terminal end of albumin binds cobalt ions at physiological conditions. However, in the presence of oxidative stress, the binding capacity decreases and the level changes in various disorders. Conventionally used ischemia modified albumin (IMA) measurement method has severe defects. In this study, it is aimed to develop an authentic new generation IMA measurement method which can be used manually also fully automatically.

Assay has three stages. At the first stage, serum apotransferrines were completely saturated with ferric ions. In the second step, cobalt ions were added to the sample for the binding by albumin. In the third step, the remaining cobalt ions were bound to new chromogen. The assay was calibrated directly using a new calibrator and the results were given as serum IMA levels and also mole bound cobalt atom per one mole albumin molecule.

It has been demonstrated that original IMA measurement method has been effected from apotransferrin and pH factors. In the new assay, these interferences were completely removed. In the conventional method, the pH value of the reaction medium was unstabilized and in the new assay the pH of the reaction medium was stabilized using a new buffer solution. In the conventional method, the results are given as absorbance in the form of AU, and the results are given as SI in the new method.

New generation IMA assay, which has different measurement principle, reagents, chromogen and calibration, has high analytical performance characteristics and it can be used automatically and maually.

Key words: ischemia modified albumin, IMA

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Young Speakers

Young Speaker 1

The importance of selenium on treatment of memory impairment: focus on TRPM2 and TRPV1 channels

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Overloaded calcium ion (Ca^{2+}) concentration in cytosol cause to elevation of mitochondrial intermembrane depolarization that main reason of excessive intracellular reactive oxygen species (ROS) production. Oxidative stress plays important role in the etiology of several kind of neurological disorders including memory impairment, dementia and Alzheimer's disease. Selenium has also important role as a cofactor of glutathione peroxidase enzyme (GPx) in the prevention of oxidative stress. It has been elucidated that low concentrations of selenium administration very useful to provide cellular viability. In many studies, the impairment of plasma selenium concentrations and GPx activity have been reported to relate with memory deficits in animal models. Transient receptor potential (TRP) channels have six subfamilies and 27 members in human. Most of these channels are responsible for the Ca^{2+} permeation especially in neuronal cells. The TRPM2 and TRPV1 channels are expressed in neurological tissues such as brain cortex, hippocampus and dorsal root ganglia (DRG) neurons and they show oxidative stress dependent activation (Yamamoto et al. 2007). Hippocampal TRPM2 and TRPV1 channel expression levels change during memory impairment and dementia. A recent theory have argued that both supporting of intracellular antioxidant system and extracellular antioxidant administration may helpful for the inhibition of TRP channels mediated Ca^{2+} influx (Balaban et al. 2017). Moreover, result of the study supported the idea by using whole-cell Patch-Clamp recordings and Fura-2 calcium signaling analyses.

In conclusion, in this work we discussed novel effects of selenium on the treatment of irregular oxidative status and memory impairment by the regulation of TRPM2 and TRPV1 channels in rats.

Keywords:
Selenium, Dementia, Alzheimer's disease, TRPM2 and TRPV1 channels

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Young Speaker 2

Is antioxidant therapy effective in sepsis?

Aslı Nur TOMRUK
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Sepsis is a complex situation involving systemic inflammatory response syndrome, tissue damage and multiple organ dysfunction syndromes. As long as sepsis is a systemic response of an organism against microorganisms and toxins, we aimed to study the antioxidant treatment in sepsis and its results.

In our review, we defined what sepsis is and explained its importance and relationship with oxidative stress. In our experience about immunopathology of sepsis, secondary stimulation of complex systems such as complement system, nitric oxide, toll-like receptors and especially free oxygen radicals results in death.

We examined the relationship between oxidative stress and immune response in sepsis. Limitless increase in reactive oxygen species (ROS) and these causing cells not having enough antioxidants results in oxidative stress. This causes an immune response resulting in

tissue damage. Thus oxidative stress has an important role in tissue damage.

The deficiency in antioxidants in sepsis sets thinking about antioxidant treatment. We analyzed the antioxidant treatments used in sepsis in both clinical and experimental studies. The positive results are seen with substances like selenium, zinc, vitamin-C, glutamine and others.

The result is that oxidative stress has a definite role on sepsis. Although some clinical and experimental studies have conflicting data, the benefits of antioxidant treatment cannot be ignored and must be thought as a supporting therapy.

Keywords: Sepsis; Antioxidant; Oxidative stress; Inflammation.

Young Speaker 3

Thermo TRP channels and chemothrepeutic agents

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Chemotherapeutic agents such as cisplatin, oxaliplatin and paclitaxel have been using in treatment of different cancer types for several years. However, severe painful neuropathy is a main complication of these cancer agents. The etiology of painful neuropathy has not been fully clarified yet. In the etiology of pain and neuropathy, calcium ion (Ca^{2+}) overload plays an important role. Ca^{2+} enters into cells by different ways including cation channels including transient receptor potential (TRP) channels.

Low and high temperature changes affect pain induction in some peripheral primary afferent fibers and the fibers are called thermoreceptors. Till today, 11 TRP channels in mammalian cells have been identified as thermosensitive TRP (thermo-TRP) channels (Uchida et al. 2017). Two TRP channels (TRPV1 and TRPV2) are activated by high temperatures. Five TRP channels (TRPV1-4 and TRPM2) are activated by different heat temperatures, although two of TRP channels (TRPA1 and TRPM8) are activated by cold and cool temperatures, respectively (Nazıroğlu and Braidy, 2017). In addition, TRPM3 and TRPC5 have noxious heat and cold sensors, respectively. Involvements of three thermo-TRP channels (TRPA1, TRPM8 and TRPV1) in chemotherapeutic agents-induced neuropathic pain were reported by the results of recent literature data (Nazıroğlu and Braidy, 2017). In the oral presentation, we discussed novel effects of chemotherapeutic agents on the peripheral pain by the regulation of TRP channels.

In conclusion, accumulating evidence suggests that neuropathic pain and painful neurotoxicity in the rodents are increased by selected chemotherapeutic agent through increased sensitization of TRPA1, TRPM8 and TRPV1. However, involvement of remaining thermo-TRP channels should be investigated by future studies.

Keywords: Chemotherapeutic agents; Peripheral pain; TRPM2 and TRPV1 channels

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Young Speaker 4

Roles of TRPM2 and TRPV1 channels in fibromyalgia: Focus on selenium

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Excessive calcium ion (Ca^{2+}) entry into cytosol of neurons causes to elevation of mitochondrial intermembrane depolarization and in turn, it induces excessive intracellular reactive oxygen species (ROS) production. Oxidative stress plays important role in the etiology of several kind of neurological disorders including fibromyalgia, because low selenium levels in plasma of patients with fibromyalgia was reported by a study (Reinhard et al. 1998). Selenium has also important role as a cofactor of glutathione peroxidase enzyme (GPx) in the prevention of oxidative stress. It has been elucidated that low concentrations of selenium administration very useful to provide cellular viability. Transient receptor potential (TRP) channels have six subfamilies and 27 members in human. Most of these channels are responsible in dorsal root ganglia (DRG) neurons for the Ca^{2+} permeation especially in neuronal cells. Expression level of the TRPM2 and TRPV1 channels are high in the DRG neurons and they show oxidative stress dependent activation (Julius, 2013). The TRPM2 and TRPV1 channel expression levels in the DRG increased in different types of pain. Since a decade, a recent theory have argued that both supporting of intracellular antioxidant system and extracellular antioxidant administration may helpful in fibromyalgia for the inhibition of TRP channels mediated Ca^{2+} influx (Yüksel et al. 2017). In the oral presentation, we discussed novel effects of selenium on the treatment of irregular oxidative status and fibromyalgia by the regulation of TRPM2 and TRPV1 channels in rats.

In conclusion, selenium may novel approach to treat FM-induced pain, mitochondrial oxidative stress and apoptosis through modulation of TRPM2 and TRPV1 channels. However, the subject should be clarified by future studies.

Keywords: Selenium, Pain; Fibromyalgia, TRPM2 and TRPV1 channels

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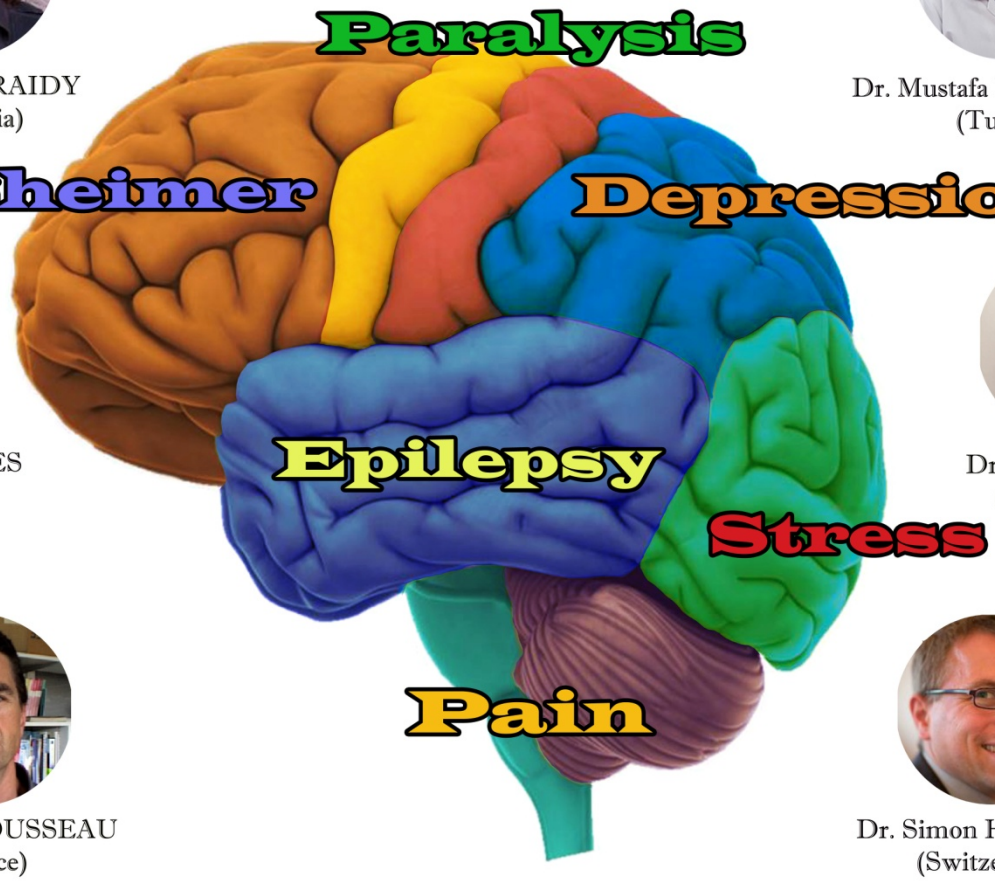

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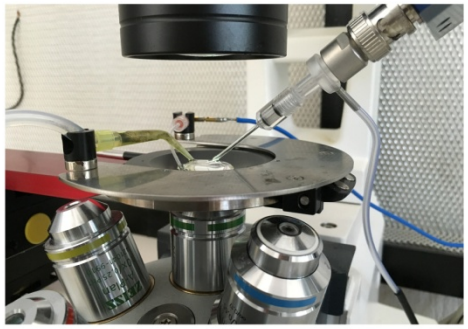

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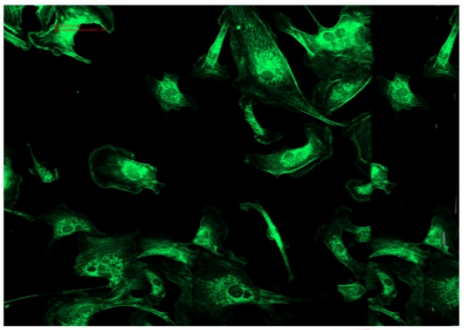

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