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Oxidative Stress, Calcium Signaling and TRP Channels

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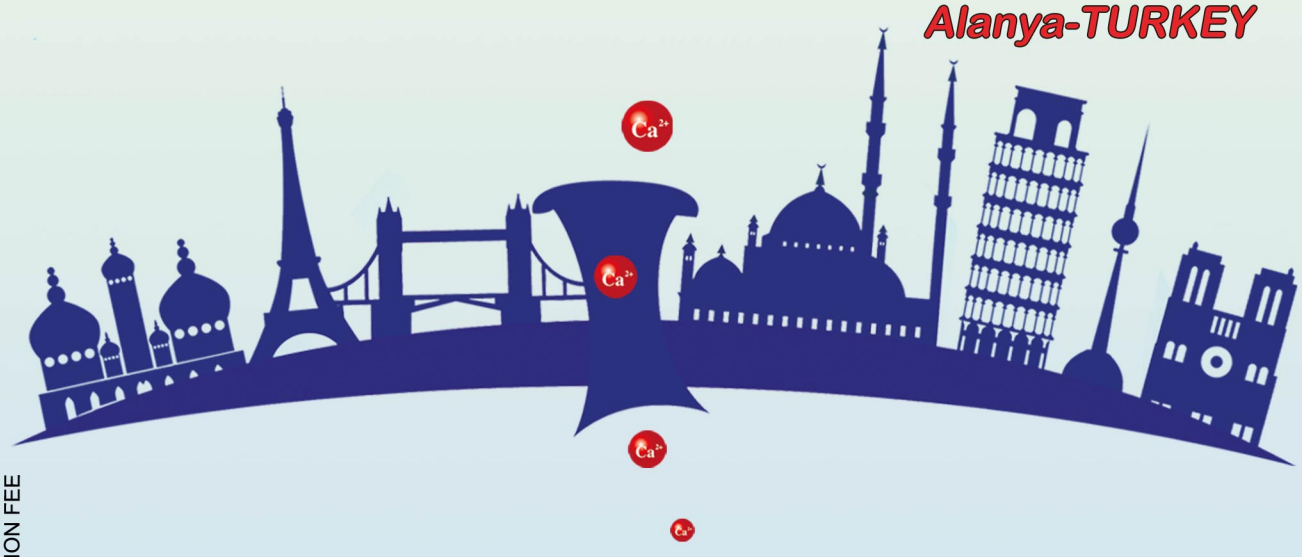

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AIM AND SCOPES
Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate 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
(Gene abnormalities. Interaction between gene and free radicals. Gene anomalies and iron. Role of radiation and cancer on gene polymorphism)

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

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Oral Presentations

Oral Presentation 1

Effect of stem cell treatment on experimental diabetic skin wound healing

Pınar Kılıçaslan SÖNMEZ[1], Fulya GÜLBAĞÇA[2], Mahmud ÖZKUT[1], Mehmet İbrahim TUĞLU[1]

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The healing of chronic diabetic skin wounds is a difficult and costly process. Stem Cells (SC) are easy to handle and reproducible and are applicable natural products used in clinic. In this study, wound healing effects of cultured cells in rat skin graft model were investigated in terms of oxidative stress and apoptosis.

Grafts 1x1 cm^2 taken from adult rat skin were placed in culture medium and $3x10^6$ adipose-derived mesenchymal (ADM) SC were implanted in high glucose medium. The grafts were transplanted in a reciprocating manner after 24 hours of incubation. On days 3 and 7 of wound healing, biopsy specimens were taken and compared with the untreated group. The samples were evaluated for H&E and MT staining in terms of epidermal thickness, number of vessels, cell infiltration, and collagen deposition. VEGF for vascularization, eNOS for oxidative stress and TUNEL for apoptosis. The cells on the graft were assessed by SEM.

The characterization was carried out for ADMKH on the graft in culture medium and they were interacted with the skin. Transplanted grafts showed a significant improvement with SC for parameters. Increased VEGF and decreased eNOS were observed with H-score. The apoptotic index was decreased.

In an experimental diabetic skin grafting, it was found that the treatment of SC was effective by increasing vascularity and reducing oxidative stress and apoptosis in wound healing. It has been thought that the application of SC to reduce the costs and increase the patient life quality by providing faster and more effective wound healing.

Keywords: Adipose-Derived Mesenchymal Stem Cell; Skin; Wound; Graft; Oxidative stress; Apoptosis; Culture.

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Oral Presentation 2

The lysosomal ion channel TRPML1 in breast cancer.

Shekoufeh ALMASI[2], Andra M STEREA[1], Barry E KENNEDY[3], Derek R CLEMENTS[3], Shashi GUJAR[3], Yassine EL HIANI[1]

Departments of Physiology and Biophysics[1], Biology[2], Pathology[3] of Dalhousie University, Halifax, NS, Canada

Despite great advances in cancer therapies, breast cancer (BC) continues to be the leading cause of mortality in women worldwide. This is in big part due to the heterogeneity known to exist within BC subtypes. The triple-negative BC (TNBC) subtype is a highly aggressive BC subtype with significant metastatic potential which is largely responsible for the morbidity and mortality of BC patients. Currently, there no approved targeted therapies for TNBC. Therefore, it is imperative to discover new pharmacological targets for TNBC therapy.

Emerging evidence suggest the important role of

targeting lysosomes function in cancer. At the base of lysosome functionality are the lysosomal ion channels which mediate the function of the lysosome through the modulation of ion influx and efflux. Here, we show that the lysosomal ion channel TRPML1is highly expressed in TNBC cells compared to normal mammary epithelial cells and that its downregulation caused a significant decrease in cell proliferation and cell-cycle arrest in G0/G1. Our data also indicate that TRPML1 downregulation inhibited the ability of migration and invasion in TNBC cells. In addition, TRPML1 down regulation abolished both mitochondrial OCR and ECAR and caused a significant reduction in mitochondrial ATP production. Most importantly, the subcutaneous injection of TNBC cells were TRPML1 was downregulated suppresses the growth and metastasis abilities of BC tumours. Meanwhile, analysis of PROGeneV2 data complements our finding and suggests that high TRPML1 expression is negatively correlated with BC patient survival. Overall, we conclude that targeted inhibition of TRPML1 function in TNBC cells hold a significant impact on TNBC tumor growth and metastasis as well as on cellular bioenergetics.

Keywords: TNBC, TRPML1, metastasis, mitochondria

Oral Presentation 3

Direct modulation of TRPA1 functionality and compartmentalization by cholesterol.

Justyna STARTEK[1], Brett BOONEN[1], Alejandro LÓPEZ-REQUENA[1], Ariel TALAVERA[2], Yeranddy A. ALPIZAR[1], Debapriya GHOSH[1], Nele VAN RANST[1], Remy LORIS[2], Thomas VOETS[1] and Karel TALAVERA[1]

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Lipid rafts are highly specialized membrane domains characterized by high concentrations of cholesterol, sphingolipids and gangliosides. This distinctive composition results in lateral phase separation and generation of a liquid-ordered domains accommodating various receptors and channels involved in numerous cellular processes.

Recently, we have shown that TRPA1 localization in the lipid rafts is a crucial factor influencing channel activity. Modification of lipid rafts composition by cholesterol depletion using methyl-β-cyclodextrin or sphingolipids hydrolysis (sphingomyelinase) decreased the responses of TRPA1 to its electrophilic and non-electrophilic agonists. Through molecular dynamics simulations and structure-function studies, we show that cholesterol sensitivity of TRPA1 depends on specific transmembrane regions in S2 and S4 containing cholesterol recognition/interaction amino acid consensus sequence. These sequences provide configuration where cholesterol molecule wraps in a “DNA-like” pattern around TM segments. Furthermore, mutation of the CRAC motif essential residues results in a reduction of calcium influx and whole cell currents. Confocal microscopy and single channel recordings revealed changes in TRPA1 distribution pattern, as mutated channels are not able to recognize lipid environment.

These findings constitute the first report of CRAC motifs presence in TRPA1 and provide novel insight in the molecular nature of TRPA1-cholesterol interaction.

Keywords: TRPA1 channel, lipid rafts, cholesterol, CRAC sequence.

Oral Presentation 4

Implication of TRPC1 in SOCE activated by the new STIM1L isoform

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Depletion of the endoplasmic reticulum (ER) Ca^{2+} store leads to a Ca^{2+} entry called store-operated Ca^{2+} entry (SOCE), which is due to the activation of Orai1 channel gated by STIM1. Our laboratory identified a new splice variant of STIM1, called STIM1L (long) that has an extra 106 aa in the C-term part. We documented that STIM1L is as efficient as STIM1 in eliciting SOCE, but still very little is known about the channel(s) gated by STIM1L. To answer this question, the whole-cell configuration of patch clamp technique and fluorescent recording of intracellular calcium fluctuations using Fura2-AM dye were applied.

Currents recorded in HEK293T cells transiently overexpressing Orai1 and STIM1 or STIM1L proteins unexpectedly reviled also the outward currents which together with the values of the reversal potentials point to the participation of other channels than Orai1 in the process. Our strong candidate was TRPC1 and its involvement in ER refiling was tested next. Indeed elimination of TRPC1 reviled the typical for calcium release-activated current (CRAC) signature of the I/V curve, strongly suggesting the endogenous participation of TRPC1 in intracellular Ca^{2+} stores refilling. These results were confirmed using Fura2-AM measurements.

Based on the above we conclude that TRPC1 actively participate in SOCE phenomenon and the activation of the non-selective cationic current is responsible for maximal activation of SOCE mediated by STIM1L isoform.

As these molecules are also expressed in muscle tissue, it remains to be determined whether they are also involved, together with other TRPCs, in human skeletal muscle SOCE.

Keywords: TRPC1 channel; STIM1 isoform; store-operated Ca^{2+} entry; patch-clamp; calcium imaging.

Funding: Swiss National Foundation (Grant 310030_166313), FSRMM, Foundation Marcel Levaillant.

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Oral Presentation 5

Calcium signaling in brain microvascular endothelium and its role in epilepsy

Beatrice Mihaela RADU[1], Paolo Francesco FABENE[2]

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Clinical and experimental studies indicate brain microvascular endothelium as important site of action for different endogenous and exogenous stimuli triggering epileptogenesis. Among the potential pharmacological targets in epilepsy have been considered muscarinic acetylcholine receptors. Although these receptors have been described in human, bovine and rat cerebral microvascular tissue, we have performed the first extensive of subtype functional characterization in mouse brain endothelium. Based on protein/ gene expression and on functional analysis, we have evidenced the expression of all muscarinic acetylcholine receptors (M_1-M_5) in mouse brain microvascular endothelial cells, with the mRNA expression for M_2, M_3, and M_5 correlating with their respective protein abundance. Functional analysis demonstrated that acetylcholine activates calcium transients in brain endothelium via muscarinic, but not nicotinic, receptors. Our study also highlighted that despite the abundance of M_1 and M_3 receptors, only a small fraction of M_1 was demonstrated to be inserted into the plasma membrane and to function in ACh-induced Ca^{2+} signaling. We also proposed an in vitro model of epileptogenesis by exposing brain microvascular endothelial cells to pilocarpine, at concentrations equivalent with the blood values in the animal models of epilepsy. We demonstrated the multiple endothelial targets (e.g. calcium signaling, tight junction proteins, adhesion molecules, cytokines release, etc.) are altered, and we concluded that blood brain barrier is an importance site of action for

pilocarpine, and the epileptogenesis mechanisms should be revisited.

Keywords: Brain microvascular endothelial cells, muscarinic receptors, calcium signaling, epileptogenesis.

Oral Presentation 6

Trafficking and local calcium signals of TRP channels in sensory nerve endings

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Our ability to perceive nociceptive pain is crucial to respond to harmful stimuli: it warns us about noxiously hot or cold objects. Sensory nerve endings that respond to pain (nociceptors) initiate an electrical signal in the periphery and transport it to the dorsal horn and eventually to higher brain centers. The detection of noxious stimuli involves the expression of nociceptive ion channels in sensory nerve endings, such as transient receptor potential (TRP) channels. Recently we found that the acute response to noxious heat relies on the functional expression of TRPV1, TRPM3 and TRPA1 in sensory nerve endings1. Calcium imaging on isolated dorsal root ganglia (DRG) is a widely accepted model to study the involvement of TRP channels in acute pain responses. However, DRGs are clusters of nerve cell bodies, present in the dorsal root of spinal nerves, far away from the skin where the physiological stimulus detection take place.

Here we present a novel approach to study TRP channels in intact skin. This allows us to study TRP activity in a model that fully recapitulate the in vivo physiology of sensory nerve endings. We use a knock-in GCaMP3 mouse line that expresses the genetically encoded calcium indicator GCaMP3 in specific neuronal cells. To our knowledge, calcium measurements in sensory nerve endings of mammalian skin have not been reported in literature yet.

Keywords: Sensory neurons; Calcium Imaging; TRP channels

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Oral Presentation 7

Oligodendrocyte acidification causes TRPA1-mediated myelin damage in ischaemia

Nicola HAMILTON[1], Circe La MACHE[1], Karolina KOLODZIEJCZYK[2], Eleni KOUGIOUMTZIDOU[2] and David ATTWELL[2]

[1]Wolfson Centre for Age Related Diseases, King's College London
[2]Department of Neuroscience, Physiology and Pharmacology, University College London

Oligodendrocytes wrap myelin around axons to increase the conduction velocity of the action potential. Failure to myelinate, damage to myelin, or loss of oligodendrocytes leads to severe debilitating mental and physical impairment. Myelin damage during ischaemia was previously thought to be mainly by activation of oligodendrocyte ionotropic glutamate receptors, which allow a detrimental influx of calcium. By patch-clamping oligodendrocytes to record their currents, while imaging their intracellular ions with ion sensitive dyes, and applying solution which mimics the conditions found in ischaemia, we found that most of the glutamate-mediated current into oligodendrocytes is indirect and caused by a rise in extracellular potassium concentration. Oligodendrocytes respond to raised extracellular potassium concentrations by acidifying their cytosol; this in turn activates TRP channels, which we identified as mainly being TRPA1, because the response is largely inhibited by specific TRPA1 channel blockers (HC 030031 and A965079), and genetic TRPA1 knock out. The calcium influx through the proton-activated TRP channels leads to separation of myelin lamellae, and conduction block, which may contribute to the decrease in conductance of the action

potential observed during ischaemia. As such TRPA1 represents a possible new therapeutic target that may decrease white matter damage in ischaemia.

Keywords: Oligodendrocyte; TRPA1; Ischemia.

Oral Presentation 8

The immunosuppressive mechanism of dimethyl fumarate involves altered intracellular Ca^{2+} handling

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Oral Presentation 9

Molecular surgery concept and TRPV1

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In general, q molecular surgery agent is a selective and potent ligand, and the target is a specific cell type whose elimination is desired through the molecular surgery procedure. These target cells have the highest innate sensitivity to the molecular surgery agent usually due to the highest receptor density being in their plasma membrane. The interaction between the ligand and its receptor evokes an overactivity of the receptor. If the receptor is a ligand-activated non-selective cation channel, the overactivity of the receptor leads to excess Ca^{2+} and Na^{+} influx into the cell and finally cell death. One of the best-known examples of such an interaction is the effect of ultrapotent vanilloids on TRPV1-expressing pain-sensing neurons. One intrathecal resiniferatoxin (RTX) dose allows for the receptor-mediated removal of TRPV1+ neurons from the peripheral nervous system. Target-specific apoptotic and necrotic processes are induced. Thus, as a nano-surgery scalpel, RTX removes the neurons responsible for generating pain and inflammation from the peripheral nervous system providing an option in clinical management for the treatment of morphine-insensitive pain conditions. In the future, the molecular surgery concept can also be exploited in cancer research for selectively targeting the specific tumor cell.

Oral Presentation 10

TRPML1 channel control prostate cancer cells proliferation through cell cycle regulation

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Prostate Cancer (PCa) is the third leading cause of cancer-related deaths worldwide. Statistically, one in eight men will develop PCa at some point during their life time. In addition to deteriorating health and productivity, the medical costs associated with prostate cancer treatment represent a significant drain on the healthcare system. Currently, PCa is diagnosed using the Prostate Antigen Test (PSA) which has an 80% false positive rate, illustrating the critical need for new therapeutic targets to improve the detection of prostate cancer and its treatment. Potential therapeutic targets include the Transient Receptor Potential Mucolipin 1 (TRPML1) ion channel which has been shown to have a critical role in many aspects of lysosomal function including proliferation, apoptosis and DNA damage. Our preliminary data shows that TRPML1 is highly expressed in PCa compared to normal cells, and that its down regulation reduces PCa cells proliferation, and causes cells accumulation in G2/M phases of the cell cycle. These effects were also concomitant with an increase in NO production and DNA damage. Based on these observations, we propose TRPML1 as a novel therapeutic target to inhibit PCa and improve its therapy.

Keywords: TRPML1; prostate cancer; Nitric oxide.

Oral Presentation 11

TRPM2 induces Akt-dependent migration and invasion in gastric cancer cell lines

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Gastric cancer is the second most common cause of cancer-related deaths in the world. However, it is mainly its high ability to form metastasis that's end up killing cancer patients. Recent studies have introduced the Transient Receptor Potential Melastatin 2 (TRPM2) as important in the invasion and migration of many types of cancer. Recently, we have reported that TRPM2 expression is negatively correlated with the overall survival of gastric cancer patients and identified TRPM2 as a key regulator of gastric cancer cell survival through the control of autophagy and mitochondrial function. Here, we aim to further investigate the role of TRPM2 in gastric cancer metastasis and its underlying mechanisms. Our data showed that TRPM2 down regulation causes a significant reduction in both migration and invasion of gastric cancer cells. In addition, TRPM2 down regulation is associated with a decreased Ca^{2+} influx and Akt phosphorylation. Meanwhile, our preliminary data also indicated that TRPM2 downregulation altered mitochondrial structure and biogenesis. Based on these finding, we hhypothesis that TRPM2 is essential in gastric cancer migration and invasion through the control of Ca^{2+} influx, which mediates Akt pathway activation, and maintains mitochondrial structure and function.

Keywords: TRPM2, gastric cancer, migration, invasion, Akt phosphorylation, Mitochondria

Oral Presentation 12

The calcium-modulating protein S100A10 is predictive of patient survival and a driver of tumorigenesis in Pancreatic Ductal Adenocarcinoma

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Pancreatic cancer is arguably the deadliest cancer type. Patients are diagnosed at advanced stages at which point therapeutic intervention is rarely successful. To date, current treatments have not been clinically efficacious. The 5-year survival of pancreatic cancer patients remains dismal (4%) without treatment and only increases to 20% after chemotherapy. The development of clinical tools for early detection and risk prediction is key for improving patient outcome and quality of life. Here, we introduce the calcium-modulating protein *S100A10* as a novel biomarker in pancreatic cancer and a driver of pancreatic tumor growth and invasion.

S100A10 belongs to the S100 family of Ca^{2+}-binding proteins that have been linked to cell proliferation, Ca^{2+} homeostasis, cellular stress, apoptosis, differentiation etc. *S100A10* is required for calcium homeostasis by regulating activity and surface translocation of the Ca^{2+} channels TRPV5 and TRPV6.

We herein demonstrate that *S100A10* mRNA and protein are overexpressed in human pancreatic tumors compared to the nearby normal ducts and non-ductal stroma. *S100A10* mRNA expression was predictive of overall survival and recurrence-free survival across multiple pancreatic cancer patient cohorts. *S100A10* expression was driven by promoter methylation and the oncogene KRAS. *S100A10* knockdown resulted in decrease in TRPV5 expression and reduced invasiveness of pancreatic cancer cell lines. Additionally, *S100A10* knockdown attenuates growth and metastatic burden of pancreatic tumor cells in vivo. In conclusion, these findings delineate, for the first time, the clinical and functional contribution of the calcium-modulating protein *S100A10* as a biomarker in pancreatic cancer.

Keywords: Pancreatic cancer, S100A10, calcium homeostasis, TRPV5, TRPV6, biomarker.

Oral Presentation 13

Effects of agomelatine in rotenone-induced Parkinson's disease model in rats

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Melatonin and melatonin analogs were demonstrated as neuroprotective, anti-oxidant and antidepressant in experimental animal models. Agomelatine is a novel analog of melatonin which is commonly used for sleep disorders and major depression in Parkinson's disease. However, the effect of agomelatine in Parkinson's disease (PD) is not known. The aim of the current study was to investigate the effect of agomelatine on neuronal injury in rotenone-induced PD in rats.

Male Sprague-Dawley rats (220-260 g) were injected with rotenone (0.5 µg, n=16) or vehicle (1 mL

DMSO, n=8) into the left substantia nigra and ventral tegmental area under stereotaxic surgery. After 10 days, PD model was assessed by rotational test following apomorphine injection (2 mg/kg, i.p.). The valid PD rats were randomly divided into two groups which received daily p.o. agomelatine (40mg/kg, n=8) or saline (2 ml/rat, n=8) for consecutively 18 days. Twenty-four hours after the last drug administration rotational test was repeated, and motor coordination was evaluated with rotarod and pole tests, just before the decapitation. Brain tissues were taken for biochemical, molecular and histopathological evaluations. The data were analysed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. $P<0.05$ is considered as statistically significant.

Agomelatine increased apomorphine induced turning behavior. Rotenone induced increase in pole test duration, and decrease in retention time in rotarod test were found to be aggravated by agomelatine administration. Agomelatine administration increased the AOPP level but did not change the increased MDA level compared to the saline administered group. Caspase 3 but not PARP1 expression was found to be increased with agomelatine administration. Rotenone induced neuronal loss was aggravated by the agomelatine administration.

These results suggest that agomelatine worsens the neuronal injury in rotenone-induced PD in rats.

Keywords: Agomelatine, Parkinson's disease, Rotenone, Rat

T. Oral Presentation 1

The antioxidant effect of *Ganoderma lucidum* on the rat sperm for male infertility

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Male infertility is still a problem for in vitro fertilization. The sperm in the damaged testicles are insufficient for fertilization. Ganoderma lucidum (GL) is a natural product as a supportive agent. It is a powerful antioxidant with the polysaccharides it contains. It has been shown nontoxic in rats and mice. In this study, the antioxidant effect of GL on sperm damage was studied in culture.

Sperm collected from the epididymis of adult male rats with TESE were incubated with RPMI media which included 10% FBS. Sperm were cultured in high glucose medium at 10, 100, and 1000 µL / ml for GL effect. Sperm motility was assessed at half-hour intervals. When immotility began, it was examined for morphology with quick-diff stainig. It was also fixed for SEM. Oxidative stress with eNOS and apoptosis with TUNEL of sperm were examined.

The motile sperm number decreased in the high glucose medium compared to the control medium. The number of abnormal sperm counts doubled. Morphological abnormalities were confirmed by SEM. The number of marked eNOS sperm and the apoptotic number indicated by TUNEL were increased. The GL application returned all parameters in a meaningful way.

Sperm maturation in male infertility is an important factor for successful fertilization and live birth. GL at its highest dose inhibited oxidative stress and apoptosis most effectively. GL is commercial product and is used for many reasons. It was thought that the use of GL in patients with infertility problems would be beneficial.

Keywords: *Ganoderma lucidum*; Infertility; Sperm; Oxidative stress; Apoptosis; Culture.

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T. Oral Presentation 2

Apoptotic effect of quercetin on human colon cancer cell line SW-480

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Cancer is the second cause of death and colon cancer is the most prevalent cancer worldwide so treatment alternatives are always on the agenda. The etiology of human colon cancer is very complex, but diet is considered to be one of the important reason of it and researches think that lots of people are at risk of colon cancer because diet style. In light of this information, we aimed to investigate whether Quercetin (Que) has apoptotic effect on SW-480 colon cancer cells.

Quercetin is a type of bioflavonoid naturally occurring in various edible plants. Also it has anti-proliferative effects. The SW-480 colon cancer cell line was cultured in monolayer model. Cells were treated with Que at 24, 48 and 72 hours of incubation. TUNEL assay were used to determine the apoptotic cells in the monolayer culture. The BrdU labeling index was used

to determine the proliferation of cells.

An IC 50 inhibition dose of Que in SW-480 colon cancer cell was 200 µM/ml at 24, 48 and 72 hours of incubation. The control group had a normal pattern of S-phase fraction and many of the SW-480 cells nuclei were observed to be positive for BrdU. TUNEL positive cells were detected after treatment with Que in the monolayer cultures. The dead cell count was higher in the SW-480 cell lines with Que applied than in the control.

We concluded that Que inhibit colon cancer growth by apoptosis with use caspase pathway. Further in vivo studies are needed to confirm our findings in humans. Three-dimensional studies, caspase analyses and AIF immunestaining analyses are still ongoing.

Keywords: Quercetin, apoptosis, colon cancer, *in vitro*

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T. Oral Presentation 3

Tympanosclerosis epidemiology in patients with chronic otitis media in Kars region and the location of computed tomography in diagnosis

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Tympanosclerosis is an inactive, irreversible otitis caused calciferous hyaline degeneration, which can occur in the lamina propia local tissue reaction. The role of tissue damage caused by free oxygen radicals (ROS) is known.

The records of the 54 patients were meet study criteria, who had been operated with tympanic membrane and middle ear between December 2011 and May 2013 and operated with the cause of tympanosclerosis operation notes, audiology records and the is 47.79% and 75.9% of the participants. All histopathologic specimens obtained from tympanosclerotic plaques, hyaline degeneration and collagen increase following increased epithelial thickness, calcification and in some case ossification were observed. Tympanosclerosis was seen in CT section as calcified or ossificated high density areas in different forms such as ovoid, linear or spider web in soft tissue in the middle ear space, thickening and density increase in the eardrum. Findings consistent with tympanosclerosis were found in CT in both ear and middle ear space. In only 3 cases (5,56%), tympanosclerotic plaque was not observed radiographically and TS diagnosis could not be established.

In conclusion, tympanosclerotic plaques were found to have a high incidence (47,79%) in the operated ears in our study, consistent with the literature. Our patient population is middle-aged women and chronic otitis is in the etiology of the patients. Histopathologic changes detected in the specimens examined were observed as hyaline degeneration and collagen increase following increased epithelial thickness, calcification and in some case ossification were observed. These patients were positively correlated with oxidative stress factors such as superoxide dismutase in accordance with the literature of tympanic calcification. Examination of histologic materials and determination of serum oxidative stress factors is necessary in terms of morbidity of the disease as well as its importance in the regulation of diagnosis and treatment of the disease.

Keywords:
Tympanosclerosis; Chronic otitis media; Sclerotic plaque; Inflammatory mediators; Serum oxidative stress factors; Free oxygen radicals; Temporal bone computed tomography.

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T. Oral Presentation 4

Silymarin promises hope for hyperglycemia treatment in HEPG2 cells

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Hyperglycemia is an abnormal condition, characterized by high glucose in bloodstream. Hyperglycemia causes several alterations in cell metabolism and signaling pathways. Silymarin is an herbal medicine, the antioxidant, anti-inflammatory properties of which were demonstrated in many studies (Crocenzi&Roma,2006). Therefore, we aimed at determining the effects of silymarin on hyperglycemia-induced HepG2 cells by examining the expression of NF-κβ and CPT1 proteins, closely associated with hyperglycemia (Ramana et al. 2004).

In this regard, we divided the cells into 4 groups as control (only ready-to-use medium), mannitol (44.5 mM mannitol), hyperglycemia (50 mM glucose) and hyperglycemia+silymarin groups (50 mM glucose+25 μg/ml silymarin). The cells were exposed to respective media for 24 h. After 24 h, immunocytochemistry staining was implemented for NF-κβ and CPT1 proteins, and classical hematoxylin-eosin (HE) was applied for morphological evaluation of the cells. MDA levels were measured by colorimetric assay to determine ROS.

As a result, NF-κβ and CPT1 immunoreactivity in mannitol group was comparable to control group. However, NF-κβ immunoreactivity and MDA levels increased but CPT1 immunoreactivity decreased in hyperglycemia group when compared to control. Silymarin treatment decreased NF-κβ, MDA levels and increased CPT1 expressions in the hyperglycemia+silymarin group. HE-stained cells were normal with euchromatic nuclei in control and mannitol groups, whereas degenerated cells with small and condensed nuclei were observed in hyperglycemia group. Silymarin treatment decreased these degenerative changes.

In conclusion, 25 μg/ml of silymarin treatment ameliorated hyperglycemia-induced cellular degenerations by decreasing NF-κβ and increasing CPT1 expressions. Silymarin can be a promising agent for the treatment of hyperglycemia.

Key Words: Hyperglycemia; Silymarin; ROS; HepG2; NF- κβ and CPT1

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T. Oral Presentation 5

Effects of rosuvastatin and amlodipine on renin-angiotensin system of kidney in NOS inhibition and salt diet induced hypertension

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Renin-angiotensin system (RAS) is an important pharmacologic target, because this system plays substantial role in the development of hypertension-related organ damage. Oxidative stress and endothelial dysfunction play an important role in pathophysiology of hypertension. Statins have cholesterol-lowering

effects and they induced to increase the expression of eNOS and improve endothelial dysfunction by reducing the production of reactive oxygen. Statins are unknown effects of Angiotensin Converting Enzyme1 (ACE1), Angiotensin Converting Enzyme2 (ACE2), Angiotensin II type 1 receptor (AT1), Angiotensin II type 2 receptor (AT2), Toll-like receptor 4 (TLR4) and renin. In our study is investigated to the effects of HMG-CoA reductase inhibitor rosuvastatin and the calcium channel blocker amlodipine on renal ACE1, ACE2, AT1, AT2, TLR 4 and renin levels in the hypertensive rats.

To produce hypertension, L-NAME which is a nitric oxide inhibitor by intraperitoneally and drinking water containing 1% of salt was given to rats for 6 weeks. As from 2th week rats were applied intraperitoneally to 10 mg / kg rosuvastatin and to 10 mg / kg amlodipine for 4 weeks. ACE1, ACE2, AT1, AT2, TLR4 and renin levels of renal tissue were measured by ELISA.

Renal levels of AT1 and TLR4 significantly increased in hypertension group but ACE2 non-significant increased. Rosuvastatin and amlodipine reduced AT1, increased ACE2 levels but not changed TLR4. Levels of AT2 and renin reduced in hypertension group but not significant. ACE1 levels not changed in hypertension. Rosuvastatin and amlodipine significantly increased AT2 levels but non-significant reduced ACE1 and renin levels.

In conclusion, renal levels of ACE1, ACE2, AT1, AT2, TLR4 and renin contribute to hypertension development is indicated that are important targets of hypertension treatment. AT1, AT2, ACE1, ACE2 and renin levels might be mediated to blood pressure lowering effects of amlodipine. Rosuvastatin may affect these parameters which associated with RAS and oxidative stress as amlodipin. Although further studies are needed to determine the effectiveness of rosuvastatin on hypertension, it has been suggested that statins might support or be an alternative for the current treatments.

Key words: Hypertension; Rosuvastatin; Amlodipine; Angiotensin Converting Enzyme1; Angiotensin II type 1 receptor1.

T. Oral Presentation 6

Immunohistochemical investigation on 8-OHDG levels in the heart of lambs with white muscle disease

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White muscle disease is an important disease seen in lamb, calf and goat. White muscle disease is a fatal disease that causes degenerative and necrotic changes in the heart and skeletal muscles resulting from deficiency of vitamin E, selenium, or both. The aim of this study is to determine if the oxidative stress in the heart muscle occurs in white muscle disease, which occurs naturally in lambs. for this purpose, the heart tissues of 10 lambs has white muscle disease and heart tissue of 10 healthy lambs brought to the slaughterhouse was taken. This tissues was stained with 8-OHdG as an important marker of histopathological and oxidative stress. When it was determined that it is a normal histological structure in healthy heart tissues, heart tissues of white muscular diseased lambs were found to have swollen, homogeneous pink color and nuclei pycnotic, and veins were congestion and locally hemorrhagic. In addition, hyaline degeneration and zenker necrosis in the muscles as well as dystrophic calcification in necrotic areas and mononuclear cell infiltration of macrophages in the majority of these areas were observed. 8-OHDG expression was not detectable in immunohistochemically investigated heart tissues of healthy lambs, whereas severe 8-OHDG expression was detected in heart tissues of white muscular diseased lambs. As a result, significant increase in oxidative stress was found in white muscle disease.

Keywords: 8-OHdG; White muscle disease; Oxidative

Stress; Immunohistochemistry.

T. Oral Presentation 7

Comparison of protective and regenerative effects of Hericium erinaceus and NGF in vitro nerve injury

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Peripheral nerve injury (PNI) is a significant health problem that is linked to sensory, motor, and autonomic deficits. Hericium erinaceus (HE), an edible and medicinal mushroom, has been extensively studied for its neurohealth properties. Nerve Growth Factor (NGF) is secreted from Schwann cells in peripheral nerves, endothelial cells, and immune hematopoietic cells. It reduces damaged nerve deaths and increases axon regeneration. In this work, we purposed to compare the neuroprotective and neuritogenic effects of HE and NGF using a laser microdissection technique in a mouse PNI model.

We prepared neuron cultures from dorsal root ganglions (DRGs) of 6-8 week aged mice, We created four study groups with the neuron cultures (Axotomy, NGF (50nM), HE (25 μM), NGF(50 nM) +HE (25 μM). We treated them in presence or absence of H. erinaceus and NGF. Axon was cut (axotomy) with a precisely controllable laser beam to model axonal injury in vitro. Axotomized neurons were imaged with fluorescent microscope system. Axotomized neurons's survival ratio and axon length was compared using the fluorescent dyes.

Both HE and NGF has protective and regenerative effect on axotomized peripheral sensory neurons. The protective capacity of HE is higher than that of NGF. Furthermore, the together therapy of HE and NGF improved axon regeneration ability of axotomized neurons more than all the other groups. Our results warrant a further investigation of HE and NGF as a potential regenerative agent to treat peripheral nerve injuries.

Keywords: DRG neurons; laser; axotomy; Hericium erinaceus; NGF, regeneration.

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T. Oral Presentation 8

Effect of methylprednisolone and heparin, used in experimental unilateral testicular ischemia-reperfusion injury, on oxidative stress in the kidney, liver and contralateral testis

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The aim of this study was to investigate the effects of methylprednisolone (MP) and heparin administration on oxidative stress in the different tissues.

Twenty-four male Sprague-Dawley rats were allocated equally into three groups. The left testes of the rats were rotated 720° for 2 h in the all groups also given MP or heparin by an intraperitoneal route 30 min prior to detorsion in the treatment groups. Left orchiectomy was performed in all rats at 2 h after detorsion. The contralateral testis, kidney and liver tissues were harvested for the measurement of malondialdehyde (MDA), protein carbonyl (PC) and nitric oxide (NO), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase.

GSH-Px in the MP group was higher than the other two groups and catalase was higher than the control group, also MDA and NO in the heparin group were lower than in the other two groups but PC in control group was lower than the other two groups in kidney tissue. NO and SOD in the heparin group were higher than the other two groups in the liver tissue. There was no difference in parameters mentioned in all groups in the contralateral testis.

MP increased antioxidant enzymes, heparin

decreased lipid peroxidation and nitrosative stress products and protein oxidation was increased by the both drugs in kidney. Heparin increased nitrosative stress and antioxidant enzyme in liver. The effect of MP and heparin on oxidative stress in kidney, liver and testis varies between tissues and oxidant-antioxidant molecules.

Keywords: Testicular ischemia-reperfusion; Methylprednisolone; Heparin; Oxidative stress; Kidney; Liver.

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T. Oral Presentation 9

An investigation on the antioxidant activity of Azoramide, a promising new anti-diabetic, on palmitate-induced insulin resistance in H9c2 cells

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Azoramide is synthesized as a regulator of endoplasmic reticulum protein folding and chaperon activity. Fu et. al (2015) showed that azoramide treatment leads to recovery of decreased insulin sensitivity and glucose tolerance in obese rats and they introduced the chemical to the literature as a potential anti-diabetic agent (Fu et al. 2015). It is remarkable that azoramide application causes a statistically significant increase in the fasting insulin level while lowering the increased blood glucose level by the end of a 1 week treatment period. Before using this promising chemical in the clinical settings it must be tested comprehensively to elucidate its mechanism of action at cellular level.

It has been shown that the insulin resistance disease model that is established in cell culture conditions adequately represents the characteristics of insulin resistance in the clinical settings (Chang et al 2016; Pierre et al 2016; Pinel et al 2016). In light of the existing data, the antioxidant effects of azoramide had been studied in palmitate-induced insulin resistant H9c2 cells. The mechanisms underlying Azoramide-induced amelioration of insulin resistance have been explored by investigating its antioxidant capacity either in cell culture or cell-free in vitro experiments through spectrophotometry.

As a result of this study, it has been shown that Azoramide has beneficial effects on palmitate-induced insulin resistance in H9c2 cells and up-regulates the antioxidant status of the cells.

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Key words: Azoramide; insulin resistance; antioxidants; H9c2 cells; palmitate

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T. Oral Presentation 10

Effects of zinc and selenium supplementation on TRPM2 channel in hypoxia-induced HEK293 cells

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Transient Receptor Potential Melastatin-2 (TRPM2) is calcium ion (Ca^{2+}) permeable cation channel (Chen et al. 2007). Hypoxia, defined as a decrease in arterial blood partial pressure (PO_2), causes damage at the cellular level (Taylor et al. 2008). Zinc (Zn) and selenium (Se) are the essential elements protecting the cell membrane and biomolecules against oxidative stress (Valko et al. 2006). The aim of this study was to investigate the effect of Zn on hypoxia exposed transfected human embriyonic kidney (HEK293) cells.

We induced four experimental groups as normoxia, hypoxia, hypoxia+Zn and hypoxia+Se in HEK293 cells. Normoxia (20% O_2, 5% CO_2 and balance N_2) and hypoxia (5% O_2, 5% CO_2 and balance N_2) groups were exposed to these gasses for 30 and 60 minutes while other groups were incubated with Zn and Se before being exposed to the gasses. In the patch-clamp experiments, Ca^{2+} currents and mean current densities of all groups were analyzed.

It was determined that compared to the groups that were exposed to normoxia for 30 and 60 minutes, Ca^{2+} current and mean current density significantly ($p<0.01$) increased in the groups that were exposed to hypoxia for 30 and 60 minutes, while the same values significantly (respectively; $p<0.05$ and $p<0.01$) decreased in the groups that were incubated with Zn. Furthermore, it was analyzed that compared with groups exposed to hypoxia 30 and 60 minutes, Ca^{2+} current and mean current density significantly ($p<0.01$) decreased in the groups that were incubated with Se.

It was concluded that hypoxia increased oxidative stress and caused cellular membrane damage, while supplementation of Zn and Se could protect the cell membrane against oxidative stress.

Keywords: Hypoxia, zinc, selenium, oxidative stress, TRPM2 channel.

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T. Oral Presentation 11

TRPM8 channel is a potential therapeutic target in prostate cancer treatment

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Accumulating evidences have indicated that disturbances in intracellular free calcium ($[Ca^{2+}]i$) concentration play an important role in the pathophysiology of prostate cancers. Ca^{2+} passes cell membrane via different channels such as chemical and voltage gated channels. Apart from the well-known cation channels, there is recently discovered channels namely transient receptor potential (TRP) family. One member of the TRP superfamily is TRP melastatin 8 (TRPM8). The Na^{+} and Ca^{2+}-permeable TRPM8 channels can be gated by different stimuli including cold and menthol. In etiology of prostate cancer, excessive Ca^{2+} entry and oxidative stress have important role (Grolez and Gkika, 206). Considering that TRPM8 is activated by menthol, mediated cell death and proliferation, and is highly expressed in the plasmalemma of epithelial cells, androgen-dependent

extracapsular prostate cancers and androgen-dependent metastasis (Bidaux et al. 2016).

Recently, we found that oxidative stress and ADP-Ribose (ADPR) treatments could induce the TRPM8 activations resulting in the overload Ca^{2+} entry, apoptosis, and mitochondrial oxidative stress. More importantly, we found that GSH could protect the Du 145 prostate cancer cells from oxidative stress-induced apoptosis via maintaining the intracellular Ca^{2+} hemostasis as well as down-regulating mitochondrial oxidative stress pathway (Unpublished data)

I concluded that the oxidative dysfunction of TRPM8 causes changes through activation of second messengers, which may lead to the pathology of prostate cancer. It seems to that the exact relationship between TRPM8 channels activation and prostate cancers still remain to be determined.

Key words; TRPM8 channel; Calcium ion; Prostate cancer; Oxidative stress, Cell proliferation.

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T. Oral Presentation 12

Role of oxidative stress in possible link between premature ovarian failure and Helicobacter pylori seropositivity: A pilot study

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Oxidative stress has been considered to one of the causative factor in the development of premature ovarian failure (POF). Helicobacter pylori has been shown to lead to extragastric inflammation and oxidative stress. In the light of this, the aim of this pilot study was to investigate a possible link between H. Pylori and POF.

A total of 39 participants were recruited for the study and divided into POF (n= 18) and control (n=21) groups. Serum levels of Cu, Zn, Cu/Zn ratio, total antioxidant status (TAS) determined along with hormonal and biochemical markers. Also the Helicobacter Pylori (HP) seropositivity was investigated.

HP seropositivity was significantly higher in POF group than control group. However, serum Cu, Zn, Cu/Zn ratio and TAS values were similar between the groups. In POF group, LH levels were positively correlated with Cu levels and Cu/Zn ratio but negatively correlated with Zn and TAS levels and Anti Mullerian Hormone levels were negatively correlated with Cu and Cu/Zn ratio but positively correlated with Zn and TAS levels. Serum trigyceride and total cholesterol levels were significantly higher in HP seropositive patients when compared to seronegative participants but TAS, LDL and HDL values were similar.

In conclusion, our results suggest that HP infection might associate with POF. This is the first study investigates this relationship. Although we could not justify systemic oxidative stress by trace elements and TAS levels, further large scale studies with more appropriate oxidative stress marker are needed.

Keywords: Premature ovarian failure; Helicobacter pylori; Oxidative stress.

T. Oral Presentation 13

Effect of antioxidants on oxidative liver injury in rabbit with obstructive jaundice

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Obstructive jaundice is one of the most frequent disease of liver and biliary tract. As a result sequence of pathologic changes occurs. Liver is the most effected

organ. Oxygen free radicals (OFR) are molecule groups which includes one more on-common electron at outer orbits (Valko et al. 2007). If the will not scavenged by antioxidants excessive production of OFR is very harmful to body cells. Hence, this equilibrium between antioxidants and OFR may change towards to the side OFR in the presence of an illness, including obstructive jaundice (Pham-Huy et al. 2008). In this study, we investigated protective effects of vitamin C and on oxidative stress in liver and biliary tract epithelium cells of rabbits with experimental obstructive jaundice.

Thirty rabbits divided in groups each including 6 rabbit. First two group (A, B) regarded as control, and C, D, E groups as medication group. Group A had only laparotomy, group B had laparotomy and choledoc ligation, Group C had laparotomy, choledoc ligation and 20mg/kg/day 21 I.M. Vitamin E for 7 days, group D had laparotomy, choledoc ligation and 20mg/kg/day 21 I.M. Vitamin C for 7 days, group E had laparotomy, choledoc ligation and 0,5 g/kg/day single dose I.V human albumin for 7 days. Antioxidant, aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and bilirubin levels were measured in the blood serum of animals. In addition, histopathological analyses in the liver biopsies were also examined.

Assessment of bilirubin values shoved statistically in significant decrease in all group according to group B. For AST, ALT,ALP and bilirubin levels , there was evident decreasing in group C and D. Serum antioxidant levels decreased in lesser amounts in group C and D. Histopathologic evaluation revealed out; less edema, limited necrosis and inflammatory cell infiltration according to group B.

In this study, it was seen that; total antioxidant capacity has decreased in obstructive jaundice. However, vitamin C and E treatment caused increase in the antioxidant capacity. It may be concluded that liver damage was caused by obstructive jaundice, can be prevented by administration of the antioxidants, vitamin C and E.

Keywords: Free radicals; Antioxidant; Liver damage; vitamin E; vitamin C

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T. Oral Presentation 14

Investigation of the relationship among oxidative status, inflammation and lipid levels in hypertension

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Hypertension is one of the major risk factors for cardiovascular diseases, and is known as a leading cause of mortality and morbidity. However, no study has been found to evaluate the association of hypertension with oxidative stress, inflammation and lipids. The aim of this study was to investigate the levels of total antioxidant status (TAS) and total oxidant status (TOS) which are the indicators of oxidative stress, and hs-CRP and lipid levels which are the some inflammation markers in hypertensive patients.

Body mass index and waist circumference of hypertensive and normotensive subjects were measured and total cholesterol, HDL, LDL, triglyceride, hs-CRP, TAS and TOS levels were analyzed in their sera. Oxidative stress index (OSI) was found by mathematical calculation.

The TOS, OSI, total cholesterol, LDL and hs-CRP levels were significantly higher ($p<0.001$); HDL level was significantly lower ($p<0.001$) in the patient groups than those in the healthy group. There was no significant difference between the two groups in terms of TAS levels. There was also a negative correlation between diastolic blood pressure and HDL levels, and a positive correlation with waist circumference in the patient group.

In conclusion, the study demonstrated that the oxidative stress index was high in hypertension. In addition, the increase in diastolic blood pressure as

HDL levels are lowered and waist circumference is increased indicates that these parameters are among the risk factors to be considered in hypertension.

Keywords: Hypertension; Inflammation; Oxidative stress: Lipids.

T. Oral Presentation 15

Inhibition behaviour of some antibiotics on glutathione S-transferase and acetyl cholinesterase activities: in vitro and in vivo

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Glutathione S-transferases (GSTs) are family of mitochondrial, cytosolic and microsomal enzymes that are primarily found in phase II metabolism. They are multifunctional enzymes for the cellular defence against xenobiotics and provide protection for organism. Acetylcholinesterase (AChE) is mainly found at neuromuscular junctions and cholinergic brain synapses. The enzyme is a critical for neurodegenerative disorders. In our study, the effects of cefoperazone, cefuroxime and cefazolin, are antibiotics, were investigated on activity of AChE and GST in vitro and in vivo. GST was isolated by GSH-affinity column chromatography and a single band was observed on SDS-PAGE gel electrophoresis. AChE was purchased commercially. For in vivo, 16 groups were formed (n=6). Control groups; were decapitated at the 1st, 3rd, 5th and 7th h, inhibitor groups; after from application at 50mg/kg cefazolin, 25mg/kg cefuroxime and 100mg/kg cefaperazon as intraperitonal were decapitated at 1st, 3rd, 5th, and 7th hour, respectively for each of inhibitor groups. Ki constants of tested inhibitors in vitro were 301.0±70, 356.1±90, and 384.4±40 µM, for AChE and 139.2±20, 1517.9±330, and 1006±110 µM for GST, respectively. All tested antibiotics showed competitive inhibition for AChE. Cefoperazone and cefazolin showed competitive inhibition, while cefuroxime showed non-competitive inhibition for GST. Cefoperazone was observed to be best inhibitor for both GST and AChE enzyme in vitro conditions. Cefazolin, cefuroxime and cefoperazone inhibited both AChE and GST enzyme activities for first 5 h and then they began to rise from the 5th h in vivo. In vivo conditions, cefuroxime exhibited a more effective inhibition profile than other inhibitors on the AChE and GST enzyme activity. These drugs were shown to cause the inhibition of both GST and AChE enzyme at micromolar level. Therefore, tested antibiotics should be used more carefully, and dosage and application times should be adjusted correctly.

Keywords: AChE, antibiotics, cefazolin, cefuroxime, cefaperazon, enzyme inhibition, GST

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T. Oral Presentation 16

The protective role of Crocin on acrylamide-induced oxidative neurotoxicity in rat

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The changes in rat brain tissues treated with Crocin as a protective agent in an acrylamide neurotoxicity model were investigated. The present study was conducted with the approval of the experimental animal ethics committee at Inonu University, Faculty of Medicine (2016 / A-59). Forty

male rats were randomly divided into 4 groups with equal number of rats (10): Control, Crocin, Acrylamide, Crocin + Acrylamide Groups. Malondialdehyde (MDA), reduced glutathione (GSH), total antioxidant status (TAS), total oxidant status (TOS), superoxide dismutase (SOD), catalase (CAT) and protein values were examined in the brain tissues. MDA, TOS levels and SOD activity increased in brain tissues of acrylamide administered rats when compared to the other groups, while the GSH and TAS levels decreased in the group ($p \leq 0.05$). GSH, and TAS levels increased but MDA, TOS and SOD levels decreased in the acrylamide + crocin administered group when compared to the acrylamide group ($p < 0.05$). In conclusion, it was observed that oral acrylamide administration altered the antioxidant/oxidant balance favoring the oxidants in male rat brain tissues, leading to oxidative stress induced neurotoxicity, while crocin administration reestablished the normal antioxidant/oxidant balance, preventing the oxidative stress induced neurotoxicity via detoxification. The present study concluded that the administered crocin dose was sufficient to prevent neurotoxicity and we recommend that adequate amounts of crocin should be consumed to prevent acrylamide-induced toxicity and improve antioxidant capacity.

Keywords: Brain, acrylamide, crocin, oxidative stress parameters.

T. Oral Presentation 17

Role of selenium in chemotherapy-induced pain: focus on calcium signaling

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Chemotherapy-induced peripheral neuropathic pain (CIP) is a dose-limiting adverse affects the quality of life and therapeutic management (Nassini et al. 2013). However the precise cellular mechanism of CIP is poorly understood. Secondary messenger calcium ion which is 10,000 times more in the extracellular environment, may help us in the assessment of this pain. After the activation of ion channels that localized in the cell membrane, a flow of calcium (Ca^{2+}) ions into the cells occurs with a concentration gradient. The change in intracellular Ca^{2+} levels provides dynamic and versatile signals that control a large number of cellular processes. The Ca^{2+} signaling integrates with other signaling cascades and controls various processes. These calcium signalizations normally occur every second in living things.

Selenium (Se) is a trace element that plays an important role in a number of biological functions. Previous studies have shown that selenium plays an important role in sustaining the physiological functions of the nervous system, such as signal transduction (Wirth et al. 2010). Se plays role as a neuroprotective agents in various neuronal diseases such as pain (Uğuz et al. 2012). In this presentation, it was discussed the role of Ca^{2+} signaling in the case of chemotherapy-induced pain. It was also assessed how Se positive contributed to this relationship.

In conclusion, Ca^{2+} signaling is disturbed by chemotherapeutic agents and consequently oxidative stress and peripheral neuropathic pain are induced in peripheral sensory neurons. It has been observed that Se can reduce these adverse effects by acting on this signaling pathways.

Keywords: Chemotherapy; Peripheral neuropatic pain; Oxidative stress; Selenium; Calcium Signaling.

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T. Oral Presentation 18

Involvement of TRPM2 and TRPV1 channels in sciatic nerve injury

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Physiological pain as an alarm system is an essential factor for body functions that warns us and helps to protect humans from tissue damage. However, pathological pain-induced by several factors such as sciatic nerve injury is usually persistent and can be excruciating in daily life. Neuropathic pain is induced by several factors including inflammation, excessive Ca^{2+} influx, oxidative stress and tissue degeneration. Inflammatory reactions in destroying neurons lead to the activation of the pain molecular pathway. In addition, destruction cell membranes induce excessive Ca^{2+} entry in the neurons, because the Ca^{2+} concentration is about 10.000 times higher in out of the neurons than in the inside of the neuron. The impairment of neuronal membrane permeability in neuronal injuries such as sciatic nerve and spinal cord injury causes activation of two molecular pathways at least. Firstly, overload Ca^{2+} influx into cytosol and it leads to excessive production of ROS in the neurons. Increased intracellular Ca^{2+} concentration through activation of several cation channels causes disruption of the Ca^{2+} contents of intermembrane space through mitochondrial permeability transition activation in the mitochondria. The dysfunction of mitochondria triggers generation of endogenous ROS. Secondly, excessive Ca^{2+} entry into the neurons induces pain.

The Ca^{2+} passes the cell membrane with several channels such as chemical gated and voltage gated calcium channels and transient receptor potential (TRP) cation channels. Some subfamilies of the TRP family, such as TRP melastatin 2 (TRPM2) and TRP vanilloid 1 (TRPV1) are activated by oxidative stress. The result of recent studies indicated involvement of TRPM2 and TRPV1 channel activation in the sciatic nerve injury induced experimental animals (Ren et al. 2015; Uslusoy et al. 2017), although sciatic nerve injury induced pain and apoptosis were blocked by blockade of the channels (Ren et al. 2015; Uslusoy et al. 2017). It was also reported that nerve injury induced excessive Ca^{2+} influx and pain were decreased by treatment of antioxidants (Berger et al. 2011). In the oral presentation, I will summarize recent reports on the TRPM2 and TRPV1 channels in the sciatic nerve injury.

In conclusion, accumulating evidence clearly suggests that the injury of sciatic nerve is involved in the generation of pain through activation of TRPM2 and TRPV1 channels.

Keywords: Sciatic nerve injury; Oxidative stress; TRPM2; TRPV1; Inflammation.

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T. Oral Presentation 19

Role of antioxidants on calcium signaling in traumatic brain injury: Focus on TRPV1 channel

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Accumulating evidences have indicated that disturbances in intracellular free calcium ($[Ca^{2+}]i$) concentration play an important role in the pathophysiology of traumatic brain injury (TBI). Ca^{2+} passes cell membrane via different channels such as chemical and voltage gated channels. Apart from the

well-known cation channels, there is recently discovered channels namely transient receptor potential (TRP) family. One member of the TRP superfamily is TRP vanilloid 1 (TRPV1). The Na^+ and Ca^{2+}-permeable TRPV1 channels can be gated by different stimuli including capsaicin and oxidative stress. In etiology of TBI, excessive Ca^{2+} entry, inflammation and oxidative stress have important role (Corrigan et al. 2016; Ma et al. 2018).

Recently, it was reported that oxidative stress in experimental TBI could induce the TRPV1 activations resulting in the overload Ca^{2+} entry, apoptosis, and mitochondrial oxidative stress. However, antioxidants such as N-acetylcysteine and selenium could protect the hippocampal neurons from TBI-induced oxidative stress and apoptosis via maintaining the intracellular Ca^{2+} hemostasis and TRPV1 channel activation as well as down-regulating mitochondrial oxidative stress pathway (Nazıroğlu et al. 2014; Ma et al. 2018)

I concluded that the oxidative dysfunction of TRPV1 causes changes through activation of second messengers, which may lead to the pathology of TBI. It seems to that the exact relationship between TRPV1 channels activation and TBI still remain to be determined.

Key words; TRPV1 channel; Hipocampus; Traumatic brain injury; Oxidative stress.

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T. Oral Presentation 20

Role of TRPV1 channel in spinal cord injuries

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Abstract Intracellular free Ca^{2+} ($[Ca^{2+}]i$) homeostasis is involved in many functions such as cellular viability, apoptosis, physiological signal transduction and excessive reactive oxygen species (ROS) production. Accumulating evidences have indicated that disturbances in $[Ca^{2+}]i$ concentration play an important role in the pathophysiology of spinal cord injury (SCI). The $[Ca^{2+}]i$ concentration is controlled by a number of membrane cation channels. Transient receptor potential (TRP) channels are a family of non-selective cation channels that have important functions in DRG neurons. The TRP vanilloid 1 (TRPV1) are calcium permeable cation channels and they are abundantly expressed in dorsal root ganglia (DRG) after traumatic injuries (Nishio et al. 2013). The TRPV1 channels in DRG neurons were demonstrated to contribute to oxidative stress-induced cell death after mechanical injuries. Recently, it was reported that oxidative stress in experimental SCI could induce the TRPV1 activations resulting in the overload Ca^{2+} entry, apoptosis, and mitochondrial oxidative stress. However, antioxidants such as Hypericum perforatum could protect the hippocampal neurons from TBI-induced oxidative stress and apoptosis via maintaining the intracellular Ca^{2+} hemostasis and TRPV1 channel activation as well as down-regulating mitochondrial oxidative stress pathway (Özdemir et al. 2016) I concluded that SCI induced oxidative stress, apoptosis and Ca^{2+} entry via TRPV1 channel was substantially reduced by antioxidants. However, the exact relationship between TRPV1 channels activation and SCI still remain to be determined.

Key words; TRPV1 channel; Hipocampus; Traumatic brain injury; Oxidative stress.

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T. Oral Presentation 21

Restoration of hypertrophy-induced by norepinephrine through opening of ATP sensitive potassium channel

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Norepinephrine (NE) has toxic effects on cardiomyocytes and induces myocardial hypertrophy, necrosis, progressive cardiac muscle damage via apoptosis. The hypertrophy has a beneficial effect on stressed-heart at early stage of it. But, it causes to increase some pathology, including heart failure or arrhythmia. ATP sensitive potassium channel (KATP) has been well documented to protect of cardiac tissue against some pathology including ischemia. The study aimed to evaluate the mechanism of protective effect of opening KATP in hypertrophic cardiomyocytes induced by norepinephrine. In the study, H9c2 cell line has used the research. It was created four groups as a control; hypertrophy; Diaxozide (Dia), one of KATP opener; Dia+hypertrophy. Distribution of actin filaments, mitochondrial membrane potential (MMP), and superoxide dismutase (SOD) enzyme activity was analyzed with proper tests, and then statistical analysis was performed. Although hypertrophy gave rise to decrease SOD enzyme activity, DIA co-treatment restored it. Hypertrophy destroyed cytoskeleton via actin distribution, but DIA ameliorated the distribution as well. Although hypertrophy caused to elevate MMP, DIA reversed its effect on MMP. Cardiomyocytes loss by oxidative stress-mediated apoptosis is an essential mechanism for norepinephrine-induced hypertrophy, and the alternations were attenuated with DIA co-treatment. Consequently, the opening of KATP has protective effects on NE-induced hypertrophy and DIA may be a candidate agent to protect the hypertrophic cell.

Keywords: ATP-sensitive potassium channel, Hypertrophy, Mitochondrial membrane potential, Actin, Cardiomyocytes.

T. Oral Presentation 22

Does HMGB1 gene silence really attenuate doxorubicin's cardiotoxicity?

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Doxorubicin (DOX) is one of the drugs for using cancer therapy, exceptionally solid and leukemia. However, its clinical utility is limited due to the drug toxicity on noncancerous tissue such as heart, liver, kidney, testis, etc. It is well known that the most adverse effect it's is seen on heart tissue. It is not still completely understood the mechanism of DOX-induced heart failure. High mobility group box 1 (HMGB1) is a chromatin protein highly conservative among the species. HMGB1 has a connection between cell's survival and death pathways. Until now, there has been no significant report refers the interaction between DOX and HMGB1 and AMP-activated kinase (AMPK) in the same experimental study. So, the study aimed to investigate whether DOX-induced heart failure mediates HMGB1 to initiate the apoptosis through (AMPK-α1) by TLR4 or not. In the study, H9c2 cell line has used the study. It was created four groups as a control, HMGB1 inhibition, DOX, DOX+HMGB1 inhibition. Silencing HMGB1 was performed with specific small interfering RNA (siRNA, 10 nM). DOX was used at two µM concentration for 36 and 48 hours. Protein and genes expressions, apoptosis was measured. Although DOX gave rise to decrease AMPK, P-AMPK, ERK1/2, PERK1/2, P38, JNK protein expression, DOX+HMGB1 inhibition led to change those protein expressions. The number of TUNEL positive and active caspase eight cells at DOX was high, although HMGB1 silencing could heal the cell numbers. HMGB1 plays an essential role as amplifying on DOX toxicity on the heart by TLR4. This study was financially supported by TUBITAK (114S118).

Keywords: Doxorubicin, HMGB1, AMPK, TLR4, apoptosis, heart muscle cell

T. Oral Presentation 23

How does AMPK Inhibition at Cardiotoxicity-Induced by Doxorubicin occur?

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Doxorubicin (DOX) is an antineoplastic agent for tumor treatment. Unfortunately, It has a toxic effect on many tissues like the heart. DOX may exacerbate defect of energy production by decreasing mitochondrial energy production, blocking the AMP-activated kinase and trigger apoptosis known as programmed cell death pathway. AMPK has associated with between cell's survival and death pathways. DOX inhibits to AMPK. However, It is not still completely understood the mechanism of AMPK by DOX. The study aimed to investigate whether inhibition of AMPK in heart failure-induced by DOX is through TLR4 and/or mTOR or not. Five groups were created as a control, DOX, DOX+TLR4 (Resatorvid, DT), DOX +mTOR (Rapamycin, DR), and DOX+mTOR+TLR4 (DRT) by using H9c2 cell line. Protein and genes expressions and apoptosis were measured. TLR4 protein expression was down at DOX group, but high at DR and DT groups. AMPK elevated at DR, PAMPK was high at DR, DT

and DRT groups. Cytochrome-c expression increased at DOX group but fell at DR, DT and DRT groups. The number of TUNEL positive and active caspase eight cells at DOX group was higher than control. However, the number of TUNEL positive and active caspase-8 cells at DR, DT, DRT was lower vs. DOX group. AMPK inhibition through the TLR4 receptor, resulting from energy deficiency via MAPK at heart failure-induced by DOX plays an essential role in triggering apoptosis.

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Keywords: Doxorubicin, HMGB1, AMPK, TLR4, apoptosis, heart muscle cell

T. Oral Presentation 24

Comparison of gender difference in terms of oxidant/antioxidant status in chronic renal failure patients before hemodialysis

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Oxidative stress is considered to play a major role in the development of end-stage chronic renal failure (CRF) complications (Palleschi et al. 2007; Dursun et al. 2008). In this study, we aimed to investigate the gender differences in terms of total antioxidant level (TAS), total oxidant level (TOS), oxidative stress index (OSI), ceruloplasmin, lipid hydroperoxide (LOOH) and total free sulfhydryl groups (-SH=total thiol) levels, paraoxonase (PON) and arylesterase in end-stage patients with CRF receiving hemodialysis treatment.

Forty seven (28 female, 19 male) patients with CRF and forty seven healthy control (31 female, 16 male) were included in the study. Serum TAS, TOS and ceruloplasmin values were measured spectrophotometrically by Erel method. Serum arylesterase, PON, -SH, and LOOH values were measured spectrophotometrically with the Abbott Architect C4000 Biochemistry autoanalyzer. Oxidative stress index was calculated using TAS and TOS values.

When CRF patients are compared in terms of gender, the mean levels of -SH and TAS, and OSI values were found to be significantly higher in male than those of female ($p=0.040$, $P=0.003$ and $p=0.016$, respectively). The serum levels of TOS and LOOH; the activities of PON, arylesterase and ceruloplasmin were not significantly different between male and female.

In conclusion, it was seen that the serum levels of TAS, -SH and OSI were higher in males compared with females, and this findings may be associated with various complications observed in gender differences of CRF patients. Considering this gender difference in CRF patients may positively contribute to preventing complications in CRF patients.

Keywords: Chronic renal failure; Paraoxonase, arylesterase; Total oxidant status; Total antioxidant status.

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T. Oral Presentation 25

Effect of therapeutic hypothermia on oxidative stress in patients undergoing abdominal surgery

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Therapeutic hypothermia (TH) is known to protect tissues against inflammation through its anti-inflammatory effect. In the present study, we aimed to investigate the effect of TH on oxidative stress.

The study included 100 patients that underwent emergency open abdominal surgery. The patients were randomly divided into two groups: (I) TH group (n=50) underwent cold therapy with local sterile frozen ice compress and (II) control group (n=50) underwent sterile compress. The serum total antioxidant status (TAS), and total oxidant status (TOS) levels were measured and oxidative stress index (OSI) was calculated on each patient on preoperative and postoperative fifth day. OSI was calculated based on the following formula: OSI (arbitrary unit) = TOS (μmol H_2O_2 Eq/L) / TAS (μmol Trolox Eq/L). The results were compared between the groups.

The two groups were similar in terms of age, gender, primary pathology diagnosis, size of incision, and wound type and size, and duration of surgery ($p>0.05$). The groups were similar with regards to preoperative TAS, TOS, OSI levels ($p>0.05$). Postoperative TAS levels were significantly higher in the TH group compared to the control group (1.618±0.253 vs 1.501± 0.232 mmol TroloxEq/L) ($p<0.017$). Postoperative TOS levels were almost similar in both groups ($p>0.182$). Postoperative OSI levels were significantly lower in the TH group (14.4±2.9 vs.16.3±3.7) ($p<0.05$).

In conclusion, we found TH to be effective in the inflammatory process by increasing TAS level. We consider that TH elevating the TAS level, eliminating reactive oxygen species and decreasing the effects of inflammatory mediators.

Key Words: Therapeutic hypothermia; Oxidative stress; Antioxidant

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T. Oral Presentation 26

Effects of voluntary and involuntary exercise on hippocampal oxidative stress and antioxidant defense in aged rats

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Brain is sensitive to oxidative damage because of the relatively low levels of both enzymatic and non-enzymatic antioxidant systems and huge amount of free radical production due to the high oxygen demand. Therefore, oxidative damage induced by free radicals also play a pivotal role in the aging process, but this situation may be reversed by regular exercise. We investigated the effects of voluntary and involuntary exercise on protein carbonyl (PC), malondialdehyde (MDA) and glutathione (GSH) levels, and superoxide dismutase (SOD) activity in the hippocampus tissue of aged rats.

The study protocol was approved by Ethics Committee of Experimental Medicine Research and Application Center, Selçuk University. Twenty aged male Wistar rats were used. The rats were randomly assigned to three groups: Control, voluntary exercise, and involuntary exercise. The voluntary exercise group was given free access to a running wheel for 90 days.

The involuntary exercise group was forced to swim for 90 days. Rats were sacrificed by cervical dislocation 24 h after the last exercise session. Hippocampus tissue was dissected for the analysis of PC, MDA, GSH, and SOD.

Hippocampal PC levels were lower in the involuntary exercise group compared to the control and voluntary exercise groups ($P < 0.05$). Although it was not statistically significant hippocampal MDA levels and SOD activities tended to decrease in both voluntary and involuntary exercise groups compared to the control group ($P > 0.05$). Hippocampal GSH levels were higher in the voluntary exercise group compared to the involuntary exercise groups ($P < 0.05$).

As a result, both voluntary and involuntary exercise trainings decrease oxidative stress and increase antioxidant defense system. Additionally, voluntary exercise seems to more effective on oxidative stress and antioxidant defense systems.

Keywords: Exercise; Hippocampus; Oxidative stress; Antioxidants.

T. Oral Presentation 27

The effect of polydatin on oxidative stress in lower extremity ischemic preconditioning model

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The prevention of ischemia/reperfusion injury of an organ through a short-time ischemia of another organ in the body is called remote ischemic preconditioning (IP). Remote IP administration is an important practice that reduces morbidity and mortality by preventing I/R damage. In this study, the effect of polydatin on oxidative stress was studied in the lower extremity IP model in rats.

Wistar Albino rats were divided into three groups. The first group underwent intraperitoneal saline injection. The second group received intraperitoneal polydatin for 3 days before the IP performance in the lower extremity. In the third group, IP in the lower extremity was performed without delivering polydatin. The blood samples were taken from the tail veins. Total Antioxidant Status (TAS) and Total Oxidative Stress (TOS) levels were measured, and oxidative stress indexes (OSI) were calculated. OSI was calculated by using the following formula: OSI (arbitrary unit) = TOS (μmol H_2O_2 Eq/L) / TAS (μmol Trolox Eq/L).

Compared to the groups, there was a decrease in TOS values and an increase in TAS values in the polydatin group, but it was not significant ($p > 0.05$). The OSI value was lower in the polydatin-received group, compared to the group that did not receive polydatin, but this decrease was not significant.

In conclusion, according to the results of this study, polydatin decreases oxidative stress even if it is not statistically significant. We believe that the use of polydatin in combination with other antioxidant methods and agents will be beneficial to reduce oxidative stress.

Keywords: Ischemia/reperfusion injury; Polydatin; Oxidative stress; Antioxidant.

T. Oral Presentation 28

Effects of anti-tumor necrosis factor alpha (infliximab) on oxidative stress and calcium signaling in neutrophil of inflammatory diseases

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Oxidative stress occurs during the several physiological functions such as mitochondria functions and phagocytosis. Reactive oxygen species (ROS) products of oxidative stress such as superoxide and hydroxyl radical are scavenged by antioxidants. Neutrophils in inflammatory reactions form the first defense barrier. The ROS products are essential in phagocytic cells including neutrophils for killing

bacteria and viruses. Involvement of oxidative stress in etiology of inflammatory disease has been known for a long time. However, the oxidative stress gates some cation channels. In turn, excessive Ca^{2+} entry induces excessive stimulation of neutrophils. Involvement of oxidative stress-induced Ca^{2+} entry in neutrophils has not been clarified yet.

Infliximab (INF) is a monoclonal antibody against TNF (Balasubramanian et al. 2017). Its affinity is high for soluble and membrane bound TNF. INF has been used therapeutically for several immune mediated disorders including rheumatoid arthritis and ankylosing spondylitis. Therapeutic molecular pathway of INF has not been totally clarified yet. However, results of recent studies in neutrophil of patients with ankylosing spondylitis and rheumatoid arthritis indicated that intracellular Ca^{2+} concentration, oxidative stress, apoptosis, caspase 3 and 9 levels were high in neutrophils of AS patients, although they were reduced with infliximab treatment (Ugan et al. 2016). In the oral presentation, I will summarize recent development of INF on oxidative stress and calcium signaling in neutrophil of inflammatory diseases

In conclusion, results of present literature information indicated that infliximab is useful agent through modulation of Ca^{2+} influx on apoptotic cell death and oxidative stress in neutrophils of patients with ankylosing spondylitis and rheumatoid arthritis, which seem to be dependent on increased levels of intracellular Ca^{2+} through activation of TRPM2 and VGCC.

Keywords: Ankylosing spondylitis; infliximab; apoptosis; calcium signaling; oxidative stress; neutrophil.

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T. Oral Presentation 29

Effect of venlafaxine on hippocampal BDNF levels in depression-induced rats

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Although antidepressant drugs have been used for approximately 60 years, very little is known about their effect mechanism. Structural abnormalities, particularly in the hippocampus, are observed in brain structures of depressed patients.

The correction of these abnormalities with treatment suggests that major depressive disorders may be associated with a decrease in cellular elasticity and structural plasticity, and antidepressant treatments may provide benefits by treating these disorders. In this study, we aimed to investigate the effect of venlafaxine treatment on the brain-derived neurotrophic factor (BDNF) and BDNF levels in the hippocampus of depression-induced rats by using the chronic mild stress (CMS) model.

In this study, 30 eight-week-old, Wistar albino male rats were divided into three groups. The first group received venlafaxine (20 mg/kg) with CMS, the second group a placebo with CMS, and the third group only a placebo (n = 10) for four weeks. At the end of the four-week period, BDNF levels in hippocampus tissues were measured.

The measurements showed that the BDNF levels of the depressed group were significantly lower than those of the control group. In our study, the hippocampal BDNF levels of the venlafaxine-administered group were similar to those of the control group and significantly higher than those of the depressed group.

In concusion, these findings show that the BDNF, which has an important function in neuroplasticity, plays a role in depression pathophysiology, and venlafaxine prevents the BDNF decrease observed in depression. This latter result supports the view that depression treatment prevents the long-term complications of the disorder.

Keywords: Depression; BDNF; Venlafaxine; Hippocampus; Neuroplasticity.

T. Oral Presentation 30

The protective effects of melatonin and caffeic acid phenethyl ester combination against cisplatin-induced nephrotoxicity

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Cisplatin used in the treatment of many types of cancers in clinical oncology for approximately 40 years has yet been discovered while no solution to the side-effect of nephrotoxicity. Although, studies on cisplatin nephrotoxicity are focused on tubular damage, there is no detailed study of the effect of cisplatin on glomerular basement membrane and podocytes. The aim of this experimental study was to investigate the effects of melatonin and caffeic acid phenethyl ester (CAPE) against cisplatin-induced nephrotoxicity in rats.

Forty-eight male rats were divided into five groups of eight animals in each group. These were constituted as saline control, cisplatin control, cisplatin+melatonin, cisplatin+ CAPE and cisplatin+melatonin+CAPE groups. Group 1, the saline control group, received only saline. Group 2 acted as the cisplatin only group and received a single 7 mg/kg dose of cisplatin intraperitoneally on the fifth day of the study. Group 3 received 5 mg/kg melatonin intraperitoneally daily for eight days and a single 7 mg/kg dose of cisplatin intraperitoneally on the fifth day. Group 4 received 10 μmol/kg CAPE intraperitoneally two days before and three days after cisplatin administration. Group 5 received 5 mg/kg melatonin intraperitoneally daily for eight days and 10 μmol/kg CAPE intraperitoneally two days before and three days after cisplatin treatment. Seven days after the last cisplatin treatment, blood samples were collected for biochemical evaluation and all experimental were sacrificed under anesthesia. Biochemical evaluation was performed by measuring glutathione (GSH) and malondialdehyde (MDA) levels. Tubular necrosis score were calculated for histopathological evaluation, and NF-κB/p65, 8-OHdG and caspase-3 staining was performed for immunohistochemical evaluation.

Cisplatin treatment increased GSH, MDA levels and TNS, 8-OHdG and caspase-3 ($p<0.05$). Melatonin and melatoinin+CAPE reduced GSH, MDA levels and TNS, 8-OHdG and caspase-3 ($p<0.05$).

In conclusion, reactive oxygen species may be candidates for the prevention of acute kidney disease in patients who use cisplatin in the treatment of malignancy. The nephrotoxic effect of cisplatin was diminished by the antioxidant effect of melatonin and CAPE.

Key words: Caffeic acid phenethyl ester (CAPE); Cisplatin; Melatonin; Kidney.

T. Oral Presentation 31

TRPM2 channel gene expression levels in bipolar disorders

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Accumulating evidences have indicated that disturbances in intracellular free calcium ($[Ca^{2+}]i$) concentration play an important role in the pathophysiology of bipolar disorders. Ca^{2+} passes cell membrane via different channels such as chemical and voltage gated channels. Apart from the well-known cation channels, there is recently discovered channels namely transient receptor potential (TRP) family. One member of the TRP superfamily is TRP melastatin 2. The Na^{+} and Ca^{2+}-permeable TRPM2 channels can be gated either by ADP-ribose (ADPR) or by hydrogen peroxide, binding to the channel's enzymatic Nudix

domain. In etiology of bipolar disorders such as bipolar I and 2, excessive Ca^{2+} entry and oxidative stress have important role. Hence, TRPM2 gene expression level is highly associated with bipolar disorders (Xu et al. 2009). Considering that TRPM2 is activated by oxidative stress, mediated cell death and gene changes, and is highly expressed in brain, the channel has been investigated in the bipolar disorders, although conflicting reports are also present (Zaeri et al. 2015). As a mutation of TRPM2, high mutation level of D543E was found in patients with bipolar disorders (Jang et al. 2015).

I concluded that the genetic dysfunction of TRPM2 causes gene changes through activation of second messengers, which may lead to the pathology of bipolar disorders. It seems to that the exact relationship between TRPM2 channels activation and bipolar disorders still remain to be determined.

Key words; TRPM2 channel: TRPM2 channel gene; Calcium ion; Bipolar disorders; Oxidative stress.

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T. Oral Presentation 32

Neuroprotective effect of royal jelly, grape seed extract, and Lycium barbarum against diethylnitrosamine-induced neurotoxicity in rats

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I aimed to investigate the effects of royal jelly (RJ), grape seed extract (GSE), and Lycium barbarum extract (LBAE) against diethylnitrosamine (DEN) induced neurotoxicity in experimental animal model.

Fifty female Sprague Dawley rats were divided into five groups (n=10): Control, DEN, DEN+RJ, DEN+GSE, DEN+LBAE. All the DEN administrated groups were intraperitoneally (i.p.) injected with three doses of DEN (200 mg/kg), dissolved in olive oil, on treatment day 0, 15, 30 of the 16-week experimental period. Then 100 mg/kg of RJ was given to DEN+RJ group, 100 mg/kg of GSE was given to DEN+GSE group, and 400 mg/kg LBAE was given to DEN+LBAE group with the daily drinking water from day 0 for 16 weeks.

RJ, GSE and LBAE treatments significantly reduced weight loss induced by DEN. The increase of malondialdehyde (MDA) level and decrease of catalase (CAT), superoxide dismutase (SOD), and glutathione (GSH) levels by DEN, was significantly suppressed by these treatments ($p<0.05$). In addition, these dietary supplements increased the total antioxidant status (TAS), calcium levels and decreased serum oxidative stress index (OSI), total oxidant status (TOS), serum ferritin levels significantly ($p<0.05$).

In conclusion, improvements were prominent in case of RJ > GSE > LBAE. Our results indicated that RJ, GSE and LBAE might be useful for prevention of the neurotoxicity induced by DEN via ameliorative effects on biochemical and oxidative stress indices.

Keywords: DEN (Diethylnitrosamine); Neurotoxicity; Royal Jelly (RJ); Grape Seed Extract (GSE); Lycium Barbarum Extract (LBAE).

T. Oral Presentation 33

We should protect our cells and telomeres from oxidative stress: A review of aging mechanisms

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Aging (senescence) is a natural biological process that is the result of several different cellular senescence mechanisms causing a progressive functional cell capacity reduction.

The most important mechanism is the free radical theory proposed by Denham Harman, also known as mitochondrial aging theory. Free oxygen radicals are extremely unstable substances with an unpaired electron in their outer orbital and their accumulation leads oxidative stress. Aging begins as the body's defense mechanisms against free radicals with a variety of enzymes and some antioxidants diminish over time. Another theory is the replicative aging theory described by Hayflick. Telomeres are specific DNA sequence repeats that make up the end of chromosomes. As a result of every cell division, telomeres become shorter and trigger aging-related mechanisms when it reaches a critical length. The telomere length is protected by addition of nucleotides which is mediated by an enzyme called telomerase, which is not present in the majority of somatic cells. Telomerase activity is regained in immortalized cancer cells, providing infinite multiplication capacity to cancer cells. Although these mechanisms seem to be independent, several studies have shown that oxidative stress is also effective in shortening of telomeres. The shortening rate of telomeres in each cell division varies, affected by the balance between oxidative stress and antioxidant defense.

In conclusion, decompensated oxidative stress plays a major role in the pathogenesis of aging related diseases such as cardiovascular diseases, Alzheimer's, and cancer. A stress-reduced lifestyle with regular exercise, an antioxidant-rich diet and avoiding alcohol and smoking seem to be our best defense against oxidative stress and, therefore, aging related diseases.

Key words: Aging; Cell senescence; Oxidative stress; Antioxidant defense; Telomerase.

T. Oral Presentation 34

Effects of free oxygen radicals on healing of fractures

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It is known that free oxygen radicals have a negative effect on wound healing. Since fracture healing, which is characterized by the new bone formation, is a type of wound healing, free oxygen radicals may also have adverse effects on fracture healing.

The presence of free oxygen radicals in the fractured hematoma was compared with plasma and the effects of free oxygen radicals on fracture healing were investigated.

Free oxygen radicals were shown to be increased in the fractured hematoma as compared to plasma. Experimentally, increasing the oxygen free radicals impair the fracture healing. In addition, disruption of the circulation also increases free radicals and affects fracture healing negatively.

In conclusion, fracture healing composed of three phases as inflammation, repair and remodeling. Several studies have reported that free oxygen radicals increase during the first 5 days of inflammation. In a previous study, after fracture, increased levels of free oxygen radicals were found in the hematoma than in the plasma. In an experimental study where free oxygen radicals were increased by exogenously by drugs, fracture healing was reported to be impaired. Free oxygen radicals can also be increased by disruption of the circulation in the presence of lymphedema. Although free oxygen radicals were shown to have adverse effects on fracture healing, studies are limited and more comprehensive studies are needed.

Keywords: Free oxygen radicals; Fracture healing; Inflammation; Trauma.

T. Oral Presentation 35

Role of oxidative stress and antioxidants on fetal development

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Human development begins with the formation of zygote by the merging of the male gametocyte (spermatozon) and the female gametocyte (oocyte). The zygote by cell division, cell migration, growth and differentiation, becomes a multi-celled person. This process includes embryonic and fetal periods. Fetus development is under the influence of genetic and environmental factors. Some substance causes malformations in pregnant women which is passed from placenta through fetal circulation to the fetus. In this case it is called teratogenesis. Free oxygen radicals are natural product of energy production processes. Increase of free radicals in the cell and their negative effects on cell functions are defined as oxidative stress.

In our studies, we investigated that effect of various medicines on the fetal development of pregnant rat. We made pregnancies on rats in our studies that we have done at different times. Drugs such as cyclophosphamide, doxorubicin, ciprofloxacin phenytoin and lamotrigine were investigated for their effects on fetal developmental effects in pregnant rats. Fetuses were taken by C-section on the 20th day of pregnancy. Thereafter, the tissues suitable for the purpose of each study were taken. These tissues were subjected to histological assessments and biochemical analyzes. Many parameters were also affected such as antioxidant parameters, enzyme levels and levels of malondialdehyde (MDA) (a marker of lipid peroxidation) were affected.

In all our studies we observed clearly that the free radical-induced oxidative damage in tissues such as fetal brain and liver. We have observed that free radical damage can be prevented by antioxidant supplementation.

In conclusion, the use of antibiotics and chemotherapy drugs in pregnancy negatively affects fetal development through oxidative stress. We think that antioxidant supplementation is important when the use of these drugs is absolutely necessary

Keywords: Antioxidants; Oxidative stress; Fetal development.

Declaration: This is a review obtained from our original researches.

T. Oral Presentation 36

Effects of anesthetic agents on TRP channels in brain

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Ion channels produce action potentials in nerves, muscles and synapses. These channels, which produce action potential, make it possible for the living organism to fulfill a range of tasks ranging from motion to sensitivity. Ion channels are the building blocks of brain functions, and many neurological and muscle deformities occur due to defects in these channels. Anesthetic agents may enable paradox stimulation and sensitization of nociceptive sensory neurons and therefore, potentially facilitate processing of pain. Since fat/water partition coefficients of general anesthetics are high, they are not homogeneously distributed in the body and accumulate in lipid-rich tissues. Anesthetic agents which pass to blood such as propofol, accumulate in excessive amounts in the brain. It has been thought that the TRP channels play a major role in the induction of propofol-induced sensory neurons in previously conducted studies. In conclusion, to reveal the effects of anesthetic agents, which reduce pain threshold and accumulate in brain, on TRP channels and shed light on the future original studies, there is a need for comprehensive reviews which covers studies in this topic.

Keywords: Anesthetic agents; Propofol; TRP channels

T. Oral Presentation 37

Inhibition of NADPH oxidase attenuates sepsis-induced acute lung oxidative damage in rats

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Oxidative stress occurs when the physiological balance between oxidants and antioxidants change in favor of oxidants (Sies, 1997). Increase in such reactive oxygen species plays a role in the molecular mechanism of sepsis (Yorulmaz, Ozkok, Ates, & Tamer, 2017). In this study; the effect of NADPH oxidase inhibitor (apocynin) on the oxidative damage of the lung tissue in the Cecal ligation and puncture (CLP) induced sepsis was investigated.

The rats were (12 weeks old, weighing 200g-250g) assigned to sham (S), sepsis group (CLP), CLP+apocynin 20 mg/kg (APO20), CLP+ apocynin 50 mg/kg (APO50). The apocynin was given intraperitoneally 15 minutes before the CLP. In the CLP group; TOS, OSI, MPO and MDA were increased, while TAS and SOD were decreased in comparison to sham. The APO20 treatment has decreased the CLP damage-induced oxidative/antioxidative averages to their basal values. In the APO20 group, in comparison to CLP group, a significant increase in the antioxidant parameters (TAS,SOD) and a significant decrease in the oxidant parameters (TOS, OSI, MPO) has been observed. Similarly to APO20; in the APO50 application, a significant difference in comparison to the CLP group in TAS,TOS, OSI, SOD, MPO and MDA values has been observed.

In conclusion, presented study demonstrated that inhibition of NADPH oxidase by apocynin provides a potential therapeutic option for attenuating sepsis induced acute lung oxidant damage.

Keywords: Apocynin; Cecal ligation and puncture (CLP) model; Lung injury; Oxidative stress; Polymicrobial sepsis.

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T. Oral Presentation 38

The biophysical properties of ERG currents in pyramidal neurons of the mice region of CA1 in hippocampus

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ERG (Ether a go go related gene) channels (Kv 11) are the members of the voltage-dependent potassium channel family, which have three subtypes, as ERG1 (Kv 11.1), ERG2 (Kv 11.2) and ERG3 (Kv11.3). Biophysical properties of ERG channels in the are yet not known in the pyramidal neurons of hippocampus in mice. For this reason, we aimed to study and biophysical properties and their functions in the pyramidal neuron of the hippocampal CA1 region.

A total of 20 mice at were used for this study. Electrophysiological characterization of ERG channels was performed using patch clamp technique in the hippocampal slices. In current clamp, application of ERG channel blockers, terfenadine (10 μM) and E-4031 (10 μM), significantly increased input resistance ($p<0,05$). They also increased a spontaneous activity and the number of action potentials (APs) induced by a square current pulse ($p<0,05$).

Tail ERG currents were measured under voltage-clamp. Steady state activation curve for ERG tail current was determined with a half-activation voltage $V_{0.5}$ −48.95 mV with a slope factor of 4,54 mV respectively. Steady state inactivation curve for ERG tail current was determined with a half-activation

voltage $V_{0.5}$ −77.35 mV with a slope factor of 10,58 mV.

In conclusion, the findings obtained in the present study suggest that ERG channels appear to contribute AP number, maintining and setting resting membrane potentials in pyramidal cells.

T. Oral Presentation 39

Effects of N–(p–amylcinnamoyl) anthranilic Acid (ACA), a TRPM2 calcium ion channel antagonist, on neurodegeneration and protein expression in a rat model of Alzheimer's disease

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Alzheimer's disease (AD), a relentless neurodegenerative disease, accounts for great majority of dementias. Current drugs are not capable of halting the progression of AD. So, more effective novel agents are urgently needed.

N–(p–amylcinnamoyl) anthranilic acid (ACA) is a blocker of transient receptor potential melastatin–2 (TRPM2) which is a non–selective, Ca^{2+}–permeable cation channel. Oxidative stress is a substantial causative entity for AD. Cellular stress leads to ischemia and Ca^{2+} accumulation by activating TRPM2 (Nazıroglu 2011). The role of ACA in neurodegeneration seen AD is not entirely known. The aim of this study was to investigate effects of ACA on spatial memory in streptozotocin (stz)–induced AD model in wistar rats. A total of 50 rats randomly divided into five groups; (1) control, (2) sham–operated, (3) intracerebroventricular (ICV)–stz, (4) ICV–stz + memantine (5 mg/kg ip) and (5) ICV–stz + ACA (25 mg/kg ip). There was no significant difference between group 3 and group 5 in Morris water maze ($p>0.05$). There were also no significant changes among the groups 1, 2 and 4 in water maze test ($p>0.05$). Western blot analysis in hippocampal tissues showed that TRPM2, but not glycogen synthase kinase–3, protein expression was markedly depressed in AD model when compared to sham-control ($p=0.0007$), and ACA treatment prevented this depression.

In conclusion, our findings showed for the first time that TRPM2 protein expression was significantly suppressed in the rat AD model, and ACA reversed this suppression. However, no improvement in spatial memory was observed.

Key words: Alzheimer's disease, neurodegeneration, TRPM2 channels

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Reference
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T. Oral Presentation 40

Administration of testosterone propionate changes significantly the expressions of ion channel genes in the mouse prostate tissues

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Testosterone is an important steroid hormone that plays a role in the development of the tissues of the male reproductive system (Asuthkar et al. 2015). The activity of the testosterone is mediated by androgen receptor (AR), a transcription factor. Androgens and AR

signals are required in prostate development and homeostasis (Zhou Y et al. 2015). They are also involved in the regulation of ion channel functions in the cell. In this study, we aimed to investigate the effects of testosterone administration on gene expressions of ion channels in mouse prostate tissues.

BALB/c mice weighing 27-32g were divided into control and testosterone propionate groups (n=10). Animals in the testosterone group received 20 mg/kg/day testosterone propionate subcutaneously for 30 days for BPH development. Fourty one ion channels expression profile of mouse prostate tissue were demonstrated by qRT-PCR.

In the testosterone group compared to the control no change in the expression level of the KCNA4 gene was observed whereas increased expression levels of KCNJ11, TRPM2-1 and TRPM2-2 and decreased expression levels of other studied genes were detected.

AR has a central role in the biology and progression of prostate cancer (PCa) and PCa progression occurs due to transient increases in serum testosterone levels. Testosterone administration has led to serious changes in the expression of many ion channel genes in mice prostate tissue. This data shows that the exogenous testosterone disrupt the homeostasis of the ion channels in the prostate tissue and thus provides favorable conditions for the emergence of many diseases such as cancer.

Key Words: Prostate; Benign Prostate Hyperplasia; Prostate Cancer; Testosterone; Androgen; Androgen receptor; Ion channel; Gene expression; qRT-PCR.

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T. Oral Presentation 41

Serotonin hyperpolarize dorsal raphe nucleus neurons in mouse by activating potassium channels

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Serotonin (5-HT) is synthesized from tryptophan amino acid is a member of monoamine neurotransmitter group. In the CNS, it is responsible for mood, appetite, memory and sleep. Some psychiatric conditions such as major depression and anxiety are related to disturbances in the serotonin signaling of the projections arising from raphe nucleus and targeted to forebrain. On the one hand the neurons of the raphe nucleus send projections almost all brain regions. On the other hand they affect themselves through auto receptors, since the dorsal raphe nucleus (DRN) neurons contain 5-HT receptors like $5HT_{1A}$, which act as auto receptors. In the current study, we aimed to study effects of serotonin on DRN neurons and its mechanism of action.

We used electrophysiological whole-cell patch clamp technique in the neurons of dorsal raphe nucleus slices from 28-33 days old Balb/c mice. The effect of Serotonin and $BaCl_2$ (GIRK channel antagonist), added to ACSF, on parameters including duration and frequency of action potentials (AP), resting membrane potential and membrane currents were studied.

In current clamp experiments, extracellular application of serotonin caused the resting membrane potential of the DRN neurons to hyperpolarize by 14.3 ± 9.4 (n=9) and caused spontaneously active neurons to stop firing. Under voltage clamp conditions, serotonin resulted in activation of an outward current with an amplitude of 25± 9.1 (n=7) when the membrane held at -57 mV, which was inhibited with extracellular application of $BaCl_2$.

In conclusion, serotonin causes hyperpolarization of the neurons of the raphe nucleus through activation of an outward current. This outward current might be mediated through GIRK channels, since it is blocked by $BaCl_2$. It appears that serotonin neurons release

serotonin locally in the dorsal raphe nucleus, which hyperpolarizes the same neurons, resulting in inhibition of these neurons by activating GIRK potassium channels.

Keywords: Serotonin, Dorsal Raphe Nucleus, GIRK channels

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T. Oral Presentation 42

Modulation of diabetes-induced Ca^{2+} entry, oxidative stress and apoptosis by TRPM2 channel: Involvement of zinc

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Impairment of insulin secretion induces to hyperglycemia and diabetes. The main stimulatory pathway for glucose-stimulated insulin secretion is ATP sensitive K^+ channels and voltage-gated Ca^{2+} channel (VGCC). In the first step, glucose is transported into beta-cells through glucose transporter 2 and the glucose leads to a change in the ATP/ADP ratio resulting from ATP production in mitochondria. This induces membrane depolarization through direct blockade of ATP sensitive K^+ channels. VGCC opens upon depolarization, causing the elevation of intracellular Ca^{2+} concentrations. Then, membrane potential changes drive pulsatile insulin secretion (Uchida et al. 2017).

Apart from the VGCC, there is recently discovered Ca^{2+} channels namely transient receptor (TRP) channels. The Ca^{2+} permeable TRP melastatin 2 (TRPM2) is part of the TRP family, members of the melastatin and vanilloid subfamilies, respectively. The TRPM2 channel was activated by poly (ADP-ribose) polymerase (PARP) pathways through the production of ADP-ribose and NAD+. TRPM2 is also potentiated by reactive oxygen species (ROS) (Sensi et al. 2009). ROS acts a central role in the β-cell death. TRPM2 channels are expressed in the pancreatic beta cells. Expression levels of TRPM2 in the pancreatic beta cells were also affected by diabetes induction. Growing interest in the therapeutic potential of TRP channels continually provides support for the hypothesis that TRP channel inhibition likely underlies many of the benefits associated with induction of diabetes (Kahya et al. 2017). In this presentation, I will summarize recent experimental research findings on how these TRPM2 channels are regulated in diabetes by Zn^{2+}.

TRPM2 is also Zn^{2+} permeable channel. Zn^{2+} contributed to TRPM2-mediated β-cell death in transfected HEK293 and beta cells lines. Apoptosis are mediated by overload Ca^{2+} entry. However, result of a recent study indicated that TRPM2-mediated Ca^{2+} entry-potentiated Zn^{2+} release underlies ROS-induced β-cell death and Zn^{2+}, rather than Ca^{2+}, plays a primary role in apoptosis.

In conclusion, results of current papers indicated that TRPM2 in diabetes is important for pancreatic beta-cell function. In addition, Ca^{2+} entry through TRPM2 channels induces Zn^{2+} release and then Zn^{2+} causes β-cell apoptosis.

Keywords: Zinc, TRPM2; Diabetes; Apoptosis; Calcium ion.

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T. Oral Presentation 43

Role of Antioxdants on Calcium signaling in ARPE-19 Cells

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As a divalent cation, calcium (Ca^{2+}), interacts as a mediator for a large number of intracellular biological processes as fertilization to cell death. Ca^{2+} can enter to the cytoplasm from either the extracellular fluid or by release from intracellular stores depending on the use.After influx to the cytoplasm, Ca^{2+} activates a number of protein kinases, proteases, phospholipases and nucleases, which then act to regulate activities such as gene expression, mitogenesis, metabolism, and motility. Transient receptor potential channels (TRP channels) are a group of ion channels located mostly on the plasma membrane which regulates Ca^{2+} homeostasis. There are about 28 TRP channels that share some structural similarity to each other. It has been reported that TRP canonical, a subfamily of TRP family ion channel has a crucial role in regulation of cellular function in ARPE-19 cells. The retinal pigment epithelium (RPE) part of the retina is located between the neural retina and the choroidal vasculature. With its tight junctions, RPE forms part of the blood-retina barrier and is important for the maintenance of retinal function. As a nutritionally essential trace element, selenium (Se) plays a critical role in oxidation, DNA synthesis, immune system etc. Moreover, Se fights cancer and other diseases. Se acts as a precursor of intracellular antioxidant enzyme glutathione (GSH). Astaxanthin is a keto-carotenoid. Astaxanthin serves as one of the most powerful antioxidants that can be absorbed by the human body. Melatonin is a hormone, produced in pineal gland. Melatonin has strong antioxidant properties and is attracting increased attention in recent years and is known to reduce oxidative stress. Here, we will discuss our findings by comparing these three antioxidant molecules and on Ca^{2+} signaling in ARPE-19 cells.

T. Oral Presentation 44

Phytochemical profile of Tanecetum erzincanense and its correlation to antioxidant and anti-proliferative activities

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Phenolic compounds are a large group of secondary metabolites of plants. Epidemiological studies show that consumption of foods which are rich in phenolic compounds have beneficial health effect on health by providing protection against diseases such as diabetes, stoke, heart diseases and cancer. Therefore studies regarding the biological activities of plant phenolic gained interest. In this study, we investigated phenolic compounds as well as antioxidant and anticancer activities of Tanecetum erzincanense in vitro.

For identification of phenolic compounds, we prepared methanol extract of the plant species T. erzincanense, and used Reversed-phase high-performance liquid chromatography (RP-HPLC) technique to detect most abundant individual phenolic compounds. In addition, total phenolic and flavonoid content have been determined by Folin ciocalteu method and Aluminium chloride colorimetric method, respectively. For antioxidant activity, we performed ABTS and DPPH assays to measure radical scavenging activity as well as ferric and cupric reducing antioxidant capacity (FRAP and CUPRAC). Finally to define antiproliferative potential, methanolic extract of T. erzincanense was tested against human three cancer cell lines namely, hepatocellular carcinoma HepG2 cells, colorectal carcinoma HT-29 cells and breast carcinoma MCF-7 cells by XTT cell viability assay.

HPLC analysis indicated that the most abundant individual phenolic compounds found in T. erzincanense are gallic acid, caffeic acid, rosmarinic acid, p-hydroxybenzoic acid, 3,4-dihydroxybenzoic acid and 2,3- dihydroxybenzoic acid. Total phenolic and flavonoid content of the extract were determined as 129,4 mgGAE/g ext. and 563,7 mgQE/g ext.,

respectively. In addition, Tanecetum erzincanense showed moderate antioxidant activity as compared to standard antioxidants namely, BHA, BHT, Trolox and α-Tocopherol. Finally, XTT assay results revealed that T. erzincanense showed more cytotoxic activity against MCF-7 cells (IC_{50}; 0.35mg/ml) compared to HT-29 (IC_{50}; 0.47mg/ml) and HepG2 (IC_{50}; 0.49mg/ml) cells. These results suggest that T. erzincanense has moderate potential biological activity.

Keywords: Phenolic compounds; Antioxidant; Tanecetum erzincanense; Anti-proliferative activitiy.

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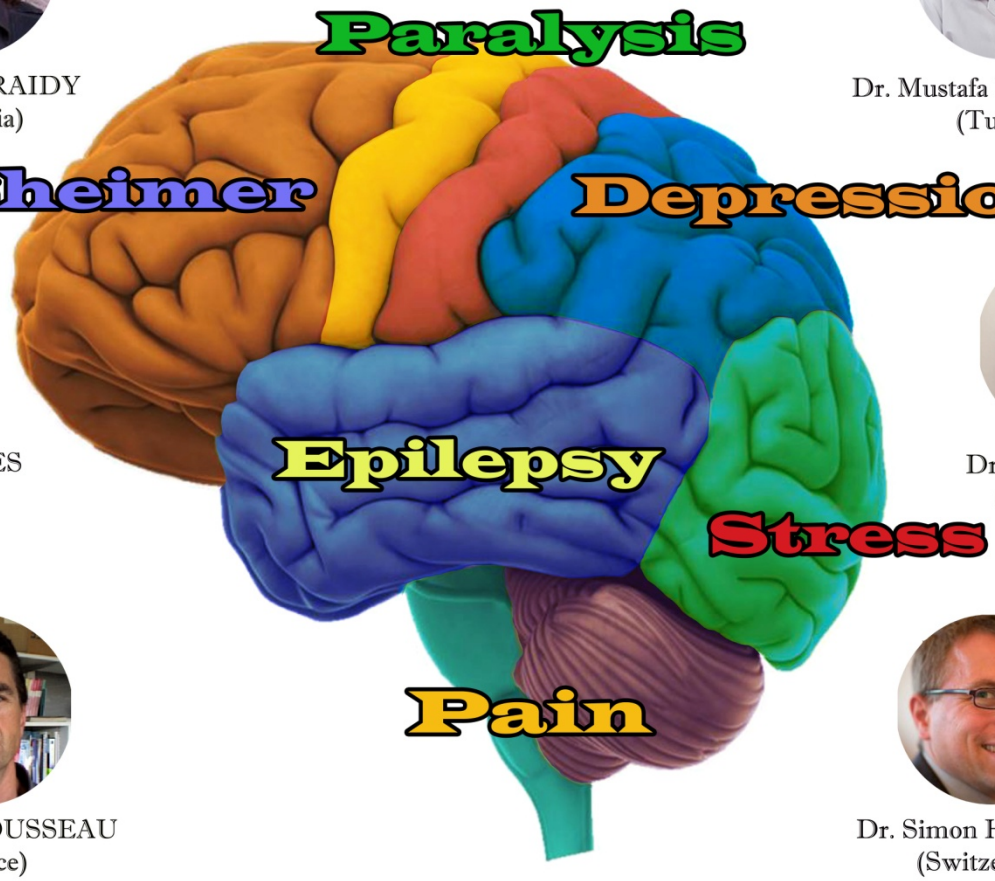

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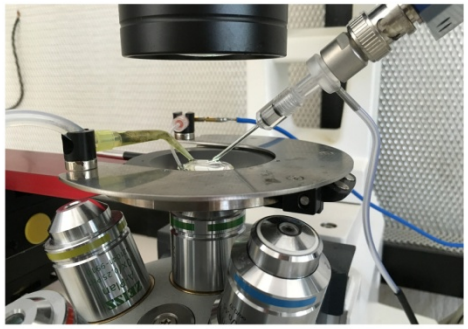

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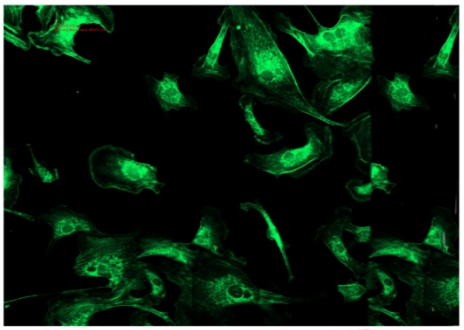

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