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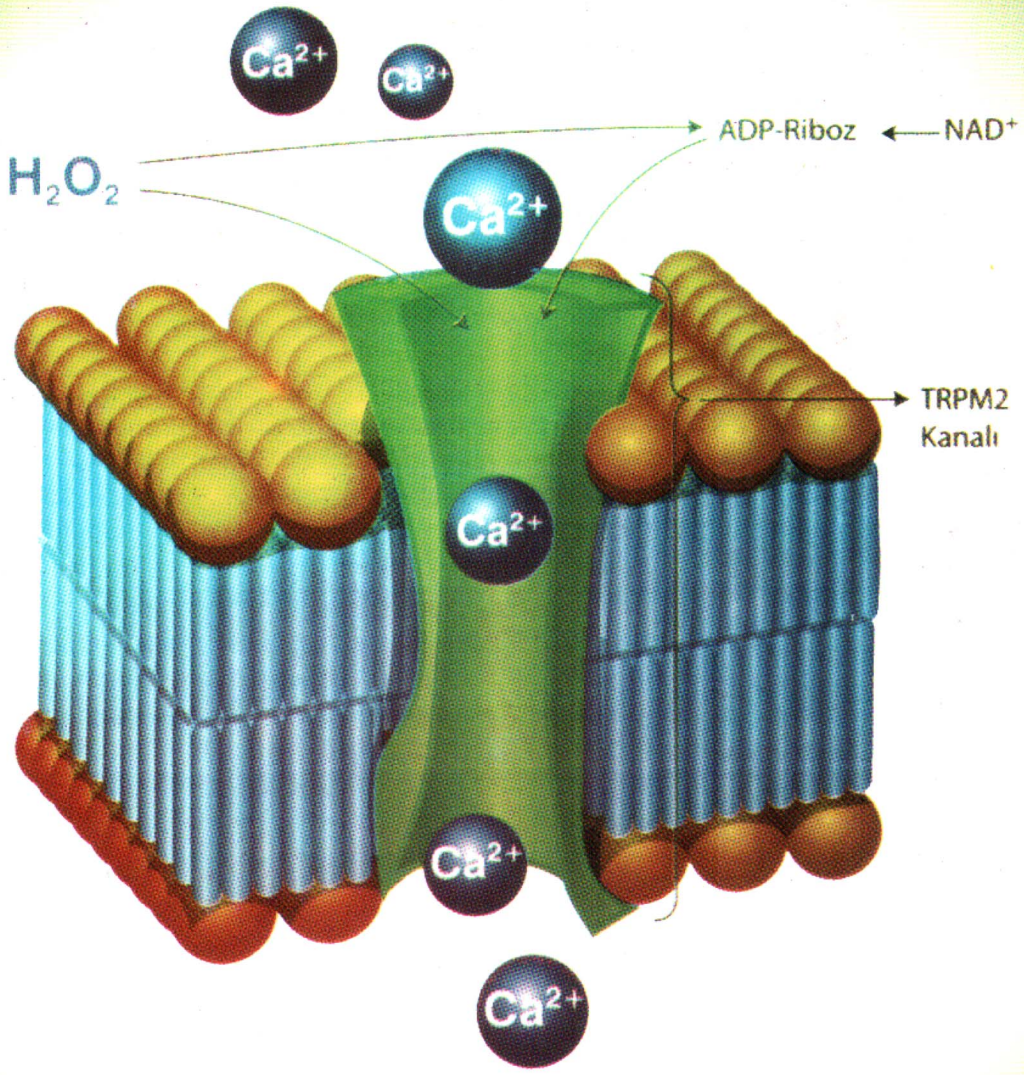

TÜBİTAK

CELL MEMBRANES and FREE RADICAL RESEARCH
Ion channels and their modulation by free radicals
(Official Journal of Society of Cell Membranes and Free Oxygen Radicals)
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Aims and Scope

Cell Membranes and Free Radical Research is a print and online journal that publishes original research articles and reviews on the molecular basis of, cell membranes, ion channels, producing free radicals from oxygen, ion channel gating. The journal is a free journal and it has been freely sending member of Society of Cell Membranes and Free Oxygen Radicals and university libraries on the world.
Areas of particular interest are:

- Signaling; signal transduction; hormones, chemicals, ions, cations
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- Cell membranes; membrane potential, membrane biochemistry
- Oxidative Stress (Antioxidant vitamins, Antioxidant enzymes, Metabolism of Nitric oxide, Oxidative stress, the biophysics of the radicals which springed up from oxygen)
- Ion Channels; Na^+ - K^+ Channels, Cl^- channels, Ca^{2+} channels, ADP-Ribose and metabolism of NAD^+, Patch-clamp applications
- Gene and oxidative stress (Gene abnormalities. Interaction between gene and free radicals as well as Gene anomalies and iron. Role of radiation and cancer on gene polymorphism)
- Therapeutic interventions and preventative medicine

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2nd International Congress on Cell Membranes and Oxidative Stress: Focus on Calcium Signaling and TRP Channels

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Conference 1

Plasma Membrane Calcium Channels

James W. Putney, Jr.

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In most eukaryotic cell types, activation of phospholipase C by G-protein-coupled receptors results in release of intracellular Ca^{2+} stores and activation of Ca^{2+} entry across the plasma membrane. The intracellular release of Ca^{2+} is most commonly signaled by the second messenger, inositol 1,4,5-trisphosphate acting on cognate receptors on the endoplasmic reticulum. Early work on mechanisms of calcium revealed that Ca^{2+} entry involves signaling from depleted intracellular stores to plasma membrane Ca^{2+} channels, a process referred to as *capacitative calcium entry or store-operated calcium (SOC) entry* (SOCE). The mechanism of activation of SOCE channels involves an endoplasmic reticulum Ca^{2+} sensor, Stim1, and a plasma membrane protein, Orai1. Orai1, and its congeners Orai2 and 3 constitute pore-forming subunits of the SOCE channel. Stim1 responds to store depletion by reorganizing into punctate structures near the plasma membrane where Orai channels collect.

Activation of phospholipase C also activates non-store-operated channels, the best example being the extensively studied TRPC channels. These channels fall into two categories; TRPC3, 6 and 7 are activated by the diacylglycerol produced by phospholipase C action. TRPC1, 4 and 5 are activated downstream of phospholipase C, but the mechanism for their activation is less clear. A contributing factor may be depletion of membrane PIP_2 which exerts tonic inhibition of the channel.

Conference 2

Structure and function of IP3 receptors

Colin W. Taylor

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Inositol 1,4,5-trisphosphate receptors (IP3R) are intracellular Ca^{2+} channels that are expressed in almost all animal cells. They mediate both the initial release of Ca^{2+} from intracellular stores evoked by the many receptors that stimulate IP3 formation and the regenerative propagation of intracellular Ca^{2+} signals. The latter depends upon both the regulation of IP3R by Ca^{2+} and the appropriate spacing of IP3R such that Ca^{2+} released by one IP_3R can regulate the activities of its neighbours. This highlights a recurrent theme in intracellular signalling: the importance of spatially organised signalling pathways. I will illustrate, using patch-clamp recording, how IP_3 dynamically regulates the assembly of IP_3Rs into small clusters wherein their behaviour is very different from lone IP_3R. This IP_3-regulated clustering re-tunes the IP_3 and Ca^{2+} sensitivities of IP_3R, facilitating the regenerative propagation of intracellular Ca^{2+} signals. A second universal theme is the integration of signals from different signalling pathways. Here too, IP_3R illustrates some of the principles. The essential regulators of IP_3R are IP_3 and Ca^{2+}, but many additional signals modulate their effects, thereby endowing IP_3R with considerable computational ability. I will focus on one example of an interaction between two ubiquitous signalling pathways, cAMP and Ca^{2+}, that serves also further to highlight the importance of spatial organization. I will present evidence that cAMP is delivered directly to IP_3R from adenylyl cyclase (AC), within junctions that are formed specifically between type 6 AC and type 2 IP_3R. These junctions function as robust on-off switches, in contrast to the responses of more typical cAMP effectors like PKA, which bind cAMP with greater affinity, and respond to local cAMP gradients extending over greater distances from AC. This defines two modes of cAMP signalling: binary (IP_3R) where cAMP is delivered directly to a low-affinity target and diffusion is sufficient to turn of the signal, and analog (eg PKA) where a higher affinity cAMP target responds to a cAMP gradient, but local degradation is required to maintain local signalling events.

Conference 3

Regulated Calcium entry pathways in the vasculature

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Calcium (Ca^{2+}) is a highly versatile second messenger that controls endothelial cell (EC) and vascular smooth muscle cell (VSMC) functions such as contraction, proliferation, and migration. The most ubiquitous pathway for regulated calcium (Ca^{2+}) entry into cells is the store-operated Ca^{2+} (SOC) entry pathway (also called Capacitative Ca^{2+} entry) that is conserved from lower organisms such as worms and flies to man. The SOC concept was proposed over two decades ago and SOC channels are defined by their activation in response to depletion of the internal Ca^{2+} stores. Influx through SOC channels is necessary for the replenishment of the Ca^{2+} stores and is also involved in cell signaling to the nucleus. Despite intensive investigations, most of which focusing

on Transient Receptor Potential (TRP) channels as molecular candidates for SOC channels, the mechanisms of activation and the identity of the key molecular players participating in this signaling pathway have long remained elusive. In the last 2-3 years however, the improvements of RNA silencing protocols combined with high throughput platforms have yielded significant breakthroughs, with the identification of Stim1 as the Ca^{2+} store sensor and Orai1 (CRACM1) as the pore-forming subunit of the archetypical SOC channel, CRAC. Here we describe the contribution of Stim and Orai isoforms to VSMC and EC Ca^{2+} signaling and show altered expression of these molecules during proliferative vascular disease. The contribution of these Ca^{2+} signaling molecules to vascular disease will be discussed.

Conference 4

Intracellular Calcium Regulation In Airway Smooth Muscle

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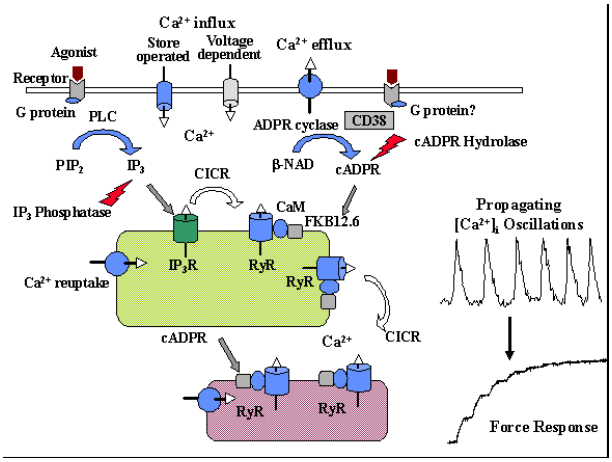
Regulation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in airway smooth muscle involves multiple mechanisms including Ca^{2+} influx and efflux across the plasma membrane, second messenger production, sarcoplasmic reticulum (SR) Ca^{2+} release and reuptake (which may themselves be feedback regulated by $[Ca^{2+}]_i$ levels). Agonists transiently elevate $[Ca^{2+}]_i$ by increasing Ca^{2+} influx and by eliciting SR Ca^{2+} release, mediated through both inositol 1,4,5-trisphosphate receptor (IP_3R) channels and ryanodine receptor (RyR) channels. Basal $[Ca^{2+}]_i$ levels are then restored by Ca^{2+} reuptake into the SR via SERCA, Ca^{2+} buffering by mitochondria, and by plasma membrane Ca^{2+} pumps. Basal Ca^{2+} levels are also influenced by leak through IP_3R and RyR channels as well as plasma membrane channels and by mitochondrial Ca^{2+} release.

Spatial and temporal differences in $[Ca^{2+}]_i$ regulatory processes exist within cells leading to intracellular heterogeneity in $[Ca^{2+}]_i$ regulation under both basal conditions and during agonist stimulation. Intracellular heterogeneity in $[Ca^{2+}]_i$ regulation may also arise from variations in the distribution of membrane receptors, production and/or diffusion of second messengers, and SR and membrane Ca^{2+} channels. Such heterogeneities in $[Ca^{2+}]_i$ regulation are evidenced by spontaneous localized $[Ca^{2+}]_i$ transients, termed Ca^{2+} sparks that have been reported in several cell types, including smooth, cardiac and skeletal muscles. Furthermore, agonist-induced propagated $[Ca^{2+}]_i$ oscillations also reflect the non-homogenous nature of $[Ca^{2+}]_i$ regulation.

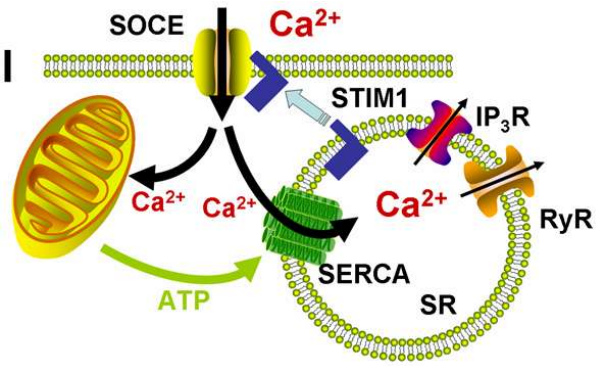


In our studies in airway smooth muscle cells, we showed that agonist (e.g., muscarinic) stimulation induces $[Ca^{2+}]_i$ oscillations that propagate through the length of the cell. We found that $[Ca^{2+}]_i$ oscillations are often initiated in regions where there is an increased incidence of Ca^{2+} sparks. Agonists increase the open probability of SR Ca^{2+} release channels, increasing the incidence of Ca^{2+} sparks that then fuse into larger transient events that propagate through the cell. Although Ca^{2+} release of through both IP3R and RyR channels is important in $[Ca^{2+}]_i$ oscillations, it appears that Ca^{2+} release through RyR channels is essential for both Ca^{2+} sparks and $[Ca^{2+}]_i$ oscillations in airway smooth muscle cells.

The intracellular pathway linking muscarinic stimulation and IP_3 production has been well-characterized. In contrast, far less is known about the coupling between muscarinic receptor stimulation and Ca^{2+} release through RyR channels. Our studies indicate that this coupling is accomplished by activation of CD38 and production of cyclic ADP ribose (cADPR), which in turn, modulates Ca^{2+}-induced Ca^{2+} release (CICR) through RyR channels. Furthermore, our studies indicate that in airway smooth muscle, cADPR increases the frequency and propagation velocity of $[Ca^{2+}]_i$ oscillations, thereby affecting global $[Ca^{2+}]_i$ regulation.

Regulation of SR Ca^{2+} refilling involves two major mechanisms: 1) store-operated Ca^{2+} entry (SOCE) across the plasma membrane, and 2) Ca^{2+} reuptake via SERCA. Recent studies suggest that the "sensing" of SR Ca^{2+} depletion and activation of SOCE is mediated via stromal interaction molecule (STIM1). Additional evidence suggests that Ca^{2+} influx into mitochondria (mitochondrial Ca^{2+} buffering) can enhance SOCE and influence Ca^{2+} reuptake via SERCA, either by modulating by phospholamban (PLB) phosphorylation or by affecting ATP availability. Physical proximity of mitochondria to the plasma membrane and SR may thus play an important role by altering local Ca^{2+} and/or ATP gradients. Mitochondria are also a potential site for oxygen free radical generation and oxidative stress. Very few studies have explored the impact of reactive oxidants on the various pathways

involved in $[Ca^{2+}]_i$ regulation.



The transient receptor potential channel (TRPC) protein, is crucial for SOCE and has been implicated as the putative Ca^{2+} influx "channel". TRPC channels appear to be important in both physiologic processes and disease states. In our work, we found that porcine airway smooth muscle expresses the TRPC1, TRPC3 and TRPC4 isoforms, with TRPC3 being the predominant isoform expressed. In human airway smooth muscle, we recently found that exposure to inflammatory cytokines increases TRPC3 (and to some extent TRPC6) expression, while other isoforms are largely unaffected. Down regulation of TRPC3 via siRNA blunts SOCE in porcine and human airway smooth muscle. However, a major issue with such siRNA studies (including our own) is that the contribution of different TRPC isoforms to overall SOCE may depend on cell type as well as the presence of other signaling mechanisms (e.g. inflammation and phosphorylation by different mechanisms). Accordingly, even if the expression or function of a single TRPC isoform is altered, it may be difficult, if not impossible, to deduce effects on SOCE, given the potential contribution of several other isoforms to overall Ca^{2+} influx.

There has been a flurry of recent interest in stromal interaction molecule 1 (STIM1) as a Ca^{2+} sensing protein that potentially mediates communication between the SR and plasma membrane and triggers SOCE in response to depletion of SR Ca^{2+} stores. The STIM1 protein is thought to function as an SR Ca^{2+} sensor via a single N-terminal EF-hand Ca^{2+} binding motif is located within the SR lumen. Some studies suggest that insertion of STIM1 from the SR to the plasma membrane, presumably via vesicular transport, is a prerequisite for SOCE activation. Indeed, this has been confirmed in functional studies. Other studies have shown that STIM1 may not necessarily be inserted into the plasma membrane, but might aggregate close enough to activate SOCE channels.

There is recent evidence for expression of STIM1 in airway smooth muscle. Indeed, siRNA inhibition of STIM1 leads to decreased SOCE in airway smooth muscle, a finding we have confirmed in human airway smooth muscle. We also found that STIM1 is expressed at a higher level in plasma membrane fractions following SR Ca^{2+} depletion in human airway smooth muscle cells.

The fact that at least some of the SR membrane is juxtaposed with the plasma membrane suggests that proximity may play an important role – the superficial barrier concept proposed by some investigators. It is possible that in juxtaposed SR, IP3R and RyR channels may be involved in the regulation of SOCE. Whether or not IP3R and RyR are directly involved in SOCE, the importance of proximity of the SR to the plasma membrane remains unknown. The limited information available suggests that physical proximity of mitochondria to the plasma membrane may also play a role in mitochondrial regulation of SOCE. In recent studies, we found that mitochondria are located in close proximity with the plasma membrane. Furthermore, inhibition of the mitochondrial Ca^{2+} uniporter using Ru360 resulted in increased SOCE in human airway smooth muscle cells. These results raise the possibility that mitochondrial regulation of SOCE also occurs in airway smooth muscle. In recent studies using time-lapse video imaging, we found that agonist-induced elevation of $[Ca^{2+}]_i$ produced movement of mitochondria away from the airway smooth muscle plasma membrane. Furthermore, in the presence of phalloidin which blocked migration of mitochondria, SOCE was significantly blunted. Local $[Ca^{2+}]_i$ (microdomain) is more important than global $[Ca^{2+}]_i$ in establishing Ca^{2+} influx into mitochondria In this regard, mitochondria may sense local microdomain $[Ca^{2+}]_i$ in the vicinity of open Ca^{2+} channels, either at the SR or at the plasma membrane. With agonist-induced Ca^{2+} release, high local $[Ca^{2+}]_i$ allows for fast mitochondrial uptake. Indeed, rapid mitochondrial Ca^{2+} uptake occurs following both IP_3 receptor- and RyR channel-mediated Ca^{2+} release in non-ASM smooth muscle. Overall, these results suggest that mitochondria buffer $[Ca^{2+}]_i$. In addition, there is now evidence that mitochondria enhance the rate of SR Ca^{2+} release by preventing Ca^{2+}-induced inactivation of IP3R and RyR channels.

In addition to mitochondrial regulation of SR via Ca^{2+}, ATP can also act as a local messenger between mitochondria and juxtaposed SR. For example, IP_3-dependent Ca^{2+} release is modulated by ATP levels. Furthermore, mitochondrial regulation of ATP may have implications for SERCA activity, affecting SR Ca^{2+} refilling. In recent studies, we found that ACh not only increased $[Ca^{2+}]_{mito}$ and $[Ca^{2+}]_i$ but also elevated mitochondrial membrane potential, suggesting agonist-induced changes in ATP levels.

Clearly, mitochondria can regulate SR Ca^{2+} dynamics via mitochondrial buffering of $[Ca^{2+}]_i$ or ATP. Physical proximity of mitochondria and SR is certainly important in these functional interactions, since, for example, microdomain Ca^{2+} gradients are affected by the distance between mitochondria and SR. In gastric smooth muscle, RyR channels are in close proximity to mitochondria, consistent with our studies in human airway smooth muscle cells. Furthermore, in studies using time-lapse video imaging of fluorescently-tagged mitochondria in living airway smooth muscle cells co-stained with fluorescent thapsigargin to detect SR, we found that under normal circumstances, mitochondria are apposed with areas of

SR. In other cell types, it has been observed that mitochondrial movement away from or towards the SR does occur under normal circumstances. In recent studies, we found that volatile anesthetics promote mitochondrial movement away from the SR, thus influencing mitochondrial Ca^{2+} buffering. Prevention of actin depolymerization by phalloidin resulted in significant reduction in mitochondrial separation from the SR. Finally, in the presence of phalloidin, isoflurane-induced delay in mitochondrial uptake of Ca^{2+} following ACh- or histamine-induced SR Ca^{2+} release was significantly abbreviated, suggesting that physical proximity of mitochondria to SR is a key player in mediating the inhibitory effects of volatile anesthetic on SERCA and SOCE.

Conference 5

From calcium signaling to mitochondrial functions – a lesson from exocrine secretory cells.

Alexei Tepikin

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Physiological calcium-releasing secretagogues ACh and CCK utilize calcium signalling cascade to trigger and regulate secretion in pancreatic acinar cells. The majority of calcium signals produced by these agonists are localised to the apical part of the cell. We utilized intra patch-pipette uncaging technique to prove that the mechanism of generation of local calcium transients depends on the long distance communication between receptors localised on the basal part of the cell, diffusable second messenger and Ca2+ release channels in the apical region of the cell. The abuility of small polarized cell to form local calcium responses depends on a high level of cytosolic calciu buffering, which we measured using the droplet technique. Using mitochondrial probes and mitochondrial inhibitors we demonstrated that the perigranular mitochondria play a major role in restricting calcium signals to the apical region. The cytosolic calcium changes trigger mitochondria calcium responses with consequent changes of mitochondria calcium concentration, mitochondria membrane potential and NAD(P)H concentration. Patterns of these signals were analysed in different groups of pancreatic mitochondria (sub-plasmalemmal, perigranular and perinuclear). The changes of ATP concentration due to calcium signals were analysed using luciferase construct. We observed moderate biphasic changes of ATP concentration induced by calcium-releasing agonists. The reverse effect of ATP depletion on calcium responses was investigated. The depletion of cytosolic ATP resulted in a drastic inhibition of both calcium oscillations and calcium influx.

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Barrow SL et al *Pflugers Arch*. 2008, 455(6):1025-39.

Conference 6

Cellular adhesion: Novel mechanisms involving voltage-gated sodium channel in human cancer cells

Mustafa B. A. Djamgoz

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Cellular adhesion is fundamentally important to a variety of physiological and pathophysiological processes, including cancer. We have previously shown that voltage-gated sodium channels (VGSCs), predominantly the 'neonatal' splice form of Nav1.5 (nNav1.5), are upregulated in metastatic breast cancer (BCa) and potentiate a variety of metastatic cell behaviours. VGSCs comprise one pore-forming α subunit with one or more β subunits. β subunits modulate functional expression and gating of the VGSC in the plasma membrane, and can potentially serve as immunoglobulin superfamily cell adhesion molecules. In studies adopting a comparative approach to weakly and strongly metastatic human BCa cells, in both MCF-7 and MDA-MB-231 cells (weakly and strongly metastatic, respectively), the β subunit mRNA expression profile was *SCN1B* (encoding β1) >> *SCN4B* (encoding β4) > *SCN2B* (encoding β2); *SCN3B* (encoding β3) was absent. However, MCF-7 cells had much higher levels of all β subunit mRNAs than MDA-MB-231 cells. Similarly, β1 protein was strongly expressed in MCF-7 and barely detectable in MDA-MB-231 cells. In order to investigate the possible role of β subunits in adhesion and migration, MCF-7 cells were transfected with siRNA targeting β1. This resulted in single-cell adhesion being reduced by 35 %, while migration increased by 121 %. In addition, the levels of nNav1.5 mRNA and protein were increased following β1 down-regulation. We conclude (1) that β1 can function as a novel cell adhesion molecule in BCa and (2) that down-regulation of β1 increases migration and, concomitantly, promotes the elevation of nNav1.5 expression. These data are consistent with VGSCβ1 subunit functioning both as a cell adhesion molecule and transcription factor, via its extracellular and cytoplasmic domains, respectively.

Conference 7

Role of calcium signalling in prostate cancer

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Major clinical problem with prostate cancer is the cell's ability to survive and proliferate upon androgen withdrawal. Indeed, deregulated cell proliferation together with the suppression of apoptosis provides the condition for abnormal tissue growth.
The aim of our work was to establish the role and regulation of calcium-permeable ion channels in prostate carcinogenesis.
1. We have demonstrated that a calcium signal can promote either cell proliferation or apoptosis, depending on the type of TRP channel involved: calcium entry via TRPC6 or TRPV6 channels stimulates cell proliferation whereas store-operated channels (represented by ORAI1 and TRPC1) are mostly involved in apoptosis induction.
2. We were particularly interested by TRPM8 channels since TRPM8 is a target gene of the androgen receptor and its expression strongly increases in prostate cancer. Recent evidence we have obtained indicate that TRPM8 may be expressed not just in the plasma membrane, but also in the endoplasmic reticulum (ER) membrane where TRPM8 may operate as an ER Ca^{2+} release channel. The "preferred" TRPM8 localization depends on epithelial cell phenotype (differentiated apical cells vs. non-differentiated basal cells) and on androgen status (androgen-dependent vs. hormone refractory).
We propose a model for the differential regulation and functional significance of plasma membrane and endoplasmic reticulum TRPM8 in carcinogenesis.

Conference 8

TRP channels, oxidant signaling and innate immunity

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Increased endothelial permeability is the hallmark of inflammatory vascular edema. Inflammatory mediators that bind to heptahelical G protein-coupled receptors trigger increased endothelial permeability by increasing the intracellular Ca^{2+} concentration ([Ca2+]$_i$). The rise in $[Ca^{2+}]_i$ activates key signaling pathways that mediate cytoskeletal reorganization (through myosin-light-chain-dependent contraction) and the disassembly of VE-cadherin at the adherens junctions. The Ca^{2+}-dependent protein kinase C (PKC) isoform PKCα plays a crucial role in initiating endothelial cell contraction and disassembly of VE-cadherin junctions. The increase in $[Ca^{2+}]_i$ induced by inflammatory agonists such as thrombin and histamine is achieved by the generation of inositol 1,4,5-trisphosphate (IP3), activation of IP3-receptors, release of stored intracellular Ca^{2+}, and Ca^{2+} entry through plasma membrane channels. IP3-sensitive Ca^{2+}-store depletion activates plasma membrane cation channels (i.e., store-operated cation channels [SOCs] or Ca^{2+} release-activated channels [CRACs]) to cause Ca^{2+} influx into endothelial cells. Recent studies have identified members of Drosophila transient receptor potential (TRP) gene family of channels that encode functional SOCs in endothelial cells. These studies also suggest that the canonical TRPC homologue TRPC1 is the predominant isoform expressed in human vascular endothelial cells, and is the essential component of the SOC in this cell type. Further, evidence suggests that the inflammatory cytokine tumor necrosis factor-α can induce the expression of TRPC1 in human vascular endothelial cells signaling via the nuclear factor-κB pathway. Increased expression of TRPC1 augments Ca^{2+} influx via SOCs and potentiates the thrombin-induced increase in permeability in human vascular endothelial cells. Deletion of the canonical TRPC homologue in mouse, TRPC4, caused impairment in store-operated Ca^{2+} current and Ca^{2+}-store release-activated Ca^{2+} influx in aortic and lung endothelial cells. In TRPC4 knockout ($TRPC4^{-/-}$) mice, acetylcholine-induced endothelium-dependent smooth muscle relaxation was drastically reduced. In addition, $TRPC4^{-/-}$ mouse-lung endothelial cells exhibited lack of actin-stress fiber formation and cell retraction in response to thrombin activation of protease-activated receptor-1 (PAR-1) in endothelial cells. The increase in lung microvascular permeability in response to PAR-1 activation was inhibited in $TRPC4^{-/-}$ mice. These results indicate that endothelial TRP channels such as TRPC1 and TRPC4 play an important role in signaling agonist-induced increases in endothelial permeability.

Conference 9

TRP channels and other agonist-stimulated cation channels in the platelet

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Platelets play a central role in the development of arterial thrombosis and cardiovascular disease. An increase in cytosolic Ca^{2+} is a key event during platelet activation, thus platelet cation channels represent potentially important anti-thrombotic targets. However, the molecular identity and relative importance of ion channels in the platelet remains poorly understood due to the difficulty of conducting electrophysiological recordings in these tiny, fragile cell fragments. Recent work has highlighted how the primary megakaryocyte represents a *bona fide* surrogate for studies of platelet signalling (eg. Tolhurst *et al.* (2005). Blood **106**:1644-51). RT-PCR screening of all known transient receptor potential (TRP) channels in murine megakaryocytes detected messages for TRPC6, TRPC1, TRPM1, TRPM2 and TRPM7. Whole-cell patch clamp recordings demonstrated functional TRPM7, a constitutively active cation channel sensitive to intracellular Mg^{2+}, and TRPM2, an ADP-ribose-dependent cation channel activated by oxidative stress. The physiological agonist ADP stimulated inward cation currents whose properties are consistent with a major contribution by TRPC6, along with a role for store-operated CRAC channels. The latter are likely conducted by Orai1, which was detected by RT-PCR in the megakaryocyte. Secretagogues also evoked repetitive transient inward cation currents through release of ATP and autocrine activation of $P2X_1$ receptors. In human platelets, secondary activation of $P2X_1$ receptors was responsible for up to ≈80% of the peak Ca^{2+} increase generated by the primary agonist collagen. Thus, with the aid of megakaryocyte electrophysiological recordings, a picture is emerging for the role of different Ca^{2+} entry pathways in platelets exposed to a variety of stimuli.

Conference 10

The Mechanism Underlying Lipid Activation of TRP channels: A Link to TRP activation by Metabolic Stress

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We have discovered that anoxia rapidly and reversibly depolarizes the *Drosophila* photoreceptor cells and induces Ca^{2+} influx into these cells in the dark. We further found that openings of the light sensitive channels, which mediate these effects, can be mimicked by mitochondrial uncouplers or by depletion of ATP in photoreceptor cells, while the effects of illumination and all forms of metabolic stress were additive. Genetic elimination of both TRP and TRP-like (TRPL) channels prevented the effects of anoxia, mitochondrial uncouplers and depletion of ATP, thus demonstrating *in vivo* that the light activated TRP and TRPL channels are sensitive targets of metabolic stress**.** A clue as to the mechanism of anoxia action came from the studies of Hardie and colleagues who found that in the DAG kinase mutant (*rdgA*), in which DAG accumulates due to the lack of its phosphorylating enzyme, the TRP and TRPL channels are constitutively active. The constitutive activity of the Ca^{2+} permeable TRP and TRPL channels, presumably leads to a toxic increase in cellular Ca^{2+} followed by photoreceptor degeneration in the *rdgA* mutant. Anoxia most likely inhibits the phosphorylation of DAG by DAG kinase and mimicked the effect of the *rdgA* mutation. This model suggests that DAG, or its metabolites PUFAs are second messengers of excitation. Because lipids were found to activate or modulate several TRP channels (e.g. DAG activates TRPC2, TRPC3, TRPC6 and TRPC7; while PUFA activates *Drosophila* TRP and TRPL and mammalian TRPV3), we examined the possibility that at least some of the lipids effects arise from open channel block removal. We used the *Drosophila* TRPL channel to examine whether lipids indeed relieve divalent open channel block, and if so, what is the underlying mechanism. We found that lipids remove open channel block without depolarization for three types of ion channels: TRPL, NMDA and TRPV3. The interpretation of these experiments is based on the findings that application of lipids, which are known to change the lipid packing of the plasma membrane, removed open channel block from all these channels without depolarization. Membrane stretching by hyposomotic solutions, also removed divalent open channel block in a similar manner to membrane lipids modulation. Lipids action was also blocked by the GsMTx–4 tarantula toxin, a specific inhibitor of mechanosensitive channels, supporting the notion that removal of open channel block by lipids is due to changes of the plasma membrane lipid packing. The results suggest that lipids do not affect the TRPL channels as second messengers but rather as modifiers of the lipid packing and of lipid-channel interactions in a manner similar to the effects of membrane lipids on stretch activated channels. The above suggestion has an important implication on understanding the gating mechanism of the *Drosophila* TRP and TRPL channels by suggesting that hydrolysis of PIP_2 by PLC together with the ensuing production of DAG change the packing of lipids in the inner leaflet of the plasma membrane resulting in direct opening the TRP and TRPL channels.

Conference 11

Role of cardiovascular TRPC channels in adaptation to oxidative stress

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Cardiovascular functions are governed by complex Ca^{2+} signalling processes based on a wide array of Ca^{2+} handling molecules such as channel and pumps, which enable cardiovascular cells to respond adequately to stress situations including alterations in cellular redox balance. TRPC proteins represent key players within the Ca^{2+} signalling network of cardiovascular cells, have been suggested as redox sensors and are considered to form classical receptor-operated cation channels. Moreover, TRPCs may as well be involved in store-operated Ca^{2+} entry processes, that are essential for cardiovascular physiolgy. The exact molecular composition of native cardiovascular TRPC channels, specifically of channel complexes that trigger cellular responses to disease-causing stimuli or mediate adaptation of cells in stress situations, is still elusive. TRPC proteins, which contribute to such „reactive“ signalling pathways associated with cardiovascular pathophysiology appear as highly attractive targets for therapeutic intervention. Aspects of redox-sensing and adaptive/reactive responses mediated by TRPC channels will be exemplified and outlined for TRPC3, which is considered as a key player in cardiac remodelling and vascular pathophysiology.

Conference 12

Protein oxidation products as mediators of enzyme damage and Ca-ATPase inactivation

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The oxidative modification of proteins plays an important role in a wide range of pathological processes and aging. Proteins are modified by numerous oxidants including H_2O_2, peroxynitrite, singlet oxygen, and radicals. More recently, an additional class of biological oxidants has been identified, peptide and protein peroxides. The latter react selectively with protein cysteine residues. The sarco/endoplasmic reticulum Ca-ATPase (SERCA) is reversibly regulated through NO-dependent *S*-glutathiolation of specific cysteine residues. The irreversible oxidation of these cysteine residues could, therefore, impair NO-dependent muscle relaxation. Here, we show that specific protein-derived (amino acid) peroxides react selectively with some of the 22 reduced cysteine residues of SERCA1, including a peptide-containing Cys674 and Cys675, where Cys674 (in SERCA2) represents one of the targets for NO-dependent *S*-glutathiolation. Of the amino acid, peptide, and protein peroxides tested, those tryptophan and tyrosine showed the highest reactivity towards SERCA, while no oxidation was detected with H_2O_2 under similar experimental conditions. Peroxides from free tryptophan showed a significantly higher reactivity than those from N- and C-terminally blocked tryptophan. Quantitative HPLC-MS/MS analysis demonstrated that the highest reactivity was observed for Cys774 and Cys938, residues within the transmembrane domains of SERCA1. This unusual reactivity cannot be solely due to the hydrophobicity of the oxidant, as peroxides from DL-tryptophan shows higher reactivity than those from N-acetyl-tryptophan methyl ester. Our data demonstrate a potential role of peptide- and protein-derived peroxides as important mediators of oxidative stress in vivo, which may cause a selective oxidation of Cys residues leading to inactivation of membrane proteins.

Conference 13

In vivo roles of TRPC3 and TRPM2 in oxidative stress

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TRPM2 and TRPC3 are transient receptor potential (TRP) protein superfamily members which are activated by oxidative stress. Treatment of cells expressing TRPM2 with H_2O_2 enhances Ca^{2+} influx and susceptibility to death. We studied oxidative stress in TRPM2 and TRPC3 knockout mice. Increasing evidence support the role of oxidative stress in development of diabetes. Glucose homeostasis was examined in TRPM2 KO mice and wild type (WT) littermates fed a standard chow or high fat diet (HFD). On chow diet, glucose infusion rates (GINF) during hyperinsulinemic-euglycemic clamp increased slightly in TRPM2 KO mice, and insulin-stimulated whole body glucose turnover was significantly increased compared to WT. Cardiac glucose uptake was increased 20% in KO. Following HFD, WT mice developed insulin resistance, indicated by significant reductions in GINF and whole body glucose turnover. HFD-fed TRPM2 KO showed significantly less insulin resistance with higher GINF and whole body glucose turnover. Although diet-induced insulin resistance caused a 70% reduction in heart glucose uptake in WT mice, the hearts of TRPM2 KO mice were protected. This suggests an important role of TRPM2 in cardiac glucose metabolism and insulin resistance. TRPC3 is an

erythropoietin (Epo)-regulated Ca^{2+} channel. We examined erythropoiesis under normal and stress conditions in TRPC3 KO and WT mice. No differences in baseline hematocrits or reticulocytes were observed. TRPC3 KO and WT mice were injected with phenylhydrazine, which causes hemolytic anemia and is a model of oxidative stress. At day 5, hematocrits, reticulocytes, and spleen wt/body wt ratios were significantly lower in TRPC3 KO compared to WT. This suggests that the lower hematocrit in TRPC3 KO is the result of defective red cell production, which is compensated for in absence of erythroid stress. These studies show that TRPM2 and TRPC3 are functionally important in vivo.

Conference 14

Effects of TRPC1 gene-silencing in vascular smooth muscle cells

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Spacio-temporal changes of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) have critical roles in all cells. Receptor-operated elevation of $[Ca^{2+}]_i$ relies on both Ca^{2+} released from internal stores and influx of extracellular Ca^{2+} through plasma membrane ion channels. Canonical transient receptor potential (TRPC) ion channels are ubiquitously expressed and partly associated with store depletion and Ca^{2+} entry mechanisms. Based on the quantitative real time RT-PCR and Western blot analyses TRPC family members are differentially expressed in vasculature. Moreover, expression pattern of some TRPC members changes reciprocally in aging rat aorta. TRPC members are suggested to construct hetero-multimeric ion channels, some of which are candidates of store-operated Ca^{2+} (SOC) entry. Within this context, post-transcriptional gene silencing (PTGS) by RNA interference (RNAi) hold great promise to investigate the nature of the altered TRPC expression profile that may have potential impacts in different disease states. (Supported by The Scientific and Technological Research Council of Turkey [TUBITAK, SBAG-3033)

Conference 15

Ionovation compact: precise automated measurement of ion channel, transporter or pore activity

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Electrophysiological investigation is one of the central tools for studying pore forming proteins. In the past, standard technological approaches have primarily consisted of various alterations of the patch clamp technique of membranes and cells. Here, we introduce an alternative to conventional methods: The Ionovation Compact – a highly flexible bench top system based on the bilayer technique. The bilayer technique is a method to record electrical currents at the single channel level. The bilayer forms a gigaohm resistance between two saline-buffer filled chambers. After incorporation of pore forming proteins (ion channels, solute channels, carriers or pumps), protein mediated currents or membrane potentials can be recorded at high resolution. As an example, the electrical activity of the reconstituted mitochondrial translocase Tom40, measured with an Ionovation Compact, is demonstrated. With respect to flexibility, the bilayer technique is a cut above the traditional patch clamp technique. Worth mentioning, both sides of the membrane are easily accessible and ion channels and pores of all membrane systems of a cell can be investigated, including intracellular membranes. The Ionovation Compact supports the scientist by a fully automated instrument operation, i.e. bilayer production and validation, capacitance control of bilayer integrity (visual control of the bilayer also possible), perfusion system for both membrane sides. In addition, the bilayer technique can be combined with other established methods, i.e. electrical and optical single-molecule observations, like fluorescence measurements or Ca-imaging, are possible. With Tom40 incorporated into the bilayer, we show the simultaneous measurement of Ca^{2+} influx and electrical activity of the translocase.

Conference16

Cumulative measurement of oxidant-antioxidant system homeostasis

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Reactive oxygen species are produced in metabolic and physiological processes. The production rate increases in some situations such as inflammation. Additionally, various oxidant molecules are also taken from the outer environment. These hazardous molecules are removed from organism via enzymatic and nonenzymatic antioxidative mechanisms. Under certain conditions, the increase in oxidants and decrease in antioxidants cannot be prevented, and the oxidative/antioxidative balance shifts towards the oxidative status. Consequently, oxidative stress, which has been implicated in over 100 disorders, develops. Serum (or plasma) concentrations of different oxidant species can be measured in laboratories separately, but the measurements are time-consuming, labor-intensive

and costly and require complicated techniques. Since the measurement of different oxidant molecules separately is not practical and their oxidant effects are additive, the total oxidant status (TOS) of a sample is measured and this is named total peroxide (TP), serum oxidation activity (SOA), reactive oxygen metabolites (ROM) or some other synonyms. On the other hand, the status of antioxidants is similar to that of the oxidants. They are named as total antioxidant status (TAS), total antioxidant capacity (TAC), total antioxidant response (TAR), total antioxidant potential (TOAP) or some other synonyms. There are not yet accepted standardizations of used methods, calibrators and terms to evaluate oxidant and antioxidant situations. Some serious analytical errors are also appeared in some used methods. We developed three novel methods for cumulative evaluation of oxidant - antioxidant status and oxidative stress. The developed reliable and sensitive methods can be used to measure total oxidant status (TOS), total antioxidant status (TAS) and oxidative stress index (OSI).

Conference17

Melatonin Receptors in Humans: Biological Role and Clinical Relevance

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In addition to its antioxidative effects melatonin acts through specific membrane and nuclear receptors. To date, two G-protein coupled melatonin membrane receptors, MT_1 and MT_2 , have been cloned in mammals, while the newly purified MT_3 protein belongs to the family of quinone reductases. Screening studies have shown that various tissues of rodents express MT_1 and/or MT_2 melatonin receptors. In humans, melatonin receptors were also detected in several organs, including brain and retina, cardiovascular system, liver and gallbladder, intestine, bone, kidney, immune cells, adipocytes, prostate and breast epithelial cells, ovary/granulosa cells, myometrium, and skin. The role of melatonin in human physiology is still under investigation. There is growing evidence that melatonin is involved in the regulation of circadian rhythms and seasonal changes. Furthermore melatonin administration is followed by a decrease in core body temperature and an increase in distal skin temperature, leading to increased heat loss. Similar temperature changes can also be found at sleep onset suggesting a connection between melatonin mediated themoregulatory effects and sleep. The hypnotic effects of administered melatonin have been extensively documented and low nighttime melatonin levels are associated with some types of insomnia. Additional effects of exogenous melatonin in humans are for example: 1) suppression of LH secretion, 2) reduction of systolic and diastolic blood pressure and blood norepinephrine levels, 3) stimulation of T-helper cell activity and interleukin production, and 4) reduction of blood coagulation activity. Furthermore in vitro studies have shown that melatonin stimulates HCO_3^- secretion in human duodenal enterocytes, exerts oncostatic actions on human breast and prostate cancer cells, and decreases the expression of GLUT4 transporter in human adipocytes. Considering the multiple localizations of melatonin receptors in the human body it is very likely that many of the functions mentioned above are mediated through these receptors. However other mechanism pathways, especially the antioxidative functions of melatonin, are also involved. The clinical relevance of knowledge of human melatonin receptors may be threefold: i) physiologically based melatonin therapy in case of impaired melatonin production/secretion, ii) administration of melatonin in pharmacological doses for the treatment of various diseases, and iii) identification of mutations of the melatonin receptor gene in diseases which may potentially be associated with melatonin. Various diseases, such as for example coronary heart disease, sepsis, fibromyalgia, cancer, alcoholism, Alzheimer type dementia, and primary insomnia, are associated with impaired melatonin secretion. Future work will provide more information about the clinical relevance of these findings, especially in regard to the applicability of melatonin as a drug in various conditions.

Conference 18

Melatonin: Helping Cells Cope with Oxidative Disaster

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The intracellular environmental is a hostile one. Free radicals and related oxygen and nitrogen-based oxidizing agents persistently pulverize and damage molecules in the vicinity of where they are formed. The mithocondria especially are subjected to frequent and abundant oxidative abuse. The carnage that is left in the wake of these oxygen and nitrogen-related reactants is referred to as oxidative damage or oxidative stres. When mithocondrial electron transport complex inhibitors are used, e.g.,rotenone, 1-methyl-1-phenyl-1,2,3,6-tetrahydropyridine, 3-nitropropionic acid or cyanide, pandemonium breaks loose within mitochondria as electron leakage leads to the generation of massive amounts of free radicals and related toxicants. The resulting oxidative stres initiates a series of events that leads to cellular apoptosis. To alleviate mitochondrial destruction and the associated cellular implosion, the cell has at itsdisposal a variety of free radical scavengers and antioxidants. Among these are melatonin and its metabolites. While melatonin stimulates several antioxidative enzymes it, as well as its metabolites

(cyclic 3-hydroxymelatonin, N^1-acetyl-N^2-formyl-5-methoxykynuramine and N^1-acetyl-5-methoxykynuramine), likewise effectivelyneutralize free radicals. The resulting cascade of reactions greatlymagnifiesmelatonin's efficacy in reducing oxidative stres and apoptosis even in the presence of mitochondrial electron transport inhibitors. The actions of melatonin at the mitochondrial level are a consequence of melatonin and/or any of its metabolites. Thus, the molecular terrorism meted out by reactive oxygen and nitrogen species is held in check by melatonin and its derivatives

Conference 19

Melatonin a promising candidate for ischemic stroke treatment

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Neuroprotection therapies have made limited progress in recent years. Several compounds shown to be efficacious in animals were tested in humans in cost-expensive trials. Unfortunately none of these studies were able to demonstrate efficacy under clinical conditions in patients. In view of previous study failures, there is a clear need to re-evaluate our strategies in drug development. As such, it has been pointed out that (i) the window of opportunity of a candidate compound, (ii) its potential side effects, (iii) its ability to pass the blood-brain barrier, as well as (iv) its utility as an add-on treatment to thrombolytics should carefully be scrutinized in preparation for neuroprotection trials. We and others have previously shown that the neurohormone melatonin, which based on its small molecular size and high lipophilicity, possesses excellent blood-brain barrier permeability and with minimal side effects in human, reduces brain injury in animal models of ischemic stroke. Furthermore, it has been found to be particularly suitable as an add-on treatment to thrombolytic drugs. In this presentation, the actions of endogenously produced and exogenously administrated melatonin in reducing ischemic brain damage are presented and outlooks for future discussed.

Conference 20

Redox Regulation of Calcium-dependent T-cell activation

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Reactive oxygen species (ROS) play an important role in the regulation of the immune response. While ROS can promote the immune response, they can also inhibit immune cell activation. The reason for this duality is unclear. We mimicked physiological conditions and show that T helper (Th) cells could sense ROS produced by macrophages. Depending on its concentration, ROS promoted or inhibited Ca^{2+} signals in Th-cells, a paradox which could be explained by the activation of cation channels, inhibition of Ca^{2+} release-activated Ca^{2+} (CRAC) channels, and release of Ca^{2+} from internal stores. We found Ca^{2+} signaling in naïve primary human Th-cells to be much more susceptible to ROS than in effector Th-cells which was explained by their lower antioxidative potential. The differential ROS effects on Ca^{2+}-signals were correlated with differences in proliferation. At a physiologically relevant concentration of around 100 μM H_2O_2 proliferation of effector Th-cells was not inhibited, whereas naïve Th-cells were depleted. At lower concentrations of H_2O_2, proliferation of effector Th-cells was even enhanced, whereas both, effector and naïve Th-cells were depleted at higher ROS concentrations. Our results can explain the duality of "positive" and "negative" effects of ROS during the immune response.

Conference 21

Dual Roles of Antioxidant Enzymes in Oxidative Stress

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Selenium-dependent glutathione peroxidase-1 (GPX1) and copper,zinc-superoxide dismutase (SOD1) are considered to be two major intracellular antioxidant enzymes. Indeed, knockout of GPX1 or SOD1 renders mice susceptible to oxidative stress initiated by reactive oxygen species (ROS) generators including paraquat and diquat, while overexpression of these enzymes confers protections against such insult. In contrast, knockout of GPX1 protects mice against neurotoxicity and lethality induced by kainic acid. Hepatotoxcity of acetaminophen is greatly diminished in the SOD1 knockout or the GPX1 and SOD1 double knockout mice, but aggravated in the GPX1 overexpressing mice. These two drugs can induce in vivo formation of peroxynitrite, a potent reactive nitrogen species (RNS). Both in vitro and in vivo evidences indicate a catalytic role of SOD1, perhaps GPX1 as well, in the peroxynitrite-mediated protein nitration. Most striking, the GPX1 overexpressing mice develop hyperglycemia, hyperinsulinemia, insulin resistance, and obesity. These mice display increased beta cell mass, insulin synthesis, and glucose-stimulated insulin secretion. However, these "favor" changes eventually lead to chronic hyperinsulinemia, and the ultimate mechanism is due to

overly scavenging ROS by the overproduced GPX1 activity in islets. In conclusion, GPX1 and SOD1 seem to exert a contrasting role in coping with ROS and RNS in vivo, and transiently beneficial effects associated with elevated activities of these enzymes may result in long-term metabolic disorder (Supported by a NIH grant DK53018).

Conference22

Telomerase protects mitochondria and lowers oxidative stress in human fibroblasts

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Telomerase is a unique reverse transcriptase which mainly functions in the nucleus to maintain telomeres. Over-expression of hTERT, the catalytic subunit of human telomerase into normal somatic cells counteracts telomere shortening and replicative senescence.
There is also evidence for a telomere-independent survival function of telomerase. However, the underlying molecular mechanism is not well understood. Telomerase is excluded from the nucleus upon oxidative stress and co-localizes with mitochondria. We show that hTERT, the catalytic subunit of human telomerase, protects human fibroblasts against chronic mild oxidative stress where hTERT is reversibly excluded from the nucleus under oxidative stress in a dosage- and time-dependent manner.
We found that in hTERT-overexpressing cells mtDNA is protected, mitochondrial membrane potential (MMP) is increased and mitochondrial superoxide production and cell peroxide levels are decreased under normal conditions and increased oxidative stress. In addition, we found a decreased level of apoptosis in hTERT over-expressing fibroblasts after treatment with hydrogen peroxide and etoposide. We performed microarray analysis and characterised signalling pathways and the bioenergetic phenotype in order to reveal mechanisms for decreased oxidative stress levels in hTERT-immortalised fibroblasts. Many changes in gene expression that forms the retrograde response (a crosstalk between dysfunctional mitochondria and nucleus) during senescence.and stress of normal fibroblasts are found to be in the opposite direction in hTERT over-expressing cells. This includes as well changes of genes involved in calcium signalling.
Our data suggest that telomerase protects mitochondria from oxidative stress-induced dysfunction by lowering mtDNA damage, decreasing mitochondrial ROS production and changing metabolic signalling.
We propose protection of mitochondria under mild stress as a novel function of telomerase.

Oral Presentation 1

Structures within TRPM2 and TRPM8 channels that determine gating and ion selectivity.

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TRPM2 and TRPM8 are closely related and both activated by multiple mechanism including binding of specific ligands and temperature but they differ remarkebly in the chemical nature and site of action of the activators. TRPM2 is gated by intracellular ADP ribose (ADPR) binding to a C-terminal Nudix box. We have defined specific amino acids that are essential for ADPR gating and provide evidence that no enzymatic activity of the Nudix box is required. Activators of TRPM8 are menthol and icillin interacting with different binding sites, as revealed by mutants in which the icillin sensitivity is selectively lost. Analogs of menthol help to understand the specific requirements for gating of TRPM8 by menthol. The S5 and S6 regions of TRPM2 and TRPM8 directly communicate with the pore. We have identified specific structures within S6 that intimately interact with the pore to an extent that single amino acid exchanges reverse the charge selectivity of the pore (from cation to anion selective). Moreover, the gating process can be modified by subtle changes in the structure of S6. An N-terminal inactive splice variant of TRPM2 lacks a stretch of 21 amino acids containing calmodulin-binding as well as PxP motifs implicated for protein-protein interaction. However, none of these motifs requires loss of function of the splice variant. --- In conclusion, studies on the structurally similar but functionally divergent channels TRPM2 and TRPM8 allow to develop concepts about the mechanisms and intramolecular structures involved in the gating of TRP channels in response to activating ligands.

Oral Presentation 2

Age-related changes in TRPC1 and TRPC6 expression: Implications for altered vascular responsiveness

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This study investigates the possible effects of aging on TRPC expression that may have functional consequences in rat thoracic aorta. The expressions of TRPC1 and TRPC6 from smooth muscle and endothelial tissues of young (8-16 week-old) and old (64-80 week-old) rats were examined at mRNA and protein level by quantitative real-time PCR and western blot, respectively. Vascular distributions of TRPC proteins were analyzed by immunohistochemistry. In addition, acetycholine, cyclopiazonic acid concentration-response curves were obtained in intact tissues. Real Time PCR and western blot analyses showed that, TRPC1 is the dominant isoform among the TRPC members studied both in endothelial and aortic smooth muscle cells. TRPC1 protein expressions were lower in old rat aorta (P<0,05), whereas TRPC6 levels were drastically higher than that of young group (P<0,01). Furthermore, immunohistochemical data demonstrated spatial changes in TRPC6 protein expression within the smooth muscle layers, with increased detection in the adventitia and endothelium from aged rat aorta. These results demonstrate selective and marked changes in TRPC protein expression with aging. These age-dependent changes in TRPC expression pattern during aging may alter store-operated calcium channel formation both in endothelium and vascular smooth muscle, possibly contributing to endothelial dysfunction and potentiated alpha adrenoceptor-mediated contractions. Supported by The Scientific and Technological Research Council of Turkey (TUBITAK, SBAG-2735 to MT)

Oral Presentation 3

Effect of nifedipine and Y-27632 on non-M_2 receptor mediated *in vitro* contractions of urinary bladder in normocholesterolemic and hypercholesterolemic rats

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Membrane cholesterol alterations effect signal transduction

and cellular functions of the smooth muscle cells. Contractile response to M3 agonists in rat urinary bladder (UB) depends on the calcium influx from L-type calcium channels and rho-kinase activation. We investigated the effects of calcium channel blocker and rho-kinase inhibitor on carbachol induced contractions of the UB strips in the presence of M2 receptor and nitric oxide synthase blockers in normocholesterolemic and hypercholesterolemic rats. 250-300 gram adult male Sprague-Dawley rats fed with standard (C, n=9) or 4% cholesterol containing chow (HC, n=8) for four weeks were used. Serum lipid profiles and the tissue cholesterol levels were measured. The cumulative dose-contraction curves to carbachol in the presence of methochtramine (10^{-5}M) and L-NAME (10^{-4}M) were obtained. They were also recorded in the presence of L-type calcium channel blocker nifedipine and/or rho-kinase inhibitor Y27632. Data was analyzed statistically. Plasma cholesterol increased in HC group (C:94.3±5.3, HC:163.3±13.4 mg/dL, P<0.001), but the elevated tissue cholesterol level was not significant. (C:8.2±1.8, HC:12.2±1.41 µg/g protein). Carbachol-induced contractions depressed in the C group by 39%, 23%, 88% and in the HC group by %68, %22, %90 respectively, in response to nifedipine, Y27632 and nifedipin+Y27632. Nifedipine inhibited the contractile response in the HC group significantly, whereas the effect of rho-kinase was not different. These findings suggest that hypercholesterolemia has impact on L-type calcium channels and detrussor cell membranes. Prolonged hypercholesterolemia may increase tissue cholesterol and the share of calcium channels in the non-M2 receptor mediated contractions. These results should be supported by more advanced studies.

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Oral Presentation 4

Role of the antioxidants on the inactivation of melastatin-like transient receptor potential 2 (TRPM2) cation channel

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Reactive oxygen species (ROS) including superoxide anion and hydrogen peroxide (H_2O_2) act as subcellular messengers in such complex processes as mitogenic signal transduction and regulation of cell proliferation when they are generated excessively or when enzymatic and non-enzymatic antioxidant defense systems are impaired. Vitamin E is a lipophilic antioxidant that interferes with the chain reaction of ROS although vitamin C is a hydrophilic molecule that can scavenge several radicals, among them the hydroxyl radical.

Melastatin-like transient receptor potential 2 (TRPM2) channel is a redox sensitive Ca^{2+}-permeable cation channel that can be gated by H_2O_2 binding to the channel's enzymatic Nudix domain. Since the mechanisms that lead to TRPM2 action in response to H_2O_2 are not understood, we examined the effects of various antioxidants on H_2O_2-induced TRPM2 cation channel currents in transfected Chinese hamster ovary cells. In our recent studies, we chosen an intracellular Ca^{2+} concentration calculated to be in the range of 1 µM. H_2O_2 (10 mM) was added extracellularly to the bath chamber. With these conditions, we were able to evoke TRPM2 currents consistently with H_2O_2. We next tested whether the vitamins C and E or glutathione (GSH) would prevent or attenuate the induction of TRPM2 currents by H_2O_2 when applied extracellularly or intracellularly. The H_2O_2-induced gating of the TRPM2 channel was not prevented or reversed by vitamin E because H_2O_2 appears to activate TRPM2 by conversion to the hydroxyl radical in the intracellular space after crossing the plasma membrane. The idea was supported by the studies of different authors and they reported that co-treatment with membrane impermeable catalase completely blocked the H_2O_2- induced Ca^{2+} entry and cell death and they also reported that a nonselective radical scavenger, mannitol, prevented cation current by H_2O_2 in TRPM2-transfected HEK293 cells, suggesting that H_2O_2 acts by generation of free radicals in cell interior.

In conclusion, TRPM2 channels were constitutively activated by H_2O_2 although we could not detect any inhibitory effect of the antioxidants on H_2O_2-induced TRPM2 cation channel currents in CHO cells.

Experimental part of the study was performed in institute of Physiology, RWTH Aachen and the study was supported by Alexander von Humbolt foundation.

Oral Presentation 5

ClC Channels

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ClC- channels play important physiological roles in all known phyla, from bacteria over plants to man. In mammalians nine isoforms have been identified. They can be divided in two branches. ClC-0 – ClC-k are expressed in the plasma membranes, while ClC-3 – ClC-7 were

found in intracellular membranes. The channels expressed in the plasma membrane were characterized very well using electrophysiological methods like two electrode voltage clamp and the patch clamp technique, while little is known about the function and the properties of the intracellular vesicular ClC-channels.
The crystallization of two bacterial ClC-channels showed that the functional unit consists of dimers, with each monomer forming its own ion pore. That result proved electrophysiological results which were done several years before the first ion channel was crystallized. During the electrophysiological analysis of the bacterial isoforms reconstituted in artificial lipid bilayers, it came out that these isoforms rather function as electrogenic Cl^-/H^+ exchangers than as ion channels. The same was shown recently for ClC-4 and ClC-5. This finding could help to stop the controversial discussion about the biophysical properties of these isoforms.
So far only two auxiliary q-subunits are known for ClC-proteins. Barttin associates specifically with ClC-K channels, while Ostm1 binds to ClC-7. Barttin dramatically increases the surface expression and influences the biophysical properties of the ClC-K channels. As ClC-K channels are expressed in kidney and in the inner ear, mutated Barttin proteins lead to Bartter syndrome IV, a disease characterized by decreased renal salt reabsorption and deafness.

Oral Presentation 6

Ncf1 controlled production of reactive oxygen species is important for resistance to experimental autoimmune encephalomyelitis in rats

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We have earlier shown the importance of reactive oxidative species (ROS) for resistance to arthritis in rats and mice. This finding was made after the *Ncf1* gene, encoding the NADPH oxidase complex subunit Ncf1 (alias $p47^{phox}$), was found to be responsible for the quantitative trait locus Pia4 in rats (1, 2). Surprisingly, we found that low ROS production increased arthritis severity in rats. This finding was confirmed when a spontaneous mutation in mouse *Ncf1* leading to low ROS production was shown to result in similar phenotypes (3). A locus controlling severity of experimental autoimmune encephalomyelitis (EAE) in rats (Eae5) has been mapped to the same region as Pia4 (4-5), thus we wanted to investigate whether EAE in rats is determined by *Ncf1*. This was done by using congenic rats carrying the *Ncf1* allele from either the disease susceptible DA strain (low ROS production) or the resistant E3 strain (high ROS production) on an identical genetic background. We found that rats carrying the functional *Ncf1* allele were more protected from severe chronic EAE induced with spinal cord homogenate than littermate controls. In addition, we found that ROS inducing agents such as phytol, earlier shown to ameliorate arthritis in rats (6), could block development of disease if injected before onset and significantly ameliorated disease if injected in the acute phase. We conclude that sufficient ROS production is crucial for resistance to autoimmunity. This finding opens up a novel pathway that can be targeted therapeutically.

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Oral Presentation 7

A practical method to measure singlet oxygen generation: Enzyme Photo-inactivation Technique

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Singlet molecular oxygen ($^1O_2$) has been investigated for 30 years because of its relation to photosensitization reactions. $^1O_2$ is a major intermediate in photochemical reactions sensitized by photosensitizers in the presence of oxygen. $^1O_2$ is responsible for the molecular mechanism of photodynamic therapy which is used for the treatment of certain type of cancers and non-cancerous disorders. The production of $^1O_2$ involves four steps: (1) visible light absorption by the photosensitizer (2) formation of the photosensitizer triplet state (3) trapping of the photosensitizer by a molecular oxygen (4) energy transfer from photosensitizer triplet state to molecular oxygen. Then, $^1O_2$ will cause destructive reactions resulting cell death in the specific targets. The decay lifetime of $^1O_2$ is 0.2 μs in living cells. Therefore singlet oxygen quantum yield (Φ_Δ) is used to determine of $^1O_2$ generation. Φ_Δ is defined as the number of singlet oxygen molecules generated for each photon absorbed by a photosensitizer and measured by employing various techniques. In the enzyme photo-inactivation technique, Φ_Δ of photosensitizers are measured by using the photosensitized inactivation of lysozyme (LYS). Briefly, Φ_Δ is determined by measuring the rate of photochemical reaction mediated by $^1O_2$. For these calculations, we accept a hypothesis defined as LYS
inactivation rate is proportional to $^1O_2$ generation rate of photosensitizer. Also, all measurements of Φ_Δ are scaled to Φ_Δ of methylene blue and the values of Φ_Δ are determined. Enzyme photo-inactivation technique led to values of Φ_Δ in good agreement with other methods including detection of luminescence of $^1O_2$ at 1270 nm (direct method), photo-thermal methods, quantitative analysis of photo-oxidation reactions, and others. This technique is highly sensitive and reproducible, requiring only a light source, a wavelength selection device, and a spectrophotometer.

Oral Presentation 8

Influence of demethoxyviridine and [1--hydroxy-demethoxyviridine] on hepatocyte Bcl-2 expression and antioxidant defence system with diethylnitrosamine and 2-acetyl-aminofluorene treated rats

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Diethylnitrosamine cause a wide range of tumors in all animal species, these compounds are considered to be an effective health hazard to human. Diethylnitrosamine initiates preneoplastic liver lesions while 2-acetylaminflourine promotes it in hepatocyte. They affect the lipid peroxidation and antioxidant defence system. The objective of this study was to determine the protective antioxidant effects of fungal metabolites; demethoxyviridine and 1-á-hydroxy-demethoxyviridine in hemolysate of two month-old Spraque-Dawley rats treated with diethylnitrosamine and 2-acetylaminflourine and Bcl-2 expression of hepatocytes. Rats in a 35 day study were divided into 10 groups of eight rats. The five of them were designed for control administrations. Another groups included two given only the inducing agent diethylnitrosamine (175 mg/kg) and the promotant 2-acetylaminflourine (20 mg/kg), and three groups that included combination of them and either demethoxyviridine (1.5 mg/kg) and same amount 1-á-hydroxy-demethoxyviridine as protectants. Bcl-2 oncoprotein expression was detected by immunohistochemically. Hemolysate were prepared to investigation of malondialdehyde level, superoxide dismutase, glutathione peroxidase, and catalase activity. The results showed that demethoxyviridine and 1-á-hydroxy-demethoxyviridine-treated rats increased in antioxidant enzyme activities in diethylnitrosamine or 2-acetylaminflourine and their combination with the exception of malondialdehyde level and decreased Bcl-2 expression in hepatocytes.

Oral Presentation 9

The Effect Of Mesna, Erdosteine And Caffeic Acid Phenethyl Ester On Oxidative Liver Injury In Rats

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The aim of this study was to investigate the possible rol of SOD, CAD and MDA in pathogenesis of cyclophosphamide (CP)-induced hepatotoxicity and to determine whether there is a putative effect of mesna, erdostein and CAPE on CP-induced hepatotoxicity in rats. A total of 50 adult Wistar male rats were divided into five experimental groups. Group I, control group; group II, CP-treated group; group III, CP+mesna-treated group; group IV, CP+Erdosteine- treated group; group V, CP+CAPE-treated group. CP was administered to CP,

CP+mesna, CP+erdosteine, and CP+CAPE groups intraperitoneally (i.p) with a single dose of 100 mg/kg on the second day of experiment. Mesna was administered to CP+mesna group i.p. with a total dose of 64.5 mg/kg divided into three equal parts 20 minutes before, 4 and 8 hours after the CP administration. Erdosteine was administered to CP+erdosteine group i.p. with a dose of 10µmol/kg 48, 24 hours and 20 minutes before CP administration. CAPE was administered to CP+CAPE group i.p. with a dose of 10µmol/kg 48, 24 hours and 20 minutes before CP administration. The activities of SOD and CAT, and levels of MDA were studied in the liver tissues of rats. In the liver tissue, the activities of SOD and CAT were decreased in CP group in comparison with control group. Erdosteine and CAPE treatment with CP increased SOD activity in the liver tissues of rats significantly in comparison with CP group. Mesna, erdosteine and CAPE treatment with CP increased CAT activity in the liver tissues of rats significantly in comparison with CP group. The levels of MDA were higher in CP group than the control group. Mesna, erdosteine and CAPE administration with CP caused a significant decrease in MDA level when compared with CP group. These results reveal that CP increases oxidative stress in the rat liver. Mesna, erdosteine and CAPE have a preventive effect on the oxidative stress via its antioxidant capacity. Erdosteine and CAPE seems to have relatively more preventive effect according to mesna.

Oral Presentation10

The antioxidant effect of Capparis Ovata on thalassemia major patients

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Introduction: The non-transferrin-bound iron (NTBI) increases in patients with thalassemia because of regular transfusion and increased iron absorption. NTBI and autoxidation of globulin chains leads to production of highly reactive oxygen radicals and cause oxidative stress. Antioxidants are used for support treatment at thalassemia. The antioxidant, antihepatotoxic, anti-inflammatuar and hipolipedimic effect of capari is known. The aim of this study is to investigate the antioxidant effects of capparis ovata.

Material and Method: A total of 40 thalassemia patient as study and control group was involved. We have given capparis marmelade with the breakfast of whom are <10 years a dessert-spoon (12.5 gr) and >10 years a soup-spoon (25 gr) for 6 months to study group. We measured hemogram, biochemical parameters and ferritin for every month and antioxidant status at the beginning and at the end of the study.

Results: We obtain a much more decrease in MDA concentration in the cappari given group (p=0.02). A significant decrease in SOD concentration at both of the groups was obtained but there was no statistically significant difference between the groups. (p=0.146) A minimal increase in Gpx (p=0.511) and not statically significant decrease in catalase concentration was found.(p= 0.838) Further more in the capparis group a significant decrease in liver function tests was occured (AST p= 0.05, ALT p= 0.01).

Discussion: The increase in MDA levels is the best sample of oxidative stres in thalassemic patients. In the present study MDA levels were high at the beginning both for control and study group, after using caparis for 6 month MDA levels decreased significiantly. In conclusion, capparis may be useful for decreasing the damage of oxidative stres and hepatotoxicity in thalassemic patients.

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Poster 1

Investigation of the mechanism of the lanthanum inhibition on calcium signaling in cultured cell types

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The inhibition of La^{3+} on Ca^{2+} signal via GPCRs and IP_3 is an unexplained effect of La^{3+}, which the mechanism is investigated. Cultured cells endogenously expressing or stably transfected with different GPCRs are used, and changes in $[Ca^{2+}]_i$ and $[IP_3]$ are tracked utilizing fluo-3 Ca^{2+} indicator or GFP-$PH_{PLC\delta 1C}$, in Ca^{2+} free bath solution, respectively. In all experiments, LEICA SP5 confocal microscope is used.

In RAT-$1_{\alpha 1b}$ cells, where α1b-adrenergic receptor is stably expressed, La^{3+} inhibits PE induced Ca^{2+} response via α1b-adrenergic receptors, and this inhibition is observed even when the agonist concentration is over the maximal dose. In HEK-293 cells where M_3 muscarinic receptor is endogenously expresed, La^{3+} did not have any inhibitory effect on ACh induced Ca^{2+} signal via M3 receptors. In LTK-8 cells, where M3 receptor is stably exspressed, La^{3+} also did not exert any inhibition. IP_3 kinetic is also not affected by La^{3+}. Similar results were obtained in RAT-$1_{\alpha 1b}$ cells, where La^{3+} also failed to inhibit ACh induced Ca^{2+} signal, when M_3 receptors are stably expressed. The dose-response graph clearly demonstrates that M_3 receptor is not affected by the presence of La^{3+}.

The outcome of these experiments is that La^{3+} do not inhibit Ca^{2+} signal via M_3 receptor, regardless of the cell type. The inhibitory effect of La^{3+} on Ca^{2+} signal is related with the receptor type.

Poster 2

Mechanisms of relaxing effect of hydrogen peroxide on bovine coronary artery smooth muscle.

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Hydrogen peroxide (H2O2), a reactive oxygen specie, is reported to play roles in the regulation of vascular smooth muscle tone. In present study, effect of H2O2 on bovine coronary artery was investigated. Experiments were done on 2-3 mm width and 10-15 mm long coronary artery strips in the isolated organ baths. After pre-contracting arteries with U46619, H2O2 (10^{-7} -10^{-}2 M) was added to organ baths cumilatively.This procedure was repeated on arterial strips incubated with tetraethylammonium (an inhibitor of Ca^{+2}-activated K^+ channels), charybdotoksin (an inhibitor of Ca^{+2}-activated K^+ and voltage sensitive K^+ channels), glibenclamide (an inhibitor of ATP-sensitive K^+ channels), uvabain (an inhibitor of Na^+ - K^+ ATPase), indomethacin (an inhibitor of cycloxygenase), L-NAME (an inhibitor of nitric oxide synthase). Each arterial strip was incubated with only one of these agents. Responses of arterial strips were recorded by a polygraph. H2O2 relaxed arterial strips in concentration dependent manner (% 90,8 4 of U46619 contractions). Removal of endothelium did not affect the relaxations. Glibenclamide, uvabain, indomethacin, L-NAME inhibited the the relaxations (% 54,5 2; %39.8 3; %52.9 3 and %41.4 3 of U46619 contractions respectively). Other agents did not affect the relaxations. According to these results, ATP - sensitive K+ channels and Na^+ -K^+ ATPase have roles in H2O2 relaxations in bovine coronary artery. Because activation of these 2 systems cause hyperpolarisation, H2O2 may relax the coronary artery by hyperpolarising the vascular smooth muscle. On the other hand, probably prostacycline (PGI2) and nitric oxide (NO) contribute the relaxations.

Poster 3

Calcium release from rat liver microsomes by using a member of *Thapsia* genus, Thapsigargicin

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As Ca^{2+} is the main requirements for the specialized functions of eukaryotic cells and many prokaryotes in their medium, the network of Ca^{2+} channels and transporters controls the intracellular Ca^{2+} concentrations ($[Ca^{2+}]i$) and the concentration of Ca^{2+} in the intracellular stores (ER; endoplasmic reticulum and SR; sarcoplasmic reticulum). Ca^{2+}-ATPase transporters are found in the plasma membrane (PMCA), in the ER/SR (SERCA), in the golgi and in the nuclear envelope. They export Ca^{2+} to the ER/SR lumen or to the extracellular spaces.

In order to examine the effect of TGC (Thapsigargicin, SERCA ATPase inhibitor and a tumour promoter) on intracellular Ca^{2+} movements, microsomes (rat liver endoplasmic reticulum subcellular fractions) were employed in this work. Spectrofluorimeter was routinely used in experiments for the measurements of Ca^{2+} movements and Fluo-3 studies were completed to follow Ca^{2+} release in microsomes. While the main intention of this work was to elucidate the effects of TGC in releasing Ca^{2+} from the intracellular Ca^{2+} stores, the outcomes were also found as significant for the comparison with another tumour promoter called TG (Thapsigargin). The results indicated that TGC has the ability to increase the intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) by means of discharging the intracellular Ca^{2+} stores. Therefore, like TG, TGC causes a drastic and specific inhibition of the ER Ca^{2+}-ATPase.

Poster 4

Ca^{2+} Movements in Digitonin-permeabilized L1210 Cells are effected by members of complex guaianolide family, Thapsigargin and Thapsigargicin

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In this study, the effect of thapsigargicin (TGC, a tumour promoter) on intracellular Ca^{2+} homeostasis has been argued to discover its role as a tool for the regulation of Ca^{2+} and to unravel the molecular mechanism behind it. In order to examine this situation, Ca^{2+} movements measured with spectrofluorimeter by using L1210 mouse lymphoma cells. During experiments with intact and digitonin-permebiliazed cells, Fura-2 and Fluo-3 studies were completed respectively, to follow up Ca^{2+} releases from these cells. The primary intention of this work was to explain and compare the effects of TGC in intact and digitonin-permeabilized L1210 cells with that of TG (Thapsigargin), qualitatively. The results indicated that, like TG, TGC has the potential of discharging intracellular Ca^{2+} stores, increasing the concentration of intracellular free Ca^{2+} ($[Ca^{2+}]_i$), and conduced a strong and specific inhibition of the endoplasmic reticulum Ca^{2+}-ATPase. In a further study, by using TGC alone, it would appear that the growth of L1210 mouse lymphoma cells have been effected in different manner with various concentrations of TGC. While the complete inhibition can be seen at 16 nM of TGC, inhibition of growth was very small at 0.16 and 1.6 nM of TGC, respectively. However, the growth inhibition by TGC was at least partially reversed by arachidonate, as has been seen for other cells with TG.

Poster 5

Calcium Signaling, Examined as an Integrated System

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Intracellular calcium (Ca^{2+}) signaling is a complex phenomenon, depends non-linearly to many different elements participating in it. In this study, all these elements are examined considering their roles forming a system. $[Ca^{2+}]$ is tracked with fluo-3 fluorescent Ca^{2+} indicator, while changes in $[IP_3]$ are determined with GFP-PH-PLCdelta chimeric protein, on confocal microscope. Cyclopiazonic Acid (CPA) is used to inhibit SERCA, and to block PMCA, lanthanum (La^{3+}) is used. Experiments in LTK-8 cells demonstrated that the ceasing of Ca^{2+} signal does not necessarily require the $[IP_3]$ to decrease, and also increments in $[IP_3]$ result in quantal Ca^{2+} release from ER. PMCA inhibition leads to an elongated time course of Ca^{2+} signal, and additionally, provides a positive feedback to quantal Ca^{2+} release, favoring the Ca^{2+} reuptake by SERCA. Intracellular Ca^{2+} oscillations are observed when the stimulus is weak, however; functional SERCA is observed to be required also for oscillatory behavior. An interesting observation was that SERCA inhibition after intracellular $[Ca^{2+}]$ increase promoted by a low stimulus resulted in a temporary interruption in the Ca^{2+} signal, which could be considered as a role of SERCA in regulating the $[Ca^{2+}]$ in the vicinity of IP_3R Ca^{2+} release channels. Summing up all these data, a minimal mathematical model, considering all these elements as an integrated system, might be implemented, which will enhance the understanding of Ca^{2+} signaling.

Poster 6

The role of Ins(1,4,5)P_3 and plasma membrane Ca^{2+} ATPase on quantal calcium release mediated by Ins(1,4,5)P_3 receptor

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After the agonist stimulation, activation of Ins (1, 4, 5) *P3* Receptor causes a graded (quantal) Ca^{2+} release from

ER. Low concentrations cause a few fold increase in the $[Ca^{2+}]_c$. Despite the continuation of agonist stimulation, this increase ceases after a while and $[Ca^{2+}]_c$ returns to its basal levels. Increasing the agonist concentration only induce a new Ca2+ release. Presence of some positive feed-back mechanisms like CICR have complicated the understanding of quantal release phenomenon. In this study we have stable transfected M3 (Muscarinic) Receptor to the LTK-8 cells.Cells which were incubated with Fluo-3 AM stimulated by acetylcholine, and changes in florescent intensity was detected by a confocal microscope. Also GFP-PHD was transiently transfected for the dynamic IP3 measurements in intact cells. Increments of IP3 in cytoplasm have been monitored again with confocal microscope with the help of GFP-PHD translocation to cytoplasm after the receptor stimulation. In our experiments during the low dose agonist stimulation the amount of IP_3 remained constant in cytoplasm. Increasing the agonist concentration led to a step-wise IP_3 increase. Therefore this will provide evidence that the stages after the IP_3 formation contributes to quantal release. We also investigated the role of PMCA in quantal calcium release. PMCA blocker La^{3+} (1mM) was added onto the cells before the acetylcholine stimulations and the quantal responds were compared between with and without La^{3+} application. La^{3+} has a noticeably effect either on removal kinetic of Ca^{2+} after the submaximal dose of acetylcholine (0.5 mM) or increasing the release after the maximal dose (100mM).

Poster 7

Hyperforin activates TRPC6 channels

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Hyperforin, a bicyclic polyprenylated acylphloroglucinol derivative, is the main active principle of St. John's wort extract responsible for its antidepressive profile. Hyperforin inhibits the neuronal serotonin and norepinephrine uptake comparable to synthetic antidepressants. In contrast to synthetic antidepressants directly blocking neuronal amine uptake, hyperforin increases synaptic serotonin and norepinephrine concentrations by an indirect and yet unknown mechanism. Our attempts to identify the molecular target of hyperforin resulted in the identification of TRPC6. Hyperforin induced sodium and calcium entry as well as currents in TRPC6-expressing cells. Sodium currents and the subsequent breakdown of the membrane sodium gradients may be the rationale for the inhibition of neuronal amine uptake. The hyperforin-induced cation entry was highly specific and related to TRPC6 and was suppressed in cells expressing a dominant negative mutant of TRPC6, whereas phylogenetically related channels, i.e. TRPC3 remained unaffected. Furthermore, hyperforin induces neuronal axonal sprouting like NGF in a TRPC6-dependent manner. These findings support the role of TRPC channels in neurite extension and identify hyperforin as the first selective pharmacological tool to study TRPC6 function. Hyperforin integrates inhibition of neurotransmitter uptake and neurotrophic property by specific activation of TRPC6 and represents an interesting lead-structure for a new class of antidepressants.

Poster 8

Elevated mitochondrial ROS blocks early cardiomyocyte differentiation through interference with Ca^{2+} signaling

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The development of cardiomyocytes from murine embryonic stem cells was monitored using a transgenic line where eGFP was expressed under control of the α-myosin heavy chain promoter. Cardiomyogenesis was unaffected by inhibition of complex IV of the electron transport chain with KCN (1mM), suggesting that anearobic ATP production is sufficient. However, heart cell development was almost completely blocked by inhibiting complex III with antimycin A (AA, 25nM). AA treatment results in production of mitochondrial reactive oxygen species (ROS) which was measured with MitoSOX Red. When the superoxide dismutase mimetic TEMPO (0.1mM) was applied to scavenge the AA-induced ROS production heart cell development could be partially restored. Interestingly AA incubation decreased cytosolic ROS levels, measured by DCF.
These findings suggest that increased mitochondrial ROS levels inhibit cardiomyogenesis and that subcellular localization of ROS is relevant.
Spontaneous Ca^{2+} spiking, known to be important for cardiac differentiation, was determined using spontaneously beating cardiomyocytes from mouse embryos (E9.5-11.5). The spiking rate was significantly lowered by AA (250nM, 42±6%, n=28) whereas subsequent addition of TEMPO

(0.5mM) partially restored spiking rate (76±10%, n=13) in 46% of the cells.
To facilitate Ca^{2+} spiking in AA treated stem cells we added the Ca^{2+} ionophore ionomycin (10µM for 2h at day 4). This partially restored cardiac differentiation, underlining the apparent involvement of Ca^{2+}-signaling. We conclude that AA arrests cardiac differentiation in pluripotent stem cell cultures by elevating mitochondrial but not cytosolic ROS levels and subsequently changing cytosolic Ca^{2+} signals.

Poster 9

Specific TRPC6 channel activation, a novel approach to stimulate keratinocyte differentiation.

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The protective epithelial barrier in our skin undergoes constant regulation, whereby the exact balance between differentiation and proliferation of keratinocytes plays a crucial role. Ca^{2+} influx is essential for this process presumably mediated by different transient receptor potential (TRP) channels. However, investigating their individual role in detail was hampered by the lack of specific stimulators or inhibitors. Since we have recently identified hyperforin as a specific TRPC6 activator, we investigated in the present study the contribution of TRPC6 to keratinocyte differentiation. Like the endogenous differentiation stimulus high extracellular Ca^{2+} concentration ($[Ca^{2+}]_{ex}$), hyperforin triggers differentiation in HaCaT cells and in primary cultures of human keratinocytes by inducing Ca^{2+} influx via TRPC6 channels. Hyperforin increases the mRNA levels of differentiation marker proteins such as Keratin 1, Keratin 10, Involucrin and Transglutaminase 1. Knocking down TRPC6 with siRNA technique and transfection with a dominant negative TRPC6 mutant prevents the induction of high $[Ca^{2+}]_{ex}$ - and hyperforin-induced differentiation. The high $[Ca^{2+}]_{ex}$- and hyperforin-induced Ca^{2+} influx in TRPC6 inactivated cells is significantly lower than in untransfected cells. As a result, expression of differentiation markers is reduced in TRPC6 down knocked keratinocytes. The present study provides evidence for the fundamental role of TRPC6 in the regulation of keratinocyte differentiation. Therefore, TRPC6 activation by hyperforin may represent a new innovative therapeutic strategy in skin disorders characterized by altered keratinocyte differentiation, such as atopic dermatitis and psoriasis.

Poster 10

Calcium dynamics

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The flow of calcium ions into the dendritic spines through the N-methyl-D-aspartate (NMDA) channels is believed to be the primary trigger for various forms of synaptic plasticity. In this study, how synaptic transmission was generated in the neuron and transmissions of calcium ions through the NMDA channels in synaptic transmission have been examined. Mathematical equations of calcium entrance and exit have been studied by using Markov Model due to the stochastic nature of synaptic transmission. We calculated analytically the calcium dynamics by pairs of presynaptic and postsynaptic spikes under different conditions and the new solutions have been compared with the known results.

Poster 11

The effect of 50 Hz electromagnetic field exposure on myocardial ion channels

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Objective: A lot of studies have been done about effects of extremely low-frequency electromagnetic fields (0-300Hz, ELF-EMF) on ion channels in different type of cells. Some of this studies have shown that EMF can effect ion channels, but others haven't corrected their results. In this study, we investigated effects of 50 Hz EMF exposure on myocardial ion channels.
Materials and Methods: Ethical approval was obtained from SDU Research Ethics Committee. In the study, we planned to use electrocardiogram (ECG) datas as the index

of myocardial ion channels activities. Twenty male Wistar Albino rats of 270-300 grams each, were divided as EMF group(n=10) and control(n=10) group. Helmholtz coils were used as EMF setup. Magnetic field intensity in between coil pair was conditioned to 1mT (1 milli Tesla) by a 50 Hz alternative power supply. A PVC plaque which can fit into coils easily, and plastic handcuffs to fix rats on this plaque were prepared. Rats were anesthetized with ketamine (10 mg/kg) and xylazine (10 mg/kg) injected intraperitoneally then they fixed on the PVC plaque and placed into setup. After 20 minutes from injections, we generated EMF in coils in EMF group and ECG datas were recorded for 1 minute. Same procedure was executed for the control group but EMF weren't generated while ECG recording. All QRS and T wave times, QRS and T amplitudes and QT intervals were acquisted in ECG datas by using Chart Pro software, and average values of this parameters were finded out for each rat. Results were analyzed with Mann-Whitney U test and the significant level was accepted as $P<0.05$.

Results

	EMF	Control	P Value
QRS time (s)	0,03293 ± 0,002395	0,03303 ± 0,000806	0,4649
QRS amplitude (mV)	268,5570 ± 23,0913	261,3513 ± 28,0005	0,6069
T time (s)	0,052179 ± 0,005342	0,053449 ± 0,014231	0,4064
T amplitude (mV)	207,6612 ± 37,3651	199,4904 ± 16,4209	0,6098
QT interval (s)	0,08469 ± 0,004399	0,08662 ± 0,014015	0,3519

Conclusion: ECG wave forms consist of total action potential of the myocardial cells. Myocardial cell action potantials can be deciphered by analyzing ECG. Ion channels which produce action potential in the ventricular muscle cell are fast Na channels, slow Na-Ca channels and K channels. Total activity durations of these channels correspond to QT interval. QRS wave is related activities of fast Na channels and slow Na-Ca channels, T wave is mainly related activities of K channels. There were no significant changes in all parameters which are obtained in this experiment. It shows that 50Hz, 1mT EMF exposure does not effect myocardial ion channels. Previous studies didn't agree concerning effects of EMF on ion channels and different results have been suggested. According to these studies, ion channels activities can be increased or decreased or not influenced in EMF exposure. That may be related dose and duration of EMF, or compensation of its biological effects by body systems. We think that these questions about effects of EMF will be answered after upcoming studies in cell levels.

Poster 12

Effects of telmisartan on mechanical responses of heart papillary muscle in rats with streptozotocin-induced diabetes mellitus

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The purpose of this study was investigated the effect of telmisartan (5.10^{-5}M), on the mechanical responses of the diabetic rat papillary muscle. In the study was used diabetic rats (8 weeks after STZ treatment) with streptozotocin-induced (45 mg kg^{-1} i.v.) and non-diabetic control rats. The contraction curves of the isolated heart papillary muscle, were recorded. We found: 1) The muscle twitch tension (P_0) were significantly smaller in the diabetic rats than in the controls. 2) Time-to-peak and half-relaxation time values were significantly longer in diabetic rats than in controls. 3) Significant differences were found in the twitch tension amplitude, the contraction rate, and the relaxation rate of electrically stimulated muscle between control and diabetic rats. 4) Telmisartan was surprisingly increased the P_o in control (C) and diabetic (D) group. 5) There was significant difference between the D and D+Telmisartan groups for time-to-peak tension and the half-relaxation time. However, the relaxation rate was also seen significant increas at telmisartan bath media. Our data suggest that the beneficial effects of telmisartan on the mechanical responses of the diabetic rat papillary muscle appear to be due to the improved. The improve effect in the diabetic group is possibly related to effects of telmisartan on components of the Ca^{2+} handling systems (increasing,of sarcolemmal Ca^{2+}-ATPase, of Na^{+} -Ca^{2+} exchanger, of L-type calcium current, of ryanodine-sensitive Ca^{2+} channels as well as increased cross-bridge cycle rate).

Poster 13

Effects of Topiramate and Vitamin E on Calcium Levels and Microsomes Ca^{2+}-ATPase Activities in Brain of Pentylenetetrazol-Epileptic Rats

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Ca^{2+}-ATPase is membrane bound enzymes and play a pivotal role in the homeostasis of Na^{+}, K^{+} and Ca^{2+} in cells. Evidence is now emerging that certain epilepsies may be a family of channelopathies with defects involving mutations in the Na^{+}, K^{+}, or Ca^{2+} channels whose activities are related to their voltage dependent conditions, or defects in the membrane- bound enzymes Na^{+} K^{+} ATPase and Ca^{2+}-ATPase that regulate the transport of ions across the cell membrane. Decreases in extracellular Ca^{2+} have been recorded in during the seizure. The aim of this study was to investigate the brain cortex calcium and microsomes Ca^{2+}-ATPase activity in rats induced epilepsy by pentylenetetrazol. Epileptic rats showed a significant decrease in brain cortex
Ca^{2+}-ATPase activity.
Forty male Wistar rats were randomly divided into five equal groups. First group was used as control and second group received a single dose of PTZ. Fifty and 100 mg/kg TPM each day were intragastrically administrated to rats constituting third and forth groups for seven days, respectively. Intragastric 50 mg TPM (each day of six days) and intraperitoneal vitamin E (150 mg/kg over day and three times) combination were given to animals in fifth group before single dose PTZ administration. Brain samples were taken at 2 hrs of PTZ administration. Tissue calcium levels were analyzed with atomic absorption spectrophotometer and Ca^{2+}-ATPase activity was measured spectrophotometrically.
Ca^{2+}-ATPase activities were lower in PTZ group than in control although Ca^{2+}- its activities increased in Topiramate supplemented group. Brain calcium levels were lower in PTZ group than in control although there is no difference between control and Topiramate and vitamin E administrated groups. Our results support the hypothesis that decreased Ca^{2+}-ATPase activities following induction of seizures with PTZ implantations. Topiramate and vitamin E treatments caused increase in the activity of the enzyme.
The study was supported by Süleyman Demirel Üniversitesi Bilimsel Araştırma Projeleri (Project number is TU-1462).

Poster 14

Investigation the effect of cinnamon protein glycosylation, Na^{+}-K^{+} ATPase, Ca^{+2} ATPase activities and lipid peroxidation levels in human erythrocytes which exposed to high glucose concentration (in vitro)

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In this study, the effect of cinnamon on protein glycosylation, Na^{+}-K^{+} ATPase, Ca^{+2} ATPase activities and lipid peroxidation levels in human erythrocytes which exposed to high glucose concentration in vitro is investigated. The blood samples obtained from healty individuals exposed to normal glucose and high glucose concentrations and then incubated with cinnamon at different concentrations. The samples which exposed to normal glucose concentration only, is used as a control group. In erythrocyte samples which exposed to high glucose concentration, Na^{+}-K^{+} ATPase, Ca^{+2} ATPase activities are found lower than control group (normal glucose concentration), and the differences between these two groups are statistically significant ($p<0.001$). The groups which exposed to cinnamon, the activities of these two membrane enzymes are increased statistically due to the increase of cinnamon concentrations. MDA and HbA_{1c} levels are increased more in high glucose group than normal glucose group. And both MDA and HbA_{1c} levels are decreased proportionally with the increase of cinnamon concentration As a result, and cinnamon increase the activities of Na^{+}-K^{+} ATPase and Ca^{+2} ATPase and decrease the level of lipid peroxidation in high glucose concentration in erythrocytes, so do in normal glucose concentrations. It is concluded that the effects of cinnamon to these parametres have a special importance on diabetes mellitus, a disease known commonly all over the world, which is characterized with its high blood glucose level.

Poster 15

Investigation the effect of capsaicin protein glycosylation, Ca^{+2} ATPase activities and lipid peroxidation levels in human erythrocytes which exposed to high glucose concentration (in vitro)

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In this study, the effect of capsaicin on protein glycosylation, Ca^{+2} ATPase activity, and lipid peroxidation level in human erythrocytes which exposed to high glucose concentration in vitro is investigated. The blood samples obtained from healty individuals exposed to normal glucose and high glucose concentrations and then incubated with capsaicin at different concentrations. The samples which exposed to normal glucose only, is used as a control group. In erythrocyte samples which exposed to high glucose concentration, Ca^{+2} ATPase activity are found lower than

control group (normal glucose concentration), and the differences between these two groups are statistically significant ($p<0.001$). In the group which exposed to capsaicin, the activity of the membrane enzyme is increased statistically due to the increase of capsaicin concentrations. MDA and HbA_{1c} levels are increased more in high glucose group than normal glucose group. And both MDA and HbA_{1c} levels are decreased proportionally with the increase of capsaicin concentration. As a result, capsaicin increased the activity of Ca^{+2} ATPase and decreased the level of lipid peroxidation in high glucose concentration in erythrocytes, so do in normal glucose concentrations. It is concluded that the effect of capsaicin to these parameters have a special importance on diabetes mellitus, a disease known commonly all over the world, which is characterized with its high blood glucose level.

Poster 16

Biophysical properties of octopus neurons of the cat cochlear nucleus: an in vitro study

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Cochlear nucleus is the first nucleus of the auditory pathway. The biophysical properties of the neuronal types in the ventral cochlear nucleus of mice have been well-characterized (Oertel et al. J. Com. Neurol, 295,136-154,1990). However, mice have high-frequency hearing only, thus mice can not be a good model for human that can hear sounds of frequencies between 20-20.000 Hz. Therefore, how auditory signals is processed in cochlear nucleus of human can be better understood by studying neurons in cochlear nucleus of the animals of both low and high-frequency hearing. For that reason in the current study, biophysical properties of octopus neurons in the cochlear nucleus of 14-day old 3 kittens were studied *in vitro* using patch clamp technique.

Octopus neurons, located in the ventral part of the cochlear nucleus, a region that is defined by a clear border in the caudal and dorsal part of the posterio-ventral cochlear nucleus (PVCN), were defined as having morphologically and biophysically extraordinary features, as they are in mice. The resting membrane potentials, input resistance and time constant of the neurons were -61±1 mV, 15±2 MOhm and 2.8±1 ms respectively (n=7). In response to DC current injections, the neurons responded with a single action potential at the beginning of the stimulus. Octopus cells were found to be sensitive to the rate of depolarizations induced by DC currents. Application of dendrotoxin (DTX) and 4-aminopyridine (4-AP) converted the onset response pattern to a tonic response pattern. For that resason, it is concluded that the extraordinary features of octopus neurons may partly be accounted for by the low threshold potassium channels (I_{KL}).

Poster 17

Permeability and Activation Properties of P2X7-Activated Pores Are Different in HEK-293 and RAW 264.7 Cells.

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$P2X_7$ is a cation channel and has been known to form a non-selective large "pore" which is permeable to large molecules. In this study, we investigated permeability properties of $P2X_7$-activated pores and role of intracellular [Ca^{2+}] in activation of these pore in HEK-r$P2X_7$R and RAW 264.7 cells by using fluorescence tracers with different charges and molecular weights. In the presence of extracellular Ca^{2+} (1mM), after P2X7 stimulation HEK-r$P2X_7$R cells permeates YO-PRO-1 and also Lucifer Yellow dyes. Interestingly, in the absence of extracellular Ca^{2+} Lucifer Yellow uptake disappeared but YO-PRO-1 did not and also YO-PRO-1 uptake was not blocked by intracellular Ca^{2+} chelation. In RAW 264.7 cells ATP application induced both YO-PRO-1 and Lucifer Yellow uptake in the absence of extracelluler Ca^{2+}. We also found that in RAW cells uptake of these dyes were not supressed by intracellular Ca^{2+} chelation. When intracellular [Ca^{2+}] is increased directly by an ionophore (Br-A23187 10 uM), without ATP application, uptake of Lucifer Yellow in HEK-r$P2X_7$R and uptake of YO-PRO-1 and Lucifer Yellow in RAW cells is activated. These findings show that more than one pathway with different permeant selectivity is responsible for the $P2X_7$ activated uptake of large fluorescent tracers in RAW 264.7 and HEK-r$P2X_7$R cells. Also these pathways can be seperated by their dependency

Poster 18

Functional consequences of TRPC1 gene-silencing in vascular smooth muscle cells

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The purpose of this study was to investigate whether there is a relationship between TRPC1 and TRPC6 expression pattern that was reciprocally altered in aging rat thoracic aorta. To test this hypothesis, rat embryonic aortic smooth muscle cells (A7r5, ECACC) cultured in DMEM/Ham's F-12 containing 10% FBS were used in expressional as well as functional analyses. Changes in intracellular Ca^{2+} were monitored in cells grown on 13 mm-polystyrene coverslips placed in separate 6-well plates. For *in vitro* gene silencing, cells were transfected with double-stranded 21mer small interfering RNA (siRNA) targeted against TRPC1 (siTRPC1, 100 nM/well) using Dharmafect2 (Dharmacon) and total RNA and protein samples were isolated after 72 h. Quantitative real-time PCR (LightCycler 2.0, Roche Diagnostic) and immunoblot analyses were performed. Effects of TRPC1 silencing on store-operated Ca^{2+} entry (SOCE) were also tested via surface spectrofluorimetry (PTI QM8/2005) in fura-2-loaded cells. Despite the decreased ($P<0.05$) levels of TRPC1 expression, there was no apparent change in SOCE induced by cyclopiazonic acid, a selective sarco-endoplasmic Ca^{2+} ATPase blocker. Although not statistically significant, TRPC6 mRNA was increased by 70% in cells treated with siTRPC1. Data suggest that decreases in TRPC1 may be compensated by elevated TRPC6 that possibly takes part in SOCE in vascular smooth muscle cells.

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Poster 19

The effect of nitroglycerine, riboflavine and alpha-tocopherol on rat electroencephalographic potentials

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Aim: To investigate the effects of different drugs on cortical electroencephalogram (EEG) in adult Wistar rats.
Material: The subject of the study was adult Wistar albino rats treated with riboflavine for 10 days and alpha-tocopherol for alternate 5 days. The EEG potentials were recorded with ADInstruments (Australia). EEG were recorded from scalp for at least 10 minute duration.
Method: Electroencephalogram potentials were filtered at 0.5-50 Hz band pass. EEG, raw signals were displayed on-line and stored for further analysis.
Results: No significant change was observed in EEG power among groups.
Conclusion: EEG power, as a measure of the amplitude of the EEG as a function of frequency (microvolts squared per Hz) has been proven useful in assessing the effects of various drugs and chemicals and it is presumed that the altered EEG power in specific frequency bands is a sensitive marker of acute and chronic drug and chemical exposure. Though it is difficult to put forward precise results because of the limited number of subjects in each group, our study shows that riboflavine, alpha-tocopherol does not effect cortical EEG significantly.

Poster 20

Effect of noise on oxidative stress parameters in the rat sera

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Objective: Sound which is transmitted through a solid, liquid, or gas materiel is a vibration whose frequencies are at 20 to 20.000 Hz and can be detected by ears. Noise is described as disturbing and unwanted sound. In this study, it is aimed to investigate the effect of noise on oxidative stress parameters in the rat sera.
Material and Method: Twenty male Sprague-Dawley rats were used in this study. Experimental group (n=10) were exposed to noise for 20 days. Control group (n=10) were hold in the same experimental conditions without any noise exposure for the same duration. Blood samples of rats were collected prior to and at the end of the experiment

and its sera were separated. Malondialdehyde (MDA), nitric oxide (NO) levels and glutathione peroxidase (GSH-Px) activity were measured in rat sera.
Results: MDA and NO levels and GSH-Px activities were found to be increased significantly at the end of experiment in noise group. No parameters were significantly different between prior to and at the end of experiment in control group.
Discussion: In our study, elevation of MDA level, an indicator of lipid peroxidation, by noise exposure indicates that there is oxidative stress in noise group. Also NO levels and GSH-Px activities were increased by noise exposure in noise group. We suggest that oxidative stress caused by noise exposure may lead to various degrees of damages in the cells such as mainly lipid peroxidation.

Poster 21

Protective effect of erdosteine on vancomycin--induced pancreatic damage in rats

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The aim of this study was to examine vancomycin (VCM)-induced pancreatic damage and to investigate the role of erdosteine, an expectorant and an antioxidant agent, on VCM-induced pancreas impairment in rats. Rats were divided into three groups: Control, VCM and VCM plus erdosteine. VCM was administrated intraperitoneally with 200 mg kg^{-1} twice daily for 7 days. Erdosteine was administered orally with 10 mg kg^{-1} once daily for 7 days. The first dose of erdosteine administration was performed 24 hours prior to VCM injection. Blood and pancreas tissue samples were taken after the study. Serum amylase, lipase, alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) activities were determined. And also, pancreas tissue samples were investigated under light microscopy. VCM administration significantly increased serum amylase, lipase, ALP and GGT activities as compared to control rats. VCM plus erdosteine injections caused significantly decreased serum lipase, amylase and GGT activities, but there was no difference at ALP activity in serum as compared to VCM administrated group. After light microscopic examination, there was significant pancreatic damage VCM given group as compared to control. Erdosteine showed histopathological protection against VCM- induced pancreatic damage as compared to VCM administrated group. Erdosteine caused a marked reduction in the extent of pancreatic damage. It is concluded that it plays an important role in the VCM -induced pancreatic damage and reduces the pancreatic damage both at the biochemical and histological levels.

Poster 22

Protective effect of montelukast against hepatic ischemia/reperfusion injury in rats

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Oxygen free radicals are involved in pathophysiology of ischemia/reperfusion (I/R) injury. This study was designed to assess the possible protective effect of montelukast, a selective antagonist of cysteinyl leukotriene receptor 1 (CysLT1), on hepatic I/R injury in rats. Wistar albino rats through clamping hepatic artery, portal vein and bile duct, were subjected to 45 min of hepatic ischemia followed by 60 min reperfusion period. Montelukast (10 mg/kg; i.p.) was administered 15 min prior to ischemia and immediately before reperfusion period. At the end of the reperfusion period, the rats were killed by decapitation. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) activity were determined in serum samples. Malondialdehyde (MDA), and glutathione (GSH) levels and myeloperoxidase (MPO) activity were determined in the liver tissue samples while formation of reactive oxygen species was monitored by using chemiluminescence (CL) technique with luminol and lucigenin probes. Tissues were also analyzed histologically. Serum ALT, AST, and LDH activities were elevated in the I/R group, while this increase was significantly decreased by montelukast treatment. Hepatic GSH levels, significantly depressed by I/R, were elevated back to control levels in montelukast-treated I/R group. Furthermore increases in tissue luminol and lucigenin CL, MDA levels and MPO activity due to I/R injury were reduced back to control levels with montelukast treatment. Since montelukast administration alleviated the I/R-induced liver injury and improved the hepatic structure and function, it seems likely

that montelukast with its anti-inflammatory and antioxidant properties may be of potential therapeutic value in protecting the liver against oxidative injury due to ischemia-reperfusion.

Poster 23

The Effect of Temperature and Duration on Protein Oxidation in Chondrocyte Culture

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One of the widely used treatment methods in degenerative joint damage is autologous chondrocyte transplantation. It often plays an important role in the protection of integrity of the locomotory system. However, the transport of a tissue to far regions lowers the success in transplantation as the number of the centers producing chondrocytes in cell culture is quite less in our country. Indeed, some biochemical alterations may occur in the cartilage tissues kept for a long time to be used in a transplantation operation. One of the most often observed problems is denaturation and oxidation of proteins in cartilage tissue. This condition leads to the development of graft versus host disease in the patients in the post-transplantation period. It has been considered that different transportation times and medium temperatures may affect protein oxidation. In this study, it was aimed to determine the optimum conditions in which protein oxidation occurs at a minimum level. For this purpose, cartilage pieces were isolated from the tars metatarsal joints of 10 cattle under sterilized conditions. They were kept in culture medium at 4°, 25° and 37°C for 1, 3 and 7 days, respectively. In the end of waiting period, the protein oxidation levels in all tissues were determined utilizing protein carbonyl group assay. The data were statistically analyzed using SPSS 11.0 and Mann Whitney U Test. In all tissues cultured at 37°C for 1, 3, and 7 days the protein oxidation levels were found to be statistically lower than that was determined in the tissues cultured at 4°C for the same time period. However, it was determined that there is no significant correlation between the protein oxidation and the incubation period. Based on these data, we can state that protein oxidation in cartilage tissue alters with change in temperature, but not with incubation period. Moreover, it can be suggested that the chondrocytes should be incubated at 37°C to obtain suitable transplantation.

Poster 24

Pycnogenol protects against renal ischemia/reperfusion injury in rats

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Oxygen free radicals are involved in pathophysiology of ischemia/reperfusion (I/R) injury.This study was designed to assess the possible protective effect of pycnogenol, against I/R-induced oxidative renal damage. Wistar albino rats were unilaterally nephrectomized and subjected to 45 min of renal pedicle occlusion followed by 3 h of reperfusion. PYC (10 mg kg^{-1}, i.p.) or saline was administered at 15 min prior to ischemia and immediately before the reperfusion period. At the end of the 3 h, rats were decapitated and trunk blood was collected. Creatinine, blood urea nitrogen (BUN) and lactate dehydrogenase (LDH) activity were measured in the serum samples, while proinflammatory cytokines, TNF-α, IL-1β, IL-6 levels were assayed in plasma samples. Kidney samples were taken for the determination of tissue malondialdehyde (MDA), glutathione (GSH) levels, Na^+, K^+ ATPase and myeloperoxidase (MPO) activity and the extent of tissue injury was analyzed microscopically. Ischemia/reperfusion caused a significant decrease in tissue GSH level and Na^+, K^+ ATPase activity, which was accompanied with significant increases in the renal MDA level and MPO activity. Similarly, serum creatinine and BUN levels, as well as LDH and IL-1β, IL-6, and TNF-α levels were elevated in the I/R group as compared to control group. On the other hand, pycnogenol treatment reversed all these biochemical indices, as well as histopathological alterations that were induced by I/R. Findings of the present study suggest that pycnogenol exerts renoprotective effects via its free radical scavenging and antioxidant activities, that appear to involve the inhibition of tissue neutrophil infiltration.

Poster 25

Protective role of caffeic acid phenethyl ester on contrast media induced oxidative stress in rat liver

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Acute renal failure frequent still occurs as a complication after radiographic examination using radio contrast media (RCM). However, RCM dependent hepatotoxicity is as yet unclear. The aim of this study was to investigate the possible protective effects of caffeic acid phenethyl ester (CAPE) on RCM induced hepatotoxicity. For the study rats were divided into three experimental groups: control group (n=10), RCM group (n=8), RCM plus CAPE group (n=10). RCM was administered intraperitoneally in the dosage of 10 ml/kg for once only. CAPE administered intraperitoneally once a day for 2 days at a dose of 10 µmol/kg. At the end of experimental period rats were anesthetized and sacrificed 24 h after the last enjection. The activities of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), and the level of malondialdehyde (MDA) were measured to investigate oxidative stress in liver tissues. We determined significantly increased MDA level in the RCM group. On the other hand, in the RCM plus CAPE group the MDA level significantly decreased when compared with the RCM group ($p< 0.05$). The activity of SOD in the RCM group significantly diminished ($p < 0.05$) when compared with the control group. CAPE co-administration with RCM resulted in significantly increased SOD activity in liver tissue when compared with RCM alone ($p < 0.05$) In our study, CAT activities not significantly between groups. Our histological parameters support biochemical parameters. In conclusion, Our results demonstrated that administertion of RCM may generates oxidative stress and hepatic damage in rat liver. However, CAPE treatment may reduce hepatic damage and oxidative stress.

Poster 26

Radiocontrast media-induced oxidative stress in rat liver: Experimental observations and the protective effect of erdosteine

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The aims of this study were to elucidate whether radiocontrast media (RCM) induces oxidative stress in liver and to evaluate the protective effects of erdosteine, a mucolytic agent. Twenty-one rats were randomized in to three groups as follows: control group, RCM, and RCM plus erdosteine. RCM was administered intraperitoneally in the dosage of 10 ml/kg for once only. Erdosteine was administered orally with 25 mg/kg once a day for 2 days. The activities of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), and the level of malondialdehyde (MDA) were measured to investigate oxidative stress in liver tissues. In addition, histological alterations in liver were evaluated. RCM administration to rats significantly increased liver MDA levels ($P< 0.005$) and decreased SOD ($P< 0.05$). However, the decrease in CAT activity was not significantly. Erdosteine co-administration with RCM resulted in significantly decreased MDA level and increased SOD activity in liver tissue when compared with RCM alone. Erdosteine showed histopathological protection against RCM induced hepatotoxicity. It can be concluded that radiocontrast media may induces oxidative stress in liver tissues and erdosteine may be a promising agent for protection against RCM-induced oxidative stress in liver.

Poster 27

Selenium normalizes kidney gelatinases in diabetic rats

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Diabetes is a syndrome associated with multi-organ dysfunction.The increase in oxidative stress plays the major role in organ dysfunction associated with both types of diabetes. Matrix metalloproteinases (MMP) 2 and 9 are enzymes known to become activated during the course of oxidant stress. There are many studies that show that oxidants per se can activate MMPs and also participate in further deterioration of the oxidant state in tissues Selenium is an essential element with powerful antioxidant effects . Several studies show an increase in circulating plasma MMPs in diabetic human and animals We hypothesized that the MMP activation and effects can be inhibited by selenium administration.
Material and Method: We used streptozotocin-diabetic rat model, and sodium selenate (15umol/kg/day) for treatment for 4 weeks. Activity and expression of MMPs were assessed by using zymography and western blotting respectively.
Results: the diabetes related increase in MMP-9 was prominent in both plasma and kidneys of animals. Selenium treatment normalized these increases. MMP-2 expression was found to be higher than control in only half of the animals.

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Poster 28

Effect of Extremely Low Frequency Electromagnetic Fields on Growth Rate of Bacteria: Correlation with ROS levels

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Electric and electronic devices used in daily life, such as GSM antennas, wireless cables, radio and television transmitters and high voltage transmission lines emit electromagnetic fields of different frequency and intensity. Many epidemiological and in vitro studies demonstrated the effect of Extremely Low Frequency Electromagnetic Fields (ELF-EMF) on biological systems. Although the mechanism of this effect has not been elucidated yet it has been suggested that this effect might be via the effect of these fields on reactive oxygen species (ROS). It was previously demonstrated that ELF-EMF affected ROS levels in eukaryotic cells. This study aimed to demonstrate the effect of ELF-EMF on growth rate of bacteria and correlate it with changes in ROS levels. Changes in growth rate and ROS levels subjected to 50Hz, 1mT ELF-EMF was determined.

Poster 29

Another vitamin which has an antioxidant effect: Vitamin-K1 (phylloquinone)

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The aim of this study was to investigate an effect of Vitamin-K1 and sodium fluoride on rat femoral fracture-healing.
As part of the study, malondialdehyde (MDA), glutathione peroxidase (GPx) and superoxide dysmutase (SOD) were analyzed in the erythrocytes of 7-month-old, 20 male Wistar albino rats (Control- (n=10) and Vitamin-K1-groups (n=10)) which underwent femoral-osteotomy followed by miniplate-screw fixation. While Vitamin-K1-group received 12mg/kg/day Vitamin-K1 in triglyceride-oil for 14-days, Control-group received only triglyceride-oil. Two-weeks after operation, we found statistically significant increase in MDA-level ($p<0.05$) that returned to preoperative-level 9-weeks after operation in the Control-group. However, there was no statistically significant difference in MDA-level either 2-weeks or 9-weeks after operation when compared to its' preoperative-level in the Vitamin-K1-group ($p>0.05$). The GPx-activity decreased at 2-weeks ($p>0.05$), however, it reached significance 9-

weeks after operation ($p<0.05$) when compared to its' preoperative-level in the Control-group. In the Vitamin-K1 group, GPx-activity decreased significantly at both 2- and 9-weeks ($p<0.05$) when compared to its' preoperative-level. SOD-activities decreased at 2-week ($p>0.05$) in both Control- and Vitamin-K1-groups. At 9-week, however, it reached significance in the Control-group, while it was insignificant in the Vitamin-K1-group. Vitamin-K1 is known with its' established effect on blood coagulation. However, accumulating studies have also reported its' accelerating effect on bone healing. Our findings suggest that Vitamin-K1 may have an antioxidant effect as demonstrated during inflammation phase of the fracture-healing period in our research.
In conclusion, vitamin-K1 may have an antioxidant effect.

Poster 30

Contractile function of the urinary bladder in hypercholesterolemic rats: *in vitro* carbachol induced contraction and cystometrography

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Hypercholesterolemia and urinary bladder (UB) dysfunction incidences increase with increasing age. Although it was shown that membrane cholesterol alterations effect smooth muscle signal transduction and cell function, its effects on function of UB has not been investigated extensively. We performed this study to examine contraction response to agonists and micturation function of the UB in the hypercholesterolemic rats. 250-300 gram adult male Sprague-Dawley rats fed with standard (C, n=24) or 4% cholesterol containing chow (HC, n=23) for four weeks were used. Serum lipid profiles and the tissue cholesterol level were measured. The cumulative dose-contraction curves to carbachol (10^{-8}-10^{-4} M) in UB strips were recorded. These responses were studied in the presence of muscarinic antagonists; methochtarmine (10^{-5}M) and 4-DAMP (10^{-7}M). Cystometrographic studies were performed under urethane anesthesia. Data was analyzed statistically. Plasma cholesterol increased in HC group (C:83.4±5.5, HC:133.9±10.4mg/dL, $P<0.001$), tissue cholesterol didn't change (C:6.3±1.3, HK:7.7±1.5µg/g protein). Dose–response curves were not different between groups. Cystometry results revealed shortened micturation intervals (C:201.4±33.6, HC:118.6±26.2 sec), decreased micturation volume (C:0.42±0.05, HC:0.24±0.06 mL) and micturation fraction (C:61.4±6.3, HC:31.7±7.4 %), elevated basal pressure (C:1.2±0.6, HC:6.2±1.5 cmH2O), elongated micturation time in HC group (P0,05). Hypercholesterolemia did not change tissue cholesterol level in rat UB, contraction response to carbachol and the share of receptors in this response. But cystometrographic data indicates that UB is sensitive to plasma cholesterol elevation. Further studies may enlighten the etiology of overactive UB.

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Poster 31

Are there any effects of stevia extract and N-nitro L- arginine on diabetes-induced oxidative stress? *

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Diabetes mellitus (DM) is a metabolic disorder, resulting in severe metabolic imbalances and non-physiologic changes in many tissues, where oxidative stress plays an important role in etiology. Several mechanisms may cause oxidative insult in diabetes, although their exact contributions are not entirely clear. Accumulating evidence points to many interrelated mechanisms that increase production of reactive oxygen and nitrogen species or decrease antioxidant protection in diabetic patients. The aim of the present study was to determine the effects of N-Nitro L-Arginine (L-NNA) (as a nitric oxide synthase inhibitor) and extract of *Stevia rebaudiana* Bertoni (SrB) leaves (as an anti-hyperglysemic plant) on hyperglycemia and oxidative stress in experimental type II diabetic rats. Female Sprague-Dawley rats of 2–3 months of age were used in this experiment. Diabetes was induced by systemic administration of nicotinamid (NA) and streptozotocine (STZ). Animals were used for the experiments 5–8 weeks after diabetes was induced. Diabetic groups were treated with SrB, L-NNA and SrB + L-NNA during to 15 days. The blood glucose levels were measured from tail vein during the experiment. After the experiment, liver tissue and blood samples were collected from the rats using appropriate techniques under ether anaesthesia. We determine the antioxidant enzymes activities such as

glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) in liver homogenate. Moreover we also measured nitric oxide synthase (NOS) and malondialdehyde (MDA) levels, a marker of lipid peroxidation in liver.
Our results shown that; the extract of SrB, which have been used for many years in the treatment of diabetes in Brazil, Paraguay and India, decreased the blood glucose concentration of the diabetic groups. There were no differences in CAT, SOD and NOS activities between the groups as compared to controls. The GPx levels of the SrB treated diabetic groups were significantly higher than controls. However, L-NNA treated groups had increased MDA levels compared to controls.

Poster 32

Oxidative stress in beta thalassemia

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Beta thalassemia is a group of hereditary disorders characterized by a genetic deficiency in the synthesis of beta-globin chains. The severity of illness depends on whether one or both genes are affected. The relative excess of unpaired globin chains, which aggregate and attach to the membrane resulting irreversible damage, high intracellular nonhemoglobin iron, and high plasma iron content may be the reasons of increased oxidative stress in thalassemic red cells. The free radicals are neutralized by a complex antioxidant system in oxidative stress. In this study we aimed to indicate the oxidant damage in beta thalassemia major . For this purpose the children with beta thalassemia major (Group I, n=35) and healthy control (Group II, n=40) whose ages under sixteen, were included in this study. After hematological analyzes, antioxidant enzymes activities of glutathione peroxidase (GSH-Px), glutathione reductase (GSH-Rd), glutathione S transferase (GST), catalase (CAT), superoxide dismutase(SOD) were measured. We also determined the level of plasma malondialdehyde(MDA) which is the end product of lipid peroxidation. As a result; no statistically significant difference was found between Group I and Group II. The normal levels of antioxidant enzymes that found in beta-thalassaemia major subjects may be the reason of presence of normal red cells owing to multiple transfusions. So this study may be carried out with untransfused beta thalassemia major patients instead of transfused.

Poster 33

The relationship between atherosclerosis and total oxidant status in obese subjects

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Obesity, the major health problems in westernized countries, is the important risk factors of atherosclerosis. It is associated with a significantly increased mortality from atherosclerotic cardiovascular disease and other causes. Furthermore, obesity is a risk factor of atherosclerosis, and are associated with increased oxidative stress. The objective of this study was to evaluate total oxidant status (TOS) in obese subjects and to establish the association between the development of atherosclerosis and TOS level in obese subjects.
Twenty-seven obese subjects and 26 controls were enrolled in this study. To determine antioxidative status of serum, total antioxidant status (TAS) was measured, and to determine the oxidant status of serum, TOS were measured. The ratio of TAC to TOS was accepted as oxidative stress index (OSI).
Serum TAC levels was significantly lower in obese subjects than in controls ($p< 0.001$), while TOS levels and OSI values were significantly higher ($p< 0.001$, both of). There were significantly negative correlation between TAC and BMI (r:-0.552, $p <0.001$), while significantly positive correlations between TOS, OSI and BMI in obesity subjects (r: 0.745, $p < 0.001$, r: 0.707, $p < 0.001$).
Our results indicate that obesity leads to oxidative stress which can contribute to pathogenesis of atherosclerosis. Furthermore, this novel method may be used as a routine test to evaluate and fallow up the levels of oxidative stress in obese subjects.

Poster34

Alpha lipoic acid treatment reduces brain edema and blood brain barrier permeability in a rat model of traumatic brain injury.

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Alpha lipoic acid (ALA), a potent antioxidant, has been shown to regenerate through redox cycling and to raise intracellular glutathione (GSH) levels. The aim of our study was to investigate the putative neuroprotective effect of ALA, in a rat model of traumatic brain injury. Sprague Dawley rats were subjected to traumatic brain injury with a weight-drop device using 300 g-1 m weight-height impact. The groups were: control (vehicle), ALA (100 mg/kg, ip), trauma and trauma + ALA (100 mg/kg, ip). 48 h after the injury, neurological examination scores were recorded and then the animals were decapitated. Brain edema was evaluated by wet-dry weight method, and blood brain barrier (BBB) permeability was evaluated by Evans Blue (EB) extravasation. In brain tissues malonedialdehyde (MDA), and GSH levels, myeloperoxidase (MPO) and Na^+-K^+-ATPase activity were assayed. Generation of free radicals was measured by luminol and lucigenin chemiluminescence (CL). The neurological examination scores mildly increased in trauma groups 48h after the induction of trauma. ALA treatment improved the altered neurological status. The MDA and MPO activity increased while GSH levels were decreased in trauma group. As a result of trauma-induced free radical generation luminol and lucigenin CL was markedly increased. ALA treatment reversed all these biochemical changes. The trauma also caused a significant increase in brain water content and this increase was partially reversed by ALA traetment. ALA treatment also reduced the EB extravasation indicating the preservation of the BBB integrity.

The present study suggests that ALA exerts neuroprotection by preserving BBB permeability and reducing brain edema probably by its antioxidant and antiinflammatory properties in the traumatic brain injury model.

Poster 35

The therapeutic effect of *Punica granatum* peel extract on ionizing radiation-induced enteritis in rats

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Radiation-induced enteritis is a well-recognized sequel of therapeutic irradiation. The objective of this study was to examine the potential radioprotective properties of Punica granatum peel extract (PGE) on the oxidative damage in the ileum of irradiation-induced enteritis.

Sprague-Dawley rats were exposed to irradiation performed with a LINAC producing 6 MV photons at a focus 100 cm distant from the skin. Under ketamine anaesthesia (100 mg/kg intraperitoneally), each rat received a single whole-body X-ray irradiation of 800 cGy. Animals were returned to their home cages following irradiation. Irradiated rats were pretreated orally with saline or PGE (50 mg/kg/day) for 10 days before irradiation and the daily treatments were continued for additional 10 days. After decapitation, trunk blood was collected to measure lactate dehydrogenase (LDH) and tumor necrosis factor-alpha (TNF-alpha) levels. Furthermore, oxidative burst of neutrophils and leukocyte apoptosis were assayed by flow cytometry. In the ileal tissues malondialdehyde (MDA) and glutathione (GSH) levels, myeloperoxidase (MPO) activity were evaluated. Plasma TNF-alpha, LDH levels and leukocyte apoptosis were increased in the irradiated rats as compared with the control group. Irradiation caused a significant decrease in ileal GSH level, which was accompanied by significant increases in MDA levels and MPO activity of the ileal tissue. On the other hand, PGE treatment reversed all the biochemical and histopathological alterations induced by irradiation.

Our results demonstrate that PGE, via its putative antioxidant action, reduces oxidative damage in the ileal tissues of irradiated rats. Thus, the present results suggest that supplementing cancer patients with PGE may support radiotherapy by improving radiation-induced enteritis.

Poster 36

Acetylcholinesterase Inhibitors and Antioxidant Enzymes in Alzheimer Disease

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Alzheimer's disease (AD) is characterized by a decrease in several brain neurotransmitters, most markedly decreased neurotransmitter is acetylcholine (ACh) (1). Because of the close relationship between clinical picture and cholinergic deficiency, most widely used therapeutic strategy in treatment of AD is to secure Ach longer at synapse (2,3). Increased oxidative stress and free radical damage has a role in the pathogenesis of AD (4). Acetylcholiesterase inhibitors (AChEIs), used for the symptomatic treatment of AD, protect cells from free radical toxicity and increase the production of antioxidants (5). Aim of our study was to investigate efficacy of cholinergic therapy and the effect of AChEIs on antioxidant enzyme activities. Oxidative stress parameters were measured in blood samples obtained from 17 healthy volunteers and 26 patients with AD, 13 treated with donepezil and 13 treated with rivastigmin throughout three mounths. The study protocol was approved by local ethics comitee. Blood samples were obtained before and at the end of treatment. Activities of plasma cholinesterase, erythrocyte superoxide dismutase (SOD) and glutathione peroxidase (GPx) were measured. Before and after treatment mini mental statement examination (MMSE), cognitive demans rating (CDR) and activity of daily living (ADL) scoring was determined. In our study there is a decrease at erythrocyte SOD activity in Alzheimer disease. SOD activity has improved after treatment with rivastigmin and donepezil (respectively, $p<0,001$, $p<0,01$). Data from our study showed that cholinesterase inhibitors might improve increased oxidative stress. Donepezil treatment showed no effect on MMSE, CDR and ADL, rivastigmin improve only ADL ($p<0,05$).

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Poster 37

Donepezil and Lipid Peroxidation in Alzheimer Disease

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Donepezil is a reversible cholinesterase inhibitor which is used symptomatic treatment of AD. Cholinesterase inhibitors prevent the breakdown of acetylcholine by inhibiting the activity of cholinesterase enzymes that metabolise acetylcholine. Lipid peroxidation (LPO) enhance in brain, CSF and plasma of patients with AD. A relationship between the intensity of LPO and the clinical picture of AD has been established, and therapeutic agents can be screened in terms of the changes they produce in the level of LPO (1). Acetylcholiesterase inhibitors (AChEIs), used for the symptomatic treatment of Alzheimer's disease, protect cells from free radical toxicity and increase the production of antioxidants (2). The aim of the present work was to assess the relationship between changes in AChE activity and the lipid peroxidation (LPO) in patients with AD. All the patients with AD were treated with donepezil throughout three mounths. Erythrocyte AChE, catalase (CAT) avtivities and malondialdehyde (MDA) levels were measured in blood samples obtained from 13 patients with AD (72,00±6,10, 8 male, 5 female) before and after treatment with donepezil and 17 healthy volunteers (67±3,69, 9 male, 8 female). The study protocol was approved by local ethics comitee. Data from our study demonstrated that donepezil may mitigate enhanced LPO.

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Poster 38

Influences of catechin on carbon tetrachloride-treated rat's histopathology and hemolysate

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In this study, the antioxidants catechin was investigated experimentally with respect to its protective effect against CCl4-induced oxidative stress in rats. Three months old and thirty-two Spraque Dawley male rats were used in the study. The rats were assigned to four groups in equal numbers. Group four received catechin (50 mg/kg/day) intragastrically (i.g) for a ten days period as pretreatments. In the second ten days period, group one received liquid oil (0.2 ml/kg/day) intraperitoneally (i.p), group two received CCl4 (0.2 ml/kg/day)(i.p) group three received catechin (50 mg/kg/day, i.g). In this period the previously treated group four received at the same dose catechin plus CCl4 daily in two divided doses. Within 24 hours after the last dose, blood samples for hemolysate were collected from the rats using appropriate techniques under ether anesthesia. Malondialdehide (MDA) levels were measured and catalase (CAT), glutathione peroxidase (GPx) activities were determined in the samples. Tissue samples were fixed in 10% neutral formalin to be used in histological studies. Slices were stained with H&E and examined under a light microscope.
Results have shown that the values obtained in only catechin treatment groups were close to values in control group, as expected. In the CCl4 treated group, free radical formation secondary to CCl4 metabolism resulted in increased MDA levels and led to oxidative damage. This damage was corrected to levels almost comparable to that of control by the free radical scavengers CAT and GPx, the activities of which were increased secondary to catechin treatments. Finally, histological studies supported that our chemical results.

Poster 39

Effect of toluene on erythrocyte membrane stability under in vivo and in vitro conditions.

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Toluene is an organic solvent widely used in the industry. Due to its high lipophilicity, it accumulates in the cell membrane impeding transport through it. Its metabolites are responsible for the formation of reactive oxygen species. Erythrocytes are prone to oxidative damage. In this study, we aimed to investigate the relationship between the osmotic fragility improving and the oxidative stress inducing effects of the toluene in the erythrocytes. Measurements of osmotic fragility, mean corpuscular volume (MCV), oxidative stress parameters (malonyldialdehyde, protein carbonyl) and antioxidant enzyme activities (catalase, glutathione peroxidase) were performed simultaneously both in the individuals exposed to toluene professionally (n=10, in vivo) and the human erythrocytes treated with toluene (n=12, in vitro). The data were analyzed statistically by Mann-Whithney U Test. Toluene increased oxidative stress parameters significantly both in in vivo and in vitro exposure, it also caused a significant decrease in the activities of antioxidant enzymes (in vitro catalase activity was lower but did not reach statistical significance). Improved osmotic fragility was observed only in the in vitro experiments. Erythrocyte MCV values didn't exhibit any change. In conclusion, the decreased osmotic fragility in in vitro toluene treated erythrocytes was a result of the membrane stabilizing effect of toluene which in turn is due to its lipophilic properties. The decrease in osmotic fragility observed in our experiments is probably due predominating membrane stabilizing action of toluene over oxidative stress induced increased fragility.

This study was granted by HUBAB (06 D05 101 003).

Poster 40

Levels of lipid peroxidation and antioxidant vitamins in plasma of patients with fibromyalgia

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Ankylosing spondylitis (AS) is an inflammatory disorder with unknown etiology that mainly affects the axial skeleton as well as the peripheral joints and extra-articular structures. In recent years, a few studies have investigated the possible role of reactive oxygen species in the etiology and pathogenesis of AS due to phagocytic cell activation. The

aim of this study was to investigate plasma concentration of vitamin A, C, E and ?-carotene and levels of lipid peroxidation (LP) in 13 AS patients with fibromyalgia and 13 healthy age-matched controls. The Bath AS disease Activity Index (BASDAI) and the visual analogue scale (VAS) were also used in all patients before the study. In addition, the patients were evaluated according to spinal involvement and peripheral involvement.
Concentrations of ?-carotene, vitamins A, C and E were significantly ($p<0.05$) lower in plasma of patients with fibromyalgia than in control although LP levels were significantly ($p<0.05$) higher in plasma of the patients than in control. levels of glutathione did not statistically change. These results provide some evidence for a potential role of increased lipid peroxidation and decreased fat soluble antioxidants in ankylosing spondylitis by its inflammatory character. These results suggested that oxidative stress and lipid soluble antioxidants play very important role in the pathogenesis of ankylosing spondylitis.

Poster 41

Is There a Role of Postmenopausal Strontium Ranelate Therapy on the Paraoxanase and Aryl Esterase Activities in the Rat Heart Tissue

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Physiological role of paraoxanase (PON 1) and aryl esterase enzymes has not completely understood. However, it is well known that they prevent the oxidation of LDL by hydrolization of lipid peroxides and act as protectors against the cellular damage caused by the toxic agents such as toxic organophosphates. It has been reported that synthesis and secretion of PON 1 were occurred in the liver. Also, it can be synthesized from the liver and spleen of fetus. In rats, it exists particularly in liver, lungs, heart, kidney, small intestine and plasma. The activity of PON 1 and aryl esterase in serum and tissues is lower in newborns and premature babies. Furthermore, the activity of these enzymes is lower in the patients requiring kidney transplantation and those with atherosclerosis, uremia, Type 2 diabetes and myocardial infarction. The women in postmenopausal period also have them at low levels. In this study, the effect of strontium ranelate on paraoxanase and aryl esterase enzyme activities was investigated in the joint damage is autologous chondrocyte transplantation. It often plays an important role in the protection of integrity of the locomotory system. However, the transport of a tissue to far regions lowers the success in transplantation as the number of the centers producing chondrocytes in cell culture is quite less in our country. Indeed, some biochemical alterations may occur in the cartilage tissues kept for a long time to be used in a transplantation operation. One of the most often observed problems is denaturation and oxidation of proteins in cartilage tissue. This condition leads to the development of graft versus host disease in the patients in the post-transplantation period. It has been considered that different transportation times and medium temperatures may affect protein oxidation. In this study, it was aimed to determine the optimum conditions in which protein oxidation occurs at a minimum level. For this purpose, cartilage pieces were isolated from the tars metatarsal joints of 10 cattle under sterilized conditions. They were kept in culture medium at 4°, 25° and 37°C for 1, 3 and 7 days, respectively. In the end of waiting period, the protein oxidation levels in all tissues were determined utilizing protein carbonyl group assay. The data were statistically analyzed using SPSS 11.0 and Mann Whitney U Test. In all tissues cultured at 37°C for 1, 3, and 7 days the protein oxidation levels were found to be statistically lower than that was determined in the tissues cultured at 4°C for the same time period. However, it was determined that there is no significant correlation between the protein oxidation and the incubation period. Based on these data, we can state that protein oxidation in cartilage tissue alters with change in temperature, but not with incubation period. Moreover, it can be suggested that the chondrocytes should be incubated at 37°C to obtain suitable transplantation.

Poster 42

Effects of Some Flavonoids on the Aluminium and Lead Induced Oxidative Neurotoxicity and NMDA Receptors

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Oxidative stress refers to the undue oxidation of biomolecules leading to cellular damage, and it is carried out by reactive oxygen species (ROS). Oxidative damage contributes deleterious effects; it may affect the DNA, which can lead to nucleotide oxidation and dimerization

and detoxification of ROS requires keeping fixed and there have been several defense systems in metabolism via function different mechanisms for this balance. Nevertheless, endogenous and exogenous triggers may cause the overproduction of ROS or the impairment of these antioxidant defense systems, therefore leading to oxidative stress.

In this study, the roles of flavonoids, the delay of destruction and the removal of oxidative stress which will take place in the rats brain with the toxicities of Al and Pb were investigated. In these inactivation mechanisms, superoxide dismutase, catalase, glutahtione peroxidase enzyme activities alterations which have antioxidative effects via removing of deleterious effects of free radicals and changes of acetylcholine esterase activity which is responsible of degredation of acetylcholine signaling in the cholinergic sinapses and lipid peroxidation, glutathione levels were determined. To determine the effects of Al and Pb-induced damage on the learning and memory functions, alterations of NMDA receptor proteins were also investigated. In conclusion, it can be said that Al and Pb at the treatment and over doses can lead to oxidative brain damage via trigering free radical production. On the other hand, a permanent therapy of neurological disorders such as Alzheimer's disease, Parkinson's disease, hiperactivity and cognitive impairments is stil impossible. Because usage of synthetic drugs is limited often by the toxic and psychotropic side effects associated with their pharmacodynamic properties. So, the results from our study suggest that treated flavonoids can be effective on prevention/elimination of neuronal damage and that eating up flavonoids riched diets can be useful to minimize toxicities of these metals.

Poster 43

Efficacies of Curcumin and Tannic Acid Against Lead and Aluminum Induced Lipid Peroxidation in Rat Liver

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Reactive oxygen intermediates (ROI) are continually generated in organisms and their production is known to be enhanced during oxidative bursts such as those caused by exposure to infection or xenobiotics. Environmental and occupational settings can offer a variety of exposures to different forms of metals. While each metal may have its own mechanisms of action, the generation of ROI by metals and the resulting effects appear to result from a common mechanism. Concerted efforts have been made in past to identify suitable antioxidants which can minimize the deleterious effects of ROI and delay the onset of degenerative disorders. Phytochemicals are naturally occurring substances found in plants and used to combat human diseases. Curcumin (diferuloylmethane) which is a low molecular weight polyphenol has antioxidant, anti-inflammatory, cancer chemopreventive and potentially chemotherapeutic properties. Tannic acid, a mixture of digallic acid and glucose falls into the hydrolysable gallotannin group and are commonly found in human diet such as tea, coffee, cocoa and wine. Tannins may act as antioxidants to scavenge free radicals and protect against oxidative damage.

In this study, the roles of flavonoids, the delay of destruction and the removal of oxidative stress which will take place in the rats liver with the toxicity of Pb and Al were investigated. In these inactivation mechanisms, superoxide dismutase, catalase, glutathione peroxidase enzyme activities alterations which have antioxidative effects via removing of deleterious effects of free radicals and lipid peroxidation levels were determined.

In conclusion, it can be said that Pb and Al at the treatment and over doses can lead to oxidative liver damage via trigering free radical production. The results from our study suggest that curcumin and tannic acid can be effective on prevention/elimination of radicalic damage and that eating up flavonoids riched diets can be useful to minimize toxicities of these metals.

Poster 44

The effects of indomethacin on apoptosis and lipid peroxidation in the newborn rats with Hypoxic-Ischemic encephalopathy injury

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Perinatal asphyxia is the one of the most important neurologic complications in the newborn. It's known that

activation of phospholipase A2, degradation of membrane phospholipids resulting in tissue accumulation of arachidonic acid, activation of cyclooxygenase which leads to formation of prostaglandin and free radical generation occur after hypoxic-ischemic damage. The aim of this study was to investigate the effect of indomethacin, a nonselective cyclooxygenase inhibitor, on apoptosis, antioxidant status and lipid peroxidation in the newborn rats with hypoxic-ischemic encephalopathy injury. For this purpose; apoptosis was evaluated by measurement of caspase 3 and 8; antioxidant capacity and lipid peroxidation were evaluated by measurement reduced gluthatione(GSH) content and catalase enzyme activity and the level of malondialdehyde(MDA), respectively. In the first group; seven-day old rat pups with model of hypoxic-ischemic cerebral injury were treated with three times indomethacin 2mg/kg/12h. and the other group; pups were given physiologic saline(Hypoxic-Ischemic Group). Sham Group had no treatment. After 72 hours, rat pups were decapitated. Activities of caspase 3 and 8 were evaluated by Colorimetric Protease Assay Kits; GSH and catalase were determined according to Beutler's Methods and MDA was assayed by Thiobarbituric acid Method in right and left brain tissues. There was statistically significant decrease in caspase 3, caspase 8 and catalase enzyme activities and GSH content($p<0.001$) in indomethacin treated group as compared to hypoxic-ischemic group. However, indomethacin didn't decrease MDA level. In conclusion, it may suggested that indomethacin has a neuroprotective effect by preventing apoptosis and enhancing antioxidant capacity although it failed preventing lipid peroxidation.

Poster 45

The association of Interleukin-6 -597G/A gene polymorphism in Patients with Myocardial Infarction

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Purpose: In recent years several studies show that inflammatory components may contribute every stage of cardiovascular diseases and increase the risk of myocardial infarction (MI). So, some of cytokines have been studied as potential new risk factors for MI. Interleukin-6 (IL-6) is a key pro-inflammatory and immune-modulatory cytokine and it is thought that it plays an important role in cardiovascular diseases. In this study, we aimed to investigate the association of the IL-6 nucleotide polymorphism -597 G/A with MI. Materials and Methods: 85 Control subjects, who were angiographically normal and 84 angiographically documented patients with MI, were included in this study. The mutations were determined by Light Cycler Real-Time PCR mutation detection kits. Results: IL-6 gene polymorphism, -597 G/A was not significantly associated with MI. 27,4% of subjects were heterozygote and 6,0% of subjects had mutations in -597 G/A in patients with MI. Conclusion: It was observed that there hasn't been any relation between IL-6 gene polymorphism -597 G/A and MI. This study could be carrying on more subjects or other polymorphisms of IL-6 such as -572 G/C and -174 G/C.

Poster 46

Determination of paraoxonase and aryl esterase enzyme activities in the smoking students under stres during the examination period

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Paraoxonase 1 (PON1) is an enzyme related to high density lipoprotein (HDL). This enzyme hydrolyzes some organophosphorus compounds and metabolizes toxic oxidized lipids associated with both low density lipoprotein (LDL) and HDL. Thus, the PON 1 activity in human serum is important for a given population. It usually varies due to certain polymorphisms (e.g. in the coding region (Q192R) and the 5' regulatory region (T-108C)) and the modulation

by various factors such as environmental chemicals, drugs, smoking, alcohol, diet, age, disease conditions. Since PON 1 plays a protective role in organophosphate toxicity, and, due to its antioxidant capacity, in cardiovascular disease, a better understanding of how PON1 can be modulated by environmental factors like smoking has potential toxicological and clinical consequences.

In this study, the effect of smoking on serum PON 1 levels in the students under stress during the examination period was investigated along with aryl esterase enzyme activity. 18 students (18-25 years old) who have been heavily smoking for at least two years were used as subjects. Control group was also gathered using the student population in the same age range, but not smoking at all. Blood were collected from all subjects during their examination period. Serum paraoxonase and aryl esterase levels were determined. The data were statistically analyzed utilizing SPSS 11.0 and Mann Whitney U Test. PON 1 and aryl esterase levels of the group including smoking students were found to be lower in comparison to those of the control group ($p<0.05$). Based on the data, it can be stated that low levels of PON 1 and aryl esterase activities will not provide sufficient protection against the peroxidation of LDL and in turn, it will enhance the susceptibility of the person to certain life threatening diseases, in particular, cardiovascular disease.

Poster 47

Serum oxidative and antioxidative status in patients with cataract.

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Oxidative stress is involved in development of many ocular diseases such as age-related macular degeneration, retinopathy of prematurity, retinal light damage and cataract. Reactive oxygen species are involved in this process. Oxidative stress is countered by antioxidants which are defined as substances that, at low concentrations relative to the substrate, inhibit the damage to the structural and functional molecules of the body, namely proteins, lipids, carbohydrates and DNA. In order to evaluate the relationship of total antioxidant status and total oxidant status with cataract, Total oxidant status (TOS), total antioxidant capacity (TAC), and oxidative stress index (OSI) were measured in sera of patients with cataract and healthy control subjects. The diabetic cataract patients' mean age was 62±12 years, the senile cataract patients' mean age was 66±8 years, the control groups' mean age was 64±8 years. Serum TAS and TOS levels were determined using a novel automated measurement method, developed by Erel. The percent ratio of the TOS to the TAS gave the oxidative stress index (OSI), an indicator of the degree of oxidative stress. TOS and OSI levels were significantly higher in diabetic cataract and higher in senile cataract subjects than in the control subjects ($P < 0.001$). TAC levels were lower in both diabetic cataract and senile cataract subjects than in the control subjects. But these differences were not significant when analyzed by student t test. The result of present study suggests that oxidative stress is responsible for the pathophysiology of cataract. It can be concluded that higher TOS activity could contribute to the higher risk of cataract formation. This possible pathophysiological association warrants further research.

Poster 48

Serum oxidative stress biomarkers in congenital cataract patients.

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Oxidative stress due to free radicals is related to the pathogenesis of many chronic disorders including cancer, inflammation and neurological diseases. Oxidative stress due to aging and light exposure is also considered to be associated with age-related macular degeneration and cataract. The ocular surface is chronically exposed to oxidative stress by means of ultraviolet light, oxygen in the air and changes in oxygen pressure due to blinking. The accurate assessment of oxidative stress in biological systems is a problem for all investigators working on the role of free radical damage in disease states. The concept of a single test that might reflect total antioxidant capacity (TAC) is an attractive one, and in this issue Erel et al

describe one such test. The ratio of TOS to TAC yields the oxidative stress index (OSI), an indicator of the degree of oxidative stress. OSI (arbitrary unit); TOS (mmol H2O2 equiv. /L)/ TAC (mmol Trolox Equiv. /L). To our knowledge, no investigation has been conducted to demonstrate the importance of TAC, TOS and OSI levels Childs with congenital cataract. Blood samples were obtained from healthy subjects (n = 20) and congenital cataract childs (n = 20). Venous blood samples were obtained and collected into tubes and serum was separated from cells by centrifugation at 1500×g for 10 min. Serum samples were run immediately or stored at -80°C. The congenital cataract patients' mean age was 4 (range, 1 to 7 years), the control group's mean age was 3 (range 2 to 7 years). TAC and TOS levels lower in congenital cataract subjects than in the control subjects (P >0.05). OSI level was significantly higher in congenital cataract subjects than in the control subjects (P<0.001).

Poster 49

Investigation of Some Antioxidant Enzymes Activities Depending On Cold Stress in Rat Liver Tissue

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The stress system coordinates the adaptive response of the organism to real and perceived stressors. Activation of the stress system leads to behavioral and peripheral changes to improve the ability of the organism to adjust homeostasis and increase its chances for survival. Exposure to extreme environments is a form of stress to be competed by the organism. The physiological components of stress response to cold are metabolic, circulatory and hormonal. Long-term cold exposure increases in mitochondrial volume density, capillary diameter, aerobic enzyme activity and tissue oxygen consumption. Cells can respond to oxidants with catalase (CAT), superoxide dismutase (SOD) ve glutathione peroxidase (GPX) enzymes.
The enzyme superoxide dismutase catalyzes the of into and . Catalase's functions include the decomposition of to and . Glutathione peroxidase reduces H2O2 to H2O by oxidizing glutathione.
In this study, catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPX) enzyme activities were investigated depending on cold stress in rat liver tissue. Twelve male wistar rats were used in this study. Animals were exposed +10 °C cold during a week. In conclusion, catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPX) enzym activities were decreased depending on cold stress.

Poster 50

Investigation of Some Antioxidant Enzymes Activities Depending on Adrenomedullin Treatment In Rat Liver Tissue

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Adrenomedullin (AdM) is a 52 amino acid peptide, with a potent hypotensive/ vasodilatory action. There are a lot of evidences that adrenomedullin plays important roles in very biological functions as otocrine, paracrine and endocrin mediators. Plasma AdM levels are increased in various diseases releated with oxidative stress such as hypertension, arteriosclerosis, diabetics and heart failure. Therefore, AdM is suggested to be a potent antioxidant and anti-hypertensive peptide, playing a critical role as a therapatic agent.
The enzyme superoxide dismutase catalyzes the of into and . Catalase is a common found in nearly all living organisms. Its functions include the decomposition of t o and . Glutathione peroxidase reduces H_2O_2 to H_2O by oxidizing glutathione.
In this study, catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPX) enzyme activities were investigated depending on adrenomedullin treatment in rat liver tissue. Animals received intraperitoneal (i.p) injection of AdM (2000ng/kg body weight) once a day during a week. In conclusion, the groups treated AdM catalase enzyme activities were decreased compared to control. There was no differences found statistically in SOD enzym activity compared with control. GPX enzym activities were increased in rat liver tissue compared to control. In conclusion, AdM has compensating effects on some antioxidant enzymes in liver tissue.

Poster 51

Effects of L- carnitine and selenium on EEG records in wireless (2.45 GHz) electromagnetic field exposed rats

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Daily exposures to various types of magnetic fields are increasing in human environment. Extremely low frequency electromagnetic fields (EMF) from power lines and public transportation systems, high- frequency EMF from mobile phones and computers, and wireless communication devices are the most familiar sources of exposure. Possible biological effects due to exposure various types EMF have become considerable public interest and concern EMF of Wi-fi and ISM frequency on wireless communication devices and using laptops may affect EEG records of biological systems by increasing free radical, which appear mainly to enhance oxidative stress, and by changing the antioxidative activities of brain thus leading to oxidative damage. L-carnitine and selenium (Se) exhibits antioxidant properties and several studies suggest that supplementation with antioxidant can influence EMF exposure induced brain toxicity although there is no info on effects of 2,45 GHz EMF on EEG records of rats. The present study was designed to determine the effects of 2,45 GHz EMF on the EEG records, and the possible protective effects of L-carnitine and Se on EEG toxicity induced by the EMF. Aim of the study was investigate effects of L-carnitine and Se effects on EEG changes in 2,45 GHz EMF exposed rats. In the current study, 30 male Wistar albino rats were used. After one week adaptation process, animals have been randomly divided to five equal groups as follows. Group 1: control group, Group 2: sham control group, Group 3: 2.45 GHz exposed group, Group 4: 2.45 GHz + L-carnitine (100mg/kg /day) ip, Group 5: 2.45 GHz + Se (1,5mg/kg/over day) ip. At the end of the 4th week, EEG records were taken from all groups. The EEG records were changed by 2.45 GHz expose although L-carnitine and Se may have protective effects on the changes. There is need further studies than in results of the study for clarifying the subject.

Poster 52

Comparing the hematological parameters and blood gases in the stable and attack periods of the patients with bronchial asthma and chronic obstructive pulmonary disease

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The attacks which are observed during the course of bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) are the important reasons for mortality and morbidity. Attack frequency proves to be higher in some patients, but its causes are not known. This study has been done in an attempt to contribute to the etiopathogenesis of BA and COPD by comparing the hematological parameters and blood gases during the stable and attack periods of these diseases. Hematological parameters and blood gases of 16 patients with BA and 17 patients with COPD who had been included in this research were studied in the stable and attack periods. Statistical analyses have been done through SPSS 11.0 software for windows and through the Student's t Test from the parametric tests. As a result of the comparisons of the hematological parameters in the attack and stable periods, a statistically significant difference which has proved to be higher in the attack period was found in patients with COPD regarding the values of white blood cell (WBC) ($p = 0.008$), neutrophil % (NE%) ($p = 0.000$), eosinophil % (EOZ%) ($p = 0.000$), NE ($p = 0.010$), EOZ ($p = 0.005$), whereas no significant difference was observed in patients with BA ($p > 0.05$). Also, as a result of the comparisons of the values of blood gases in the attack and stable periods, no significant difference was detected in patients with BA ($p > 0.05$). On the other hand, a statistically significant difference which has proved to be lower in the attack period was found in patients with COPD regarding

the value of pO_2 ($p = 0.000$). These results indicate that there occurs an increase during inflammation process in the attack periods of patients with COPD. The inflammation process is considered to be capable of increasing the release of both mediator and free radicals, and thus causing the air current to be limited by the bronchial obstruction and oxidative stress to increase.

Poster 53

The Effects of Cinnamon and Sugar Tea Extracts on Oxidative Stress in STZ-NA Diabetic Rats*

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Diabetes mellitus (DM) is a syndrome characterized by abnormal insulin secretion, derangement in carbohydrate and lipid metabolism, and is diagnosed by the presence of hyperglycemia.

Oxidative stress in diabetes mellitus may play an important role in the pathogenesis of early and long term complications of human diabetes. Protein glycation and glucose autoxidation can generate free radicals that can catalyze lipid peroxidation. Other potential mechanisms of oxidative stress include the reduction of anti-oxidant defense.

The aim of the present study was to determine the effects of cinnamon and sugar tea extracts on antioxidant defense system in STZ-NA diabetic rats.

Female Sprague-Dawley rats of 2–3 months of age were used in this experiment. Diabetes was induced by intraperitoneally administration of nicotinamid (NA) and streptozotocine (STZ). These animals were used for the experiments 12 weeks after diabetes was induced. Diabetic groups were treated with cinnamon and sugar tea extracts during to 30 days. After the experiments tissues and blood samples were collected from the rats using appropriate techniques under ether anaesthesia.

We measured antioxidant enzymes activities such as glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT) and malondialdehyde (MDA) in liver homogenate.

In this study we found that; tissue SOD levels were increased at sugar tea and sugar tea+cinnamon (250 mg/kg) treated diabetic groups; MDA levels were decreased at cinnamon (250 mg/kg) and sugar tea+cinnamon (250 mg/kg) treated diabetic groups according to diabetic control group; GPx levels were decreased at diabetic control groups although it were increased at cinnamon and sugar tea treated diabetic groups according to diabetic control groups. There were no differences in CAT activities among the all groups.

Poster 54

Effect of Strontium Ranelate Treatment on Oxidative Stress in Ovariectomized Rat Liver

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Strontium exists in varies food substances and tap water in very small quantities. It is similar to calcium. The ranelate form of this element is usually administered at therapeutic doses. Strontium ranelate enhance the formation, but, reduces the resorption of bones. It is composed of two stable non-radioactive strontium atoms and ranelic acid compound. In literature it has been shown that strontium ranelate prevents bone loss by reducing bone resorption and enhancing its formation in ovariectomized rats. Clinical studies also support the use of strontium ranelate in the treatment of postmenopausal osteoporosis. However, it is not certain that the use of strontium ranelate alters the antioxidant/free radical balance. In this study, the influence of the strontium ranelate treatment on oxidative stress in the ovariectomized rats was investigated. 28 Wistar Albino rats were used and they were divided into 4 groups. Each group consist 7 animals. Group I was determined as the control group and was not treated. Group II was received strontium ranelate for three months. Group 3 was ovariectomized and not received any treatment. Group 4 was administered strontium ranelate for three months following the three month-recovery period after ovariectomization operation. Liver tissues of animals in all groups were isolated and lipid peroxidation levels were determined using malondialdehyde (MDA). To determine the antioxidant levels glutathione peroxides (GSH-Px) and catalase levels were investigated. All data were statistically analyzed using SPSS 11.0 program and Mann Whitney U Test. In the end of this study, it was found that MDA levels increase significantly in the Groups of 2, 3, and 4 in comparison to the control group. Also, GSH-PX level

decreases in Group 3, but increases in Group 4, upon comparison with the control group. Catalase level in Group 4 was found higher than the control group. Based on the results, it can be stated that the treatment with strontium ranelate triggers lipid peroxidation in the body and the antioxidant system involves compensating this condition.

Poster 55

Investigation of Lipid Peroxidation in Isolated Muscle Tissue Following In Vitro Application of Indoxacarb

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Pesticides have an impact on the environment because of their widespread use in agriculture to enhance crop production. Pesticides are unique in that they are intentionally released into the environment to protectagricultural products from pests. However most of them are neither specific nor selective to pest and therefore are hazardous to nontarget organisms as well as humans.. Exposure to several classes of pesticides is known to increase lipid peroxidation a metabolic endpoint of reactive oxygen species produced in vivo. Indoxacarb is an insecticide in a new class of chemistry with a new mode of action now registered for use on apples and pears. Indoxacarb is in the oxadiazine class of chemistry and it works as a sodium channel blocker. In this study, we investigated the effects of indoxacarb administration in isolated frog sartorius muscle on lipid peroxidation levels and antioxidative enzymes. 16 adult frogs (*R. ridibunda*) were used in this study. After decapitation of all frogs, their M. sartorius muscles were isolated. The isolated muscles were divided into experimental (n=8) and control group (n=8). Muscles of experimental group were incubated in a solution of indoxacarb (10 mM) at room temperature for one hour. On the other hand, the control group was incubated in saline at room temperature for the same period of time. In order to determine the lipid peroxidation in two groups, malondialdehyde (MDA) levels were investigated. Antioxidant activity in two groups was found by determining the catalase levels. The MDA levels and the catalase activity values of the group incubated with indoxacarb were statistically higher than those of the control group ($p<0.05$). Based on the results, it can be stated that indoxacarb induced intoxication of muscle tissue enhances the lipid peroxidation, but the tissues are protected against oxidative stress by antioxidant system.

Poster 56

N-acetyl L-cysteine depress 50 Hz electric field-induced lung impairment in guinea pigs: Assessment of heme oxygenase-1, protein carbonyl content, malondialdehyde, nitric oxide, hydroxyproline

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The extremely low frequency (ELF)-electric (E) field expoure which is caused by power lines and electrical appliances due to development of technology has raised the research activities in many countries to determine its effects on living organism. In order to explain the epidemiological observations associated with ELF electromagnetic (EM) field exposure, experiments have been conducted in multiple laboratories to examine alterations of biological functions by EM field. Severalstudies have indicated risk of cancer among people and, in particular, among children living in homes where magnetic fields are measured near power lines. People near power lines are usually exposed to electric fields in different directions, strengths, and periods in the range of several kV/m. The minimum E field level of a 750 kV power line is 1 kV/m at cord maximal height, but it is 12 kV/m at cord minimal height.

We aimed to determine the influences of ELF E field exposure (50 Hz, 12 kV/m, 7 days/ for 8h/day) on oxidative and nitrosative stress and collagen synthese in lung tissue of guinea pigs. To this end, we investigated the pulmonary levels of heme oxygenase-1 (HO-1), protein carbonyl content (PCO), Malondialdehyde (MDA), Nitric oxide (NO) and Hydroxyproline (HP). We also examined the success of external antioxidant treatment such as N-acetyl-L-cysteine (NAC) on ELF E fields-induced stress. PCO level significantly increased ($p<0.05$) but change in HO-1, MDA, NO and HP levels were insignificant ($p>0.05$) for electric field exposure groups compared with sham. PCO and HO-1 levels in groups treated with N-acetyl-L-cysteine (NAC) were significantly lower than E field applied groups ($p<0.05$).

We conclude that NAC has protective effect on electric field induced stress. Decrease in radical levels in NAC applied groups compare to E field exposed groups shows that NAC is successful at removing E field exposure induced radicals

Poster 57

Antibody Response to The Human Stress Protein BIP in Ankylosing Spondylitis

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Chaperones have hitherto been recognised as having only intracellular functions to protect cells from stress by preventing denaturation of proteins and thereby apoptic cell death. Bip (Grp 78) is a key chaperone of endoplasmic reticulum (ER) function due to its roles in protein folding and assembly, targeting misfolded protein for degradation, and controlling the activation of ER stress sensors. ER stress has been suggested to be involved in various diseases, such as diabetes, cardiovascular diseases, neurodegenerative diseases, and cancer. Ankylosing Spondylitis (AS) occurs due to misfolding of HLA-B27 protein. This misfolding causes ER stress and this stress trigger autoimmunity. Theaim of the present study is to investigate antibodies against BÝP which are suggested to present in HLA-B27-associated Ankylosing Spondylitis. Thirty serum samples from patients with Ankylosing Spondylitis and thirty controls were analysed for the presence of Anti BIP by means of Enzyme Ýmmunosorbent Assay using method of Bodman. There were no significant differences between patients and controls in the samples. Although HLA-B27associated AS is suggested to cause ER stress, the indirect marker of ER stress anti BIP was absent in our patient group.The mechanism by which Grp78 autoimmunity is triggered or initiated is still remaining unclear. Further investigations are still needed to be performed.

Poster 58

Does hypercholesterolemia alter relaxation response to isoproterenol in rat detrussor strips?

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Function of the urinary bladder (UB) to store the urine and to evacuate stored urine in time depends on detrussor contraction and relaxation. Smooth muscle cell functions and signal transduction is affected by membrane cholesterol alterations. We investigated the effect of hypercholesterolemia on adrenergic relaxation response in rat detrussor strips. 250-300 gram adult male Sprague-Dawley rats fed with standard (C, n=9) or 4% cholesterol containing chow (HC, n=6) for four weeks were used. Serum lipid profiles and the tissue cholesterol levels were measured. Strips were precontracted by 10^{-5} M carbachol, after stabilization, cumulative dose-relaxation curves to isoproterenol (10^{-9}–10^{-4}M) were obtained. Relaxing effect of isoproterenol was also studied in the presence of L-NAME (10^{-4} M) and methochtramine (10^{-5} M). Data was analyzed statistically. Despite the increased plasma cholesterol in HC group (C:87.8±3.8, HC:170.2±11.1 mg/dL, $P<0.001$), tissue cholesterol did not change (C:6.7±2.1, HC:10.2±1.5 µg/g protein). Maximal relaxation with isoproterenol was observed in HC group (C:35%, HC:49%), relaxation curves were not different between groups. L-NAME did not change the effect of isoproterenol in both groups. Although methochtramine augmented the relaxing effect of isoproterenol in the control group($P<0.05$), it did not change the response in HC group. Since the relaxation response to isoproterenol in carbachol stimulated detrussor strips is more prominent in the hypercholesterolemic rats, it can be suggested that mechanisms involved in the relaxation of the UB are sensitive to cholesterol alterations. This enhanced relaxation response may be due to the lack of the relaxation limiting action of M_2 receptor activation.

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Poster 59

Organophosphate pesticides (OPs) and oxidative stress

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Residual amounts of organophosphate pesticides (OPs) have been detected in the soil, water bodies, vegetables, grains and other food products. The widespread use of organophosphate pesticides in agriculture, public health and household environments results in continuous exposure of human populations.

In agriculture, organophosphate pesticides are commonly used for achieving better quality products, increased production rate and controlling pest population. However, they are also toxic substances. These pesticides lead to generation of reactive oxygen species such as hydrogen peroxide (H_2O_2), superoxide ($O^{2\cdot}$), and hydroxyl ($^{\cdot}OH$), which have harmful effect on human health. The reactive oxygen species may react with biological macromolecules, cause enzyme inactivation, DNA damage and initiate lipid peroxidation in tissue by accumulating in polyunsaturated fatty acid (PUFA). If these oxidants can not be removed by antioxidant defense systems they cause oxidative stress. As a result of oxidative stress, pathological formations like DNA damage and cancer are observed. We researched malondialdehyde (MDA) indicator of oxidative stress end product of lipid peroxidation on twelve agriculture workers' in blood serum. Eight people not effected directly by pesticides are chosen as a control group. Concentration of MDA analyzed by UV spectrophotometer. According to the analyze, it is determined that the MDA concentration in blood serum is higher in agriculture worker than control group. This high MDA concentration can show the oxidative stress as one of the indicator. Tablo 1 shows MDA concentrations of agriculture workers and control group.

Tablo1. Concentrations of agriculture workers and control group

	MDA
Control n=8	0.32 µmol/L
Agriculture workers n=12	1.4 µmol/L

Poster 60

Antioxidant or/and prooxidant activity of new phenyl-piperazine derivatives

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Oxidants play a significant role in the pathogenesis of a inflammation and rheumatoid arthritis leading to oxidative stress. The processes associated with inflammatory responses are complex and often involve of reactive oxygen species. There are many mediators, which initiate and amplify the inflammatory response such as histamine, serotonin and metabolic products of arachidonic acid. In this study, new phenylpiperazine derivatives of hydantoin differ in area of phenylpiperazine phenyl ring, at 3-N of hydantoin ring as well as in area of hydroxypropyl chain were synthesized and evaluated for anti-oxidant activity. Next, the Trolox equivalent antioxidant capacity (TEAC) assay was used with slight modifications, measuring the scavenging capacity of a compound to the blue–green ABTS cationic radical resulting in a colorless product. The amount of ABTS•+ scavenged by the antioxidants in the investigated compounds was measured after a 10 sec and 30 min incubation at 37^{O}C, by the degree of decolorization, measured spectrophotometrically at 414 nm. In our study, the TEAC value reflects the scavenging capacity of used dose of phenyl-piperazine derivatives expressed as the equivalent concentration (in mM) of Trolox, a water-soluble Vitamin E analogue. To a fixed concentration of an antioxidant, ABTS in a variable concentration (1 mM, 2,5 mM, 5 mM, 10 mM) was added. In conclusion, it was found out that the compounds possess antioxidant or/and prooxidant activity. However, the mechanism(s) responsible for the anti-oxidant activity of the new phenyl-piperazine derivatives remain to be elucidated, as is the overall clinical impact of this property and should be further investigated.

Poster 61

Effect of Sulfite Treatment on Total Antioxidant Capacity, Total Oxidant Status, Lipid Hydroperoxide and Total Free Sulphydryl Groups Contents In Normal and Sulfite Oxidase Deficient Rats Plasma

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Sulfites, which are commonly used as preservatives, are continuously formed in the body during metabolism of sulfur-containing amino acids. Sulfite oxidase (SOX) is an essential enzyme in the pathway of the oxidative degradation of sulfite to sulfate protecting cells from sulfite toxicity. This article investigated the effect of sulfite on Total Antioxidant Capacity (TAC), Total Oxidant Status (TOS), Lipid Hydroperoxide (LOOH) and total free sulphydryl groups (-SH) contents in normal and sulfite oxidase (SOX) deficient male albino rats' plasma. For this purpose rats were divided into four groups: control (C), sulfite treated (S), SOX-deficient (D), and sulfite treated SOX-deficient (DS) groups. Sulfite oxidase deficiency was established by feeding rats a low molybdenum diet and adding to their drinking water 200 ppm tungsten (W). Sulfite (70 mg/kg) was administered to the animals via their drinking water. SOX deficiency together with sulfite treatment caused a significant increase on the plasma LOOH and total oxidant status levels. -SH content of rats plasma significantly decreased by both sulfite treatment and SOX deficiency compared to the control. There was also significant decrease in plasma TAC level by sulfite treatment. In conclusion, sulfite treatment affects the antioxidant/oxidant balance of the plasma cells of the rats toward oxidants in SOX deficient groups.

Poster 62

The effects of various propolis concentrations on biochemical and hematological parameters of rainbow trout (*Oncorhynchus mykiss* Walbaum, 1792)

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Propolis is a natural product that honeybees collect from plants. Propolis is a sticky dark-colored material showing a very complex chemical composition. The major compounds of propolis are flavonoids and caffeic acid esters which are also responsible for biologic activity of propolis.

In this study, biochemical parameters and hematological parameters in blood tissue of rainbow trouts exposed to various concentrations of propolis were determined. In the present study, the effect protective doses of propolis were compared to control group in hematological parameters and biochemical parameters. A statistically significant increase ($P<0.05$) in total leukocyte count (WBC), as well as granulocytes values for rainbow trout exposed to 20 ppm and 30 ppm propolis doses groups was found. However, there was a statistically significant decrease in agranulocytes values ($P<0.05$), and also in erythrocyte, hemoglobin and hematocrit values for fish exposed to 30 ppm and 20 ppm propolis, but MCV and MCH values ($P<0.05$) significantly increased. The erythrocyte number, hemoglobin amount and hematocrit value of 30 ppm propolis-treated rainbow trouts were significantly lower than that of control animals ($P<0.05$). A statistically significant changes ($P<0.05$) were found with administration of 20 and 30 ppm propolis in values of biochemical parameters in blood. Hematological and biochemical parameters in various doses -treated rainbow trout was investigated, and the effects of 10 ppm propolis were outlined, evidencing their preservation role on hematological and biochemical parameters. The results show that propolis has an important effect on biochemical parameters and hematological parameters at 10 ppm levels, whereas 20 ppm and 30 ppm dosage appears to be unfavourable for blood of rainbow trouts. This study opens a new perspective on the investigation of propolis biological properties, mainly with respect to the hematological and biochemical parameters in blood of rainbow trout.

Poster 63

The effects of the synthetic organoselenium compounds on total RNA levels in some tissues of DMBA-induced albino wistar rats

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The effects of novel synthetic organoselenium compounds (SeI and SeII) on total RNA in tissues of DMBA-induced rats were investigated. DMBA (7,12-dimethylbenz[a]anthracene) is a polycyclic aromatic hydrocarbon (PAH) known to cause tumors in rats. Selenium is an essential trace element. Two series of organoselenium compounds were synthesized. Synthetic organoselenium compounds can be tailored to achieve greater chemopreventive efficacy with minimal toxic side effects by structural modifications. Therefore, we undertook the present study to evaluate the chemopreventive potential of the novel synthetic organoselenium compounds (SeI and SeII) in the well-established DMBA-treated rat model by monitoring the extent of total RNA. Determination of total RNA levels was studied as for deriving introductory information about the enzyme levels which plays a central role the control and secretion of stress hormons. Total RNA levels were found to be significantly increased by the effect of DMBA in hypothalamus and adrenal medulla of rats ($P<0.05$). Total RNA levels was also decreased in heart tissue of DMBA treated groups ($P<0.05$). It was also found that total RNA levels in SeI and SeII treated rat tissues was also a statistically significant convergence in comparison to the control group values ($P<0.05$).

Poster 64

Natural plant antifreeze causes oxidative stress-induced liver toxicity in rat: A pilot study

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Previous plant studies have shown that the generation of free radicals is increased by Thiobacillus administration due to oxidation of iron. Natural plant antifreeze (NPA) is containing Thiobacillus and NPA has been taking by animal and human. We investigated effects of NPA administration on oxidative stress-mediated pancreas and liver toxicity in rats by evaluation of lipid peroxidation (LP), total glutathione (GSH) and nitric oxide (NO) levels. Twenty nine male Wistar rats were randomly divided into two groups. First group (n=9) was used as control. 0.35 ml of NPA ($3.5x10^3$ bacillus in 0.35 ml)/day was given to rats consisting second group (n=20) for 40 days. LP and NO levels in liver and pancreas, and body weight gain were significantly ($p<0.001$) higher in NPA group than in control group although GSH levels decreased. In conclusion, NPA had toxic effects on liver and pancreas by increasing free and nitrogen radical and suppressing GSH levels.

Poster 65

Possible Health Effects of Wireless Devices

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Wireless computer networks have become common place in our environment. Wireless hotspots are found in many public areas and, increasingly, in homes and schools. Wireless networks use low-powered radiofrequency (RF) transmitters called access points to communicate with other low-powered transmitters called client cards that are located in users' laptop computers or other portable equipment. Nearly all of these wireless networks use Wi-Fi technology. Despite the very low power at which wirelessnetworks operate, some citizens have questioned the possibility that the RF signals associated with the networks might pose a health threat. This article gives a brief summary of the biological effects and health aspects of RF radiation wireless devices.

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Poster 66

An investigation about the effects of RF technology on human tissues.

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With the increasing use of Radio Frequency (RF) waves in recent five decades, the health effects of electromagnetic radiation is an important investigation subject. While the RF is well known, it is difficult to investigate the health effects of RF radiation, because of the komplex metabolism of human body. However, by the experimental and theorical studies, a lot of significant health effects of RF radiation have been discoveried. But, there are probabilities that RF can have much more adverse health effects. In this study, the adverse consequences by RF radiations have been evaluated and its interaction with tissues have been investigated. It is very important, in recent years, to have knowledge about the effects of RF radiation, because of increasing use of mobile phones and increasing TV and radio stations. Investigations show that, there are no significant health effects of RF radiation at low intensity. But, for a long exposure time at high intensity, there are some adverseconsequences. So, for the RF sources, there are national and international intensity limits. For human exposure, as long as one is exposed to the radiation below these standards, there is no definite adverse effects of RF radiation for human health. So, it is wrong to say the RF radiation is very harmful. On the other hand, it is wrong to say RF energy does not induce adverse health effects; it depends on frequency, intensity and exposure time.

Poster 67

Antioxidant effect of green tea and grape seed on oxidative stress

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Cells continuously produce free radicals and reactive oxygen species as a part of metabolic process. These free radicals are neutralized by a complex antioxidant system. Oxidative stres is an imbalance between reactive oxygen species or free radicals and antioxidant system and can cause irreversible damage at important cell compartments. Tea (*Camellia Sinensis*) is the second largest consumed beverage in the world. Epidemiological studies have shown that a high intake of tea is associated with a low incidence of carcinogensis. This apparent anti-carcinogenic activity is believed to be associated with antioxidant activity, especially the catechin antioxidant components from gren tea. Oral supplementation with tea extract can lead to an increase in *ex vivo* plasma antioxidant activity. Antioxidant components from green tea are principally the catechin derivatives, e.g. epigallocatechin (EGC), epigallocatechin gallate (EGCG), epicatechin (EC), epicatechin gallate (ECG).

Various naturally occurring antioxidants are known to be present in grape seeds, notably phenolic compounds, whose content may range from 5 to 8% by weight . It is well established that grape seeds contain principally flavonoids such as catechins, epicatechin and epicatechin-3-Ogallate, and dimeric, trimeric and tetrameric procyanidins. These molecules possess a structure that confers on them an antioxidant property, which has been demonstrated to exert a novel spectrum of biological, pharmacological, therapeutic, and chemoprotective effects against oxygen free radicals and oxidative stress.

Dietary intake of natural antioxidants can neutralize harmful free radicals and their noxious tissue- and organ-damaging effects and may be an important defense mechanism of our body against oxidative stress.

Poster 68

Effect of L-Carnitine on Doxorubicin-Induced Liver Damage in Rats

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Doxorubicin (DOX) is a chemotherapeutic agent, which is widely used in cancer treatment. The most common side effect of DOX is on cardiovascular system. However, there are some studies suggesting a constituonal change on liver, kidney, pancreas and small intestine tissues related to DOX administration. Various methods have been tried to prevent DOX-induced side effects. In this study, we aimed to investigate whether L-Carnitine (LC), a fatty acid co-factor, has a protective effect on hepatic tissue against a possible DOX-induced damage. Twenty-four male Wistar albino rats weighing between 200-250 grams were included in this study. All animals were divided into three equal groups: Group-I (controls), Group-II (2,5 mg/kg of DOX injected group) and Group-III (single dose of DOX and ten dose of 50 mg/kg LC given group). After ten days, liver tissues removed to study antioxidant values and histopathologically examined. DOX administration resulted in prominent lipid peroxidation. Beside this, it caused a decrease in reduced glutathione, beta-carotene, vitamins A, C and E levels and glutathione peroxidase activity in liver. The parameters were slightly affected by LC administration and no difference was found between Group-II and Group-III . In liver tissue samples of Group-II, there were mononuclear cell infiltrations, vacuolar degeneration, hepatocytes with basophilic nucleus and sinusoidal dilatations. Similiar findings were present in Group-III except that of a slight decrease in mononuclear cell infiltration, but this difference was not istatistically significant. In conclusion, DOX caused increase in lipid peroxidation levels of liver in rat although antioxidant values decreased. The changes did not recovered by LC administration.

Poster 69

50 Hz horizontal electric field effect on lipid peroxidation and antioxidant enzyme activities

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Living organisms are developed with natural electric and magnetic fields for millions of years. However, the level and the type of the electromagnetic fields that humans exposed are changed due to technological improvements and increased need of electricity. For instance, power lines, household appliances; transformers are certain exposure sources of electric (E) and magnetic fields. Level of exposed electromagnetic fields mainly differs with respect to the polarization of the field and distance from the source. In this study, effect of 50 Hz horizontal electric field in the strengths of 0.3 kV/m, 0.6 kV/m, 0.8 kV/m and 1 kV/m on lipid peroxidation and antioxidant enzyme systems. Study was executed by 50 guinea pigs totally, 10 animals in one group. Groups were determined as one control and groups of E field exposure in 4 different strengths (0.3 kV/m, 0.6 kV/m, 0.8 kV/m and 1 kV/m). Exposure durations are determined as 3-day-exposure period for 8 hours daily (between 9 a.m. and 5 p.m). After the last exposure day, the guinea pigs were anesthetized by the injection of ketamine and xylazine and killed by decapitation. Malondyaldehide (MDA) levels and adenosine deaminase (ADA), xanthine oxidase (XO), myeloperoxidase (MPO), superoxide dimutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT) activities were analyzed in the extracted brain tissues. Statistical analyses of the obtained results were carried out using SPSS software (SPSS 11.5 for windows, SPSS Inc., Chicago, USA). The one-way analysis of variance (ANOVA) and post hoc multiple comparison tests were performed on the data of biochemical variables to examine the difference among groups. The result of the analysis revealed no difference in all exposure groups with respect to controls ($p>0.05$). In the light of these results, effects of stronger electric field exposure should be taken into consideration in further studies.

Poster 70

Mobile phone radiation effects on oxidative and nitrosative stress: role of antioxidant treatment.

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Biological effects of mobile phones are one of the scientific subjects that become popular recently since it is the unique electromagnetic field source that humans carry with themselves in daily lives. Today relation between production of reactive oxygen, nitrogen and mobile phone radiation is mentioned in certain researches.
In this research, hepatic effects of 10 and 20 minutes daily exposure to 1800 MHz GSM mobile phone radiation during 1 week on oxidative and nitrosative stress and antioxidant enzyme activities were investigated. Furthermore, in this study, it is observed if the antioxidants taken as nutrition may reduce the adverse health effects of mobile phone radiation. With this aim, we used epigallocatechin-3-gallete (EGCG) which is one of the green tea polyphenols and known as a good antioxidant. In the experiment, Guinea pigs were exposed to mobile phone radiation (GSM 1800, 0.4 W/kg) during 10 minutes and 20 minutes daily for a week. After the last exposure day, the guinea pigs were anesthetized by the injection of ketamine and xylazine and killed by decapitation. The levels of malondyaldehide (MDA), nitrate (NO_3), nitrite (NO_2), total level of nitric oxide (NO_x) and myeloperoxidase (MPO), superoxide dimutase (SOD), glutathione peroxidase (GSH-Px), were analyzed in the extracted liver tissues. Statistical analyses of the obtained results were carried out using SPSS software (SPSS 11.5 for windows, SPSS Inc., Chicago, USA). The one-way analysis of variance (ANOVA) and post hoc multiple comparison tests were performed on the data of biochemical variables to examine the difference among groups.
The result of the analysis showed that mobile phone exposure changed the hepatic level of MDA, NO_3, NO_2 and NO_x, also activities of MPO, SOD and GSH-Px with respect to control. Moreover, it is observed that EGCG administration depressed the effects of mobile phone radiation in these parameters. In other words, EGCG has pro-oxidant effect on hepatic oxidative and nitrosative stress which caused by mobile phone radiation. Since health effects of mobile phones are not definite yet, individual health precautions may be realized by eating foods rich from antioxidants in order to prevent adverse health effects of mobile phones.

Poster 71

Vitamin E and Selenium Combination Modulates biochemical values in Pregnant Rat Exposed to 7 Gray Radiation: Effects of hematite

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Radiation may affect biological systems by increasing free radical, which appear mainly to enhance lipid peroxidation (LP), and by changing the antioxidative activities of liver thus leading to oxidative damage. Vitamin E (VE) as a major fat soluble antioxidant and selenium (Se), an active component of glutathione peroxidase, exhibits antioxidant properties and several studies suggest that supplementation with antioxidant can influence 7 gray radiation exposure induced liver biochemical values changes. There are some recent publications that hematite including walls may be having also protective effects on radiation exposure. In recent years, there has been a need for compact shielding design such as self-shielding of a radiation source or upgradation of radiation machinery in existing facilities. In these cases, high performance shielding materials are needed. Generally, the radiation strength becomes stronger when machinery is upgraded. The present study was designed to determine the effects of radiation on the liver biochemical system system, and the possible protective effects of vitamin E selenium combination on liver toxicity induced by radiation in walls with hematite (%50) in 2 cm thickness.

Forty-eight pregnant and 48 non pregnant female Wistar albino rats were divided into two groups namely hematite and concrete. Each of the two groups were divided four subgroups namely control, Se and VE administrated group, pregnant control and pregnant plus VE+Se group. VE (100 mg/kg) and Se (1.5 mg/kg) administrated VE and Se received groups over day and for 19 days. Radiation in a dose of 7 gray for 4 min was given at 5th and 12th days of experiment

Total Bilirubin, direct bilirubin, LDH and ALP levels were higher in pregnant groups than in non pregnant groups. Direct bilirubin, LDH and GGT levels both in pregnant and non pregnant groups were lower in VE+Se administrated groups than in controls. There are no statistically important protective effects of hematite in 2 cm thickness on investigated values.

It can be concluded that VE+Se may prevent 7 gray radiation-induced biochemical values changes in blood serum by strengthening the antioxidant defense system although there is no significant effects of the concrete slabs with that thickness.

Poster 72

Inhibition of Telomerase Activity by Tannic Acid in MCF-7 Cell Line*

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The hydrolysed tannins, commonly called tannic acid, are polyphenolic compounds. Tannic acid is found in a variety of common foods including nuts, beans and grapes. Tannic acid has also been recently recognized as possessing anti-carcinogenic, anti-oxidants, anti-mutagenic, anti-microbial, anti-allergic, anti-inflammatory and astringent properties. Telomerase is an RNA-dependent DNA polymerase with reverse transcriptase activity that adds hexameric repetitive sequences (TTAGGG) to chromosome ends in dividing cells to ensure chromosomal stability and prevent ageing. Regulation of telomerase activity in human cells plays a significant role in the development of cancer. In the study, we aimed to investigate the effects of tannic acid on telomerase activity in MCF-7 cell line. These cells were incubated for 24, 48 and 72 hours with 25, 50 and 100 μM concentrations of tannic acid. Telomerase activity was determined by the telomere amplification repeat protocol (TRAP assay) using the TeloTAGGG Telomerase PCR ELISA ^{PLUS} kit. Tannic acid inhibited telomerase activity in MCF-7 cells in a dose- and a time- independent manner and it was obtained that tannic acid as a potent inhibitor of telomerase activity in MCF-7 cells.

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Effects of Resveratrol on Telomerase Activity in Caco-2 Cell Line*

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Telomerase, a specialized ribonucleoprotein, plays an essential role in cell proliferation as a protective mechanism against end-replication problem by adding TTAGGG repeats to the telomeres. Most normal human cells have no detectable telomerase activity, but it is observed in most cancer cells. Resveratrol (3, 4', 5 trihydroxystilbene) is found in many plants, including grapes, peanuts, berries and root of Polygonum cuspidatum. It is known as an antioxidant, anti-carcinogenic, anti-inflammatory, anti-mutagenic, anti-proliferative, antiviral, antibacterial, and estrogenic and vasodilator agent. In our study we aimed to investigate the effects of resveratrol on telomerase activity in CaCo-2 cell line. CaCo-2 cell line was cultured and then exposed to different concentrations (25, 50 and 100 μM) of resveratrol for various periods (24, 48 and 72 h). After treatments, telomerase activity was determined using TeloTAAGGG Telomerase PCR ELISA^{PLUS} kit. Our data show that resveratrol inhibit dose- and time-independent telomerase activity of CaCo-2 cells. In this study, we found that resveratrol may be potent inhibitor of telomerase activity in CaCo-2 cell line.

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Effect of Be^{2+} on the membrane systems.

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Bilayer lipid membranes (BLM) and liposomes are commonly used as models for cell membranes to study their interaction with inorganic ions. The electric field distribution at the boundaries of phospholipids membranes was intensively studied in many different aspects concerning its biological importance. It was previously shown that the principal electrostatic and thermodynamic effects of Be^{2+} at the model membrane systems are in good agreement with Gouy-Chapman-Stern theory of diffuse double layer and theory gives the value of binding constants for Be^{2+} about $400M^{-1}$ and 10^4 M^{-1} for uncharged phosphotidyl choline (PC) liposomes in gel and liquid-crystalline states of the lipids, respectively. In comparison with other divalent cations Be^{2+} adsorption is about 100 times more effective for model membrane systems and induces cooperative changes of the surface properties of the membrane: changes of polar head group conformation of lipids and reorientation of water molecules near the membrane. The present study includes also the influence of Be^{2+} on the light-induced membrane potential of the plasmatic membranes of water plant *Elodea Canadensis*. It was established that the presence of the Be ions in the medium decreases the magnitude of the membrane potential and its depolarization speed, also causes disappearing of the primary transition phase. It was supposed that Be^{2+} influences on the redox type proton pumps of the plasmatic membranes by depressing their functioning.

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