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INTEGRATIVE POWER OF PATHOPHYSIOLOGY IN POSTGENOMIC ERA OF PRECISION MEDICINE

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From a broader prospective, the living human body may be viewed as an open system with the permanent import and export of mater/energy and information with the environment. Living body is fully dependent on oxygen, macronutrients and some micronutrients import. Daily produced and used biological energy enables structural and functional channelling of informational exchanges between the genome and environmental demands. In addition, some categories of macromolecules, generated within the body subsystems, serve as the information-containing and conveying units. The information and energy interplay serves as a driving principle that maintains the basic structure and physiology of the body. From the conception of zygote on, throughout development, growth, maturation and body involution, the bi-directional open system is governed by a set of internal rules. Quantity and quality of human body responses are guided within the limits of life compatibility. At the level of clinical phenomenology body physiology shows a high reactive variability, adaptive and chronobiological plasticity. Genome provides basic biological information pool which is used and maintained during the individual life span. Transcriptomic, proteomic and reactomic genome expression is guided by the permanent physiological demands. Self-maintenance and functional performance from cellular to whole-body level may be analysed as a response to the environmental conditions. For example, antigens, mechanical trauma and body exercise do turn on complex patterns of inflammation/immune, repair/regeneration and reactivity build-up, respectively. Components of those challenges are recognized by human body as unique sets of information to which adaptive responses are generated. Body adaptive responses are usually described to follow nonlinear patterns. Nonlinearity stems from several levels of body functional organization. They include macromolecular functional features (e.g., enzyme kinetics, molecular turn-over), cellular level (e.g., integration of multiple signals, triggering division versus death pathways), tissues levels (e.g., remote effect of hormones/cytokines) and regulatory levels (e.g., endocrine/neural homeostasis, mirror-j physiology), etc. Nonlinearity contributes to a complexity pattern of natural responses in health and disease. The complexity of human body physiology, additionally, stems from parallel pathways, multiplicity of regulatory homeostatic/homeodynamic loops (feedback and feed-forward), biological redundancy, genomic variability, inter-dependence on physiological gradients, chronobiological alterations of reactivity robustness and plasticity of function/structure maintenance.

The nature of scientific method in biomedicine is dominantly reductionistic quantitative approach. Tacit scientific reasoning implies that knowledge of the elements will necessarily tell us the story of the whole system. Understanding of biomedical life phenomena is thought to be reducible to the levels of chemistry, physics and information. Simplified models are developed and widely used. Those models provide testable, reproducible, and ethically approvable condition. They are easily controlled, and thus suitable for extensive quantitative analysis. In depth knowledge gain is facilitated by sophisticated methods and their growing refinements. We learn and reason in a way of "more and more about less and less". Out of methodological simplification the whole body reactivity has been envisioned as the sum of elementary mechanisms. Integrative physiology of the organism as whole has tacitly been derived from elements, with rarely proper testing of integral reactivity. All those approaches have inherent problem of simplification and methodological "ignorance" of complexities. In general, they tend to ignore parallel pathways, regulatory loops, biological redundancy, inter-dependence on physiological gradients, chronobiological alterations (etc) that are functional in the integral body system. It is obvious especially with the big data of omics-methodologies, which are pending for a new interpretations schemes and their integration into the classical phenomenology.

The study of human physiology in health and disease is faced with two demands related to two different and partially overlapping dimension of the same problem. The clinical pragmatisms to deliver the health benefits and the nature of scientific investigation of the integral complex systems emerge as the two central pivots of medicine. Both sides generate relevant data and construct putative patterns of body reactivity. Both sides silently impose their own methodological, conceptual and professional guidelines to their approaches, and thus contribute to ways of interpretation of human body phenomena. Both sides contain strong and weak features with respect of certainty of interpretations and integration. Results, methodical strategies, comprehensive insights and visions of both sides, should serve as raw material in attempts

of integrative understanding of physiological performance of the body. Medical doctors are inclined to reason along a macro-scale knowledge and diagnostics of clinical reality. They include a qualitative interpretation and perception along with available quantitative diagnostic data. Therefore symptomatology and semeiology of disease processes at clinical level are seen as highly variable, nonlinear, often redundant and with low predictability. Physician's practical teleology is a benefit of a patient. The precision medicine and demands of personalized approaches to individual patient's problem have been additional enforcing the need of integrative synthesis. Such demand reiterates the cognitive and diagnostic issues of the whole body versus local reactivity. Understanding of etiology and pathogenesis networking and their relations to symptoms, signs and dysfunctions remains the critical challenge. Due to a complexity of body structure/function dynamics the principal etiology is not always identifiable, and thus therapeutic interventions are not necessarily corrective at the right (causative) place. They often achieve positive clinical effect via interference with secondary, tertiary (etc) pathways. For example, therapeutic reduction of fever improves patients' condition regardless of its real cause.

The mission of general pathophysiology studies is to enable a synthetic view of heterogeneous types of information and to stimulate an integrative study process. Stemming from nanomolecular and macromolecular level, general pathophysiology makes bridges towards inheritance, subcellular, cellular and tissue as well as organism level. It aims towards study of common etiopathogenatic pathways. It tries to figure out a reliable frame of reference of pathobiological processes responsible for a given clinical problem. Synthetic pathophysiology outlines and crystallizes pathways, taxonomic orders, distribution of disease phenomena and describes the dynamics of processes. General pathophysiology has been defined as …" an integrative branch of medicine which deals with the causative (etiological) and processual (pathogenetic) aspects of disease…" (The Beijing Declaration -***International Society for Pathophysiology***). Etiological factors (chemical, physical, live agents, inherited genomic polymorphisms) induce a variable set of body reactions, which differ both in a quantity and in a quality. Pathophysiology uses clinical and basic data and knowledge and applies new methods, with a growing sophistication of existing methods - imported methods coming from chemistry, physics, biology, information technologies (etc).

Proper pathophysiological framework should integrate vertical, horizontal and longitudinal dimensions of the disease/disorder states. It should facilitate a rational usage of both quantitative scientific knowledge and qualitative descriptive knowledge information plethora and mastering professional demands. In order to improve the efficacy of teaching/learning approach we developed the ***algorithmic analysis/synthesis method***, which became attractive and friendly to students, as well as from teachers point of view. The method is a matrix-guided educational model with four steps. The first part is ***the exposition of problem***, which provides short presentation of "raw data" derived from patient records, selected publications with experimental data, etc. The second part is ***the repetition of relevant knowledge***, which is a multiple choice test, whose statements is related to the exposition and referred other teaching materials (textbooks, websites etc). The third part is ***algorithmic workout of the pathogenesis***, a task in which students, out of given 25-30 units of etiopathogenesis, build-up the cause-consequence sequence of events, with positive and negative feedback loops, and parallel and contextual events. The fourth part is the ***feedback integration of the problem*** which deals with additional relations, systematization and quantitative aspects of the same problem.

There is general natural tendency of etiopathogenetic pathways to form the common crossing points of reactivity. ***The etiopathogenetic clusters*** are the points where, very often, many unrelated pathways converge to the common units of pathogenesis. It appears that pathways belonging to heterogeneous types of diseases tend to group together, spontaneously, around certain etiopathogenetic element. Such common units are formed at certain deviation of electrolyte concentration (like hyponatraemia, hyperphosphatemia, hyperchloremia, etc), macromolecular alterations (e.g., hypoproteinemia, dyslipidemias, etc), and than on cellular and organ functional levels (e.g., acute renal failure, seizures), as well. Such common „hubs" of the response we named the etiopathogenetic clusters (EPC). We consider them as important integrators of natural pathophysiological processes. Such clusters integrate multiple inputs and multiple exits in the natural development of various diseases and altered conditions in human body. Thus, EPC may have both theoretical and practical importance in study of medical pathophysiology. The EPCs have tendency to form a network, with connecting pathways among them. For example, the EPC of acute renal failure leads to the EPC of the metabolic acidosis, and to the EPC of the hyperkalaemia, and to the EPC of the consciousness disorder, and so on. One could speculate that such EPC networking reflects the inherent capacity of human body to react. EPC networking thus follows the general patterns of natural body reactivity. The EPCs have importance in clinical reasoning and clinical interventions. These clusters are often targets of therapeutic interventions. Correction of EPC' deviation from reference value leads to immediate clinical improvement, both locally and generally.

CALORIC RESTRICTION STABILIZES BODY WEIGHT AND ACCELERATES BEHAVIOURAL RECOVERY IN AGED RATS AFTER FOCAL ISCHEMIA

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Obesity and hyperinsulinemia are risk factors for stroke. We tested the hypothesis that caloric restriction, which reduces the incidence of age-related obesity and metabolic syndrome, may represent an efficient and cost-effective strategy for preventing stroke and its devastating consequences. To this end, we placed aged, obese Sprague Dawley aged rats on a calorie-restricted diet for 8 weeks prior to the experimental infarction. Stroke in this animal model caused a progressive decrease in weight that reached a minimum at day 6 for the young rats, and at day 10 for the aged, *ad libitum*-fed rats. However, in aged animals that were calorie-restricted prior to stroke, body weight did not decrease after stroke, but we noted accelerated body weight gain shortly thereafter starting at day 5 post-stroke. Moreover, in calorie-restricted animals, the weight gain was associated with improved behavioural recovery on tasks requiring complex sensorimotor skills, or on tasks requiring cutaneous sensitivity and sensorimotor integration or spatial memory. In turn, these improvements in calorie-restricted rats were associated with post-stroke increases in serum glucose, insulin and IGF1 levels, and with specific changes in the expression of gene transcripts involved in glycogen metabolism, IGF signalling, apoptosis, arteriogenesis and hypoxia. In conclusion, our study shows that recovery from stroke is enhanced in aged rats by a dietary regimen that reduces body weight prior to infarct.

Keywords: aging; stroke; calorie restriction; body weight; neuroprotection; behaviour; transcriptomics

ZINC THERAPY, A HOPE IN DIABETIC NEUROPATHY

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Zinc has been shown to be essential to the structure and function of a large number of macromolecules and for over 300 enzymic reactions. Streptozotocin-induced diabetes in Wistar rats can be considered a good experimental model for the study of the type I diabetes mellitus (insulin-dependent). It is also known that in the context of this illness the metabolism of the whole body is disrupted, as the oxidative stress is major and the deficient immune defense is associated with abnormalities in the circulating lymphocyte subtypes and the autoantibodies. The main objective of the current article is to investigate the diabetic polyneuropathy of diabetes mellitus and its complications. The effect of Zn in streptozotocin diabetic rats was studied. Zn was administered by gavage, daily, for 16 weeks to Wistar rats that have been rendered diabetic by a single i.v. injection of streptozotocin (55 mg/kg body weight). Dysalgesia was investigated under the conditions of nociceptive stimulation through the following tests: the thermoalgesic mechanism through the tail-flick test, the hot plate test and the plantar test, and the mechanoalgesic mechanism through the algesimetric test. Thermal hyperalgesia detected in the diabetic group is significantly reduced through the administration of Zn. Diabetes-associated mechanical hyperalgesia decreased significantly ($p<0.001$) probably through the inhibition of the NMDA receptors. Excitatory glutamatergic synapses are characterized by a postsynaptic electron-dense membrane thickening. The present data suggest a favorable effect of Zn in inhibiting diabetic complications by several mechanisms. Zn, antagonists of NMDA may constitute an alternative therapy to normalize pain reception.

PROTECTIVE BRAIN EFFECTS OF SOME NATURAL COMPOUNDS ON AN EXPERIMENTAL MODEL OF ANXIETY-LIKE BEHAVIOR

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Anxiety disorder can associate with oxidative stress and behavioral changes. β-Carboline-3-carboxylic acid N-methylamide (FG- 7142) administration has been chosen to induce anxiety-like behavior in rats. The aim of this study was to evaluate the effects of natural compounds, i.e. Quercetin (Q), *Hypericum maculatum* (HM) and *Hypericum perforatum* (HP) on an experimental model of FG 7142 – induced anxiety. 42 Wistar rats were divided into 7 groups (n=6): Control, Carboxymethylcellulose(CMC), FG, Alprazolam + FG (APZ+FG), Q+ FG, HM+ FG, HP+ FG. APZ (0.08 mg/kgc), Q (30 mg/Kgc), HM and HP (350 mg/kg-1) were orally administered for 21 days. FG (7.5 mg/kgc) was intraperitoneally administered 1 hour before the behavioral tests, i.e., Open Field Test (OFT) and Elevated Plus Maze (EPM). Brain oxidative stress biomarkers, brain GABA levels and plasma corticosteron levels were also assessed. Q reversed ($p<0.05$) the inhibitory effect of FG on the general and peripheral locomotion in OFT and on total entries in the EPM. Q, HM and HP treated animals travelled a greater distance, made more entries and spent more time in the center of the OFT as compared to FG ($p<0.05$). Q and HP increased the GABA levels in frontal lobe as compared to CMC ($p<0.05$). APZ increased the GABA levels in hippocampus as compared to FG, CMC and control ($p<0.01$). Q diminished the MDA levels in hippocampus, while HM and HP decreased lipid peroxidation in frontal lobe ($p<0.05$). APZ, Q, HM and HP decreased plasma corticosteron levels. In conclusion, Q, HM and HP administration may offer brain protection and have anxiolytic effect on induced anxiety-like behavior.

THE ROLE OF AQP-4 IN THE PREVENTION OF CEREBRAL OEDEMA IN ISCHEMIC STROKE

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According to the WHO (World Health Organization) statistics, stroke affects, each year, about 15 million people, among which about 5 millions decease and other 5 millions are left with important sequelae, this pathology representing, worldwide, the second cause of death in persons over 60. Currently, the only known non-surgical treatment for stroke, the use of osmotic diuretics such as mannitol, does not prevent the formation of sequelae caused by this pathology, as it becomes effective a few days after the formation of cerebral oedema. Therefore, the development of more efficient treatment methods for this pathology is necessary, a first step being the clarification of the mechanisms of formation of cerebral oedema and the attempt to find prevention methods of its installment. To that effect, the study of AQP-4 -a channel protein located predominantly in the brain and involved in the bidirectional transport, according to the osmotic gradient, of water from one side to the other of the semipermeable cell membrane - could be useful for the clarification of the etiopathogenic mechanisms of stroke and for its prevention. It is well known that the blocking of this channel protein can prevent the formation of cytotoxic oedema in stroke and that, furthermore, an increase in the levels of this protein can have a protective effect on the formation of vasogenic oedema.The study which is the subject of this presentation aims to elucidate the mechanisms of formation of stroke by the analysis of the interactions between AQP-4 – a protein whose modulation can have a neuroprotective effect in the stroke-induced oedema – and other proteins located in the brain (like alpha-syntrophin or Kir4.1) with which this interacts.

THE APPLICATION OF CLINICAL PATHOPHYSIOLOGY IN ORDER TO DETERMINE THE ETIOLOGY OF SEVERE HYPONATRAEMIA AND THE EFFECT ON ITS MANAGEMENT IN THE INTENSIVE CARE UNIT SETTING

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Fluid and electrolyte balance is of paramount importance to the practice of intensive care medicine. Hyponatraemia is the most common disorder of fluid and electrolyte balance encountered in clinical practice. It generates a wide spectrum of functional derangements and clinical manifestations, which are associated with increased mortality, morbidity and length of hospital stay. In this presentation, we discuss the value of the clinician's intimate knowledge of pathophysiologic processes in accurately distinguishing between the syndrome of inappropriate ADH secretion and cerebral salt wasting syndrome, which are associated with diametrically opposed treatments. We illustrate this in a case report of severe hyponatraemia, where the correct diagnosis was established, thus expediting therapy.

CHANGES OF NEUROLOGICAL STATUS AND PROTEINURIA IN HYPERTENSIVE PATIENTS UNDERGOING THERAPY

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High blood pressure (HBP) is probably the most important public health problem in developed countries. Through the morphopathological changes and cardiovascular, renal and cerebrovascular complications that it leads to, HBP is a major public health problem. The study was conducted on 40 patients, during October 2016-April 2017. The selection criteria implied that the patients had been previously diagnosed with HBP (except drug-induced HBP, like HBP in rheumatic patients, treated with Cyclosporin A) and also that they had been hospitalized at least twice during the aforementioned period, in order to be able to assess their evolution under hygieno-dietetic and antihypertensive treatment. The changes in neurologic status and proteinuria under treatment were evaluated. The neurological examination determined that 4 patients (10% of the group) presented with changes concerning the neurological status (1 patient – right hemifacial hypoesthesia, 2 patients – pupilar photosensitivity disorders, 1 patient – speaking disabilities). According to proteinuria, we distributed the patients in 4 categories: normal proteinuria, <300 mg/24h – 27 patients; 300-500 mg/24h - 7 patients; 500-1000mg/24h-4; >1g/24h - 2 patients. On the second visit we noted a drop in proteinuria values in 4 patients (10% of the group), without changes in the neurological status. Furthermore, the patients with severe renal impairment had a persistent proteinuria, presenting with the same high values. Only in 1 patient from the examined group we noted an increase in protein excretion, despite the antihypertensive treatment.Once the clinical manifestations are installed, the renal impairment with nephroangioslerosis and proteinuria (CRI) are rarely reversible.

THE PATHOPHYSIOLOGIC MECHANISMS INVOLVED IN BALANCING ARTERIAL PRESSURE

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The current tendency is to try to identify new therapeutic targets for the development of optimal strategies of arterial hypertension prevention. The aim of this study is to estimate the influence of the association between the renin inhibitor (Aliskiren) and the polyphenolic extract on biochemical parameters and systolic and diastolic blood pressure on an L-NAME induced experimental model of arterial hypertension (AHT). The rat blood pressure values were recorded using a CODATM . Blood Pressure System, which uses a non-invasive blood pressure measuring method.

Polyphenolic extract from *Sambucus nigra* reduce systolic and diastolic arterial pressure values in rats with drug-induced AHT, a phenomenon more pronounced when polyphenols are associated with Aliskiren. The combination between the Aliskiren and polyphenolic extract produce superior hypolipidemic and antioxidant effects than in the case of separate administration within experimental AHT. In the hypertensive rats which received *Sambucus nigra* extract, the polyphenolic extract provided protection, ensuring the integrity of the vascular endothelium and keeping within normal limits the elastic elements from the media, as well as the internal elastic limiting membrane. The polyphenolic extract has cardio-protective effects and could be used as a nutritional supplement in chronic cardiovascular and metabolic diseases.

In conclusion, the proposed areas of study provide experimental basis for a trial study in which the combination of two different classes of substances, namely renin inhibitors and natural polyphenols will have increased effectiveness in reducing blood pressure and reducing the side effects of the major classes of antihypertensive agents used so far as monotherapy.

IMPACT OF MELATONIN ON BLOOD PRESSURE REGULATION: FOCUS ON NITRIC OXIDE

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The pineal hormone, melatonin (N-acetyl-5-methoxytryptamine), shows potent receptor-dependent and -independent actions, which participate in blood pressure regulation. Besides the interaction with the vascular system, this indolamine may exert part of its antihypertensive action through interaction with the central nervous system (CNS). The aim of our study was to find out whether melatonin can affect blood pressure, nitric oxide synthase (NOS) activity, eNOS and nNOS protein expressions in rats with metabolic syndrome (SHR/cp). Rats were divided into four groups: 6-week-old male WKY and SHR/cp and age-matched WKY and SHR/cp treated with melatonin (10 mg/kg/day) for 3 weeks. Blood pressure was measured by tail-cuff plethysmography. NOS activity, eNOS and nNOS protein expressions were determined in the heart, aorta, brain cortex and cerebellum. MT(1) receptors were analysed in the brain cortex and cerebellum. In SHR/cp rats, blood pressure was decreased after melatonin treatment. In the same group, melatonin did not affect NOS activity and eNOS protein expression in the heart and aorta, while it increased both parameters in the brain cortex and cerebellum. Interestingly, melatonin elevated MT1 protein expression in the cerebellum. Neuronal NOS protein expression was not changed within the groups. In conclusion, increased NOS activity/eNOS upregulation in particular brain regions may contribute partially to BP decrease in SHR/cp rats after melatonin treatment. Participation of MT(1) receptors in this melatonin action may be supposed.Since melatonin acts favourably on different levels of hypertension, including organ protection and with minimal side effects, it could become regularly involved in the struggle against high blood pressure.

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NEUROTOXICITY OF BISPHENOL A AND THE IMPACT OF MELATONIN ADMINISTRATION ON OXIDATIVE STRESS, ERK/NF-kB SIGNALING PATHWAY AND BEHAVIOR IN RATS

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Bisphenol-A (BPA) is a synthetic xenoestrogen widely used in the production of polycarbonate plastics, known for its adverse effects on the functions of the nervous system. However, the effects of BPA exposure on different areas of the brain and underlying molecular mechanisms and the impact of Melatonin (MEL) administration are still largely unknown. The aim of the study was to investigate the effect of two doses of MEL (20 mg and 40 mg/kg b.w.) on BPA (2 mg/kg)-induced cognitive impairment, oxidative stress and extracellular signal-regulated kinase (ERK) ½ levels in hippocampus, cerebellum and frontal lobe of Wistar rats. DNA damage and the expression of nuclear transcription (NF)-kB and monocyte chemo attractant protein (MCP)-1 in hippocampus and histological changes were also evaluated. A low dose of BPA induced some alterations in the locomotor activity and enhanced anxiety in parallel with increased lipid peroxidation and ERK ½ levels, especially in hippocampus. 20 mg/kg b.w. of MEL diminished the oxidative stress in the frontal lobe, increased the MCP-1 expression in hippocampus in response to inflammation and improved the emotionality of animals. Hippocampal lipid peroxidation, ERK ½ levels and MCP-1 expressions diminished after high dose of MEL in parallel with increasing and activation of NFkB. The both doses of MEL, administered for 14 days before BPA exposure, significantly reduced DNA lesions and attenuated the BPA-evoked histopathological alterations in hippocampus. These data indicate that MEL mediates neuroprotection against BPA-induced neurotoxicity and improves the behavioral changes suggesting a real potential as protective agent in brain toxicity.

ASSESSING CARDIO-VASCULAR RISK USING ATHEROGENIC PLASMA INDEX AND LEPTIN TO ADIPONECTIN RATIO

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Risk models based on lipid profile and inflammatory markers are common practices in in cardio-vascular medicine. In current guidelines, younger than 40 years old and a non obese status are considered low risk predictors. Therefore, we have conducted a descriptive study, to test the hypothesis of an existing relationship between adipose tissue dysfunction and dyslipidaemia in a young non obese population, considered as preliminary pathophysiological events of the vascular disease. 93 young adults (average age =23 y) without metabolic syndrome were included in the study. Dysfunction of adipose tissue was estimated from the leptin to adiponectin ratio and dyslipidemia from the atherogenic plasma index (AIP = log TG/HDL). Statistical tests (distribution, correlation and regression analysis) were performed using an SPSS (Statplus for Mac, 2016) software.

According to the AIP value, 21.6% of the participants were included in the high risk and 15 (18%) in the medium risk category. The linear correlation coefficient with leptin to adiponectin ratio revealed a fair, significant correlation (R=0.20, p=0.05). In conclusion, the high incidence of high risk values of the AIP in otherwise considered low risk populations for cardio-vascular disease supports the need to develop a panel of earlier and more specific biological predictors. Our findings suggest that longitudinal studies should include in the prediction algorithm the evaluation of the adipose tissue dysfunction.

THE SYMPATHOLYTIC AND PARASYMPATHICOTONIC EFFECTS OF MIDASOLAM ASSESED BY CHANGES IN HEART RATE VARIABILITY

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Study's objective was to determine the changes in cardiac vegetative tonus after administration of midazolam solution by measure of heart rate variability (HRV). The study was performed at Institute of Emergency Medicine and was approved by Ethic Committee. The group of study consists from 47 patient scheduled for elective surgery with age 38.9± 12.4 years and BMI – 24.5±3.2 kg/m^2. The changes in cardiac vegetative tonus were appreciated by modification of HRV measured by Holter device. For HRV analysis the continuous ECG was registered the first 5 minutes before premedication, 5 minutes after administration of Fentanyl 1,0 mkg/kg and the first 5 minutes after administration of midazolam 0.2-0.3 mg/kg and Fentanyl 2.0 mkg/kg. Administration of midazolam reduces the total power of HRV by 49%. The power of LFun spectrum, which reflects the sympathetic tonus of the heart was reduced with 1.7%, meantime the power of HFun spectrum, which is the parameter of parasympathetic cardiac tonus was increased by 4.7%. The ratio LF/HF which reflects the sympatho -parasympathic balance of the heart reduces from 3.11±0.34 in pre-anesthetic time to 2.54±0.24 after induction with midazolam. In conclusion, intravenous administration of midazolam solution is associated with decreased sympathetic cardiac tonus and increased parasympathetic cardiac tonus.

ACTIVATION OF PURINERGIC RECEPTORS P_2Y_{11} IMPROVES VASCULAR FUNCTION IN RAT AORTA AFTER ANGIOTENSIN II STIMULATION

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Purinergic signaling via the ATP binding-P2 receptors family plays a crucial role in cardiovascular regulation via the modulation of vascular tone/remodeling, inflammation and coagulation. The P_2Y_{11} receptor is one of the most abundant subtype expressed in the endothelium.The present study was aimed at evaluating the role of P_2Y_{11}-mediatedvascular responsein the presence of angiotensin II (Ang II). To this aim, aortic rings were isolated from rats, suspended in organ chambers and used for isometric force measurements. The rings were treated or not with Ang II (100 nM, 30 min) in the presence or absence of activator of P_2Y_{11}receptors (NF_{546}, 10 µmol/L) with or without the P_2Y_{11} antagonist (NF_{340}, 10 µmol/L). The results revealed that activation of P_2Y_{11} receptors reduced the vascular contractility to phenylephrine and improved the endothelial-dependent relaxation to cumulative doses of acetylcholine after Ang II stimulation. These effects were reversed in the presence of the inhibitor of P_2Y_{11} receptors. In conclusion, activation of P_2Y_{11} purinergic receptors alleviated endothelial dysfunction elicited by acute ex vivo exposure to Ang II, an observation that requires further investigation in order to elucidate the signal transduction mechanisms.

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THE EFFECTS OF FOOD ON ARTERIAL STIFFNESS

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The present presentation aims to review the main food components associated with arterial stiffness and destiffening and their mechanisms of action, considering recent experimental and clinical studies. A diet rich in fruits and vegetables reduces arterial stiffness due to its antioxidant and anti-inflammatory effect, improves endothelial function and lipid profile. Lycopene can play an important role in improving vascular function and the primary and secondary prevention of cardiovascular disorders, considering its antioxidant and anti-inflammatory effect, the ability to improve endothelial function and the metabolic profile, reduce arterial stiffness and size of the atherosclerotic plaque. Mediterranean diet is involved in destiffening due to the synergistic effect of its components. Polyunsaturated fatty acids reduce synthesis of proinflammatory mediators, blood pressure and LDL cholesterol and increase availability of nitric oxide (NO) in the vascular wall. Cocoa increases production of NO and prevents its degradation by reactive oxygen species, reduces the level of adhesion molecules and has a metabolic effect due to its high flavonoids content. Caffeine increases arterial stiffness and negatively impacts vascular health, but several studies show contradictory results. Habitual tea consumption, especially green tea, may have a protective vascular effect, due to catechins. The vasoactive properties of dietary proteins depend on the amino acid composition and source. A high sodium intake was associated with an increased arterial stiffness, related to endothelial dysfunction regardless of blood pressure values. Several studies revealed the association between potassium level and arterial stiffness, related to its effect on endothelial function and blood pressure. Dairy products improve endothelial function due to its mineral content and lactotripeptides. Vitamins have antiatherogenic effects, they improve endothelial function and the metabolic profile, but the effects on arterial stiffness were beneficial only in some study populations. A healthy destiffening diet should be rich in fruits and vegetables, polyunsaturated fatty acids, cocoa flavonoids, tea catechins and dairy products.

MONOAMINE OXIDASE INHIBITION IMPROVES VASCULAR FUNCTION AND REDUCES OXIDATIVE STRESS IN RATS WITH LIPOPOLYSACCHARIDE-INDUCED INFLAMMATION

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Oxidative stress is a central pathomechanism in vascular dysfunction associated with both acute and chronic inflammation. We have previously demonstrated that monoamine oxidases (MAOs) with 2 isoforms, A and B, are contributors to the endothelial dysfunction associated with acute inflammation in mice. The present study was purported to assess whether MAO-related oxidative stress impairs vascular function in the setting of experimental inflammation induced with lipopolysaccharide (LPS) in rats. To this aim Wistar rats were subjected to treatment with lipopolysaccharide (LPS, 8 mg/kg, single injection, 12 hours before experiments). Aortic rings were used for qPCR to assess MAOs expression and for organ bath studies. In the latter case, cumulative concentration-response curves to phenylephrine followed by acetylcholine in the absence versus the presence (30 min incubation) of several MAO inhibitors (Clorgyline - an irreversible MAO-A inhibitor, 10 μM; Moclobemide - a reversible MAO-A inhibitor, 10 μM; Selegiline - an irreversible MAO-B inhibitor, 10 μM). Hydrogen peroxide production was assessed in aortic rings harvested from animals in the presence versus the absence of MAO inhibitors using the Ferrous iron xylenol (FOX) orange OXidation assay. The results showed that LPS exposure increased expression of both MAO-A and MAO-B, whereas incubation with all MAO inhibitors improved vascular function and reduced oxidative stress. In conclusion, MAO-A and B isoforms are both expressed in the vascular system and induced in response to LPS treatment in rats. Inhibition of MAOs restored normal vascular function and mitigated oxidative stress in a rodent model of acute inflammation.

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VITAMIN D AND OXIDATIVE STRESS IN VASCULAR AND ADIPOSE TISSUES: KILLING TWO BIRDS WITH ONE STONE

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We currently face a globally evolving epidemic of obesity that is intimately linked with the occurence of type 2 diabetes mellitus (DM) in both adults and children, hence the term "diabesity". Several pathomechanisms have been incriminated as being responsible for this ‚dangerous liaison', including a chronic state of low-grade inflammation, the excessive secretion of adipokines, the overflow of lipids from the adipose tissue, and the increased oxidative stress. There is unequivocal experimental and clinical evidence for the association between hypovitaminosis D and the risk for obesity/ metabolic syndrome and DM on one side, and also for the antioxidant property of vitamin D on the other. Monoamine oxidases (MAOs) with two isoforms (A and B) are mitochondrial enzymes that that catalyze the electron transfer from biogenic amines to molecular oxygen with the constant generation of hydrogen peroxide (H_2O_2) in both vessels and adipose tissue. We here present evidence that: i) suboptimal vitamin D status is associated with increased reactive oxygen species (ROS) in adipose tissue and vascular samples, ii) *in vitro* administration of the active vitamin D alleviated both oxidative stress and vascular dysfunction, iii) the protective effects of vitamin D are related, at least partly, to a decrease in MAO expression. Experiments are ongoing to further elucidate the signal transduction pathways responsible for the beneficial effects of vitamin D.

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VITAMIN D MODULATES HYDROGEN PEROXIDE PRODUCTION IN ADIPOSE TISSUE ISOLATED FROM PEDIATRIC PATIENTS SUBJECTED TO ELECTIVE SURGERY

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Adipose tissue is an important component of body mass having an essential role in lipid, carbohydrate, and energy metabolism. It also contains an inflammatory cellular infiltrate correlated with the degree of evolution of obesity, aspects that make it a proinflammatory, prothrombotic and proaterosclerotic condition. The common aspect of all these complications is the excessive generation of reactive oxygen species (ROS). Recent studies have identified vitamin D responsible for reducing oxidative stress in adipose tissue, but the mechanisms are far to be elucidated. The present work was purported to assess the effects of vitamin D on oxidative stress at the level of human adipose tissue. To this aim adipose tissue (visceral and subcutaneous) was isolated from children undergoing general surgery. The samples were treated with increasing concentrations (1 nM, 100 nM, 10 microM) of the active form of vitamin D, 1,25$(OH)_2$-D3 for different periods of time (1 h, 12 h, 24 h) and used for hydrogen peroxide (H_2O_2) measurements (FOX assay), qRT-PCR and immune histology. The results showed that in both types of adipose tissue, when applied in the lower (1 nM) and physiological (100 nM) concentrations (but not in a higher concentration - 10 microM), 1,25 (OH)2-D3 was able to significantly reduce the amount of ROS. In conclusion, the active form of vitamin D is able to dose-dependently modulate ROS production in human adipose tissue. Further experiments are required to elucidate the underlying pathomechanisms of this differential response since vitamin D supplementation in children is widely indicated in order to prevent/treat its deficit.

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MITOCHONDRIAL RESPIRATION OF PLATELETS IS COMPROMISED IN PATIENTS WITH METABOLIC SYNDROME

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Emerging experimental and clinical research has provided evidence that measurement of mitochondrial function in peripheral blood cells is an useful diagnostic tool to assess the overall bioenergetic health of an individual. Thrombocytes are nowadays recognized as early predictive markers of mitochondrial dysfunction induced by metabolic stress with a promising potential use in monitoring the progression and therapeutic response in several chronic pathologies. Therefore, the study of platelets and platelet mitochondrial function will provide a better understanding of mitochondrial physiology and pathogenic mechanisms, allowing the translation of mitochondrial research to human disease. The aim of this study was to measure mitochondrial respiration using high-resolution respirometry in patients with metabolic syndrome. Blood samples were obtained from age-matched healthy adult donors and patients with metabolic syndrome and were subjected to two-step centrifugation in order to obtain a platelet-rich plasma sample (1000 x 10^6 /mL). Respiration of isolated human platelets was assessed at 37°C using the Oxygraph-2k (Oroboros Ltd.), after plasma membrane permeabilization with digitonin (1µg/1 x 10^6 platelets), according to the Substrate-Uncoupler-Inhibitor-Titration (SUIT) protocol adapted to evaluate both complex I and complex II-dependent respiration. Respiratory parameters were impaired in patients with metabolic syndrome as compared with control ones. We conclude that the assessment of mitochondrial function in platelets isolated from peripheral blood by high-resolution respirometry represents a reliable method to monitor the bioenergetic profile in humans and to detect the presence of mitochondrial dysfunction as potential novel biomarker in cardio-metabolic diseases.

OBESITY-INDUCED INFLAMMATION: EFFECTS ON ADIPOSE DERIVED STEM CELLS PROLIFERATION AND DIFFERENTIATION

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Adipose tissue (AT) is composed mainly of two different cell categories: adipocytes, which are the main parenchymal cell type; and the stromal vascular fraction (SVF) containing the remaining cellular components. This SVF includes preadipocytes, fibroblasts, endothelial cells, immune cells and multipotent stem cells. Stem cell population from AT (adipose derived stem cells, ASCs) are characterized as CD39/CD44/CD73/CD90/CD105/CD45/CD31 cells. ASCs from morbidly obese patients obtained from subcutaneous adipose tissue (SAT) at the moment of bypass gastric surgery revealed a lower proliferation and adipogenic differentiation potential compared with ASCs from non-obese subjects that underwent liposuction. It is important to highlight, that morbidly obese patients represent a late stage in the development of obesity where metabolic syndrome is already established and where the pro-inflammatory signals have been maintained for a long period. ASCs from morbidly obese patients loss their stemness showing a pre-adipocyte-like differentiated phenotype, and that the impartment in the transcriptomic profile is higher in ASCs from obese patients with metabolic syndrome and clus tering of several cardiovascular risk factors s than in ASCs from obese metabolically healthy.

OBESITY AND TYPE 2 DIABETES. THE ROLE OF BARIATRIC/METABOLIC SURGERY

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Objective. Obesity is known to be associated with type 2 diabetes and a high cardiovascular risk, commonly explained by the chronic inflammation and oxidative stress status. Bariatric/metabolic surgery is currently the most successful treatment for morbidly obese leading to a significant long term weight loss and an important remission/amelioration of type 2 diabetes. The aim of this study was to analyse the impact of sleeve gastrectomy (SG) on some parameters of glucose homeostasis, chronic inflammation and oxidative stress.

Materials and methods. We investigated 34 morbidly obese patients before and six months after SG. We evaluated the BMI (body mass index), %EBMIL (the percent of excess BMI loss) and the fasting serum levels of insulin, hsCRP (high sensitivity C reactive protein), TNF-α (tumor necrosis factor alpha), chemerin, nitrite and nitrate (NOx), total oxidant status (TOS) and total antioxidant response (TAR). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated.

Results: Six months after SG there was a significant change (decrease) of the BMI ($p<0.001$) and hsPCR ($p=0.044$) levels. No significant changes of chemerin ($p=0.605$), TNF-α ($p=0.287$), NOx ($p=0.137$), TOS ($p=0.158$) and TAR ($p=0.563$) values were observed by the end of the study. However, we revealed a significant time effect on fasting blood glucose variable ($p=0.052$), fasting insulin ($p=0.025$) and HOMA-IR ($p<0.001$).

Conclusions. There was an important reduction in glucose homoeostasis parameters and, although except for hsCRP, we observed no significant changes in other parameters of chronic inflammation and oxidative stress indicating that other mechanisms might be involved in the amelioration of insulin resistance.

CROSSTALK BETWEEN ARTERIAL STIFFNESS, VITAMIN D, HIGH SENSITIVITY C REACTIVE PROTEIN, LDL AND OXIDIZED LDL CHOLESTEROL IN HYPERTENSIVE PATIENTS

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The present study aimed to assess the relationship between arterial stiffness and vitamin D, high sensitivity C reactive protein (hsCRP), LDL and oxidized LDL (LDLox), respectively in hypertensive patients. A total of 40 hypertensive patients, aged 47±6 years, 60% males, were investigated using a Mobile-O-Graph to assess pulse wave velocity (PWV), augmentation index (AI), augmentation pressure (AP), arterial age, central and peripheral blood pressure variables. Additionally, hsCRP, LDL, LDLox and 25-hydroxy-vitamin D3 were assessed.The following values were obtained for hsCRP, LDL cholesterol, LDLox and 25-hydroxy-vitamin D3: 0.45±0.48 mg/dl, 144.82±42.92 mg/dl, 261.37±421 ng/ml, and 25±11 microg/l, respectively. PWV, AI and AP were, as follows: 7.16±0.66 m/s, 19±13.83 and 7.9±7.22 mmHg, respectively. Significant Bravais-Pearson correlations were obtained between LDLox and AP and AI (r=0.517 and 0.25, respectively). Biserial correlation coefficients were significant for the relationships: hsCRP>0.1 mg/dl-early arterial aging (EAA) and patological increased PWV-hsCRP (rpb=0.35 and 0.4, respectively). Logistic regression analysis showed also significat associations between hsCRP, EAA and pathological increased PWV, respectively. An increased hsCRP was the most sensitive predictor for pathological increased PWV, and increased LDLox, the most specific. Low vitamin D level was the most sensitive predictor of pathological AI, and increased LDLox the most specific. LDL exceeding 100 mg/dl and LDLox were the most sensitive and specific predictors of EAA. In conclusion Vitamin D, high sensitivity C reactive protein, LDL and oxidized LDL provide valuable information in middle-aged hypertensive patients related to arterial stiffness and early arterial aging.

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PHYSIOPATHOLOGICAL IMPLICATIONS OF BODY COMPOSITION IN CHRONIC HEPATITIS C

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Chronic hepatitis C (CHC) may be involved in body composition changes, both in the body mineral metabolism impairment (osteopenia/osteoporosis) and in the body adipose and lean tissues impairment (hepatitis C associated dysmetabolic syndrome - HCADS). Interactions between virus C, visceral adipose tissue and host genetic factors contribute to the pathogenesis of HCADS. Prospective cohort study based on a cohort of patients with CHC, assessed with DXA (Dual Energy X ray Absorptiometry) and compared with a control group. We used parameters of bone and soft tissues (adipose and lean tissues) and we evaluated the correlations of these parameters with demographic, anthropometric parameters (age, sex, smoking, body mass index - BMI) and disease parameters (degree of hepatic impairment, viral load, treatment). There was a significant decrease in total and trunk adipose tissues in CHC patients compared to the control group, which involves the presence of lipodystrophy. Bone mineral density was significantly decreased in CHC patients (osteopenia/osteoporosis) compared to the control group. These body composition changes correlated with smoking, low BMI and antiviral treatment. The impairment of body composition represents a disease complication in CHC patients, closely related to the presence of the virus and administration of antiviral therapy.

RADIO-IMAGISTIC STAGING OF LIVER STEATOSIS

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We present preliminary results from a research study regarding correlations be-tween the biological and morpho-pathological evaluation of the fatty liver and radio-imagistic investigations. The purpose is to establish the utility and accuracy of radio-imagistic evaluation of fatty liver and to suggest an radio-imagistic staging of hepatic steatosis. We evaluated 2 groups of patients – group A: 262 patients, examined using radio-imagistic methods (ultrasound, computed tomography and magnetic resonance) and liver biopsy and group B: 150 patients, examined using ultrasound and steatotest. The obtained *results* demonstrate that the radio-imagistic evaluation is a reliable diagnostic method for liver steatosis, with over 81% overall accordance with the biological and morphopathological data, and over 89% accordance in case of homogeneous steatosis, with involvement of the entire liver parenchyma.

THE INVOLVEMENT OF OXIDATIVE STRESS (OS) IN HEMATOLOGICAL MALIGNANCIES

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OS is defined as the imbalance between the production of reactive oxygen or nitrogen species (ROS/RNS) and the total antioxidant capacity (TAC) of the organism. It is involved in many physiological (activation of enzymes, gene expression, protein-kinase activity, cell signaling, apoptosis, immune response, ageing) and pathophysiological processes (altered immune response, chronic inflammation, carcinogenesis, atherogenesis, Alzheimer's, Parkinson's, diabetes mellitus). Many experimental or clinical studies (on laboratory animals or patients with acute/chronic leukemia, malignant lymphomas, and malignant monoclonal gammopathies) argue the involvement of OS in hematological malignancies.

Currently, in the Laboratory of Oxidative Stress Evaluation, University of Medicine and Pharmacy of Craiova, funded by the ARES grant – Center for experimental research of normal and pathological ageing, research about OS involvement in chronic myeloid leukemia (CML), (Ph)-negative chronic myeloproliferative neoplasia (CMPN) and myelodysplastic syndromes (MDS) is undergoing, taking into account that the hybrid CML gene BCR-ABL is associated with increased ROS levels in hematopoietic cells (Rodrigues, 2008) which synthesize the abnormal bcr-abl protein that activates multiple signaling pathways: MAPK, PI3K, JAK/STAT and Hedgehog, considered to be involved in disease progression (Long, 2001). These signaling pathways are involved in important processes for leukemogenesis and disease progression: increase of cell proliferation, apoptosis inhibition, alteration of leukemic cells – medullary microenvironment interaction, and genetic instability of leukemic clone (Cross, 2011). Increased ROS levels in CML have two major consequences: lesions of the biomolecules, including DNA mutations, favoring genetic instability, and overexpression of RedOx-sensitive signaling pathways (Cross, 2011). High levels of OS markers (MDA and protein-carbonyl groups) and low GSH levels in plasma of CML patients compared to control groups (Singh R, 2009; Ahmad, 2008). OS increases in the accelerated phase of CML and at the same time non-enzymatic antioxidants levels decrease; individuals with genic polymorphisms related to reduced gluthation-S-transferase activity have an increased risk of CML development and a poor prognosis (Sailaja, 2010).

Regarding CML treatment, isocyanates function as pro-oxidants, decreasing the GSH pool and selectively destroying CML cells resistant to 1st generation TKIs (imatinib mesylate), without affecting normal hematopoietic cells (Zhang, 2008). Adaphostin, a tyrphostin kinase inhibitor, produces increased ROS levels, DNA lesions, apoptosis of cells expressing the BCR-ABL gene, including imatinib-resistant isoforms (Chandra, 2006). Our research aims to establish correlations between OS level, additional chromosome abnormalities, clonal instability, mutational status, disease progression and TKI resistance development.

Regarding (Ph)-negative CMPN, studies have shown increased ROS levels through activation of pro-inflammatory pathways (NF-kB, NF-E2), and OS involvement in thrombotic events in polycythemia vera (Hasselbalch, 2014; Bjorn, 2015; Kaufmann, 2012; Durmus, 2014). On the other hand, in CMPN, the hematopoietic stem cell niche is characterized by decreased catalase activity, leading to increased OS level, oxidative alteration of DNA, clonal instability and myelofibrosis/ acute leukemia progression (Marty, 2013). Recent studies have shown that ROS overproduction offers a growth advantage to JAK2-positive clones (Marty, 2013; Haselbalch, 2014; Xu, 2013). Considering this data, we aim to evaluate OS level in different CMPN and to establish possible correlations between OS level, presence of JAK2V617F mutation, therapeutic regimen and development of complications.

Numerous studies have shown increased ROS levels in CD34+ cells extracted from the blood of MDS patients. Iron overload following increased need of transfusion, altered hematopoiesis, increased serum ferritin and hemoglobin decrease are associated with increased OS levels (Saigo, 2011), and iron chelation therapy is believed to decrease OS (Ghoti, 2011). Starting from these considerations, we will evaluate ROS levels and TAC in correlation with different MDS subtypes, iron metabolism, therapeutic regimen and clonal expansion.

Keywords: oxidative stress, reactive oxygen species, total antioxidant capacity, CML, CMPN, MDS.

HOW TO IMPROVE THE CYTOTOXICITY OF TRITERPENES? A CASE STUDY ON MASLINIC ACID

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Natural products remain on of the best sources of drugs and drug leads. They possess enormous diversity being unsurpassed by any synthetic library. They are evolutionary optimized as drug-like molecules.

Among natural products, triterpenes play a special role, and more than 20.000 of them have been isolated so far. Triterpenes and triterpenoids are often bioactive and present a huge therapeutic potential. One of the most interesting scaffolds is represented by pentacyclic maslinic acid – an oleanane-type triterpene. This molecule can be extracted from olives or is easily synthesized in good yields from commercially available oleanolic acid. While the parent compound is of minor cytotoxicity, simple derivatization led to analogs being highly cytotoxic for a variety of human cancer cell lines while being significantly less cytotoxic for non-malignant cells.

Bioactivity-driven optimization finally led to analogs acting as mitocans and showing nano-molar EC50 values as well as to analogs whose cytotoxicity can be switched on/off at will. The presentation will provide a roadmap for the synthesis of highly active compounds including structure-activity relationships.

A MASLINIC ACID DERIVATIVE ELICITS LOCAL BENEFICIAL EFFECTS AND DECREASES MITOCHONDRIAL ROS PRODUCTION IN A MURINE MODEL OF CHEMICALLY-INDUCED SKIN CARCINOMA

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The present study was purposed to assess the effects of a benzylamide derivative of maslinic acid (EM2) in mice exposed to chemical agents and on isolated liver mitochondria. SKH1 male and female mice were randomly assigned to one of the following groups: 1) NO TRTM (mice with chemical-induced skin carcinoma - first 2 weeks - topical application of 7,12-dimetilbenzantracen (DMBA, 0.025% solution, once per week), followed by repeated applications of TPA solution (12-a-13-ethyl-decanoilphorbol, twice per week), 2) BLANK HG(mice with chemical-induced carcinoma plus with topical application of blank hidrogel, twice per week), and 3) EM2 (mice with chemical-induced carcinoma plus with topical application of the EM2 1% hydrogel, twice per week). Local treatment was initiated in the presence of papillomas. At the end of the experiment liver mitochondria were isolated by differential centrifugations, respiratory parameters for complex I (CI) and II (CII)-supported respiration were measured by high-resolution respirometry, and reactive oxygen species (ROS) production was assesed by the Amplex Red technique.

The EM2 treated groups developed fewer papillomas as compared to the untreated and blank HG groups, respectively. As concerning mitochondrial respiration, a substrate-independent decrease in all respiratory rates in treated vs. non-treated male (but not female) animals was recorded. In both males and females, EM2 treatment significantly decreased H2O2 production in mitochondria respiring on complex I (and to a lesser degree on complex II) substrates.

In conclusion, topical application of the maslinic acid derivative elicited a protective effect against the development of skin lesions, a substrate-dependent decrease in ROS production and a substrate-independent decrease of respiratory parameters in isolated liver mitochondria.

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NANOBIOSENSORS FOR CANCER DIAGNOSIS AND MONITORING

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Many conventional technologies for cancer diagnosis or monitoring report different handicaps such as high cost and time required for sample preparation, intensive sample handling or various side effects that can become troublesome to patients. In the past years, nanotechnology has been proposed to reduce some of these difficulties. While a usual biosensor includes biorecognition probes (to detect specific chemical compounds from a specific biochemical reaction) and a transducer element (to convert a biorecognition event into a suitable electrical, thermal, or optical signal), nanostructures linked to various biorecognition probes allow the control, manipulation and detection of molecules with diagnostic interest, even at the single molecule level.

This presentation will focus on several personal recent results showing synthesis and evaluation of controllable size gold nanoparticles and magnetic nanoparticles with a low polydispersity coefficient. We will also explore ways to attach these nanomaterials with biorecognition probes and to analyze the reported signal. Finally, the presentation aims at providing a brief survey on nanobiosensing strategies in some types of cancer.

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Keywords: nanoparticle, nanobiosensor, cancer

THE INVOLVEMENT OF OXIDATIVE STRESS (OS) IN MYELODYSPLASTIC SYNDROMES (MDS)

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Many studies have demonstrated elevated levels of reactive oxygen species (ROS) and decreased levels of the total antioxidant capacity (TAC) in plasma of MDS patients, especially in RAEB1 and RAEB2 subtypes of the WHO classification. Our aim is to confirm OS involvement in MDS. Our study comprises two groups: a control group of healthy volunteers and a study group of MDS patients (sex ratio = 7:10, mean age = 72 years, mostly classified as RA or RAEB) diagnosed and stratified according to the WHO classification. 22 MDS patients are enrolled in the study (informed consent obtained) and the enrollment is on-going. Patients were treated with supportive care (RA) and low dose Cytosar (RAEB 1, RAEB 2). Evaluation of ROS/TAC is done using a microplate reader/flow-cytometer in the Oxidative Stress Laboratory. At the moment of acute myeloid leukemia progression, 8–hydroxy-guanosine level, a marker of DNA oxidation, will be measured. Also, we will evaluate iron metabolism parameters. The evaluation of ROS and TAC is ongoing and preliminary results will be presented at the conference. We expect high ROS levels compared to the control group, as well as low TAC in comparison to healthy individuals. Moreover, we expect to find a link between the levels of ferritin and MDS progression to AML. OS and iron metabolism in MDS patients need to be monitored to establish correlations between the ROS level, ferritin and hemoglobin values.

THE INVOLVEMENT OF OXIDATIVE STRESS (OS) IN CLONAL INSTABILITY IN CHRONIC MYELOID LEUKEMIA (CML) AND TYROSINE KINASE INHIBITOR (TKI) THERAPY RESISTANCE DEVELOPMENT

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CML is a clonal malignant proliferation of the hematopoietic stem cell developed as a result of bcr-abl oncoprotein; OS is an important etiopathogenic factor in CML. Currently, TKIs are considered the standard treatment. The main objective is to evaluate OS in CML in order to establish a correlation between the OS level and the molecular response in TKI-treated patients. Currently, our study includes healthy volunteers and 19 patients diagnosed with CML in the Hematology Clinic of Filantropia Hospital, Craiova; ROS level/antioxidant capacity will be determined using a flow cytometer/microplate reader. The study group consists in 10 females and 9 males, aged between 20 and 85 years, all in the chronic phase of CML, in treatment with 1st or 2nd generation TKIs/hydroxyurea. The obtained data are stage results and are to be interpreted during the study. We expect: an existing correlation between the OS level and the bcr-abl transcript value in CML, OS to be involved in clonal expansion in CML and in switching to advanced disease, OS involvement in primary/secondary TKI resistance mechanisms, the influence of disease progression on the existence of gene polymorphisms for antioxidant enzymes. We expect the obtained results to support literature data: the involvement of ROS in genomic instability and auto-mutagenesis, responsible for the TKI resistance of the leukemic clone. The results and conclusions will be used to elaborate the Ph.D. thesis with the same title and will be disseminated accordingly.

GLIMPSES FROM THE HISTORY OF THE PATHOPHYSIOLOGICAL DEPARTMENT OF THE CLUJ FACULTY OF MEDICINE DURING THE XXTH CENTURY

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The prelude of the modern pathophysiology was done in Cluj at the Hungarian Faculty of Medicine – founded in 1872. Important professors were: Endre Högyes. Arpad Bokaly etc.

In 1919 in Cluj was created the Romanian Faculty of Medicine. During the interwar period the Pathophysiological Department was named "Institute of General Pathology and Experimental Medicine". In 1919/1920 the teaching activity was supplemented by Titu Vasiliu - Associate Professor at the Pathology Department. In 1920/1921 the Chair was led by the prestigious physician Professor Constantin Levaditi.

Then between 1923 and 1941 the Chair was led and organized by Professor Mihai Botez.

During the refuge of the Faculty in Sibiu the head of Department was the skilful pathologist Professor Rubin Popa.

In 1948 after the reform of the academic learning from Romania the Chair was named "Pathophysiology". Since 1949 until 1951 the head of the Department was Pavel Ciurdariu.

In 1951-1962 the Chair was directed by Professor Ion Baciu who gave an experimental and exploratory orientation to the research activity. Between 1962 and 1990. the chief of the Department was Professor Laurenţiu Tomuş. In 1990/1991 Associated Professor Vasile Ban led the Chair.

Between 1991 and 2015 the head of the Chair was Professor Luminiţa Pleşca Manea who developed the activity of this Chair.

PROFESSOR PAUL RIEGLER FOUNDER OF ROMANIAN MODERN VETERINARY SCIENCES

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Paul Riegler was born on December 11th 1867, in Roman, a small town in Moldavia, Romania. In 1888, after graduating the primary and secondary school in his native town, he entered the Veterinary Medical School in Bucharest that he graduated in 1893. In 1900, after a competition, Paul Riegler became Head of the Department of General Pathology (Pathophysiology), Microbiology and Pathological Anatomy, to which he devoted himself with great love till his death. One of his great concerns regarded pulmonary glanders, showing that some other nodular lesions, may be mistaken for it (published in "The Journal of Comparative Pathology and Therapeutics", London, 1905, p. 277). V. Babes, together with P. Riegler, C. Motaş, Al. Ciucă etc. carried out investigations regarding the epidemiology of rabies, anthrax, tuberculosis etc., high incidence diseases that produced victims among humans and animals. This led him, after many efforts, to the creation of the "Institute for serum and vaccines", which started to operate in 1910 and was named after Pasteur in 1922. He actively participated in the organization of the National Congresses of Veterinary Medicine in 1904 (second congress) and in 1913 (third congress) and the Congress of Zootechny and Veterinary Hygiene in 1924. Next to I. Cantacuzino (physician and biologist), I. Athanasiu (veterinarian) and D. Voinov (biologist), he contributed to the establishment of the Bucharest branch of Biological Society in Paris, branch where many Romanian researchers asserted themselves and which he directed several times. He participated in the activity of Veterinary Medical Society, the President of which he was for a long time. He participated in different International Congresses for Veterinary Medicine (Baden–Baden 1899, Budapest 1905, Hague 1909), as well as in the Comparative Pathology Congress in 1912 in Paris, where he presented three papers.

UROTHELIAL CANCERS IN CATTLE: AN ANIMAL MODEL FOR HUMAN DISEASE?

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Urinary bladder tumours are rather common in adult cattle grazed on pasturelands rich in bracken fern. The prevalence of such tumors in these animals may be ≥90%. Ptaquiloside, the major bracken carcinogen of bracken, along with some infectious agents, in particular bovine *Deltapapillomavirus*, appear to play a crucial role in urothelial cell transformation. Although urothelial tumors of cattle have significant biological differences, however, they share many phenotypical features with their human counterparts; therefore, it has been suggested that the morphological classification of human bladder tumors adopted by the World Health Organization is appropriate also for bovine urothelial tumors. Indeed, like humans, bovine bladder cancer is characterized by a very strong epithelial plasticity. Furthermore, bovine and human bladder cancer shares some molecular pathways. Inactivation of pRb and overexpression of E2F3 are common events in human and bovine urothelial tumors. AKT signaling appears to be involved both in human and bovine urothelial tumorigenesis. Human and bovine urothelial tumor cells share the expression of many proteins implicated in bladder tumorigenesis such as uroplakin III, COX2. Only approximately 10% of bovine urothelial carcinomas metastasize. Unlike humans, an unaltered expression of GM3 ganglioside and an overexpression of decorin and lumican, factors believed to modulate the metastatic potential of bladder malignancies, have been shown in bovine bladder cancer. Among the hitherto characterized pathogen recognition receptors (PRRs), Mincle receptor that belongs to C-type lectin receptors (CLRs), has just been described in bovine urothelial cancer cells, which could open new avenues in the immunotherapy of human bladder tumors.

SOME FACTS OF THE PATHOGENESIS OF BRONCHOPNEUMONIA IN PIGLETS

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Aim of the study was to evaluate the role of the various components of innate immunity in the pathogenesis of lung disease in piglets. The study was conducted on 3.5 month old piglets (6 patients, 6 healthy). The functional activity of blood neutrophils, lysozyme and bactericidal activity of blood serum, the concentration of C3 fraction of complement, the level of circulating immune complexes were determined by methods described Morozov & Khavinson (1980). It was shown that the indicators characterizing the activity of cellular and humoral components of innate immunity were unstable in acute bronchopneumonia. Cellular factors of nonspecific protection of ill piglets had no significant difference from the level of intact animals, but the contents of phagocytic neutrophils (phases adhesion and capture were reviewed), the activity of lysosomal cationic proteins of neutrophils had tendency to decrease. Among the humoral factors of nonspecific protection in the course of the disease was observed only normalization of bactericidal activity of blood serum. The level of circulating immune complexes of ill piglets before treatment do not differ significantly from intact animals, to the 7th day of observation was increased ($P<0.05$) by 1.5 times, maintained at a high level at 14 days, declining to 35.0±7.55 to the 21st day, which was 2.5 times higher ($P<0.05$) initial values. Thus, the starting mechanism of the development of immunopathological process in bronchopneumonia of piglets should be considered the inadequate elimination of complexes antigen-antibody. The high level of circulating immune complexes, the tendency to decrease levels of C3 component of complement in the blood, the oppression of phagocytic activity of blood neutrophils of piglets are an important diagnostic criteria in the course of the disease.

Keywords: pathogenesis, bronchopneumonia, piglets

TRESS – ETIOPATHOGENIC FACTOR IN FELINE IDIOPATHIC CYSTITIS

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The feline urologic syndrome describes a variety of pathological conditions encountered in domestic cats, characterized by hematuria, polakiuria, stranguria, dysuria, as well as variable degrees of urethral obstruction. FIC has a complex ethiopathogeny, involving local conditions but also nervous and endocrine disturbances, representing a real challenge for veterinary therapeutics. The aim of this study was to assess the stress role in the development and also the therapeutic management of feline idiopathic cystitis (FIC). Two cats, aged 6 and 8 years old, have been presented to veterinarian because of difficult urination. Following the clinical and paraclinical medical examination they have been FIC diagnosed. The onset of FIC was related to the death of the owner, respectively the frequent change of house. The third cat was a stray one, of approximately 6 years old, which was rescued to be housed. In order to be adopted, the cat was neutered and sent to the shelter. Few weeks later the cat developed FIC. The therapeutic management included anti-inflammatory drugs and diet change, but the relief of stress was the decisive factor for the long term healing. The chronic stress suppresses the adrenal cortex, which lead to ACTH increase and sympathetic nervous system (SNS) activation (Westropp JL., 2005). The disproportionate activation of noradrenergic outflow related to an inappropriate adrenocortical steroids outpouring impairs the epithelial permeability (Chew DJ., 2009). The subsequent activation of sensory nerves induces local release of neurotransmitters by bladder sympathetic fibers, promoting neurogenic inflammation. Conclusions: The stress plays an important role also in the development and the therapeutic strategy in feline idiopathic cystitis.

Keywords: stress, feline idiopathic cystitis, ethiopathogeny, therapeutic management

THE IMPACT OF INFRARED RADIATION ON THE RELEASE OF LEUKOCYTE ALKALINE PHOSPHATASE AND SELECTED PLASMA ANTIOXIDANT INDICES DURING CARDIOPULMONARY BYPASS - OBSERVATIONS IN A SWINE MODEL

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Background. Cardiopulmonary bypass (CPB) has been associated with many deleterious effects on blood cells. Near infrared radiation (NIR) is known for its cytoprotective properties. The potential use of NIR during CPB has not been studied yet. To assess whether NIR influences the leukocyte enzyme release and blood antioxidant status during and after CPB. 24 pigs were connected to CPB for 1 hour. No surgery was performed. In 12 of them, blood in the oxygenator was irradiated with NIR. Number of leukocytes (WBC), activity of leukocyte alkaline phosphatase (APh), serum catalase (Cat) and ferric reducing antioxidant power (FRAP) were measured prior to and after 30 minutes of CPB, after weaning from CPB, and in the 6th, 12th and 24th hour of experiment. In both groups all the parameters were comparable at the beginning of the experiment while during the CPB the WBC initially decreased. Starting from the 6th hour of experiment a slow increase of the WBC was observed until the 24th hour. Those changes in WBC were accompanied by the increased release of APh. Leukocytes activation using zymosan activated serum (ZAS) intensified this process. In control group, the FRAP and Cat activity achieved the initial value in the 24th hour of experiment, after decreasing during CPB. In NIR exposed blood the FRAP and Cat activity remained lower in the 24th hour of observation. Limited APh release from leukocytes, decreased FRAP and Cat activity during CBP and after NIR, suggest that exposing blood to NIR might alleviate the effects of blood contact with a foreign surface.

Keywords: cardiopulmonary bypass, leukocyte enzyme, blood antioxidant status

THE INFLUENCE OF GLUCORTICOIDS ON EQUINE PLATELET FUNCTION AND OXIDATIVE STATUS

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Haemostatic disturbances participate in pathophysiological changes occurring in horses with increased levels of endogenic or iatrogenic cortisol. However, the role of platelets in these changes is not clear. The aim of the study was to evaluate influence of glucocorticoids on the expression of the p-selectin (CD 62P) and activity of catalase in equine platelets. Blood from 10 healthy horses was incubated with dexamethasone or hydrocortisone. Obtained platelet-rich plasma (PRP) was divided into two samples, one of which was activated with thrombin. The expression of p-selectin was evaluated by flow cytometry and the catalase activity was quantified in samples without thrombin using the spectro-photometric assay. The expression of p-selectin in platelets increased significantly after activation with thrombin. None of steroids seemed to have significant influence on CD62P expression in resting platelets. In contrast, among activated platelets those previously incubated with dexamethasone showed increased CD62P expression. Dexamethasone also appeared to increase the activity of platelet catalase. Both examined parameters were lower in samples incubated with hydrocortisone. The study suggests that steroids may change the activity of equine platelets and may contribute to the haemostatic disturbances in diseases such as laminitis.

INFLUENCE OF NIR EXPOSURE ON BLOOD COAGULATION PARAMETERS IN DIALYZED SHEEP AFTER BILATERAL NEPHRECTOMY

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Disturbances in coagulation are serious problems in patients with renal failure. Repeated hemodialyses additionally intensify tendency to bleeding and/or thrombo-embolism risk. Near infrared radiation (NIR) can modificate interactions between water and amino acids, proteins. The question is: does NIR affect plasma proteins participating in coagulation processes? Assessment of results of NIR exposure on blood coagulation parameters in dialyzed sheep after bilateral nephrectomy. 10 bilaterally nephrectomized sheep were dialyzed every day. During dialyses, the blood of 5. sheep was exposed to NIR. The prothrombin time (PT), the activated partial thromboplastin time (APTT), the thrombin time (TT), the fibrinogen (Fb) concentration and coagulation factors II – XII activity were measured in plasmas obtained from blood of all animals, before and after 1,2,4,6,7,10 dialyses. A radical nephrectomy caused prolongation of aPTT and TT without changes in PT, increase in Fb concentration and decrease in coagulation factors activity. Consecutive dialyses and NIR irradiation led to increase in factors activity and subsequent shortening of aPTT and TT. Nephrectomy caused the hypocoagulative status of all sheep which was partially corrected after 1st dialysis. Corrections of coagulation parameters was stronger and more stabilized after next dialyses and simultaneous NIR exposure. Activation of the coagulation factors was not accompanied by imidiate shortening of aPTT and TT.

NEW DATA ON OXIDATIVE STRESS PROPHYLAXIS WITH FUNCTIONAL FOODS

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Oxygen, in addition to its beneficial effects, also has untoward effects that manifest in certain circumstances when forming reactive oxygen species (ROS). In the body, the level of oxide-radicals is maintained by enzymes such as superoxide-dismutase (SOD), catalase, glutathione and its enzymes (glutathione-peroxidases), etc. The target of oxidative changes is proteins, which modify, destabilize cell morpho-physiology, especially when the cytoskeleton is affected. Also, ROS attacks membrane lipids due to double bonds in the polyunsaturated fatty acid structure, the most efficient initiators of the lipid peroxidation process being ultraviolet radiation, especially UV-A. Among the „preventive" antioxidants that retain the transition metals, preventing the Fenton reaction, are: ferritine, transferine, lactoferrin, ceruloplasmin, albumin. Recent concerns about the prevention of oxidative stress through the use of functional foods or ingredients that have a positive impact on individual human and animal health and the stimulation of physical, behavioral or mental performance. These functional foods contain natural antioxidants like tocopherols, ascorbic acid, plant extracts such as rosemary, lycopene flavonoids, etc. Synthetic antioxidants such as: butylated hydroxyanisole - BHA, butylated hydroxytoluene - BHT, gallate propionyl - PG, tertiary butyl - TBHQ hydroquinone are also used, in addition animals can also use ethoxyquin - EQ. Of course, the beneficial effects of oxidative stress by participating in the generation of oxidants that compete with bactericidal activity, as well as the synthesis of biologically active molecules such as eicosanoids (prostaglandins), the ROS level must be rigorously controlled, via multiple enzymatic and enzymatic pathways, to prevent alteration of the cytoskeleton and membrane lipids.

HEMATHOLOGICAL, BIOCHEMICAL AND BEHAVIORAL ASPECTS IN ORGANIC SELENIUM SUPPLEMENTED FODDER ROSSO CHICKENS

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Selenium is a trace mineral with antioxidant proprieties, which, by mediating the glutathione, indirectly protects the hemoglobin against the risk of oxidation by peroxides through three antioxidant enzymes: superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase The experiment was done on 20 laying chicks from the Rosso race, 6 weeks old at the start. The chicks were divided in 2 batches, and one of the batches received feed enriched with organic selenium (Sel-Plex). After 180 days, biological samples were colected by cubital vein puncture and hematological and biochemical determinations were made. We also made following determinations: body weight, body temperature and computerized thermography of the comb and wattle The results were tabled, graphically represented and biostatistically interpreted. In the experimental batch significant growths were observed in the erythrocyte constants: erithremie, hemoglobinemy, hematocrite and MCH. Of the biochemical markers significant growths were observed in: ascorbinemic acid, alkalin phospahasis and selenium. The following parameters dropped significantly : proteinemia, amylase and MCV. Changes were also observed in cholesterol, calcium, magnesium and other parameters, but without statisticaly value. In the present paper we have shown the beneficial role of organic selenium on some haematological and biochemical markers, resulting in a growth of erythropoiesis, and at the same time a intensification of the metabolic processes in the experimental group.

METHODS AND TECHNIQUES OF INVESTIGATION USED FOR THE STUDY OF THE INDUCED OBESITY IN LABORATORY ANIMALS: THEORETICAL CONCERNS AND PRACTICAL CHALLENGES

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Introduction. Obesity is defined as a body mass index over 30 kg/m2 and represents a significant health risk, because it increases the risk of diabetes, cardiovascular disorders, stroke and colon cancer [1].

Aim. To characterize different methods of inducing obesity in laboratory animals, as well as to detail various examination techniques used in research.

Discussion. There are several types of obesity regarding the method of inducing: diet induced (hipercaloric diets), drug induced, chemical agents induced, surgically induced obesity and the one encountered in monogenic and polygenic models [1]. For the study of obesity the most used method of inducing it is the use of hipercaloric diets for laboratory animals, because it can be viewed as an experimental model for the studied of human obesity [2]. The main investigation technique is the biochemical examination. It is used to determine the blood levels of lipids (especially triglycerides and cholesterol). This exam also reveals glucose levels and several hormones involved in the development of obesity (Leptin, insulin) [3]. Other methods of investigation involve: weekly measurement of body weight, daily dosing of food intake, anatomopatologic examination and immunohistochemistry (to differentiate between the brown, beige and white fat) [4]. Some of the practical challenges that can be encountered are animal deaths in chemically induced obesity, wrongful calculation of the hipercaloric diet, inconclusive results of immunohistochemistry examination [4].

Conclusions. Current animal model of obesity can be used for the study of obesity associated human diseases and for testing different therapeutic agents.

Keywords: obesity, methods, investigation, laboratory animals

EFFECT OF WHOLE BLOOD TRANSFUSION ON BIOCHEMICAL AND PLASMATIC OXIDATIVE STRESS IN HOLSTEIN CALVES

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Introduction. Blood transfusion is an act of administering blood or any of its components to an animal (Bell, 2006). The transfusional therapy in cattle determines a lot of changes in the biochemical and plasmatic oxidative stress parameters and an appropriate analysis of transfusion effects is essential for a successful therapy act (Weiss, 2010).

Aim. Investigation of transfusional therapy influence on some biochemical and plasmatic oxidative stress parameters, in different transfusion types.

Materials and method. Twenty-one Holstein male calves (BW=105±11.85 kg) were randomly assigned either to control group (C-G) (n=7) or in one of the two treated groups (n=14). All the calves were subjected to the anemia induction protocol (AIP) at the beginning of the experiment. The hetero-transfusion group (HT-G) received a transfusion with compatible blood and the auto-transfusion group (AT-G) received their own blood. The transfused blood volume was the equivalent of 65% of the extracted blood during the AIP, for both treated groups. The biochemical determinations were made by spectrophotometric methods using Konelab 30 I Thermo Fisher. Total antioxidant activity, Total Oxidant Status (TOS), Nitric Oxide (NO), Thiols and Oxidative Stress Index were determined as plasmatic oxidative stress parameters. The statistical analysis were made using ANOVA.

Results and discussions. Total Proteins (TP) level was statistical significant higher ($P<0.05$) for heterotransfusion group, three days in a row after transfusion (day 3= 6.03±0.15 g/dl, day 4= 6.27±0.25 g/dl and day 5= 6.73±0.95 g/dl), compared with control group. The Globulin (Glob) levels were also significant higher ($P<0.05$) in the second group from day 3 to day 5 (day 3=3.20±0.10 g/dl, day 4= 3.37±0.15 g/dl and day 5= 3.30±0.35 g/dl), compared to control group. Similar to TP and Glob, the Albumin (Alb) levels were higher ($P<0.05$) in the heterotransfusion group compared to control, in the same time interval (day 3=2.83±0.06 g/dl, day 4= 2.90±0.10 g/dl, day 5=2.80±0.10 g/dl). For the Total Bilirubin (TB) there was no significant variation recorded and for the Direct Bilirubin (DB) levels only in day 9 (0.07±0.01 mg/dl) was recorded a lower value of HT-G compared to the first group ($P<0.05$). Regarding the Indirect Bilirubin (IB) levels, a significant difference ($P<0.01$) between HT-G and AT-G was observed in day 3 (HT-G=0.06±0.00mg/dl, AT-G= 0.10±0.01mg/dl). Aspartate Aminotransferase (AST) levels were significant higher in HT-G compared to C-G ($P<0.01$) in days 6 and 7. In AT-G, AST levels were higher compared to control in days 4 and 7 ($P<0.05$). Also, there were significant differences ($P<0.01$) of AST levels between treated groups in day 7 and 11, with higher values recorded in HT-G. In the plasmatic oxidative stress parameters were few statistical significant differences recorded: TOS level was higher ($P<0.05$) in HT-G (day 14= 17.91±0.59 µmol H2O2 equivalent/L) compared to control. OSI index was also higher ($P<0.05$) for HT-G (16.54±0.54), compared to control.

Conclusion. The biochemical changes represents the most important issues as transfusion side-effects, while plasmatic oxidative stress has a lower impact in transfusion therapy subjects.

Keywords: cattle, transfusion, hematology

COMPARATIVE MIRNAS EXPRESSION ANALYSIS IN HUMAN AND CANINE BREAST CANCER

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Introduction. Comparative oncology represents an important field of biology, with roles in cancer research and drug development. High incidence and mortality in human breast cancer, ranking first in women worldwide, make it imperative to improve the existing diagnosis methods, and to find suitable animal models for new biomarkers and therapeutic strategies. Histological and molecular similarities between 2 species breast cancers showed that dogs could be reliable models for this pathology. Circulating miRNAs give important information regarding development and progression of many cancers. The purpose of study was to identify a common panel of microRNAs with biomarker potential and possible therapeutic targets.

Material and methods. We performed a Next Generation Sequencing followed by qRT-PCR study on cell lines and tissue samples from both species, to find molecular similarities and identify the signalling pathways modulated by the most relevant common microRNAs.

Results and discussions. We compared human and canine breast cancers with healthy controls and found 21 common miRNAs with altered expression in both human and canine breast cancer. The two most overexpressed miRNAs were miR-21-5p and miR-29b-3p, further studied regarding their target genes and the canonical pathways in which they are involved, most altered being associated with cancer, cell cycle, apoptosis, and invasion.

Conclusions. By integrating and interpreting the results of our study, we concluded that the common microRNAs involved in human and canine breast cancer might have potential biomarker role for the diagnosis and pathology characterization, an important tool for comparative oncology with benefits in both human and veterinary medicine.

NEUROPROTECTIVE EFFECT OF *COMBRETUM MICRANTHUM* ON STREPTOZOTOCIN–NICOTINAMIDE INDUCED DIABETIC RATS.

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Diabetes mellitus is associated with mild cognitive impairment anxiety and depression. *Combretum micranthum* (CM) known as ”Herbal tea of long life” or ”plant to heal”, is a widely used plant in Afircan traditional medicine, for various conditions including diabetes. The aim of this study is to assess the ability of CM leaves extract to prevent the cognitive impairment in diabetic rats. Diabetes mellitus was induced in adult Wistar male rats by using the streptozotocin (STZ) –nicotinamide (NA) model. Animals with glycaemia above 250 mg/ dL were divided into four groups, non-treated diabetes, group receiving classic diabetes therapy (glycoside 5 mg/kg b.w. d.), and two groups were treated with CM in doses of 200 and 400 mg/kg b.w. d., for eight weeks long. Body weight, blood glucose, glycated hemoglobin, lipid profile and insulin levels were measured. Additionally we assessed the general locomotor activity and anxiety were assessed using open field test (OFT) and elevated plus maize (EPM). In the end of the study brain histopathological changes and the levels of oxidative stress (MDA, SOD, CAT, GPx) were additionally investigated. The CM therapy significantly decreased the glycaemia from the first week of study, prevented the body weight loss and improved other parameters of glycaemic and lipid profile. CM therapy prevents diabetic encephalopathy, down regulates the brain oxidative stress.

In conclusion the present research work, we demonstrated that CM provided neoroprotection on experimental diabetes mellitus model.

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IMMUNE CELLS AND THEIR PRODUCTS INVOLVED IN ALLERGIC INFLAMMATION

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Background. Inflammation is a response of the organism to aggression, being a way to protect the body. Sometimes the process is inducing damages to tissues and ends in diseases, as it happens in allergic diseases. Allergens are presented by antigen presenting cells (APC) to T lymphocytes which became Th2 type and secrete IL-4 and IL-13 inducing IgE switch in B lymphocytes. All this may help us to diagnose and may be therapeutic targets. For example specific IgE is a a diagnostic tool to be evalute in vitro (serum evaluation) and in vivo (skin testing), and also is used to dose the monoclonal antibody (MoAb) therapy with omalizumab (humanized anti-IgE MoAb) in asthma and chronic spontaneous urticaria (CSU). Other MoAb may be used having as target eosinophils. Mast cells and basophils are the mediators release cells after the link between allergens and specific IgE bound to specific receptors. Some of the mediators may be used in diagnose (as is tryptase, leukotrienes).

The aim is to understand to importance of different cells and their mediators involved in allergic diseases able to induce inflammatory damages.

Methods. We evaluate our patients (1500) with allergy by measuring total and specific IgE (tIgE between 30-over 10.000 kU/L; specific IgE between 0.35 to over 100 kU/L). The asthmatic patients with high IgE had a good respond (100%) to Omalizumab therapy during 12 month. We used also Omalizumab in 36 patients with CSU for 4 month, with improvment in 90% of our pts. The evaluation of tryptase descoverd pts having silent mastocytosis (Tryptase over 11 ng/ml in 4 pts), pts with high risk for side effects during immunotherapy. In 45 pts with drug allergy, we are using basophil degranulation tests to diagnose (with high specificity, 96%).

Conclusion. Understanding the mechanism of allergic inflammation may provide elements for diagnosis and helped us to choose the best therapy for our patients.

Keyword: inflammation, allergy, IgE, mast cells, lymphocytes

EOSINOPHILS IN PROTECTIVE IMMUNITY AND PATHOLOGY

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Eosinophils are predominantly tissue-dwelling cells whose functions in health are not entirely understood. Eosinophils are key immune cells involved in both allergic inflammation and certain clonal myeloproliferative disorders. Peripheral blood or tissue eosinophilia is seen in a wide array of diseases, ranging in severity from mild to life-threatening, and as a result of several mechanisms. When activated, eosinophils release mediators and active substances that can damage tissues and contribute to disease pathology. Normal eosinophil biology, the mechanisms of eosinophilia, tissue damage by eosinophils, and the major causes of eosinophilia are discussed in this paper. Moreover, the authors aim to present an approach to the underlying causes of eosinophilia, with a highlight on critical elements of differential diagnosis of disorders affecting eosinophils in patients who were addressed to the Allergy Department of the "Professor Doctor Octavian Fodor" Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania.

CELL ADHESION MOLECULES AND THEIR ROLE IN ALLERGIC INFLAMMATION

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Allergic IgE mediated reaction involves a chronic inflammatory process demonstrated over the last 20 years. The event that initiates the inflammation cascade is the activation of LTh2 by presenting the allergen by the APC and sensitization to the allergen. IgE is synthesized by lymphocyte B after interaction with TL at MHC class 2 on BL and the TL antigen receptor, this interaction occurs in the secondary lymphoid organs. When LTh2 is stimulated by an allergen, it induces IgE synthesis at the B lymphocyte level via the cytokines IL-4 and IL-13. IgE have the capacity to bind to the mast cells and basophiles. They bind to their surface the specific IgEs against the allergen that produced the sensitization. The mast cells and basophiles degranulate to a new contact with the sensitizing allergen and release the mediators contained in their cytoplasm granules (preformed) and newly synthesized mediators (de novo mediators) having inflammatory properties. These mediators are responsible for the appearance of symptoms characteristic of allergic diseases.

Preformed mediators are responsible for the acute phase of allergic inflammation characterized by allergic rhinitis of nasal and ocular itching, sneezing and rhinorrhea. In the allergic reaction, early mediators initiate a complex network of inflammatory phenomena that lead to the expression and activation of cell adhesion molecules ICAM-1, VCAM-1 and E-selectins. Activation of these cell adhesion molecules favors the migration of tissues to proinflammatory cells such as eosinophils and neutrophils.

Method. We evaluated 79 patients with allergic rhinitis in Allergology department, and and a batch of 30 healthy volunteers as a control batch.

Results. 79 patients with an average age of 30.44 ± 9.9 were investigated, of whom 49.36% were women, and most of the 83.54% came from the urban environment; the group of healthy volunteers with similar characteristics. Various markers that can grow under the conditions of an allergic disease have been analyzed from the serum. Most of the mean values of the markers of inflammation obtained in the study group were significantly higher in AR patients than in healthy volunteers except for E-selectins (ICAM-1: $p = 0.001$, VCAM-1: $p = 0.000$, E-selectins: $p = 0.764$). The cell adhesion molecules ICAM-1, VCAM-1 and E-selectins were not influenced by the type of allergen sensitizer, keeping them in approximately equal proportions in subsets of patients with allergen sensitization from the outside, inside the home or both.

Conclusions. Allergic rhinitis is a disease of the young adult from the urban environment (besides the genetic factor, western lifestyle plays an important role in this disease). The predominant form is moderate- persistent allergic rhinitis. The severity of the disease did not correlate with the degree of systemic inflammation due to CAM levels (E-selectins, ICAM-1, VCAM-1). Most probably in the respiratory tract, CAM is more pronounced than at the systemic level. The mean values obtained in the study of markers of inflammation are higher than the healthy volunteer values for ICAM-1 and VCAM-1, and we may consider that patients with AR have a significant degree of systemic inflammation.

BLOOD DONATION: MULTIDISCIPLINARY APPROACH

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The paper has the main aim to present sequentially, the rejection reasons of potential blood donors, the management of professional attitude and the future strategy which should be developed according to regional realities. The study is a descriptive and analytic one, being evaluated medical records afferent to the period of time 01.01.2014-31.12.2016. Due to the large number of assessed individual the study is a population one, being taken into account the number/gender/age and blood donor category. Each potential/blood donor was reported according to rejection/allowance to blood donation, each criteria: medical (clinical and paraclinical) and non-medical. Is proven that the panel of diseases which will reject (temporary or definitive) the individual is very large, with the predominance of hepatic function disturbance (ALT level), followed by cardio-vascular diseases; regarding paraclinical parameters, the predonation level of hemoglobin significantly fingerprints the rate of temporary deferral of potential blood donors, and in case of postdonation (for blood donors) rejection criteria, the viral markers, mainly the presence of AgHBs. The assessed data, show the importance of professional responsibility of the physician who rules the predonation medical examination, to support the transfusion safety golden rules, for both blood donor and transfusion recipient. Also, should be recognize the interface of the blood centres physicians/lab workers, with the other specialists, mainly with the general practitioner, in order to report, to collaborate each other, for a rapid and correct diagnosis, a proper treatment, with a higher quality of life.

PLASMA LIPIDS AFFECT DABIGATRAN ETEXILATE ANTI-COAGULATION IN RATS WITH UNBALANCED DIABETES MELLITUS

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Dabigatran etexilate (DE) appears to ensure similar efficacy for stroke prevention in patients with and without diabetes mellitus (DM). However, the benefit of reducing major bleeding was not seen in diabetics. We aimed to investigate the anticoagulant response to DE and the biological predictors of this response using an experimental DM model. Six control (C), eight DE-treated control (CD), five diabetic (D), and eight DE-treated diabetic rats (DD) were investigated. Plasma glucose (GLU), triglycerides, total cholesterol (CHOL), high- and low-density lipoprotein (LDL) cholesterol, and plasma creatinine were measured. Corelations with the diluted thrombin time (dTT) were ascertained. When corrected for similar DE intake, dTT was significantly higher in DD compared to CD ($p<0.001$). Among DD, there was a significant negative correlation between creatinine clearance and dTT ($r=-0.91$, $p<0.01$). Additionally, dTT positively correlated with CHOL ($r=0.96$, $p<0.01$), LDL ($r=0.75$, $p=0.04$), and GLU ($r=0.83$, $p=0.02$). In multiple regression analysis, CHOL ($r=0.93$, $p<0.001$) and LDL ($r=0.74$, $p<0.01$) remained independent predictors of dTT. This study indicates significantly more intense DE-induced anticoagulation in diabetic rats, that does not seem to be solely related to kidney dysfunction, and demonstrates that plasma cholesterol can significantly affect DE-anticoagulation in this setting. These results could explain the similar benefit of DE on stroke prevention in patients with and without DM, as well as the lower benefit of reducing major bleeding in diabetics.

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CHANGES IN THE LEVEL OF CELL INJURY MARKERS DURING EXPERIMENTAL HEMORAHIC SHOCK AFTER TREATMENT WITH RAVITEN

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Background. Clinical management of patients with hemorrhagic shock (HS) represents a complex and difficult process. Multiple patogenetic loops involved in onset and evolution of HS underlie the need for searching new remedies with antihypertensive, cytoprotective and antiinflammatory effects, which could diminish the degree of cellular injuries. STUDY'S OBJECTIVE was to determine the ability of inhibitor of NO-synthase *Raviten*, to reduce the serum level of enzymes subsequent to cell injuries during experimental HS.

Materials and methods. HS with a length of 120 min. in rats was performed by effusion of 30% from total blood volume via femural artery. Rats were then resuscitated for 90 min. with isotonic solution alone and isotonic solution plus NO-synthase inhibitor *Raviten* (20 mg/kg BW). At 90 min after resuscitation the blood was collected and was determined the level of markers of cellular injury: ALT, AST, GGTP, GLDH, pancreatic amylase, pancreatic lipase, LDH, creatinkinase.

Results. Administration of *Raviten* after 120 minutes of HS reduced levels of ALT, GGTP, GLDH, pancreatic amylase and creatinkinase by 16% ($p<0.05$), 41% ($p<0.05$), 13% ($p<0.05$), 34% ($p<0.05$), respectively, when comparing the level of these enzymes in animals with HS which were resuscitated only with isotonic solution without Raviten. The serum level of AST, pancreatic lipase and LDH didn't show significant differences between animal groups.

Conclusions. Raviten is an isothiourea derivative with inhibitory action on NO-synthase, by this way diminishing the inflammatory component of HS, such preventing the cellular injuries with subsequent reduction of cell injury markers in the blood.

STREPTOZOTOCIN-INDUCED DIABETES MELLITUS INCREASES INTRINSIC PLATELET REACTIVITY, BUT DECREASES IN VITRO PLATELET AGGREGATION

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Higher platelet reactivity is accepted as a ubiquitous feature in diabetic patients. However, studies of platelet function are rather inconsistent, some studies reporting higher platelet reactivity in diabetics, while others showed no change. We aimed to evaluate platelet indices and *in vitro* platelet aggregation in rats with long-lasting (28 weeks) diabetes mellitus (DM). Twelve control (C) and 14 diabetic (D) rats were investigated. In the D rats, diabetes was induced at 11 weeks of age using streptozotocin (60 mg/kg, i.p.). Platelet count and indices, and *in vitro* adenosine diphosphate (ADP), protease-activated receptor 4 (PAR4), and arachidonic acid (AA)-induced whole-blood platelet aggregation were assessed in C and D rats at the age of 38 weeks. Compared to their non-diabetic controls, D rats presented significantly lower platelet count and plateletcrit (both $p \leq 0.001$), and significantly higher mean platelet volume ($p < 0.01$). ADP- ($p = 0.04$) and AA-induced ($p < 0.01$) platelet aggregation were significantly lower in D compared with C rats, whereas PAR4-induced platelet aggregation was similar between the two groups ($p = 1.00$). The present study demonstrates a paradox of high intrinsic platelet reactivity and low *in vitro* ADP- and AA-induced platelet aggregation in rats with streptozotocin-induced DM compared with non-diabetic controls. However, the relevance of in vitro platelet aggregation to the contribution of platelets to *in vivo* DM-related thromboembolic complications remains questionable.

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PATHOPHYSIOLOGY OF CHRONIC ITCH

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Pruritus is a worldwide phenomenon, occurring in every age group, with a great impact on quality of life. It is the most common symptom in dermatology and, like pain, represents suffering. Except well known chronic pruriginous skin diseases as atopic dermatitis and *prurigo nodularis*, it is frequently described in various systemic (uremia or cholestasis), psychiatric and neurological conditions. It also occurs as a result of medication intake and is common in patients on hemodialysis.

Several mechanisms which lead to pruritus have been described and proved that the immunological background of each disease is different. It is currently hypothesized that in each disease, different mediators are mainly responsible for the transmission of itch. Clinical presentation may reflect the differences in the mediators involved in pruritus in each disease. This may explain why some patients strongly scratch their skin, while others never scratch even if they suffer from itch. Thus, current research focuses on receptors, neuropeptides, cytokines and other factors including immune cells in the blood, peripheral and central nervous system in an attempt to elucidate the mechanisms that drive itch transmission in each of the different diseases. Treatment is yet difficult and controversial as it is more to be discovered about pathophysiology of itch.

NON-ANTIBIOTIC EFFECTS OF RIFAXIMIN

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Rifaximin is an oral non-absorbable semisynthetic antibiotic derivative of rifampin, characterized by a broad spectrum of antibacterial activity (Gram-positive and -negative, aerobic and anaerobic bacteria). It is used in the management of several gastrointestinal infectious diseases, mainly travelers' diarrhea, colonic diverticular disease and for reduction of the risk of recurrence of hepatic encephalopathy in patients with cirrhosis. Unlike other antibiotics, rifaximin shortens the duration of infection without eradicating enteropathogens and without significantly changing the intestinal microbiota. This suggests that rifaximin has mechanisms of action other than direct antibiotic activity. Some pre-clinical studies showed that rifaximin has effects on both the pathogen and host. Direct effects on pathogenic bacteria (reduction of the expression of some bacterial virulence factors) as well as changes in epithelial cell physiology leads to reduced bacterial adherence on epithelia, reduced bacterial internalization and reduced inflammatory cytokine release by host cells. Because of the very small amount of intestinal absorbtion, rifaximin is a relatively safe antibiotic for the patients with advanced liver disease, who need a modulation of gut microbiota. In patients with hepatic encephalopathy, rifaximin has been proved to have beneficial effects on cognitive function, reducing endotoxemia and bacterial translocation as well. It appears that these effects are linked to a modulation of gut microbes functionality, that enhances the production of favorable metabolites. In a study group recieving rifaximin there was a significant increase in serum saturated fatty acids (myristic, caprylic, palmitic, palmitoleic, oleic and eicosanoic) as well as unsaturated (linoleic, linolenic, gamma-linolenic and arachnidonic).

AUTOMATIC VS MANUAL DNA EXTRACTION METHODS FROM SALIVA

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Saliva represents a unique body fluid, easy and non-invasive to collect and may be useful as an alternative to blood source of genomic DNA for large scale genetic studies. In this study, we evaluated the DNA yield and the suitability of isolated DNA for real-time PCR amplification (which is the most used molecular technique in genetic studies) using an automatic nucleic acids extractor, a commercial DNA extraction kit and a simple cost-effective protocol with ammonium acetate under different storage conditions of saliva samples. The participants, 20 in total (age range: 19-57), were asked to rinse vigorously their mouth for 45-60 seconds with 15 ml of a 2% saline solution. The samples were divided into 4 tubes containing equal amount of sample and were submitted to different storage conditions. The first tube was used for immediate DNA extraction (C1), the second tube was stored at -20°C for 1 week (C2), the third tube was immediately centrifuged at 10000 rpm for 5 minutes and the cell pellet stored at -20°C for 1 week (C3) and the final aliquot was mixed with ethanol to a final 70% concentration and stored at room temperature for 1 week (C4). Real-time PCR reactions were performed using a commercial human beta-globin control assay. Saliva is a viable alternative source of real-time PCR amplifiable DNA and even storage in 70% ethanol solution for one week at room temperature, still provided DNA sufficient for several real-time PCR reactions without affecting the PCR amplification results.

META-ANALISYS REGARDING PERIODONTAL ISSUES IN PATIENTS WITH OSTEOPOROSIS

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Osteoporosis and periodontal disease are two chronic diseases with high prevalence, that share certain pathophysiological elements. The study consisted of a meta-analysis of published studies that researched the relationship between osteoporosis and periodontal disease. The analyzed articles were *in-extenso* texts, published between 1997 and 2016. The database used was PubMed.org. We analyzed 10 studies, that were published before 2007. Among these, 6 concluded that there are statistically significant differences between the osteoporotic group and the control group – in the case of the osteoporotic patients a correlation between bone mineral density (BMD), interproximal alveolar bone loss and clinical attachment level was found. The other 4 studies did not show an association between the aforementioned matters. We also analyzed 11 in-extenso articles, published after 2007. 10 studies showed a correlation between osteoporosis and periodontal disease, in terms of number of absent teeth, oral hygiene status, clinical attachment level, interproximal alveolar bone loss and bleeding on probing. controversial findings regarding the existence or absence of an association between osteoporosis-periodontal disease have mainly been found in studies published before 2007. In the last 10 years, after 2007, we have noticed a tendency towards uniformity in the sense that a consensus seems to be settling, the vast majority of studies concluding that there is an association between osteoporosis and periodontal disease. An explanation for previous differences of opinion and uniformity of opinion at present may be the consensus on diagnostic criteria for both osteoporosis and periodontal disease.

INFECTIVE ENDOCARDITIS OF ORAL ORIGIN – CASE REPORT

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Infective endocarditis (IE) is an inflammation of the endocardium, caused by bacterial infection. There are two pathogenic mechanisms required for endocarditis: a predisposing abnormally of the endocardium and the concurrent presence of microorganisms in the bloodstream. Causative microorganisms vary by source of bacteremia and host risk factors, but overall, streptococci and *Staphylococcus aureus* are resposible for most IE cases. Oral streptococci may cause IE, but the incidence is difficult to estimate and the pathogenesis is not well understood. A 47-year old male with a history of hypertension was admitted in the Prof. Dr. Matei Bals National Institute of Infectious Diseases, Bucharest, for enterocolitis with *Clostridium difficile*. During the hospitalizion he presented fever and we isolated from blood culture *Streptococcus gordonii*, an oral Gram-positive bacterium, that has a high affinity for tooth surfaces. *S. gordonii* plays a key role in the initiation of dental plaque formation, but it can also bind to damaged endothelium and synthesizes a wall protein called platelet adherence protein A (PadA) that specifically interacts with platelet GPIIb/IIIa. The interaction between PadA and GPIIb/IIIa resultes in firm platelet adhesion, dense granule secretion and activation. This process can lead to enhanced platelet deposition and the formation of IE vegetations. An echocardiogram confirmed the diagnosis of IE; the patient followed a 6-week course of antibiotherapy, with a favourable outcome. The presence of oral bacteria in the blood may represent an important risk factor for IE, in the setting of endothelial damage.

THE PHYSIOPATHOLOGICAL MECHANISMS INVOLVED IN THANATOGENESIS - CLINICAL AND MICROSCOPIC STUDY

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Thanatogenesis is based on a series of chained physiopathological mechanisms that will eventually lead to that „point of no return" from which the body / cell can no longer regenerate or survive. Presentation of the most frequent thanatogenesis mechanisms in the case of a group of patients from the Pathology Department in Tîrgu Mureş. Patients were divided into groups, according to the primary organ system, to which secondary mechanisms were added. For the cardiovascular system, acute coronary heart disease prevailed. For the respiratory system, lung infections or lesions prevailed due to chronic diseases. For the digestive system, upper or inferior digestive hemorrhage or Clostridium Difficile infections have prevailed. Hepatic pathology was represented by various types of cirrhosis. The urinary system had in the first place, chronic kidney disease, associated or not with diabetes mellitus. An important part of the patients died of malignancies. The malignant pathology was predominated by cases of lung carcinoma, colo-rectal carcinoma, cervical carcinoma and haematological neoplasms. The infectious pathology has been focused on HIV and AIDS infections. Most deaths occurred at ICU, from Surgery, Internal Medicine, Oncology, or Infectious Diseases Clinic. Beside the clinical aspects of the cases, the paper also presents microscopical features of death-related injuries. The most common causes of death were cardiovascular diseases and various types of cancer, in correlation with statistics in the published literature. .

SKIN LYMPHOMAS THROUGH THE VIEW OF THE PHYSIOPATHOLOGIST AND THE MORPHOPATHOLOGIST

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Lymphomas represent neoplasms with T and B cell origins. Lymphomas differentiates from leukemia by the fact that they are originated in lymph nodes or peripheral lymphoid organs and affects only late or not at all the hematogenous bone marrow. Leukemias has as starting point, a malignant tumor transformation of the haematopoietic stem cells, and affects lately the lymph nodes and peripheral organs. Cutaneous lymphomas represents a characteristic group of lymphomas, with primary cutaneous affecting. A brief presentation of the pathophysiological mechanisms by which the skin is affected, in the case of cutaneous primary lymphomas or cutaneous secondary determinations. The paper presents correlations between the pathophysiological mechanisms of the different types of cutaneous lymphomas and their histopathological appearance. Immunohistochemical investigations are mandatory for establishing an exact diagnosis and for an appropiate differential diagnosis. Full blood count, paraclinical investigations and clinical data are essential for clinical-pathological correlations. Cutaneous biopsy and histopathological examination are mandatory. Most skin lymphomas are T type. Mycosis fungoides is the most common type of T-lymphoma. The skin may be affected secondary to both lymphomas and leukemias.

IMMUNOHISTOCHEMICAL FEATURES OF ANTIGEN PRESENTING CELLS IN CUTANEOUS MELANOMA WITH REGRESSION - PATHOPHYSIOLOGICAL, PROGNOSTIC, THERAPEUTIC CORRELATIONS

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Melanoma is the most dangerous type of skin cancer. The rising incidence in general population, increased incidence in young patients and high mortality rate in melanoma patients have been frequently reported in medical literature in recent years. Lack of adequate treatment in different stages of the disease represents important issues facing clinicians and researchers. The opportunity and relevance of understanding the inflammatory phenomena involved in cancer pathogenesis, which is considered essential for the development of potentially promising treatments, has become increasingly obvious. Cutaneous dendritic cells play multiple physiological roles and are involved in various pathophysiological processes. Nevertheless, the role of dendritic cells in melanoma regression phenomenon is not well understood. One of the essential phenomena in the evolution of melanoma is spontaneous tumor regression. Melanoma regression is the result of a complex interaction between malignant melanocytes and the immune response of the host. Currently, the investigation of dendritic cells able of presenting antigens, especially of Langerhans cells, could be the premise of the development of effective anti-melanoma vaccines. Recent studies emphasize that research on dendritic cells involved in melanocytic regression will help in elucidating the current failure of anti-tumor mechanisms in melanoma (both natural and therapeutic).In this work, we will present the results of the immunohistochemical studies of the skin dendritic cells obtained by our multidisciplinary team in recent years. We will also perform a brief review of the role of dendritic cells in inflammatory melanoma infiltrate. These antigen presenting cells are involved both in the induction of immune tolerance towards the tumor and in the production of anti-tumor immunological responses.

Concluding, in the context of limited knowledge of variable evolution of melanoma subtypes, we propose further studies of the tumor's inflammatory infiltrate, especially antigen presenting cells Langerhans, in relation to the biological behavior of tumor cells (proliferation, invasiveness and metastasis).

EXPERIMENTAL-INDUCED LIVER FIBROSIS FOR THE STUDY OF THE HEPATOPROTECTIVE POTENTIAL OF DIFFERENT NATURAL COMPOUNDS WITH ANTIOXIDATIVE ACTIVITY

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Liver fibrosis, a common condition occurring during the evolution of almost all chronic liver diseases, is the consequence of hepatocyte injury that leads to the activation of Kupffer cells and hepatic stellate cells (HSC). Reactive oxygen species (ROS) and some cytokines are among the most potent activators of HSC. There are a lot of experimental models to induce liver fibrosis and we performed two of them: CCl4-induced fibrosis and bile duct ligation (BDL). We aimed to evaluate different protective strategies with natural compounds using these experimental models in order to establish their potential to inhibit the initiation and the progression of liver fibrosis: Silymarin (Si), an herbal product, Chitosan (CS) a polysaccharide obtained from chitin and silver nanoparticles loaded with chitosan.

In order to quantify liver injury and protective effects of these natural compounds in early and late phases of experimentally induced liver fibrosis we assessed: hepato-cytolysis (aminotransferases and LDH), oxidative stress (malondialdehyde, protein carbonyls, GSH/GSSG ratio), inflammation (different interleukins and intracellular pathways), fibrosis (histological score, hyaluronic acid), transforming growth factor TGF-β1, markers of HSC activation (α – SMA expression by western blot) and activation of Kupffer cells (CD 68) by immunohistochemistry. We have also used the immunohistochemical assay for cytocheratin 19 and proliferating cell nuclear antigen (PCNA). Our data showed the protective effects of Silymarin, in different doses, in early and late phases of liver fibrosis, the protective effects of chitosan during the early stages after BDL and no clear beneficial effects of silver nanoparticles loaded with chitosan in the early stages of liver cholestasis.

LEFT VENTRICULAR NON-COMPACTION: A COMPREHENSIVE APPROACH

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Left ventricular non-compaction (LVNC) of the myocardium is a genetically heterogeneous disorder that can be linked to mutations in mitochondrial, cytoskeletal and sarcomeric proteins. This cardiac abnormality is characterized by an embryonic failure of full maturation of the myocardium due to an arrest in the compaction process. Familial occurrence is frequent with autosomal dominant and X-linked transmissions. The classical triad of complications are heart failure, arrhythmias, including sudden cardiac death and systemic embolic events. Here, we present a rare case of a 21 years old male that showed up at the emergency room with syncope and marked fatique on exertion. The ECG findings consisted of 2:1 Mobitz II block alternating with total atrioventricular block. When echocardiography was performed we found segmental thickening of the left ventricular myocardial wall, consisting of a thin compacted epicardial layer and a thickened noncompacted endocardial layer with prominent trabeculations and deep recesses, with noncompaction to compaction ratio ≥ 2. The patient required permanent cardiostimulation, therefore we performed the implantation of a Pro-MRI bicameral cardiac pacemaker. Although two-dimensional echocardiography is the first line diagnostic investigation, some non-compaction criteria were occasionally found in other heart diseases. Importantly, patients with dilated cardiomyopathy, hypertrophic cardiomyopathy and LVNC share common pathogenetic mutations as well. Thus, a comprehensive diagnostic assessment, including multimodality imaging and a systematic screening of all first-degree family members, may provide solid information to further clarify the diagnosis.

PHYSIOPATHOLOGY OF HIV-ASSOCIATED PREMATURE AGING UNDER CART

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Highly active antiretroviral therapy (HAART) has significantly increased life expectancy of the human immunodeficiency virus (HIV)-infected population. However, a premature and accelerated aging of HIV-patients has been observed, potentially caused by continuous viral stimulus in spite of efficient viral suppression or by adverse effects of antiretroviral therapy. Mitochondrial oxidative stress, shortening of chromosome telomere and accumulation of excess lamin A precursors are considered to be the basis of HIV-induced accelerated senescence.The nucleoside reverse transcriptase inhibitor (NRTI) antiretroviral drug class is recognised to cause depletion of mitochondrial DNA via inhibition of the mitochondrial specific DNA polymerase-γ. Other antiretroviral drug classes, for example protease inhibitors, also cause severe mitochondrial damage by inducing aforementioned oxidative stress. NRTI triphosphate-induced inhibition of telomerase and prelamin A accumulation caused by protease inhibitors are the other two main contributors to premature aging in HIV infection. This paper reviews how HIV infection and antiretroviral therapy cause premature aging and to the emergence of HIV-associated non-AIDS illnesses (HANA).

HIV PRIMARY INFECTION PRESENTED AS ACUTE ENCEPHALITIS – PATHOPHYSIOLOGY AND DIAGNOSTIC CHALLENGES

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Acute encephalitis is a life-threatening condition. A wide variety of infectious agents are implicated and in many patients no cause is found. HIV infection of the central nervous system (CNS) is associated in most cases with a chronic evolution. HIV primary infection rarely presents as acute encephalitis. HIV encephalitis is characterized by diffuse myelin damage, neuronal loss, microglial nodules and lymphocytic infiltrates. Envelope glycoproteins cause the membranes of infected macrophages to fuse forming multinucleated giant cells – the hallmark of HIV encephalitis.A 67-year old man was admitted to Prof. Dr. Matei Bals National Institute of Infectious Diseases, Bucharest, in october 2016 with fever, confusion, drowsiness and tremor of extremities. Neurological examination showed finger to nose test dysmetria, positivity of Noica test, bilateral hyporeflexia. Lumbar punction revealed pleocytosis and slightly increased proteins. Magnetic resonance imaging revealed bilateral inflammation of the hippocampus –suggestive for viral encephalitis. All available specific laboratory tests for viral identification including cerebrospinal fluid polymerase chain reaction were negative. The HIV test was also negative. He had a favourable outcome following two weeks of nonspecific therapy (corticosteroids), with complete remission of symptoms associated with encephalitis. After two months from discharge the patient was tested again for HIV and the serology was positive. The diagnosis was confirmed and he started antiretroviral therapy. Although HIV usually affects the brain as a result of a longstanding infection, the primary infection may also lead to CNS inflammation and the consecutive encephalitis can pose significant diagnostic challenges.

CHARACTERISTICS OF BODY COMPOSITION IN PATIENTS RECEIVING ANTIRETROVIRAL THERAPY (ART)

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The increased use of combination antiretroviral therapies has led to significant improvements in mortality among HIV-positive patients. However, multiple metabolic complications, proved to have complex etiology, have been described in HIV infection. The aim of this study was to explore body composition abnormalities and bone demineralization among patients with HIV infection. A cohort of patients confirmed with HIV infection, undergoing antiretroviral treatment (ART), has been evaluated using dual-energy X-ray absorptiometry (DXA). The results were compared to healthy controls (a cohort of subjects without HIV infection). The associations between changes in body composition and lifestyle data, the parameters related to viral infection and antiretroviral medication use, were analyzed. In the group of HIV-infected patients receiving antiretroviral therapy, low adipose tissue mass and reduced lean tissue mass were found, in comparison to the control group, mostly correlated with protease inhibitors treatment. Among HIV infected men, bone mass was lower compared to the control group; these changes were related to ART type, smoker status and body mass index. The results of the study show that body composition changes are common in HIV infected persons, in association with specific HIV factors and long-term

PHYTOTHERAPY IN OXIDATIVE STRESS

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The oxidative stress is defined as an imbalance between reactive oxygen species (ROS) production and the antioxidant mechanisms. Reactive nitrogen species (RNS), which include NO•and peroxynitrite ($ONOO^-$), together with ROS are responsible for oxidative/nitrative stress. The consequences are generalized oxidation resulting in post-translational modifications that alter the function of important cellular proteins and signalling pathways, leading to cell dysfunction, necrosis or apoptosis. Further studies also confirmed that $ONOO^-$ has physiological functions like a role in triggering ischaemic preconditioning and ischaemic postconditioning.

An important way to manage the oxidative stress risk is controlled diet containing antioxidant bioactive nutrients. Among these the group of polyphenols might be most promising, because they are exerting antioxidative, anti-inflammatory, cardioprotective, cancer chemopreventive and neuroprotective effects. Furthermore, it was found that plant-derived polyphenols can have dual antioxidant and prooxidant activities depending on the environmentental conditions because phenolic antioxidants behave like prooxidants under the conditions that favor their autoxidation. Moreover, there is a growing consensus that a combination of antioxidants, rather than single entities, may be more effective over the long term.

Experimental studies were designed to investigate whether diets supplemented with some plant extracts rich in polyphenols could positively affect the oxidative status in acute inflammation and myocardial ischemia in rats.

ANTIOXIDANT EFFECT OF FLAVONOIDS IN CEREBROVASCULAR DISEASES

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The investigation of the mechanisms that leads to neuronal apoptosis in cerebral ischemia is under research all over the world. The enhancement of oxidative stress in brain neurons is one of the most important pathophysiological mechanism associated with cerebral ischemia. The antioxidant effect of flavonoids can be one important mechanism for modulation of neuronal apoptosis and death in neurovascular diseases as are stroke or chronic cerebral ischemia due to atherosclerosis. In addition to their influence on the cerebral blood flow, flavonoids interact with signalization cascades that lead to the inhibition of neuronal death by oxidative stress apoptosis and thus promote neuronal survival and synaptic plasticity. Acting on the intracellular antioxidant mechanisms the flavonoids can become a balance regulator for production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Addition of flavonoids to dietary components can constitute an adjuvant therapy for neuroplasticity enhancement after stroke or in chronic cerebral ischemia. The aim of this work was to review the antioxidant effects of flavonoids in cerebro-vascular diseases and their benefits according with the new research.

GRAPES PRODUCT INFLUENCE ON MALONDIALDEHYDE AND FATIGUE SENSATION IN MODERATE PHYSICAL TRAINING

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The aim was to assess the influence of a grapes extract product (GEP) on malondialdehyde (MDA) and muscle fatigue sensation (MFS), in moderate physical exercise training (PT). Volunteer sedentary subjects (n=12 men) were divided into two groups: control (C=6) without GEP; who received GEP (G=6). Training consisted of running on an Excite + Run MD treadmill, at 40 watts, daily, for a week. GEP was administered for one month before PT and during PT. MDA and MFS measurings were: 1 day before PT (T1); on the 4rd (T2) and last day (T3) of PT; on the 3rd day after the ending of PT (T4). Statistical evaluation was done using the Student test. Differences between groups: a) MDA was significantly increased at C, compared to G (T2, $p = 0.04$, T3, $p = 0.002$, T4, $p = 0.02$); b) MFS was significantly increased at C, compared to G (T2, $p = 0.04$, T3, $p = 0.003$, T4, $p = 0.01$). In conclusion 1) Under the GEP influence, MDA and MFS were significantly reduced to G group compared to C. 2) GEP acted on MFS more intense than on MDA. 3) The GEP effect on MDA and MFS was maintained after the physical training. 4) We suggest the GEP use for MDA and MFS modulation, in moderate physical training, in sedentary people.

REMEMBERANCE – 2015 PATHOPHYSIOLOGY CONGRESS IN IASI

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Two years ago we had the pleasure and honour to to be the organizer of the National Congress of the Romanian Physiopathology Society, with international participation. It took place in Iași, between the 7th and the 10th of May 2015. The congress was organized under the patronage of the University of Medicine and Pharmacy „Grigore T. Popa, a renown institution, dedicated for the last 137 years to the formation of medical doctors and pharmacists, always in the service of man, training people that will be able to pass on to next generations the reciepe for a valuable medical act. The congress was attended by reputed professors from all the university centers in Romania, as well as famous guests from the field of world pathophysiology. Thus, we have been honored by the presence of Prof. Dr. Olga Pechanova, Head of Institute of Normal and Pathological Physiology, Slovak Academy of Sciences in Bratislava, President elect of International Society of Pathophysiology, Prof. dr. Francesca Romana Patacchioli, Associate Professor of Pharmacology, Department of Physiology and Pharmacology University "La Sapienza" of Rome, Italy and Professor Zdenko Kovač, Chair of Pathophysiology, President of Teaching Comitee, University of Medicine Zagreb.Through its themes, conferences and debate, this meeting definitely marks a milestone in the development of physiopathology, giving us the oportunity of a meeting with profound professional and emotional meaning. We wish with all our hearts that this meeting represented an important moment on the ascending road of recognition of this scientific field.

DESIGN OF A CUSTOM ALGORITHM FOR IMAGE ANALYSIS OF VASCULAR PREPARATIONS STAINED WITH DIHYDROETHIDIUM

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Oxidative stress is both a central pathomechanism and an important theraputic target in cardiometabolic disease. Dihydroethidium (DHE) is a widely used ratiometricmarker that has been reported by several (but not all) authors to be specific for superoxide anion ($O_2^{\bullet -}$). The reaction between $O_2^{\bullet -}$ and DHE generates an oxidized compound that displays red fluorescence. The aim of the present study was to design an automated image analysis algorithm that will allow to circumvent the autofluorescence of elastic lamina in vascular preparations. Aortic rings were harvested from adult male Wistar rats, snap frozen in Tissue-Tek OCT, cut in thin sections (20 um) and incubated with DHE for 30 minutes at room temperature. Representative images were acquired on an Olympus FV-1000 confocal laser scanning microscope. We used dual channel detection, at 461 nm for autofluorescence mask and 560 nm for the DHE stain. Image analysis was performed in Icy, an open source platform. A custom algorithm was designed to quantify DHE staining in rat aortas by using the following operations: channel extraction, threshold based segmentation, Boolean region of interest (ROI) operation to generate a final ROI, followed by ROI statistics export in an Excel file. Batch image analysis is assured by including all processes in a folder loop. By changing the detection settings, the same algorithm can be used for other fluorescent markers, thus rendering versatile the proposed algorithm. In conclusion, we set up a user-friendly algorithm in an open source platform to quantify fluorescently labeled, dual channel images that allows removal of autofluorescent elements from the final measurements.

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ACUTE RESPIRATORY DISTRESS SYNDROME - LINKING PATHOMECHANISMS TO IMAGING FINDINGS

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Acute respiratory distress syndrome (ARDS) is a life-threatening acute respiratory failure with variable progression associated with high morbidity and mortality when diagnostic and appropriate therapy are delayed. The present work was aimed at establishing a relationship between the chest X-ray, ultrasound and computed tomography (CT) findings and the stage-related pathomechanisms in ARDS. We evaluated 5 patients admitted to the intensive care unit of the county hospital of Timişoara with the diagnostic suspicion of ARDS. Early radiographic changes include the appearance of increasingly confluent alveolar infiltrates, mimicking a pulmonary edema pattern.The subacute phase of ARDS (2–10 days after lung injury) is characterized bydecreased lung volumes and signs of consolidation that are noted clinically and radiographically. These findings are the results of type II pneumocyte and fibroblast proliferation in the interstitium of the lung. CT is mandatory for the cases with questionable diagnosis on x-rays, and for evaluating the chronic phase of ARDS (after 10–14 days), when fibrosis, emphysema, and pulmonary vascular obliteration occurs.Understanding the pathophysiology of ARDS is crucial for the correct stage-related diagnostic as well as for the adequate therapeutic approach.

CAROTID INTIMA-MEDIA THICKNESS AND WEIGHT GAIN PATHOPHYSIOLOGY

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Weight gain can lead, in time, to overweight and obesity, the latter becoming pathologies that are more and more frequently met in this century's diagnoses. From pathophysiology point of view, obesity is the result of an imbalance between energy intake and consumption, with the occurrence of genetic and environmental factors. Many hormonal mechanisms have been elucidated to help regulate appetite and food intake, fat storage patterns, and the appearance of insulin resistance and atherosclerosis. Aim: we investigate the relationship between weight gain and carotid intima-media thickness, a well-known early marker of subclinical atherosclerosis.

Patients and methods. We carried out a sectional, analytical and observational study conducted on a number of 100 subjects divided as follows: 17 normal weight subjects; 83 overweight and obese subjects.

Results. Analyzing the relationship between carotid intima-media thickness (IMT) and weight status, there are highly significant statistical differences between normal weight and overweight, obese vs normal weight. Mean carotid intima-media thickness is significantly greater in patients presenting metabolic syndrome. Studying the connection between mean values of serum cytokines (hsCRP, E-selectin, MCP-1) in patients with carotid intima-media thickness ≥0.9 mm, value considered as certain cardiovascular risk factor, one observed that, although they are greater than in patients with intima-media index < 0.9 mm, the difference is statistically significant ($p<0.05$) only in the case of hsCRP, which is also proven in the case those with metabolic syndrome.

Conclusions. Carotid intima-media thickness is increased to mean ≥ 0.9 mm values in asymptomatic overweight and obese subjects, being significantly higher in those who associate a metabolic syndrome. We discovered a close causal relationship between body mass index, carotid intima-media thickness and the presence of systemic inflammation. Ultrasound measurement of carotid intima-media thickness can be an inexpensive screening method, available to clinicians in order to detect subclinical atherosclerosis in overweight and obese patients.

Keywords: carotid intima-media thickness, obesity, overweight, cytokines, early atherosclerosis.

IMPORTANCE OF IMMUNOLOGICAL MARKERS IN THE DIAGNOSIS AND TREATMENT OF PATIENTS WITH BREAST CANCER

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Breast cancer (BC) occupies first place in female cancer mortality. Hormonal receptors (HR), along with Her protein, Ki67 cell proliferation index, have a prognostic value and underpin the molecular classification of BC. The aim of the study is determination of the importance of immune markers in therapeutic decision of Her2+ positive BC patients. 44 patients with Her2+ BC from IOCN were included. Immunohistochemistry assessed the carcinoma type, presence of HR, Ki67 index. Patients were divided according to these parameters in luminal B and positive array carcinoma. Correlations between demographic characteristics, Ki67 density, molecular type of carcinoma and toxicity along with treatment response were made through Fischer and Chi square test. 75% of patients had invasive ductal carcinoma (IDC), 18.2% of them had IDC and ductal carcinoma in situ, 6.8% IDC and invasive lobular carcinoma. Estrogens and progesterone receptors higher than 10% was in 56.8% and 38.6% of patients while, Ki67% was higher than 15% in 86.4% of patients. According with the presence of HR, patients were divided into luminal B 59% and positive array 41%. Neoadjuvant chemotherapy was performed for 41% of patients whereas 59% of patients underwent surgical intervention followed by adjuvant chemotherapy. The response rate of treatment was better at patients classified as positive array. The expression of ki67 was higher in younger women. Immunological markers have a major impact in classification, prognosis and treatment of BC. Positive array patients correlated with favourable response of chemotherapy. Ki67 represents an aggressive marker, suggesting the need for aggressive treatment.

THE EXPERIMENTAL ANTIOXIDANT EFFECT OF *LYCIUM BARBARUM* ON THE BODY EXPOSED TO PHYSICAL EFFORT

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The main objective of the study is to follow the antioxidant effect of *Lycium barbarum* (Goji) natural juice on the body exposed to physical exercise. We studied the oxidant-antioxidant balance indicators during subacute physical exercise on 6 groups of Wistar breed rats (n = 6 each) using the swimming test. Some groups were only subjects of subacute physical exercise while others were subjects of subacute physical exercise and received an additional daily intake of *Lycium barbarum* natural juice. Nitro-oxidative stress was measured by serum determination of total oxidative status (TOS), total antioxidant capacity (TAC), malondialdehyde (MDA), total thiols, nitrites and nitrates. Increased TAC and serum thiol levels confirmed the antioxidant potential of *Lycium barbarum* during subacute physical exercise. The daily intake of *Lycium barbarum* natural juice led to the reduction of oxidative stress and, implicitly, of lipid peroxidation, as evidenced by the decrease of serum MDA values. In conclusion, *Lycium barbarum* could represent a natural, non-doping alternative to improve sport performance, due to its energizing and antioxidant effects.

ARNICA MONTANA IN SURGERY AND SPORTS, FROM THE PERSPECTIVE OF PUBMED PUBLICATIONS

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The objective was the evaluation of research concerning Arnica Montana (AM) in surgery (SG) and sports (SP), from the perspective of PubMed publications. 1947-2016 period was assessed by the total number of publications (N) and the average number of publications per year (ANP), using keywords: ”AM”, ”AM and P” (AMP), ”AM and SG” (ASG), ”AM and SP” (ASP). Analyzed filter for AM was age, with subfilters: 0-18, 19-44, 45-64 and >65 years. Statistical evaluation was made on the basis of the Student test. N for AM increased between 1930-2016, the highest being in 2016. N were more numerous: a) for AMP (68.9% of AM) than for ASG (6.98% of AM) and ASP (3.9% of AM); b) for 19-44 years (36.3 of AM). There were no publications with: ASG, between 1930-2000; ASP, between 1930-1990. For NMA, differences were: a) insignificant between AM-AMP; b) significant, between AM-ASG (p=0.000094) and AM-ASP (p=0.000063). In conclusion, 1) N for AM for 69 years was 370. 2) There were favorite the AM studies with subjects between 19-44 years old and the AMP studies. 3) Publications have shown on ASG since the 2000s and on ASP since the 1990s. 4) The theme of Arnica Montana and Surgery and Sport, reflected by chosen keyword and PubMed filter, even if it is still limitedly explored, it exist as a research concern.

RETROSPECTIVE ANALYSIS OF PUBMED PUBLICATIONS ON GRAPES, GREEN TEA AND OXIDATIVE STRESS

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The objective was the evaluation of research concerning grapes (GP), green tea (GT) and oxidative stress (OS) relationship, by the retrospective analysis of PubMed publications. 1994-2015 period was assessed, by the total number of publications (N), using keywords combinations: ”GP and OS” (GPOS), ”GT and OS” (GTOS). Analyzed filters: a) ”species” with the sub-filters ”other animals” (AN) and ”humans” (H); b) ”sex”, with subfilters ”male” (M), ”female” (F). Statistical evaluation was made on the basis of the Student test. N for GPOS and GTOS increased between 1994-2017 and 1998-2015 respectively, the highest being 2010-2015. Publications were more numerous: a) for AN (52.8% of GPOS; 53.8% of GTOS) than for H (34.2% of GPOS; 38.8% of GTOS); for M (9.7% of GPOS; 11.12% of GTOS) than for F (6.8% of GPOS; 9.45% of GTOS). There were no publications with: M, F for GPOS between 1994-1999; M for GTOS, between 1998-1999. In conclusion 1) N for GPOS for 21 years, was 441 and N for PTOS for 17 years,was 1079. 2) Studies with animals and human male predominated. 3) Publications on GPOS and GTOS have shown interest since the 1990s, and have steadily increased until now. 4) Theme of grapes, green tea and oxidative stress, reflected by chosen keyword and PubMed filters, even approached only in the last 20 years, is of growing interest.

MORPHOLOGICAL CHANGES IN EXPERIMENTAL HEMORRHAGIC SHOCK AFTER TREATMENT WITH RAVITEN

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A high role in the study of hemorrhagic shock (HS) is given to cellular injuries, the degree of which depends on severity of bleeding and reperfusion. Nowadays, the optimal strategy for resuscitation remains controversial and the clinical as well as the experimental studies are oriented toward strengthening of the „conventional" treatment and implementation of alternative methods of pathogenetic treatment.

Study's objective was to determine the character of morphological injuries during experimental HS treated with Raviten. HS with a length of 120 min., in rats was performed by effusion of 30% from total blood volume via femoral artery. After 90 min., rats were resuscitated with isotonic solution and isotonic solution plus NO-synthase inhibitor Raviten (20mg/kg BW). At 90 min. after resuscitation rats were sacrificed and the livers, kidneys, lungs and myocardium were immediately removed. Tissues specimens were fixed using standard methods and stained with hematoxylin and eosin. After treatment with Raviten leukocytes infiltration in the centrilobular hepatocytes was reduced. At the level of cardiomyocytes was observed that cell tumefaction, capillary stasis and interstitial bleeding were diminished. Alveolar edema, alveolar and bronchial bleeding, fibrinoid intumescence with leukocytes reaction at the level of interalveolar septa in the lung and vacuolar and granular dystrophy at the level of epithelium of the convoluted tubules in the kidneys were reduced. All these morphological changes were compared with those put into evidence in animals which were resuscitated without Raviten. The intensity of morphological changes in the liver, lung, heart and kidney in animal resuscitated with Raviten were less than in animals with HS treated without Raviten.

PRELIMINARY RESULTS OF INTRON 22 INVERSION DETECTION IN A ROMANIAN GROUP OF HAEMOPHILIA A PATIENTS

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The World Federation of Hemophilia defines severe hemophilia A as a hereditary coagulopathy with FVIII clotting level < 1 IU/dL or < 1% of normal and normal von Willebrand factor activity. In 40-50% of cases, the severe form of the disease is caused by an inversion occurring in intron 22 (inv22) of the FVIII gene. Inv22 is considered the most common mutation that leads to severe hemophilia A. Our aim is to detect inv22 in a group of Romanian hemophiliacs. The study group consisted of hemophilia A patients currently treated in our centre, from which we collected peripheral blood (informed consent obtained). Genomic DNA was isolated using the standard extraction procedure and the concentration was measured spectrophotometrically. Isolated DNA was subjected to LD-PCR, following a protocol previously described by Poláková et al, 2003. PCR product was loaded onto a 0.6% ethidium-bromide stained agarose gel and electrophoresis began at 70V for 18-20h. Preliminary results of the study will be presented at the conference. We expect similar inv22 mutation rates as described in the literature (45-50%). Molecular genetic testing is extremely important in hemophilia A, yet it is not currently practiced in Romania. This is the first study to describe the inv22 frequency in Romanian patients and to predict inhibitor risk development based on their mutational status for inv22.

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THE EVALUATION OF OXIDATIVE STRESS IN MYELOID METAPLASIA WITH MYELOFIBROSIS (MMM)

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MMM has been classified by the World Health Organization (WHO) as pertaining to the BCR-ABL1-negative myeloproliferative neoplasia, together with polycythemia vera (PV) and essential thrombocythemia (ET). A rare hematological disorder, arisen from haematopoietic stem cell abnormalities, it can be either primary (agnogenic) or secondary to other diseases (PV, ET or chronic myeloid leukemia). JAK2V617F, CALR or MPL somatic mutations are sometimes present. Oxidative stress, defined as an imbalance between the level of reactive oxygen/nitrogen species (ROS/RNS) and the total antioxidant capacity (TAC) of the organism, is believed to play a role in MMM. The main objective is to evaluate oxidative stress in MMM. Our study involved two study groups: 20 healthy volunteers (control group) and 10 MMM patients: 3 patients with primary MMM, and 7 patients with secondary MMM (informed consent obtained). MMM diagnosis was established based on the revised 2016 WHO criteria. JAK2V617F mutational status was determined in all cases. ROS level and TAC were determined by the free oxygen radical testing (FORT), and free oxygen radical defense (FORD) assays, respectively. JAK2V617F mutation was present in one case of primary MMM and 5 cases of secondary MMM (4 after PV and one after ET). FORT values were increased ($p<0.05$) and FORD values were decreased ($p<0.05$) in MMM patients, especially in JAK2V617F-positive patients ($p<0.05$), in comparison with the control group, which registered normal values (FORT <2.3 mmol/L H_2O_2; FORD: 1.07–1.53 mmol/L). In conclusion our results confirm increased ROS levels and decreased TAC in MMM patients.

THE EFFECTS OF DIFFERENT DOSES OF METHYLENE BLUE OVER NOCICEPTION

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Methylene blue (MB) is a synthetic redox compound, it improves mitochondrial respiration and the metabolic rate by stimulating mitochondrial IV complex by up to 30% and also NO-synthases (ROS), monoamine oxidases A (MAO) and disulfide reductases. The aim of our study was to assess the effect of different doses of MB over nociception after a single dose, intrapertioneal administration. To evaluate the effect of MB over nociception we chose the doses of 1 mg/kg, 5 mg/kg respectively 10 mg/kg bw administered intraperitoneal. Mice were BALB/C male mice (n=24), 30+/-2g, nociception was evaluated using the tail flick (TFT) and hot plate test (HPT) that were performed at 30, 60, 120, 180 and respectively 4h after administration. Statistical analysis was performed with repeated measures ANOVA and student t test in SPSS v19.0. On the TFT only 10 mg/kg bw have shown antinociceptive effect ($p = 0.03$) with gradual increasing in the latency. On the HPT administration of 10 mg/kg bw lead to an analgesic effect 30 minutes with a maximum effect at 1 respectively 2h after administration. 5mg/kg bw had an analgesic effect on the HPT ($p<0.01$, $F(1,18)=21.15$), a time effect and an interaction between the two with statistical significance ($p<0.01$) with a progressive increase in pain perception (7.57±2.27 at 30 mins to 8.4±3.18 at 4h). The study demonstrated that methylene blue has an analgesic effect, and even if it requires further investigation, the data suggests that the effect may be related to serotonergic mediation.

THE TIMED EFFECTS OF DIFFERENT DOSES DISULFIRAM OVER NOCICEPTION

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Disulfiram (Dis) manages to produce an irreversible hepatic inhibition of mitochondrial aldehyde-dehydrogenase (Mt-Aldh).Another action of this compound is interference with mitochondrial membrane polarization often leading to apoptosis. In order to test the effects of disulfiram on nociception, we tested doses of 50 mg, 100 mg and 200 mg/kg respectively given by gavage. The mice were BALB/C male mice (n = 32), 30 +/- 2 g and nociception was evaluated using the tail flick (TFT) and hot plate test (HPT). The 50 mg/kg dose led to decrease in the TFT that was recorded in the first 30 minutes post-administration with statistical significance recorded at one hour post-administration. The same effect was also observed at 3 hours post-dose and was maintained at 5 hours, respectively 6 hours post-dosing. 100 mg/kg disulfiram had the same antinociceptive effect on the Hot Plate test response and the statistical significance was recorded 3 hours post-administration. After this interval, there was a decrease in the response time to 100 mg/kg but still retained statistical significance at 4 hours respectively 300 minutes after administration. The administration of 200 mg/kg of disulfiram gavage had effects similar to the 100 mg/kg dose, with an increase in the latency period during the experiment showing statistical significance three hours post-administratio. Although the effect of Dis over nocicpetion can bring novelties to pain therapy, more researches are needed to clarify the exact mechanism of action.

THE INFLUENCE OF GLICATED HEMOGLOBIN ON WHOLE BLOOD VISOSITY IN PATIENTS WITH DIABETIC NEPHROPATHY

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The complications, especially those affecting microcirculation, exhibit great importance in the assessment and follow-up of patients with diabetes mellitus. Blood viscosity plays its most important role in the microcirculation where it contributes significantly to peripheral resistance and may cause sludging in the post capillary venules. The effect of whole blood viscosity in patients whit diabetic nephropaty is still unclear. The aim of this study was to examine the influence of glicaemic control measured by glicated hemoglobin on rheological parameters, and especially on whole blood and plasma viscosity in patients with diabetic nephropaty. Blood viscosity is an important determinant of local flow characteristics. Blood exhibits shear thinning behavior: its viscosity decreases exponentially with increasing shear rates. Estimation of whole blood and plasma viscosity was made on 32 patients, comparing different stages of diabetic nephropathy and with different values of glicated hemoglobin. Depression of the regulatory mechanisms of microvascular blood flow as well as decreased tissue perfusion indicated the restricted blood flow in microcirculatory network in diabetic nephropathy. In conclusion blood viscosity was elevated in the patients with major organ complications and not in the patients without or with early complications, in correlation with poor glicaemic control.

SINGLE PORT DONOR NEPHRECTOMY WITH VAGINAL EXTRACTION: SURGICAL MANAGEMENT OF A CASE OF CHRONIC KIDNEY DISEASE WITH MASSIVE PROTEINURIA

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Proteinuria causes progressive kidney damage by inducing the synthesis and activation of molecules with vasoconstrictor, proinflamatory and profibrotic effects, such as endothelin 1, monocyte chemoattractant protein 1, RANTES, IL-8, NF-kB, TGF-β, TNF-α, C3 and C5b-9. We present the case of a 19-year-old male, diagnosed with Chronic Kidney Disease at the age of six with uncontrolled proteinuria (10861 mg/24h). His aunt, a 61-year-old woman volunteered to donate a kidney. Subsequent to compatibility and imaging tests, the left kidney was chosen for donation. Under general anesthesia, a single port was inserted through an umbilical incision, having 3 cannulas for the surgical instruments. After the kidney dissection, a kidney-sized compatible colpotomy was performed through the posterior fornix and an endobag was introduced through the incision. The graft was placed into the bag and, following vessels stapling, it was extracted using the vaginal route. The kidney was perfused with cold solution and then delivered to the recipient's operating room. The procedure was completed with neither perioperative complications nor the requirement of extra ports. The donor was ready for discharge after three days. Her creatinine level was 0.9 mg/dL and no analgesic drugs were prescribed. In conclusion proteinuria is an important factor that leads to ESRD (End Stage Renal Disease) which requires kidney transplantation or dialysis. Single Port Donor Nephrectomy with Vaginal Extraction is a feasible procedure with excellent cosmetic outcomes - the surgical scar is hidden by the umbilicus - that might contribute to the increase of the number of living donor nephrectomies.

METHYLENE BLUE IMPROVES VASCULAR FUNCTION IN EXPERIMENTAL DIABETES

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Diabetic mellitus (DM) is associated with abnormal vascular function and increased generation of reactive oxygen species (ROS) that contributes to accelerated atherosclerosis. Methylene blue (MB) was reported to exert protective effects in the cardiovascular system but the mechanisms are partially understood. The present study was purported to assess the effects of MB in acute administration on vascular function and ROS generation in vascular rings harvested from rats with streptozotocin-induced DM. Aortic segments were isolated from rats with streptozotocin-induced diabetes mellitus (single intra-peritoneal injection, 50 mg/kgc; evolution of diabetes 1 month) and controls (CTL). Hydrogen peroxide (H_2O_2) production in rat aortic segments was measured spectrophotometrically bymeans ofthe Ferric iron xylenol orange OXidation (FOX Assay, Sigma Aldrich). Organ bath experiments were performed in rat aortic rings the presence vs. the absence of methylene blue (0.1 microM). Endothelium-dependent relaxation to cumulative concentrations of acetylcholine (ACh) was recorded after preconstriction with phenylephrine (80% of the contraction elicited by KCl 80 mmol/L). *Ex vivo* incubation with MB reduced contractility, improved relaxation and attenuated H_2O_2 production in diabetic arteries. In conclusion, MB treatment might be useful in restoring the endothelial response in conditions associated with increased oxidative stress and vascular dysfunction, such as diabetes mellitus.

VASCULAR PROTECTION MEDIATED BY ATP-DEPENDENT CHANNELS IN EXPERIMENTAL DIABETES

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We have previously demonstrated that novel synthetic benzopyran analogues, KL-487, KL-1492, KL-1507 elicited a dose-dependent modulation of respiratory function and decrease in reactive oxygen species (ROS) production in isolated rat heart mitochondria, effects that have been associated with cardioprotection via the ATP-dependent potassium channels. Whether these compounds exert beneficial effects on vascular function in diseased vessels it is not known. The present study was purported to assess the effects of the benzopyran compounds on vascular reactivity and reactive oxygen species (ROS) production in aortic rings isolated from rats with streptozotocin-induced diabetes mellitus (DM). The effects of KL-1487, KL-1492, KL-1507 (10 μmol/L) on endothelium-dependent relaxation (EDR) were assessed in organ bath and H_2O_2 production measured by means of ferrous oxidation xylenol orange (FOX) assay have been studied in diabetic vs. non-diabetic rats. In diabetic vessels we found an important increase in contractility, a decrease in EDR and an increased H_2O_2 generation. Incubation of vascular segments with all investigated compounds attenuated H_2O_2 production, reduced contractility and partially restored EDR in vessels with intact endothelium (but not in denuded vessels). In conclusion, in type 1- experimental diabetes the novel benzopyran analogues improved vascular function and mitigated oxidative stress in an endothelial-dependent manner.

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COMPARATIVE EFFECT OF SARTANS AND ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN DIABETIC RETINOPATHY

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Purpose. The aim of this study was to evaluate the effect of Sartans treatment and Angiotensin-Converting enzyme inhibitors (ACEi) on diabetic retinopathy (DR) evolution in patients with type 2 diabetes mellitus and associated hypertension.

Method. 4 study groups were evaluated: group 1- patients with DM type 2 and non-proliferative (NP-DR; group 2 - patients with DM type 2, NPDR and untreated associated hypertension (HT); group 3- patients with DM type 2, NP-DR and associated HT treated with Sartans; group 4-patients with DM type 2, NP-DR and associated HT treated with ACEi. DR assessment was made by ophthalmoscopic examination and visual function evaluation by Early Treatment Diabetes Retinopathy Study (ETDRS) chart, contrast sensitivity chart (Pelli-Robson chart) and visual field (static automated perimetry). Laboratory tests as are basal glycemia, glycated hemoglobin (HbA1C), total cholesterol (CST), LDL-CST, HDL-CST and C-reactive protein (CRP) were evaluated. Arterial blood pressure was also assessed. All the parameters above were tested at the first admission in the hospital (T1) and after 1 year (T2).

Results. Both groups 3 and 4 had a significant low blood pressure at T2 compared with T1 ($p<0.01$) and compared with group 2 at T2 ($p<0.01$). Sartans treatment significantly reduced also the levels of lipids compared with ACEi treatment ($p<0.01$). The visual function parameters were also better in the Sartans group treatment compared with ACEi group treatment.

Conclusions. Beneficial effects of Sartans treatment on diabetic retinopathy evolution can represent a new perspective for clinical practice in diabetic retinopathy management.

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THE EFFECT OF VITAMIN D SUPPLEMENTATION ON INTERMUSCULAR FAT IN EXPERIMENTAL SARCOPENIA

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Sarcopenia (atrophy that accompanies the physiological process of aging) is characterized by a loss in both fiber size and number with fiber type II transitioning to type I. Many studies indicates that vitamin D has an essential role in many tissues including skeletal muscle. Increasing evidence indicate myopathy associated with severe vitamin D deficiency indicated a potential association between vitamin D and muscle. Indeed, skeletal symptoms were found to be responsive to treatment with vitamin D but, the mechanisms remained undefined.

The study was conducted on a homogenous group of 20 male Wistar rats (age: 10 – 20 months old, weight: 385 – 520 g). They had been exposed to artificial light 12 hrs / day, for 9 months. Once a week, the animals from groups 3 and 4 were administered vitamin D, i.e. 0.25 ml vitamin D3/100g body weight, while the groups 1 and 2 were administered palm oil. The present study sought to elucidate the effect of vitamin D on histopathological and ultrastructural changes in skeletal muscle in a rodent model of vitamin D deficiency and sarcopenia. The striated muscle tissues sampled from both young and old rats who had been administered vitamin D presented homogenous muscle fibres, without triglyceride accumulation.

ETIOPATHOGENIC INTERRELATIONS BETWEEN INFLAMMATION, OBESITY AND CARDIOVASCULAR RISK FACTORS

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Systemic arterial hypertension (HTN), diabetes mellitus (DM) and obesity are important cardiovascular risk factors, and it is presumed that inflammation could represent a common pathogenic way. The study group consisted of 100 patients with HTN, a majority of 85% with HTN 3rd degree. We followed associations between degree of HTN, presence of DM type 2, and degree of obesity, as well as correlations between glycemic and lipid metabolism markers and inflammatory profile expressed by fibrinogen and C reactive protein (CRP) levels. In the studied patients, obesity was associated more frequent with higher levels of arterial blood pressure, being 41.2% obese in HTN stage 3 compared to 16.7% in HTN stage 2. Also, the glycemic control (glycemia, glycated hemoglobin) was more altered in HTN stage 3, while cholesterol and LDL levels were significant increased in HTN stage 2. Also, the concentrations of CRP were significant increased in patients with 3rd degree HTN. Obesity and DM type 2 were frequently associated with HTN 3rd degree, while these patients had higher levels of inflammatory markers, demonstrating a chronic inflammatory state in patients with increased cardiovascular risk.

OBSTETRIC OUTCOMES ASSOCIATED WITH MATERNAL OBESITY AND CHRONIC INFLAMMATION

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Obesity has reached epidemic proportions in our patients who are of childbearing age, with pregnant patients of normal weight being in the minority. In particular, maternal obesity is linked to numerous metabolic complications including subfertility, gestational diabetes, hypertensive disorders of pregnancy and thromboembolism with potential long-term health consequences for both mother and child.Pregnancy is associated with altered immunity. The underlying pathophysiology is likely to involve alterations in glucose and lipid metabolism, inflammation, perturbances in adipokines and vascular dysfunction.

The aim of this study was to characterize placental inflammatory mediators and macrophage accumulation in relation to peripheral inflammation in obesity.

In conclusion, the chronic inflammation state of pre-gravid obesity is extending to *in utero* life with accumulation of an heterogeneous macrophage population and proinflammatory mediators in the placenta. We hypothesized that the placenta develops exaggerated inflammation in response to obesity. The resulting inflammatory milieu in which the fetus develops may have critical consequences for short and long term programming of obesity.

Keywords: obesity, pregnancy, placenta, inflammation, cytokines, obstetric outcomes

RELATIONSHIP BETWEEN STRESS AND OBESITY IN ADOLESCENTS

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The human body responds to any stress situation by releasing specific hormones and accelerating the heart and respiratory rate, and the brain needs more oxygen to focus on the problem in order to coordinate other systems or mechanisms to respond as quickly as possible. The problem, however, occurs every time when the stress level causes loss of control, fear and long-term anxiety - associated with lasting physiological changes. The study of a group of 28 adolescent subjects with obesity revealed significant differences between the physiological and psychological variables analyzed as being responsible for basal physiological changes. From a psycho-behavioral perspective, the ability to respond to stress is determined by the identification of stress-inducing factors and the control of the psychostatic situation in the first few minutes on the general condition of the body. We report a positive correlation between the calculated BMI and the stress level estimated by the Perceived Stress Scale (PSS), and high intensity of stress felt by obese subjects, which demonstrates an important link between these variables. The results obtained contributed to the objective identification of the relationship between stress inducing factors and obesity in adolescents as well as the possibility to intervene through counseling in order to obtain a positive psychic state.

THE IMPACT OF OBESITY ON WHITE ADIPOSE TISSUE OXYGEN CONSUMPTION: A PRELIMINARY DATA REPORT

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Overweight and obese patients present an enlarged intra-abdominal visceral fat mass which plays important endocrine and metabolic functions in health and disease, yet the bioenergetics of adipose tissue is still poorly understood in humans. The aim of the present study was to evaluate the effect of obesity on oxygen consumption in adipose tissue in young and adult patients. Human adipose tissue was harvested during elective surgery performed in children (n = 8) and adult (n = 12) patients, that were both randomized in two groups of control (normoponderal patients) and obese patients. Adipocyte oxygen consumption was measured at 37°C high-resolution respirometry using the Oxygraph-2k equipment. Substrates (glutamate + malate) were added to provide electrons to complex I for basal respiration (state 2 respiratory rate), followed by ADP to stimulate oxidative phosphorylation (state 3 respiratory rate), while the uncoupled respiration was measured after the addition of a classical uncoupler (FCCP). A significant decrease in all mitochondrial respiratory parameters (basal, active and uncoupled respiration) as compared to controls was recorded in adipose tissue samples harvested from obese children; at variance, only state 2 respiratory rate was significantly reduced in obese adults. Our preliminary data are suggestive for an impairment of oxidative phosphorylation in visceral adipose tissue of obese children (but not adults) an observation that requires further investigations in order to characterize the underlying mechanisms/adaptive changes .

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SALIVARY CORTISOL AND STRESS RESPONSE

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In modern society, stress is everywhere and affects people of different ages, including children. Psychological stress can be defined as psychological tension or strain that is difficult to manage or endure. The body and brain adapt to acute stress through the activity of the hypothalamic-pituitary-adrenal (HPA) axis . Stress can lead to alterations in the (HPA) axis, glucose metabolism, insulin sensitivity, other appetite-related hormones and hypothalamic neuropeptides. Uncontrollable stress changes eating patterns and salience and consumption of hyperpalatable foods. This could trigger neurobiological adaptations that promote increasingly compulsively behavior and obesity. These effects could be correlated with salivary cortisol. Stress response depends on intensity, duration and type of stressor. ***Challenge stressor***, a demanding but controllable situation that activates the sympathetic-adrenomedullary (SAM) system, with fight/flight response, which shuts down digestion. For this type of stressor the body has the resources to cope with. ***Threat stressor***, for which the body does not have the resources to cope with or social stress (public embarrassment or failure, feeling defeated) activates HPA axis with cortisol release. Chronic stress, especially when people live in a palatable food environment, induces HPA stimulation, excess glucocorticoids, insulin resistance, which lead to inhibition of lipid mobilization, accumulation of triglyceride and retention of abdominal fat.

SALIVARY ALPHA-AMYLASE – A BIOLOGICAL MARKER OF ACUTE STRESS IN CHILDREN

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Stress is one of a factor which may influence behaviors and health especially when an individual faces challenges that surpass his or her coping skills.

Stressors can be either acute (minutes to hours) or chronic (days to months). There are varying conceptions of an acute stressor depending on whether the participant is animal or human. The stress response, which maintains allostasis, is comprised of a cascade of adaptive responses originating in the central nervous system as well as in the periphery. It is well accepted that psychological stress is capable of activating the sympathetic-adrenal medullary (SAM) system and the hypothalamic-pituitary-adrenal (HPA) axis, however the physiological effects of stressors are highly variable between individuals.

The SAM system produces physiological changes and is integral to the stress response. The SAM system involves intricate communication between the sympathetic nervous system (SNS) and the adrenal medulla within the adrenal gland. The SNS activates the adrenal medulla to secrete catecholamines including adrenaline and noradrenaline. Measurements of salivary adrenaline and noradrenaline do not appear to reflect SNS activity.

Recently alpha-amylase has been proposed as a valuable indirect salivary biomarker reflecting catecholamine activity.

Numerous studies applying stress protocols have demonstrated that salivary alpha-amylase (sAA) is highly sensitive to stress-related changes. SAA responsiveness to acute stress has been assessed in adults, rarely in children.

The study's objective was to determine pathophysiological changes in the SAM system in response to a number of stress factors in children. / This study was designed to clarify pathophysiological changes of the SAM system responses to psychosocial stressors in children. Children from this study (n = 30) will give saliva samples during a laboratory session in which they were exposed to a series of stressors.

In conclusion, the major points of this study are the induction of a acute stress factor to children. The response to stress will be assessed by measuring the salivary enzyme. Based on the available data, we will highlight that there is a pronounced disorder of the SNS under acute stress conditions.

LIPID ACCUMULATION DURING ADIPOGENIC DIFFERENTIATION OF HUMAN DERIVED SUBCUTANEOUS MESENCHYMAL STEM CELLS IN OBESE BARIATRIC PATIENTS

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Introduction. The adipocyte expansion is a critical process with implications in the pathogenesis of metabolic syndrome and insulin resistance associated to obesity. Impaired adipogenesis leads to dysfunctional, hypertrophic adipocytes, local inflammation and peripheral insulin resistance.

Methods. Our pilot study includes 17 obese patients, 6 males and 11 females, mean age= 38.76 ± 8.89 years and mean BMI= 46.06 ± 6.48 kg/m2 referred for bariatric surgery. We performed adipose derived stromal /stem cells (ADSC) isolation from the subcutaneous adipose tissue and after 80% confluence we incubated sample wells with adipogenic cocktail (DMEM, 10% FBS, 1% ITS, Dexamethasone, IBMX, Indomethacin) and for control wells we continued with mesenchymal proliferation medium. At day 21±3 of adipogenic protocol specific lipid dye with Oil Red O was used together with fluorescent nuclear dye (DAPI) for the obtained adipocytes. After pigment elution, spectrophotometric absorbtion at 492-504 nm using a plate reader evaluated the differentiation versus control. Fluorescent nuclear dye based cell count was performed using FACS Tissue Gnostic Fluorescent camera and software.

Results. The obtained adipocyte lipid accumulation was between 12.5% and 108.76% with significant correlation with insulin resistance index: HOMA-IR ($p=0.01$), C peptide ($p<0.05$) and morning cortisol levels ($p<0.05$) which indicates the relationship between the differentiation capacity of ASC and the metabolic disorders associated with obesity.

Conclusion. The adipocyte expansion is a critical process with implications in the pathogenesis of metabolic syndrome and insulin resistance and also, a highly individualized method to determine the metabolic risk for obese patients.

ADIPOSOFT: IMAGE ANALYSIS SOFTWARE FOR THE QUANTIFICATION OF THE HEMATOXYLIN-EOSIN AND OIL RED O SECTIONS OF ADIPOCYTES

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The microscopic analysis of adipocyte cellularity in histological sections provides a reasonable cost-benefit ratio compared with the other methods. In this type of analysis, histological images are captured using a wide-field optical microscope, printed or screened, and then manually analyzed to count the number and measure the diameter of every cell. In this article, we reported the results obtained using Adiposoft, opensource software that provides fast and accurate quantitative measurements of adipose tissue cellularity in histological sections. Abdominal subcutaneous (SAT) adipose tissue was obtained from human participants undergoing bariatric surgery. Adipose tissue biopsies were Formalin-fixed, embedded in paraffin and hematoxylin and eosin (H&E)-stained. Preadipocytes were isolated, proliferated and differentiated in adipocytes. Culured adipocytes were then fixed in paraformaldehyde and dyed with oil red O and DAPI (blue) for nuclei. H&E and oil red coloration sections were assessed using a wide-field optical microscope and acquired photos were analyzed using Tissue FACS v4.0 and Tissue Gnostics vX.X software. We used an Image analysis software - Adiposoft 1.13 to quantify the area of the individual adipocytes in hematoxylin and eosin (H&E) and oil red O sections of adipocytes. We describe the steps of image analysis implemented by the program.Changes in the morphometric measurements of the adipocytes (perimeter, diameter, and area were reported.

THORACOABDOMINAL AORTIC ANEURYSM - OBSERVATIONS REGARDING THE ASSOCIATION WITH ATHEROMATOUS ARTERIAL DISEASE

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A histological description of the atherosclerotic lesions located within thoracic and abdominal aneurysm, in 20 patients, 17 men and 3 woman, with mean age of 64 years (46 to 80 years) is presented. The study was made in a period of 5 years, between 2012 and 2016, on surgery aortic specimens processed using routine histological methods. In these cases, the affected aorta showed various degrees of ATS lesions in relation with associated RFs and revealed the ATS grading in relation with degree of destruction of the arterial wall on surgical resected aortic segments. The paper also studied the ATS aneurysm in association with severe complications, resulting the necessity of continuous monitoring of these patients.

SCINTIGRAPHIC PATTERNS IN PARATHYROID PATHOLOGY

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Hyperparathyroidism is characterized by an increase in the synthesis and release of parathormone (PTH) and it can be primary, secondary or tertiary. The parathyroid glands can be visualized with the help of several imagistic methods: scintigraphy, ultrasonography, CT and MRI, the most utilized ones being ultrasonography and scintigraphy. We are exemplifying a few cases of primary, secondary and tertiary hyperparathyroidism studied in Hiperdia Brasov's Nuclear Medicine department. Parathyroid scintigraphy represents the imagistic method of visualizing pathological parathyroid glands utilizing radioactive isotopes. The scintigraphic imaging technique that was utilized was with dual-tracer (subtraction technique) using ^{99m}Tc-Per-technetate for studying the thyroid gland and ^{99m}Tc-Sestamibi for studying the parathyroid glands. The images were acquired with a dual detector Symbia E gamma camera (SIEMENS). The acquired images are early planar static (at 10-15 minutes after administering the radiotracer i.v.) and late (at 1.5-2.5 hours after injecting). While the radiopharmaceutical is eliminated from the normal thyroid gland, in the abnormal parathyroid tissue the radioactivity is maintained. The images were centered on the cervical region and included the mediastinum as well. The planar study was supplemented with SPECT acquisitions performed immediately, obtaining the multiplanar reconstructions, offering a greater sensibility and accuracy to the examination.Following the studies, cases of primary hyperparathyroidism by parathyroid adenomas, including ectopic sites (the most frequent) and secondary and tertiary hyperparathyroidism (with a lower frequency) were diagnosed. The imagistic methods allow a good visualization and localization of pathologically modified parathyroid glands, frequently by parathyroid or ectopic adenomas; normal parathyroid glands are not observable. Parathyroid scintigraphy remains an important imagistic technique which enables a correct evaluation of parathyroid pathology.

GGT – EVIDENCE AND CONTROVERSIES – THEORETICAL CONSIDERATIONS

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Serum gamma-glutamyl transferase (GGT), a sheath enzyme which plays a key-role in the cycle ϒ-glutamyl, considered for a long time as a diagnostics marker for liver affections and alcohol consumption, has relatively recent been connected with cardio-vascular diseases and mortality rate growth. The correlation between the increase of serum values of the gamma-glutamyl transferase and a wide range of chronic diseases has been studied, the increase of GGT being considered as an independent risk factor for the general mortality. Part of glutathione metabolism and of leukotrienes' synthesis, this enzyme shows certain particularities about the distribution mode at cellular level and the promotion of carcinogenesis. The presence or the absence of the expression of this enzyme at tumoral level has proofed to be linked to the tumoral sensibility towards chemotherapy. We propose you an incursion through some molecular mechanisms which are at the basis of gamma-glutamyl transferase's role in the pathophysiology of some diseases which determine an increased morbi-mortality in the general population.

EFFECT OF NOISE AND MUSIC ON ANXIETY AND GLYCEMIA, IN MENTAL STRESS

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The objective was to evaluate how noise (NS) and music (MS) can influence anxiety (A) and glycemia (G), in intense mental stress. Volunteer healthy subjects (n=24 men) were organized into 3 groups: control (C=8) without NS or MS; under NS (N=8); under MS (M=8). All groups were subjected to the same mental stress: a demanding mathematical exercise. NS and MS were applied starting one hour before and during stress. NS was urban traffic. MS was Concert no.21. by WA Mozart. A and G measurings were: ***1h (T1) and 15min (T2) before stress; 15min (T3) and 4h (T4) after stress***. Statistical evaluation was made on the basis of Student test. Differences between groups: A was significantly increased at N, compared to C (T2, p=0.02, T3, p=0.04, T4, p=0.05) and M (T2, p=0.001; T3, p=0.004; T4, p=0.01); G was significantly increased at N, compared to C (T2, p=0.05, T3, p=0.02, T4, p=0.02) and M (T2, p=0.03; T3, p=0.002; T4, p=0.003). In conclusion 1) Mental stress increased A and G at T2, T3, T4, the highest values being at T2. 2) NS supplemented the mental stress effect on A and G values. 3) MS reduced stress effect on A and G. 4) Listening to Mozart's MS, before and during intense mental exercise, can be a useful, economical and affordable factor for antistress protection.

CAN SMOKING INFLUENCE THE EVOLUTION OF RHEUMATOID ARTHRITIS?

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The aim of this study was to examine the effects of smoking on the development of rheumatoid arthritis, following clinical aspects (onset, extraarticular manifestations, stage of disease expressed through present erosions) and paraclinics (seropositivity expressed by the presence of rheumatoid factor and Ac anti-CCP). A prospective study was performed on a group of 277 patients with rheumatoid arthritis, registered in the Rheumatology Department of the Medical Clinic II, St. Andrew's Hospital, Constanţa. Demographic, clinical and biological variables have been analyzed, with particular reference to their correlation with smoker status. We have entered the information into a database using the Microsoft Office Excel program. We used MedCalc software to calculate the odds ratio to assess the differences between smokers and non-smokers. We considered statistically significant $p<0.05$. Smokers develop rheumatoid arthritis earlier 5.3 years than non-smokers. Smoker status (onset or ever) correlates with the presence of FR ($p = 0.314$) and Ac antiCCP ($p = 0.0493$). Current smoker status correlates with the presence of erosions ($p = 0.426$) and extraarticular manifestations ($p = 0.225$). The presence of ankyloses does not correlate with smoker status. In conclusion, smoking influences the evolution of rheumatoid arthritis.

RETROSPECTIVE ANALYSIS OF PUBMED PUBLICATIONS, REGARDING THE RELATIONSHIP BETWEEN MUSIC AND STRESS

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The objective was the evaluation of research concerning music (M) and stress (S) relationship, by the retrospective analysis of PubMed publications. 1950-2017 period was assessed, by the total number of publications (N) and the average number of publications per year (ANP), using keywords combinations: ” M and S” (MS), ” M and S and cortisol” (MSC). The analyzed filters were: a) ”species” with the sub-filters ”other animals” (AN) and ”humans” (H); b) ”sex”, with subfilters ”male” (M), ”female” (F), ”male+female” (MF). Statistical evaluation was made on the basis of the Student test. N for MS increased between 1950-2017, the highest being between 2010-2017. Publications were: a) more numerous for H (84% of N) than for AN (3%); similar for M (53%), F (54%), M+F (63%); reduced for MSC (9.5% of N). For ANP, with respect to MS, differences were: a) significant, between AN-H ($p = 0.04$); B) insignificant between M-N, F-N, M + F-N. Between 1950-1980 there were no publications with MSC. For ANP, MSC-N difference was insignificant. In conclusion 1) N for MS, for 67 years, was 934. 2) There were favorite studies with human subjects, male+female. 3) Publications on MSC have shown interest since the 1980s and have steadily increased until now. 4) Theme of music and stress, reflected by chosen keyword combinations and PubMed filters, is of great and growing interest.

MODIFICATIONS OF THE ORAL CAVITY INDUCED BY SYSTEMIC SCLERODERMA: CASE REPORT

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Systemic scleroderma (SSc) is a chronic autoimmune disease, and its pathophysiological mechanism involves two main elements: obliterating microanghipathy and fibrosis. Clinical manifestation involves, mainly, skin, mucosa, and viscera. Given the role of the oral mucosa and alveolar bone in functions of the dento-maxillary system, SSc will causes several pathological changes, sometimes knows as dento-maxillary disharmony.

We report the case of a 38-yers-old patient, from the Rheumathology and Interal Medicine Clinic of "Dr. I. Cantacuzino" Hospital. The symptomatology started in Februrary 2014. At the first presentation the following were detected: skin thickening, fatigue and drastic weight loss (12 kg in 3 months). However the modifications of the oral cavities were present, but not related with de disease: isolated dental cavity, whose long-time evolution was obvious, absence of periodontal impairment detectable on computer-tomography (CT), the height and width of the alveolar bone being in normal range. In August 2015, the patient started treatment with biological agents, under chemoprophylaxis for tuberculosis. The clinical examination of the oral cavity revealed: fibrosis of perioral tissues (microstomia), severe gingival retraction, vertical and horizontal resorbtion of the alveolar bone. Given the fact that the modifications of oral mucosa and alveolar bone is well know as a manifestation of SSc, the severity of the disease is not reliant only on the factors related to the body, but also with environmental factors, such as, oral hygiene, diet, vicious habits. Knowing the etiology, clinical manifestations, evolution and management of the disease is imperative for the dentist, in order to achieve the best results by reestablishing the fuctions of dento-maxillar system – esthetics, phonatory function, mastications.

ETANARCEPT TREATMENT AND THYROID FUNCTION IN PATIENTS WITH PSORIASIS VULGARIS

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Psoriasis vulgaris, a chronic inflammatory skin disorder, requires a long term medication, in order to avoid relapsing episodes. TNF-alpha, one of the targeted molecule in therapy, seems to be also involved in pathogenesis of thyroid disorders. The aim was to evaluate the relationship between anti TNF-alpha therapy and thyroid parameters: serum level of triiodothyronine (T3), free thyroxine (FT4), thyroid-stimulating hormone (TSH) and antithyroidperoxidase antibody (AbTPO) in treated population.

Materials and methods. The study was performed on 44 patients with psoriasis vulgaris from the Dermatology Department of Emergency County Hospital Cluj (20 patients under anti-TNF alpha treatment (etanercept), 24 patients with no previous systemic therapy). A thyroid ultrasonographic evaluation was also performed for each patient.

Results. The mean serum level of FT4 was significantly higher in patients with no systemic treatment ($p<0.05$). The patients treated with etanercept had a significantly higher level of TNF-alpha ($p<0.05$). No significant difference was observed for the other evaluated parameters. Also, we found a significant negative correlation between TNF alpha and TSH levels ($r=-0.366$, $p=0.015$).

Conclusions. we only found that the mean serum level of FT4 was significantly higher in patients with no systemic treatment. Also, a negative strong correlation was seen between serum level of TSH and TNF-alpha. Based on our data, comparison with other anti TNF-alpha therapies might be of interest in future studies.

Keywords: psoriasis, TNF-alpha, etanercept, thyroid

MECHANISMS OF HUMAN PAPILLOMAVIRUS VERTICAL TRANSMISSION

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Human papillomavirus is a viral infection recognized as a risk factor for anogenital warts and cervical cancer among adults. Low-risk HPV types (HPV-6 and HPV-11) are most frequently involved in the vertical transmission of the infection. It is not yet completely understood how the fetus becomes HPV positive. The frequency of vertical transmission is low and ranges from 1 to 20%. Recent studies suggest that HPV infection may impair fertility and effectiveness of assisted reproductive techniques. HPV-infected men can transmit viral DNA to oocytes, which can cause trophoblastic apoptosis and reduce the endometrial implantation of trophoblastic cells, thus increasing the risk of miscarriage. Also, vertical transmission may be involved in the pathogenesis of preterm rupture of the membranes, leading to preterm birth. Perinatal transmission is supported by the presence of HPV-induced lesions at birth, such as laryngeal and anogenital lesions simultaneously with the detection of HPV DNA in the amniotic fluid, placenta and the umbilical cord. Perinatal transmission is considered to be the result of the fetus coming into contact with infected cells of the vagina and cervix during birth. Studies have shown that there is both an increased rate of HPV detection among newborns by vaginal delivery (51.4%), compared to those delivered by cesarean section (27.3%) and an increased incidence of juvenile respiratory papillomatosis after prolonged delivery (more than 10 hours). Given all this, it is important to review the manner in which the virus can be transmitted to the newborn along with the clinical relevance.

MINOXIDIL AND SPECTRAL TOPICAL APPLICATION REINFORCED BY LOW-LEVEL LASER THERAPY ON AN ANIMAL MODEL OF ALOPECIA - NEW ZEALAND RABBITS

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Several factors are involved in the etiopathogenesis of hair loss: the genetic determination, the excess of androgens, local vasoconstriction, hypoxia and inflammation. The aim of this reasearch was to evaluate on an animal model (New Zealand Rabbits) the hair regrowth effects of Low-Level Laser Therapy (LLLT) as monotherapy or concomitant therapy with topical application of two chemical treatments that are used in human patients with hair loss: Minoxidil 2% or 5% and Spectral DNC. Eleven squares on 2 cm^2 each (10 for testing and 1 control) were denuded on the dorsal part of 10 New Zealand rabbits. Daily topical treatment with 0.5 ml Minoxidil 2%, Minoxidil 5% and Minoxidil 5% was performed as single therapy on 3 squares. LLLT with the HairMaxProfessional12, 3 times/week, was applied 1 minute 30 seconds on one sqaure and 3 minutes on another. The rest of 6 squares received combined treatment of each topical compound with each exposure to LLLT. The hair regrowth effect was evaluated after 3 months by macroscopical images (photographs), trichoscopy (with a dermatoscope) and histopathological assessment. At the beginning and at the end of the experiment, the systolic blood pressure was measured and the tested areas were examined by a Doppler ultrasound study. Our results show that LLLT induced significant hair regrowth, the topical therapy did not increase the systolic blood pressure and the vasodilation was significantly increased in the areas treated with Spectral. This study proves the combined therapy is more efficient than the single use of LLLT or topical treatment.

THE IMPACT OF PATHOPHYSIOLOGICAL MECHANISMS ON THE TREATMENT OF ACNE

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Affecting mostly adolescents and young adults, ***Acne vulgaris*** represents one of the most common chronic inflammatory skin disorders. The exact worldwide incidence and prevalence are currently unknown, although registries in the USA are suggesting that approximately 40–50 million people are affected by this condition. Understanding the importance of the pathophysiological mechanisms underlying acne vulgaris, it's precise cellular and molecular biology and identifying any potential candidate trigger factors are the current challenges in treating this disease. Even though its precise pathogenesis has remained enigmatic, overproduction of sebum, bacterial colonisation by ***Propionibacterium acnes*** within the pilosebaceous units and altered keratinisation are generally agreed as causal factors. Lipid-rich sebum is hydrophobic in nature and it facilitates lubrication and protection of the skin while ***P. acnes*** hydrolyses triglycerides in the sebum, causing the release of free fatty acids which increase the chance of bacterial adherence. This is why, in order to use an effective treatment, we need to first understand the impact of pathophysiological mechanisms involved in its development. In this poster we present the relevance of certain substances used in the treatment of various types of acne lesions present in clinics (depending on the mechanism underlying the formation thereof), such as retinoids, benzoyl peroxide, antibiotics.

THE PATHOPHYSIOLOGICAL PARTICULARITIES OF CUTANEOUS FUNGAL INFECTIONS IN IMMUNOSUPPRESSION CONDITIONS CAUSED BY UV RADIATION

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The skin represents an important part of the body protection against external pathogens due to its capacity to generate an immune response. It has already been demonstrated that prolonged exposure to ultraviolet (UV) radiation compromises the immune system's ability to fight against these pathogens, both locally and systemically. UV radiation determines immunosuppression by depleting cutaneous Langerhans antigen presenting cells (APCs), causing leukocyte apoptosis, stimulating keratinocyte production of interleukin (IL)-10 which enters the bloodstream and generates a systemic suppression of the immune response by blocking Langerhans cells' capacity of presenting the antigen to the T-lymphocytes, and also stimulates the production of reactive oxygen species which can also affect APC function.The existence of serious local and systemic fungal infections in immunosuppressed patients is cited in medical literature. This paper exemplifies this characteristic of fungal infections through the case of a 7 year old patient who, after prolonged exposure to UV radiation presents an extensive tinea corporis infection, 1 day after contact with infected cats. What is particular about the aforementioned case is the shortened incubation period (compared to an average of 1 to 3 weeks), possible because of the immunosuppresion caused by the prolonged UV radiation exposure. In conclusion, diagnosing and choosing the correct treatment for cutaneous fungal infections is made difficult by the fact that the pathophysiological mechanisms involved are not fully understood.

A LITERATURE ANALYSIS OF THE PHYSIOPATHOLOGICAL LINK BETWEEN HIDRADENITIS SUPPURATIVA AND BACTERIAL SUPERINFECTION

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Hidradenitis suppurativa, also known as acne inversa, is a chronic, inflammatory disease, which determines extremely painful abscesses and sinus tracts formation with muco-purulent secretion, leading to functional impairment and important psychosocial impact. The prevalence of the disease is 1-4%, females are more frequently affected. The cause of the disease is not completely understood, a multifactorial physiopathological mechanism being involved. In order to elucidate the cause of the disease, two theories have been stated. The follicular theory describes disorders of the basement membrane of the hair follicle on which external stress factors act, causing an inflammatory response of the keratinocytes and follicular obstruction. Clinical manifestations appear after the rupture of the cyst epithelium and extravasation of the content. The non-follicular theory studies the involvement of apocrine glands aberrant secretion, resulting in epidermal invagination. Bacterial infection represents an essential element in completing the clinical picture. In the majority of secretion tests, Gram-negative bacteria have been revealed. Bacteria secrete a protective polysaccharide matrix, resulting in a biofilm. Failure of standard antibiotic therapy when treating bacterial infection could be caused by the biofilm that prevents the penetration of the antibiotic. To conclude with, research on physiopathological mechanism is essential for the introduction of new therapeutic alternatives.

NON-SCARRING ALOPECIAS – FROM PATHOPHYSIOLOGICAL MECHANISMS TO TREATMENT

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Hair loss (alopecia) is often a major source of distress for patients. The main forms of nonscarring alopecias are androgenic alopecia, alopecia areata and telogen effluvium. Despite their high frequency and the relevance of their psychological impact, the pathogenesis is not completely understood, being influenced by genetic, hormonal and environmental factors. In addition, response to treatment varies according to the patient's age, disease extent and duration or other co-morbidities such as anemia, low iron stores, endocrine dysfunction, low vitamin D, systemic illnesses or autoimmune diseases. Androgenic alopecia is a prevalent condition, but with limited approved therapeutic options. Finasteride and minoxidil have the highest proven efficacy. The response of the hair follicle to minoxidil consists of an increase in the proportion of follicles in anagen, a reduction in telogen follicles and an increase in hair follicle size.Topical minoxidil could also be a reasonable candidate drug for telogen effluvium, based on its pathogenesis. Alopecia areata is a $CD8^+$ cell, Th1-type autoimmune reaction against anagen stage hair follicles.Among the various therapies available for it, the most common approach is the use of intralesional and topical steroids. In conclusion an organized approach to recognizing characteristic differential features of hair loss disorders is the key to diagnosis and management.

EVALUATION OF OXIDATIVE STRESS IN ACUTE EXPERIMENTAL INFLAMMATION AFTER CURCUMIN TREATMENT

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Curcumin, a natural phenolic compound is an anti-tumor agent with anti-inflammatory and anti-oxidant properties. The aim of this research was to evaluate oxidative stress levels, antioxidant activity and high performance liquid chromatography (HPLC) Curcumin concentrations in an acute experimental inflammation induced by Turpentine oil (intramuscular 0.6 mg kg-1 body weight) and to compare a prophylactic versus a therapeutic regimen of Curcumin (oral suspension of 150 mg Curcumin kg-1 rat weight). Sixteen adult male Wistar rats were assigned to four groups: Control, Group I (Curcumin only), Group II (Curcumin administration, then induced inflammation after 1 hour) and Group III (induced inflammation then Curcumin administration after 2 hours). Oxidative stress was assessed by measuring serum malondialdehide and carbonylated proteins, while systemic and local total antioxidant capacity was determined by ABTS. Local tissue changes (muscle, kidney, liver) were analyzed by histopathological tests. Results showed that acute inflammation significantly increased lipid peroxidation in Groups II and III compared to Control and Group I. A reduced total antioxidant capacity (ATBS) in serum, kidney and muscle tissue was present in Groups II and III. ABTS levels were significantly increased only in the liver tissue of the animals with induced inflammation ($p<0.05$ as compared to Group I). Curcumin concentration decreased in a time-dependent manner in all study groups and was the lowest in Group III. The study proved the potential of Curcumin in reducing oxidative stress in both prophylactic and therapeutic regimens.

HEART RATE AND GLYCEMIA MODULATION, IN ACUTE PHYSICAL STRESS, WITH SCHISANDRA CHINENSIS

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The objective was to highlight the heart rate (HR) and glycemia (G) modulation with Schisandra chinensis product (SCP), in intense and acute physical stress (PS).

Volunteer sedentary subjects (n=24 men) were divided into three groups: control (C=8) without SCP; who received SCP 3 weeks before PS (SC1=8); who received SCP 6 weeks before PS (SC2=8). PS was done the day after ending treatments, and was represented by intense short duration physical exercise, made with a Monark Ergomedic 839E cycleergometer. HR and G measurings were: 1 day before SC1 and SC2 treatments (T1); 15min (T2) before PS; 15min (T3) and 4h (T4) after PS. Statistical evaluation was done using the Student test. HR was significantly increased at C, compared to SC1 (T2, p=0.01, T3, p=0.03, T4, p=0.04) and SC2 (T2, p=0.002; T3, p=0.004; T4, p=0.02); G was significantly increased at C, compared to SC1 (T2, p=0.05, T3, p=0.01, T4, p=0.02) and SC2 (T2, p=0.04; T3, p=0.001; T4, p=0.003). Under SCP influence, parameters were significantly reduced, HR immediately pre- and post PS, and G post PS. Reduction of HR and G was greater in SCP2. Influence of SCP was slightly higher on HR than on G. 4) SCP may be an effective, safe and accessible modulation path for stress caused by intense and acute physical exercise, in sedentary persons.

RESEARCH ON NATURAL PEPTIDES WITH TUMORICIDAL PROPERTIES

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Cytotoxic peptides are small cationic molecules such as those found in venoms, e.g lycotoxin I and II in wolf spider, dermaseptin from frog or mammalian defensins and cryptdins. Many studies have highlighted the tumoricidal properties of some natural peptides. In order to assess the viability / proliferation of tumor cells in the presence of the native peptide may be used the Trypan Blue viability test with propidium iodide (PI) and MTT (4,5-dimethylthiazol-2,5-diphenyltetrazolium bromide). The membrane of living cells has selective permeability to Trypan Blue, which can cross only the membrane of dead cells. The recorded fluorescence intensity is directly proportional to the amount of damaged DNA. MTT viability test is based on the ability of mitochondrial succinate dehydrogenases of the living cells to reduce the MTT tetrazolium soluble salts and form insoluble crystals of formazan (purple). Since the MTT reduction can occur only in metabolically active cells, the level of activity is a measure of cell viability. Water insoluble formazan can be solubilized with isopropanol or dimethyl sulfoxide (DMSO) and revealed by colorimetric method. In apoptosis, phosphatidylserine (PS) is translocated to the outside of the membrane. PS is evidenced by the binding of Annexin V coupled with a fluorescent substance. Molecular biology techniques indicate that these structures modify cell membranes via interaction with intrinsic ion transport proteins and/or formation of ion channels. These two mechanisms of action lead to changes in second messenger systems that further augment the abnormal activity and distortion of the signal transduction causing cell death.

EFFECT OF *ALLIUM MONTANUM*, *ALLIUM FISTULOSUM* AND *ALLIUM SATIVUM* ON INFLAMMATION-INDUCED NITRO-OXIDATIVE STRESS

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Introduction. Ethnobotanical studies from Romania mention 32 wild and cultivated species of *Allium L*. These plants have been valued for many centuries for their use in seasoning food, medicinal properties, and in some parts of the world, their use in religious rites. The antioxidant activity of *Allium species* is due to a variety of sulphur-containing compounds and their precursors, in addition to other bioactive compounds such as polyphenols, dietary fibre and microelements. Therefore, the aim of the present study was to evaluate the antioxidant effects of extracts from *Allium montanum, Allium fistulosum* and *Allium sativum*.

Materials and methods. Plant extracts were prepared by a modified Squibb repercolation method, producing a 1:1 (w:v) extract.

Wistar male rats were assigned to 12 groups (n=5). Each extract was administrated by gavage (1ml/day, po) in three dilutions (100%, 50%, 25%) for 7 days. A negative control and an inflammation group with 0.9% saline solution (1 ml/day, po), a diclofenac group (20 mg/day/kg b.w, po), and an allicin group (8 mg/kg/day, po) were also included. Excepting the negative control, in the 8th day acute inflammation was induced by turpentine oil (0.6 ml/100g b.w. i.m.). In the 9th day blood samples were harvested. Oxidative stress was evaluated by measuring total nitrites and nitrates, total oxidative status, total antioxidant response, oxidative stress index, malodialdehyde and total thiols in the serum.

Results. All allium samples reduced significantly nitro-oxidative stress by lowering nitrates, total oxidative status, total antioxidant response, oxidative stress index, and malodialdehyde and increasing total thiols in the serum. The effects were comparable with diclofenac and allicin.

Conclusions. Extracts of *Allium montanum*, *Allium fistulosum* and *Allium sativum* had inhibitory effect on inflammation-induced nitro-oxidative stress. The effects seem to be mostly due to allicin content.

Keywords: *Allium montanum*, *Allium fistulosum*, *Allium sativum*, nitro-oxidative stress

ANTI-INFLAMMATORY AND ANTIOXIDANT EFFECTS OF *MAHONIA AQUIFOLIUM* EXTRACTS

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Introduction. Oxidative stress and inflammation are interlinked processes that seem to play an important role in aging. The present work aimed to test the antioxidant and anti-inflammatory activity of ethanolic Mahonia aquifolium leaves (ML), flowers (MF), green fruits (MGF), ripe fruits (MRF) and bark (MB) extracts in an experimental acute inflammation.

Materials and methods. Six polyphenols and four alkaloids were measured by HPLC. The radical scavenging activity was measured by DPPH test. Inflammation was induced in rat with turpentine oil. Anti-inflammatory activity was evaluated with serum nitric oxide (NOx) and TNF-alpha, and oxidative stress with total oxidative status (TOS), total antioxidant reactivity (TAR), oxidative stress index (OSI), 3-nitrothyrosine (3NT), malondialdehyde (MDA), and total thiols (SH). Extracts were administrated orally (100%, 50%, 25%) for seven days prior to inflammation. The effects were compared to diclofenac.

Results. The most abundant polyphenol was chlorogenic acid, and alkaloids were identified only in MB. The DPPH assay was good, excepting MB. All extracts decreased NOx, TOS, 3NT, and increased SH. TNF- alpha was reduced, and TAR increased only by ML, MF MGF. MDA was not influenced.

Conclusion. Our findings suggest that M. aquifolium has anti-inflammatory and antioxidant effects that support the use in primary prevention of the inflammaging process.

Keywords: mahonia aquifolium, anti-inflammatory, antioxidant, polyphenols, alkaloids

ASSESSMENT OF THE MASLINIC ACID DERIVATIVE EFFECTS IN AN EXPERIMENTAL MODEL OF PHOTOCHEMICAL SKIN CARCINOMA IN FEMALE MICE

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The present study was purposed to assess the effects of a benzylamide derivative of maslinic acid (EM2) in mice exposed to photochemical damage and on mitochondrial respiration in isolated liver mitochondria, respectively. To this aim SKH1 female mice were randomly assigned to one of the following groups: i) NO TRTM (mice with photochemical-induced skin carcinoma - first 2 weeks - exposure to ultraviolet B radiation (UVB) followed by the topical application of 7,12-dimetilbenzantracen solution (DMBA) 0.025% (once/week), and by repeated applications of TPA solution (12-a-13-ethyl-decanoilphorbol, twice per week) and exposure to UVB radiation, 30 minutes before TPA topical application), ii) BLANK HG (mice with photochemical-induced carcinoma plus with topical application of blank hidrogel, twice per week), iii) EM2 1% (mice with photochemical-induced carcinoma plus with topical application of the EM2 1% hydrogel, twice per week). At the end of the experiment mice were sacrificed and liver mitochondria were isolated by the differential centrifugations technique. Mitochondrial respiration was assessed by high-resolution respirometry in the presence of complex I (CI) and II (CII) respiratory substrates and ROS production was assessed by the Amplex Red assay. At the end of the experiment the treated group showed fewer papillomas. With respect to the mitochondrial respiration, a substrate-independent increase in all respiratory rates in treated vs. non-treated animals was recorded. Interestingly, the maslinic acid derivative did not influence the ROS production in female mice.

In conclusion, topical application of the maslinic acid derivative and hydrogel in female mice with photochemically-induced carcinoma was associated with a decrease in skin lesions and adaptive changes in respiratory function but no effect on oxidative stress in isolated liver mitochondria.

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THE PEER TUTOR PROGRAM IN PATHOPHYSIOLOGY AT ”VICTOR BABEȘ” UNIVERSITY OF MEDICINE AND PHARMACY OF TIMIȘOARA - A BIRD’S EYE VIEW

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The Peer Tutor Program in the Pathophysiology Department at ”Victor Babeș” University of Medicine and Pharmacy of Timișoara, Romania has started since 2013 with 2 major branches, tutorship in teaching and research activities, respectively. Regarding the teaching program, students from IVth year in Medicine were selected after an interview and in recognition of their performances in Pathophysiology (a grade of 10 is mandatory) to participate in the educational process by teaching practical laboratories to students enrolled in the Ist year in the specialization General Nursing. By providing peer support in and out of the classroom tutors improved both their communication skills and knowledge of the topic, an opportunity that has been unanimously recognized as highly advantageous in clinical years. Accordingly, the tutorship activity was continued for the next 2 years when the Vth and VIth year tutors taught the Pathophysiology labs to the IIIrd year students in Medicine, both Romanian and English sections; in the latter case, an opportunity to improve their medical English was equally provided. This activity not only helped tutors to consolidate and enhance the understanding of disease but also provided the teaching staff with a continuous feed-back from the students regarding the relevance of information taught in Pathophysiology for the clinical years. As concerning the research activity, participation of the students in experiments currently performed by PhD students and postdocs allowed them to gain practical skills, attend scientific meetings for young researchers and finalize license theses. Overall, students agree that tutorship might be regarded as the first step in pursuing an academic career.

FIRST ACTIVITY REPORT OF THE MEDICAL SCIENTIFIC SESSIONS

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Although regarded as low evidence in the hierarchy of biomedical research evidence, case reports are essential for training of medical students and represent a type of manuscript to which undergraduates can contribute. „Medical Scientific Sessions" (Romanian: „Sesiunile Științifice Medicale") is a project organised by the SSMB – Standing Committee on Medical Education department. We aim to present the first activity report regarding the previous academic year. We have designed a medical education project as an opportunity for undergraduates to practice skills needed for scientific study and to prepare case report presentations to be discussed during scientific sessions. Students could either participate independently or seek the aid of the organising committee in search for scientific coordinators. Eight medical specialties were addressed: Gastroenterology, Internal Medicine, Cardiology, Infectious Diseases, Obstetrics&Gynecology, and Paediatrics (Paediatric Neurology/Neonatology included, despite being separate specialties). One scientific session was dedicated to Fundamental Sciences (reserved to original studies/mini-reviews) and another to foreign students enrolled in the English Teaching Groups. A total of 40 active participants presented case reports during the events, attended also by another 500 passive participants. Case reports are useful teaching tools for medical students and can be equally constructive for undergraduates considering research activities. Our project provided helpful information for medical students and complimentary activities to the faculty curriculum which does not offer academic writing courses.

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RAISING STUDENTS' MOTIVATION IN MEDICAL TRAINING

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According to recent studies the motivation gradually decreases during "academic career", especially at the passing of threshold level between different scholar levels (e.g. high school and faculty). These evidences emphasize the importance of elaboration and implementation of some programs aiming the academic motivation rise, implementation of different medical study methods in university curriculum which would tilt the motivational "balance" towards performance and education. Feasibility of new knowledge depends mainly on their integration in the previously gained knowledge in passed disciplines. Thus, a necessity appears concerning the development in students of ability to apply knowledge in the consolidation of well-discriminated clinical thinking. In this regard a key tool is developing in students of professional behavior towards the patient, as well as interrogatory logistics. At the chair of Physiopathoogy and clinical physiopathology has been extracurriculary tested the new method of study: CASE BASED ON CLINICAL ARGUMENT (CBCA) involving 36 students of 3-rd year, faculty of Medicine I devided in 4 gropups, and as consultans have been the collaborators of the chairs of Pathophysiology, Internal Medicine II, Hematology, Endocrinology, Cardiology. The full course of CBCA included 10 cases of 2 to 2.5 hours each. At the end of course of training by clinical case analysis the students have been investigated regarding CBCA. In conclusion. The questionnaire analysis shows that the majority of students underline that clinical case discussion develops clinical thinking coming closer to clinical disciplines, and contributes to knowledge acquiring and consolidation as well as augments the motivation of students to study and self-training.

CLASSIC AND MODERN APPLICATIONS OF POLYLACTIC ACID (PLA) REGARDING TISSUE ENGINEERING IN EXPERIMENTAL BONE DEFECTS

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Polylactic acid (PLA) development has driven considerable interest in the engineering and utilization of the polymer throughout the years. Due to its advantages is used as a biomaterial in various medical applications (tissue engineering, orthopedic devices and drug delivery systems). The main purpose of this review is to highlight PLAs development and application since its discovery. This review also summarizes the role of this biomaterial and its copolymers, blends or composites in bone regeneration. Polylactic acid has four advantages which are renewability, biocompatibility, processability and energy saving (Xiao Lin et al, 2012). Biocompatibility is the most attractive property of PLA with respect to the biomedical field. The bone has the capacity of self-regeneration, but because of certain cronical metabolic pathologies, traumas and aging, deficient bone regeneration appears (Gomez et al., 2011). Modern strategies aim for accentiated bone tissue healing, through the implantation of varied molecules: cells, biomaterials and combinations of these, for the acceleration of the healing process. The purpose of biomaterials is to repair, help, substitute or regenerate bone tissue (Pearce et al., 2007). Further we discuss the polymer's utilization in bone tissue grafting on different experimental protocols on laboratory animals incorporating better understanding of its successful utilization. In vivo research has been the preferred experimental system in bone tissue research. Animal bone defects models allow the evaluation of biocompatibility of the polylactic polymer and are a keystone in translational technologies into human use.

Keywords: polylactic acid, 3D printing, bone defect, tissue regeneration

3RS PRINCIPLES AND THE ALTERNATIVE METHODS TO ANIMALS TESTING

LUCIAN FARCAL

BIOTOX SRL / Douglas Connect GmbH

The 3Rs principles refer to Replacement, Reduction and Refinement of animal testing, first defined by the scientists William Russell and Rex Burch in ‚The Principles of Humane Experimental Technique' in 1959. The increasing concern about the use of animals for toxicity studies and other effects of substances has led to widespread support of alternative method development. Therefore, alternative test methods have been developed to replace the use of animals with non-animal systems, reduce the number of animals in a test, or refine the procedures to make them less painful or stressful to the animals under study. Currently, the Directive 2010/63/EU on the protection of animals used for scientific purposes includes an explicit reference to the 3Rs principle, the regulatory authorities have endorsed the principle of the 3Rs and accepted to some extend for regulatory purposes. The alternative methods that are developed to reduce or replace animal experiments are typically based on either *in vitro* systems or on computer-based (*in silico*) models.

In this context, the University of Agricultural Sciences and Veterinary Medicine from Cluj-Napoca, has supported the establishment of the Romanian Centre for Alternative Methods (ROCAM; http://rocam.usamvcluj.ro/) which promotes the development and application of the alternative methods and their acceptance by regulators. Since its inauguration in 2015, ROCAM acted as a platform to disseminate the 3Rs approaches, facilitated and provided training in the area of 3Rs. Moreover, its aim is to support research activities for the development, optimization, validation and application of such integrated testing strategies and alternative methods to animal testing.