ABSTRACT

Aluminum Excytotoxicity and NeuroAutoImmunity: the Role of the Expression of CD32a$^+$ (FcγIIa) and ICAM-1$^+$ in the Rat Brain

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Background: In the central nervous system (CNS) microglia is a crucial for defense of the brain against invading microorganisms, tumors and following trauma [1]. However, uncontrolled activation of these cells may have deleterious outcomes [2] by activation of Fcγ and the complement 3 receptors as well as by opsonin-dependent phagocytic reactions induced [3]. One of the contributing proteins in these reactions is the intercellular adhesion molecule-1 (ICAM-1) [Couchair et al., 2006]. ICAM-1 binding to the CR3 receptors of the complement and LFA-1 (lymphocyte function associated antigen-1) expressed on the microglial cells and astrocytes may facilitate autoimmune inflammatory reaction in the brain.
Results: The expressions of CD32$^+$(FcγIIA receptor) as a round shaped cells between the pyramidal cells of the hippocampus, near to the site of injection of aluminum showed immunohistochemicaly were detected and quantified by computing imaging. Expressions of ICAM-1$^+$ immunoreactive cells significantly increased in the hippocampus and in the choroids plexus. Dark brown staining localized in the CA3 region of the hippocampus showed assembles of activated microglia while the clusters of ICAM-1$^+$ in the choroid plexus indicating upcoming inflammatory reactions into the brain after intracerebral injection of aluminum salt.
Conclusions: The pattern of expression of CD32$^+$(FcγIIA receptor) near to the site of injection of aluminum, indicate a phagocytic role of microglia may play at the site of aluminum induced excitotoxicity in the brain. Significant expression of ICAM-1$^+$ immunoreactive cells with the clusters in the choroid plexus suggests a consequently neurotoxic autoimmune reactions induced by microglial hyperactivation in injured brain.

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ABSTRACT

Thyrotropin-Releasing Hormone (TRH), Cancer-related Fatigue and the Immune System

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Introduction: Decades of research have shown that thyrotropin-releasing hormone (TRH) is widely involved in the control of behavioral, metabolic and immunological homeostasis, far beyond its role as a regulator of the hypothalamic-pituitary-thyroid axis (1). In various clinical situations and disease states TRH agonism exerts normotrophic, state dependent therapeutic effects which manifest as restorations of homeostasis, including that of the immune system (2). In instances of behavioral depression TRH agonism exerts arousing and analeptic actions.
Cancer-related fatigue (CF) is a highly prevalent symptom with a significant negative impact on quality of life. No evidence-based pharmacological interventions exist to treat this serious clinical problem. CF can be viewed as a failure of homeostasis involving several body systems (3). Evidence suggests that CF is associated with immune dysfunction and may be due to the actions of proinflammatory cytokines released as a result of the disease process or in response to radiation and/or chemotherapeutic treatment interventions. In a pilot, randomized, placebo-controlled, crossover study, we investigated the efficacy and safety of TRH as a treatment for fatigue in patients with cancer. We also evaluated the impact of TRH administration on the immune system in these patients.
Methous: Patients with cancer experiencing clinically significant fatigue without any medically reversible causes of fatigue were enrolled in this study. The primary outcome measure was the visual analog scale for energy (VAS-E) assessed at 3, 7 and 24 hour post TRH and saline (placebo) intravenous administration. The secondary outcome measures included the profile of mood states (POMS) questionnaire, a six-minute walking test (6-WT), the Hospital Anxiety and Depression scale (HADS), the Leeds Sleep Questionnaire (LSEQ), and quality of life using the Functional Assessment of Cancer Therapy scale (FACT-G). We evaluated selected serum markers of inflammation including C-Reactive Protein (CRP) and specific cytokines.
Results: We enrolled 11 patients in the study. A total of 8 patients completed the study. Two patients did not meet the study eligibility criteria and one patient was withdrawn due to exacerbation of migraine headaches. No unexpected side effects were seen. Clinically significant improvement in fatigue level was seen with the VAS-E, the primary outcome measure and the fatigue and vigor subscales of the POMS ($p < 0.05$). Increase in energy level was associated with functional improvement as measured by the 6-WT and improved quality of life with trend towards significance on several subscales of FACT-G. Improvement in fatigue level with TRH administration also correlated with decrease in serum CRP levels.
Discussion & Conclusions: TRH administration was efficacious in the treatment of CF with a positive impact on quality of life. TRH administration was safe and tolerable. Improvement in fatigue level with TRH administration was associated with a positive impact on the CRP levels. These results provide a crucial impetus for pursuing TRH systems as a target to treat cancer-related fatigue.

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ABSTRACT

Immunoglobulin and antibody interventions during aging: theoretical and therapeutic considerations of damage reversal

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Physiologic autoantibodies are part of our normal immune repertoire where they function to maintain homeostasis by performing physiologic functions. Evidence suggests that the body uses autoantibodies to prevent disease and to self-treat diseases once started. This suggests a potential therapeutic role for autoantibodies, or, even better, a way to use them to prevent disease.
Since the role of physiologic autoantibodies in removing senescent and damaged cells is probably the best example of a physiologic autoantibody, complete with well established function, this will be used, initially, as an example. IgG autoantibodies bind to altered band 3 anion exchanger protein on senescent cells and trigger their removal by macrophages. Oxidation is a primary mechanism for altering band 3 and generating senescent cell antigen (SCA). Band 3 isoforms are found in all cells, tissues, and membranes, and in all species examined. The innate immune response to band 3 membrane proteins and their regulation of cellular lifespan and therapeutic potential will be presented.
Examples of other potential innate and physiologic autoantibodies include intravenous immunoglobulins, neuroprotective antibodies to amyloidgenic toxic peptides, and antibodies to oxidized LDL (OxLDL) which modify the natural progression of atherosclerosis.
Intravenous immunoglobulins are used to successfully treat many diseases. One of the proposed mechanisms of action of intravenous immunoglobulins in treatment of disease is that they provide natural immunoregulatory antibodies which modulate inflammation. The list of the many immunoregulatory effects of intravenous immunoglobulins includes modulation of activities that fall within the general categories of Fc receptors, inflammation, B cells and antibodies, T cells, and cell growth. The last category, cell growth, includes regulation of apoptosis and inhibition of lymphocyte proliferation.
Antibodies to beta amyloid may protect neurons against amyloidgenic toxic peptides. Humans have naturally occurring antibodies to toxic Abeta and amyloidgenic non-Abeta species in plasma and cerebral spinal fluid (CSF). Most individuals show antibody activity against peptides unique to autosomal dominant forms of dementia. IgGs isolated from plasma of AD patients or healthy controls protected primary neurons from Abeta toxicity. IgGs to oligomeric perpartations of Abeta1-42 decline with age and advancing Alzheimer's disease (AD). This suggests that these naturally occurring antibodies could be used therapeutically.
The role of innate and physiologic autoantibodies and their peptide antigens in health and disease, and their therapeutic potential will be discussed.

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ABSTRACT

Does aging need its own program, or the program of development is quite sufficient for it? Stationary cell cultures as a tool for search of anti-aging factors

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We guess that the aging process is caused by cell proliferation restriction-induced accumulation of DNA damage in cells of an organism or in cell population. For cell cultures, the proliferation restriction is related to the contact inhibition and to the Hayflick's limit, and for multicellular organisms - to appearance, in the process of differentiation, of organs and tissues consisting of postmitotic and very slowly dividing cells. It is assumed that proliferation of intact cells prevents accumulation in a cell population of various errors. However, the continuous propagation of all the cells in a multicellular organism is absolutely incompatible with its normal functioning. Thus, program of development, when it generates postmitotic or slowly dividing cells, automatically leads also to onset of the aging process (mortality increase with age). Therefore any special additional program of aging simply becomes unnecessary. This, however, doesn't reject, for some organisms, the reasonability of programmed death which makes possible the elimination of harmful (for the species) individuals. It is also very important to emphasize that increase or decrease of organism's life span under effect of various external factors are not always necessarily related to modification of the aging process.

The experimental-gerontological models similar to the Hayflick's model are "correlative" since they are based on some correlations only and not related necessarily to the gist of the aging phenomenon. If the rationale of the "Hayflick phenomenon" is used, we can't explain why we age. Nevertheless, many authors virtually put a sign of equality between aging in vitro and aging in vivo, which generates conclusions that are quite doubtful. A classic illustration of that is the telomere concept of aging, originally formulated at the beginning of seventies by A. Olovnikov and used by him to explain the limited "proliferative" life-span in vitro of normal cells. At the moment it looks like the telomere shortening contributes to aging in vitro only, but not to aging in vivo because an organism never realizes all proliferative potential of its cells. Besides, the most "responsive to aging" are the organs and tissues consisting of postmitotic cells, for which the concept of proliferative potential practically loses any meaning. We developed another "correlative" model - a model for testing of geroprotectors and geropromoters - so called "cell kinetics model". It is based on the well-known correlation between "age" of cultured cells (age of their donor) and their saturation density. The model allowed us to preliminary test a lot of different compounds and factors interesting from gerontological point of view, but it revealed no information about real mechanisms of aging. However, the second model we use in our studies - the "stationary phase aging" model - obviously, is a "gist" model. It is based on the assumption that in the cells of stationary cultures various intracellular changes similar to those of aging organism can be observed. And, indeed, "age" changes which are well known from organismal studies were shown to really occur in our experimental stationary cell culture model. Such experiments can be carried out on nearly any type cells of various biological species. Thus the evolutionary approach to analysis of the data is provided. Moreover, the changes in the stationary cell cultures become detectable already in 2-3 weeks. All this allows us to suppose that the "stationary phase aging" model should provide a very effective approach to testing of different substances and their cocktails on their activities in terms of accelerating or retarding aging - of course, if their effect is realized on the cell level only.

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ABSTRACT

Aging, Alzheimer's disease, Cancer and the LEARn (Latent Early-life Associated Regulation) model

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Current research suggests that aging-related disorders and cancer share some common features. Particularly, neurodegenerative disorders, such as Alzheimer's disease (AD), manifest late in life and are characterized by progressive loss of neuronal and synaptic markers. The sporadic nature of most AD cases strongly argues for an environmental link that may drive AD pathogenesis. However, the triggering factors and the period of their action are unknown. In addition to genes, environmental factors, including diet, metals and life style, play an important role in human behavior and the development of disease phenotype. Our goal is to understand the nature and timing of such 'Gene-Environment' interaction. We have proposed that primary gene sequence variation is often not an immediate operator in neurobiological pathology; instead, environment acts upon the genetic substrate, producing a "Somatic Epitype" (Lahiri & Maloney, *Nat Rev Neurosci*, 2006). We investigated how early-life environmental factors affect the manifestation of a later life disorder. In addition to AD, neuropsychiatric and affective disorders, such as schizophrenia and major depressive disorder, respectively, have broad ranges of age of onset and symptoms. However, all share uncertain etiologies, with opaque relationships between genes and environment. We propose a "Latent Early-life Associated Regulation" (LEARn) model, positing latent changes in expression of specific genes initially primed at the developmental stage of life. In this model, environmental agents epigenetically disturb gene regulation in a long-term fashion, beginning at early developmental stages, but these perturbations might not have pathological results until significantly later in life. The LEARn model operates through the regulatory region (promoter) of the gene, specifically through changes in methylation and oxidation status within the promoter of specific genes. The LEARn model combines genetic and environmental risk factors in an epigenetic pathway to explain the etiology of the most common, i.e., sporadic, forms of neurobiological disorders (Wu et al, *J. Neurosci*, 2008; Lahiri et al, *Mol Psychiatry*, 2009). The LEARn model provides a mechanism of the imposition of a methylation-dependent "somatic epitype" of a promoter due to reaction to environmental stressors such as exposure to heavy metals, nutritional variation, or maternal care, resulting in a pathogenic or pathologically vulnerable phenotype. Thus, AD, as it usually appears in senescence, would be a 'long-latent' condition, and its etiology would be that of a 'two-hit' disorder, similar to those found in currently accepted models of cancer etiology. In the case of AD, this second hit would be a broad spectrum of changes in gene expression, especially upregulation of inflammatory factors, which has been shown to be a function of normal aging. Application of the LEARn model would suggest potential therapeutic strategies. Supported by NIH grants to DKL.

ABSTRACT

Cytoprotection and immunomodulatory effects of transferrin [Tf]: relevance to neuroimmunomodulation and aging

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Human life expectancy has increased progressively leading to a substantial growth of the "elderly" population. In this population certain disorders occur with high prevalence. Some of these, in particular autoimmune disorders, are thought to be related to thymic involution that reflects alterations in the interplay of neural, endocrine and immune factors in the course of aging. We have established a murine model of thymic involution induced by stereotactically placed electrolytic lesions in the anterior hypothalamic area. The events observed in this model mimic those observed during senescence including thymus involution, enhanced glucocorticoid reaction to distress, and obesity. Previous in vivo studies showed that administration of transferrin (Tf) modifies allogeneic and xenogeneic interaction in a way that favors the induction of immunological unresponsiveness [1,2]. The studies in mice showed that Tf has a profound cytoprotective effect on the thymus. Tf also exhibits stress- and immune-protective properties and interferes with proliferative responses and programmed cell death. In human mixed lymphocyte cultures, the addition of Tf as well as Tf-derived glycans (Tf-Gly) inhibited selectively alloantigen-driven cell proliferation by down-regulating immunostimulatory and by up-regulating immunosuppressive cytokine expression [3]. Preincubation of human marrow with Tf/Tf-Gly effectively protected cells against apoptosis induced by gamma-irradiation, TNF-alpa and agonistic anti-Fas MAB. Both immunomodulatory and anti-apoptotic activity of Tf were not mediated via CD-71, the classic Tf-receptor type 1 (TfR1). The cytoprotective effect of Tf was confirmed in several in vivo models including Fas-mediated hepatotoxicity in mice. Tf protects hepatocytes against Fas-induced cell death via the mitochondrial pathway by reducing BID cleavage, inhibiting caspase-3 and -9 activation and up-regulating survival signals such as Bcl-xL. The Tf-mediated protection of hepatocytes against Fas-induced injury is mediated by TfR2 [4]. These and other data indicate that Tf exhibits additional important functions aside from binding and transporting iron. Being involved in the regulation of alloreactivity and apoptosis, Tf (or part of its molecule) might participate in the maintenance of "self-identity" mechanisms, which are tightly linked to the capacity of the immune system to recognize and react against any noxious agent. Senescence is characterized by a progressive decline of self-recognition capacity that inevitably followed by autoimmune, neoplastic and degenerative (age-associated) diseases. The described properties of Tf can be exploited to modify immune responses and provide cytoprotection against pro-apoptotic and cytotoxic signals when neuroimmunomodulatory mechanisms are impaired, e.g. during aging. The use of the hypothalamus/thymus model in genetically modified mice will develop a clearer understanding of the interplay of neural, endocrine and immune factors during different pathologic states and thereby develop a basis for novel preventive or therapeutic strategies.

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ABSTRACT

Cancer as the main aging factor for humans and reversal of cancer-induced aging processes on metabolic and immune reactions by pineal hormones other than melatonin: the fundamental role of 5-methoxytryptamine

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The progressive alterations of the circadian rhythms, the enhanced-free radical production, the anomalous neuroendocrine regulations of the immune responses and the diminished pineal function represent some of the most important biological dysfunctions occurring with age.Several experimental studies have suggested that aging processes may be at least in part counteracted through a neuroendocrine modulation with agents such as the pineal hormone melatonin (MLT). However, MLT would simply represent the most investigated pineal hormone, but at present we know that it simply constitutes one of the several pineal hormones. In particular, according to the data available up to now, at least another pineal indole hormone has to be taken into consideration on the basis of its biological activities, the 5-methoxytryptamine (5-MTT). In vitro, 5-MTT has been proven to play an antitumor antiproliferative effect superior to that of MLT itself. As well as MLT, 5-MTT may also exert a potent anti-oxidant action and an anticachectin property, due to an inhibition of TNF-alpha secretion. Finally, as far as the immunomodulatory effects are concerned, 5-MTT would modulate the macrophage function, by counteracting macrophage-mediated suppression of the anticancer immunity, whereas T helper-1 lymphocyte would constitute the main target cell for MLT action in stimulating the anticancer immune response. The recent advances in the knowledgements of the psychoneuroimmunology of cancer have allowed us to identify the endocrine, neuroendocrine and immune alterations occurring with cancer progression. If we compare cancer-related immunoendocrine alterations with those which characterize the aging processes, we may observe that cancer onset and progression are depending on an anticipation and on amplification of the same neuroimmune anomalies occurring in aged subjects. In fact, immunoneuroendocrine dysfunctions, such as the progressive loss of the circadian biological rhythms, the decline in the endocrine pineal function, the diminished IL-2 endogenous production and the enhanced macrophage suppressive activity have been described in both cancer patients and aged subjects.Therefore, cancer may be reinterpretated as an anticipation of the common immune and neuroendocrine mechanisms occurring with age. Several clinical studies have demonstrated that MLT may exert an anticancer efficacy in advanced cancer patients, including those for whom there is no other standard anticancer therapy. Moreover, it has been proven in humans that the anticancer action of MLT is associated with a correction of some cancer-related neuroimmune disorders, such as the desynchronization of cortisol circadian rhythm, IL-2 deficiency and enhanced production of inflammatory cytokines, namely IL-6 and TNF-alpha. Preliminary clinical studies would suggest that the therapeutic endocrine and immune properties of MLT in the neoplastic diseases may be amplified by a concomitant administration of pharmacological doses of 5-MTT during the light phase of the day, since its administration during the dark period of the day would immediately induce the transformation of 5-MTT into MLT because of the activation of the NAT enzyme during the night.

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ABSTRACT

Thyrotropin releasing Hormone (TRH) promotes insulin producing cell proliferation

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The best-characterized physiologic role of TRH is the stimulation of the pituitary-thyroid axis [(1)]. However, TRH has many other effects not only in the brain, such as the regulation of neuronal growth, controlling appetite behavior and immunity on pineal gland [(2)], but also in extra-CNS locations such as the pancreas [(3)]. TRH levels in the β cell peak during the stages of late embryonic and early neonatal development [(4)]. These observations are consistent with a linkage of TRH to islet cell proliferation and differentiation. The growing population of diabetics in the world generates a requirement for the development of effective agents for diabetic therapy. Utilizing TRH as a glucose regulatory peptide by enhancing pancreatic islet β cell function is an innovative approach to enhance the therapeutic options available. In this presentation, we describe the distribution of the TRH receptor in the pancreas and the novel effects of TRH in β cell function by identifying its special molecular signals [(5)]. *In vivo* studies, with GFP positive labeled bone marrow transplants in diabetic animal models, showed that TRH improved _ cell function, apparently by attracting bone marrow migration into the injured pancreas to repair islet injury and facilitate _ cell regeneration. Evidence from our preliminary studies provides a pathway to future developments for normalizing blood glucose in human diabetes.

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ABSTRACT

Reactive astrocytes are key players in nigrostriatal neurorepair/regeneration: relevance for parkinson's disease

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Parkinsons'disease (PD) is a common neurodegenerative disorder characterized by the presence of tremor, muscle rigidity, slowness of voluntary movements and postural instability. One of the pathological hallmark of PD is loss of dopaminergic (DAergic) neurons in the subtantia nigra pars compacta (SNpc). The cause and mechanisms underlying the demise of nigrostriatal DAergic neurons are not completely clarified, but interactions between genes and environmental factors are recognized to play a critical role in modulating the vulnerability to PD. Current evidence points to reactive glia as a pivotal factor in PD, but whether astroglia activation may protect or exacerbate DA neuron loss is presently the subject of much debate. Astrocytes and microglia by secreting an array of pro- and anti-inflammatory cytokines and chemokines act as double-edged swords, exerting both detrimental and neuroprotective effects (Marchetti and Abbracchio, 2005). Emerging evidence suggest that early life events, including embryonic life exposure to endotoxins, virus, hormones or neurotoxicants, may significantly influence DAergic neuron vulnerability in adulthood. Within this frame, this work will underline the cardinal role of the astroglial cell compartment and its mediators. Based on its dualistic role, inflammation can contribute in both a "protective" or "destructive" way, leading to either neurodegeneration and/or neuroprotection. Importantly enough, the final outcome of gliosis also depends on complex interactions between genetic, hormonal and environmental factors. Given the crucial role of glia-neuron interactions in neuronal growth, survival differentiation, neurogenesis and synapse formation, alterations in glia-neuron crosstalk as observed with the aging process may increase DAergic neuron vulnerability to environmental neurotoxicants, also through glial negative modulation. Then, injury-induced inflammatory cascade via glial activation serves as a prompt mechanism initiated to eliminate damaged neurons on the one hand, while on the other, it simultaneously activates endogenous self-repair processes aimed at re-establish neuronal function. While uncontrolled glial reaction may impair the survival and proliferation of neuroprogenitors and/or block repair processes, efficient neuron-glial crosstalk, as induced by cytokine-activated glia may promote neurogenesis and neurorepair. Overall, glia and its pro-/anti-inflammatory mediators represent a final common pathway through which genetic, hormonal and environmental influence can modulate resistance or susceptibility to PD. Drugs developed to target astroglia, by modulating both the inflammatory detrimental component, while, in the mean time, activating glial neuroprotective capacities are being studied with the hope to contribute to the development of novel therapeutic treatment strategies for Parkinson's disease and possibly other neurodegenerative disorders.

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ABSTRACT

Aortic wave velocity; a measurement of the stiffness index (SI) of arteries and the results of certain supplements that appear to improve the SI

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Aortic velocity, arterial stiffness index, pulse pressure wave, myocardial infarction, cardiovascular, stroke, Bio-Clip, carnosine, aminoguanidine, resveratrol, arginine

There is a growing opinion that the two most important factors for determining the risk of a cardiovascular or stroke related event are the patient's blood viscosity and their arterial stiffness, to wit 'thin' viscosity and 'soft' arteries are highly favorable. Until recently, the methods of measuring arterial stiffness were complex and costly. However, the arrival of photopletysmography finger clamps and software programs to evaluate the arterial elasticity have allowed for a simple, fast and accurate measurement to be enabled.

This lecture looks briefly into its methodology and reminds of the need for such procedures to help reduce the cost of the traditional 'treatment' of cardiology by shifting its emphasis into prevention.

In addition, some patients' evaluations are shown- patients who consumed some specific supplements indicating a significant arterial stiffness improvement within relatively short periods of time. The lecture ends with an analysis of the different supplements potential common factor of action/ benefit.

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ABSTRACT

Telomere shortening is a sole mechanism of aging in mammals

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The proofs adduce of that telomere shortening is a sole mechanism of aging in mammals. All apparent contradictions, and first of all the absence of inverse correlation between residual telomere length and donor age, are explained within the bounds of telomere theory. It is explained in what way telomere shortening might be the cause of aging and life-span restriction. It is also shown the inability of oxidative theory to explain a number of undisputable facts, easily explained by telomere theory such as malignant growth of tumor cells and why our children start to age not from the level reached by the cells of their parents at the moment of conception but from zero. We postulate that if oxidative damage was entirely absent telomeres would, nevertheless, shorten with each mitotic cycle because such is the mechanism of DNA replication, and aging would occur all the same, and it is the very thing we can observe under effect of any antioxidants. But if telomeres do not shorten, as it is in transformed cells because of working telomerase, aging will do stop and transformed cells will show no senescence. And we also observe it in spite of damaging effect of reactive oxygen species which is even more intensive than in normal cells.

ABSTRACT

Plasticity of neuroendocrine-thymus interactions during ontogeny and ageing: role of zinc and arginine

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Thymic re-growth and reactivation of thymic functions may be achieved in old animals by different endocrinological or nutritional manipulations such as, (a) treatment with melatonin, (b) implantation of a growth hormone (GH) secreting tumour cell line (GH3 cells) or treatment with exogenous GH, (c) castration or treatment with exogenous luteinizing hormone-releasing hormone (LHRH), (d) treatment with exogenous thyroxin or triiodothyronine, and (e) nutritional interventions such as arginine or zinc supplementation (Fabris et al., 1997). These data strongly suggest that thymic involution is a phenomenon secondary to age-related alterations in neuroendocrine-thymus interactions and that it is the disruption of these interactions in old age that is responsible for age-associated immune-neuroendocrine dysfunctions. The targets involved in hormones-induced thymic reconstitution may directly or indirectly involve hormone receptors, cytokines, arginine, and a trace element such as zinc, which is pivotal for the efficiency of neuroendocrine-immune network during the whole life of an organism (Fabris et al., 1997). The effect of GH, thyroid hormones, and LHRH may be due to specific hormone receptors on thymocytes and on thymic epithelial cells (TECs), which synthesize thymic peptides. Melatonin may also act through specific receptors on T-cells. In this context, the role of zinc, which turnover is reduced in old age, is pivotal because of its involvement through zinc fingers in the gene expression of hormone receptors (Shankar and Prasad, 1998). In addition, the effects of zinc are multifaceted: from the reactivation of zinc-dependent enzymes, to cell proliferation and apoptosis, to cytokines expression and to the reactivation of thymulin, which is a zinc-dependent thymic hormone required for intrathymic T-cell differentiation and maturation as well as for the homing of stem cells into the thymus (Hadden, 1998). Zinc is also required for arginine action, via NO pathway (Mocchegiani et al., 1993). The role of zinc is therefore crucial in neuroendocrine-thymus interactions. According to data in animals and humans, the above reported endocrinological manipulations (GH, thyroid hormones, and melatonin) or arginine treatment may also act via zinc pool in restoring thymic activity in ageing allowing improvements on peripheral immune efficiency (Mocchegiani et al., 1994). As a consequence, the association of some hormones and zinc or arginine may be a valid anti ageing strategy as well as in preventing the appearance of some age-related diseases, such as cancer, arteriosclerosis and type 2 diabetes taking into account that zinc homeostasis and alterations in immune performances and neuro-endocrine pathways are common events both in ageing and in age-related diseases.

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ABSTRACT

Our endogenous "pineal clock" and cancer. Cancer and non-cancer. Strategies for early detection, prevention and cure of neoplastic processes

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I propose here that cancer, similarly to most diseases such as cardiovascular, autoimmune and neurodegenerative diseases is simply, in most cases, the final expression of an early or late derangement of central neuro-endocrine-immune control, defined now as "immunological surveillance", leading to a loss of non-proliferative control of pre-existing and "dormant" pre-neoplastic or neoplastic cells in the body. The "hormonal-immune" alteration preceding and anticipating onset of cancer, does not depend only on a chronic quantitative changes of hormone synthesis and release, but on a desynchronization of their rhythmic, circadian release, in which the pineal network plays a major role. Being the immune system totally controlled by the circadian, day-night cyclic periodicity of hormones, the resulting alteration of hormone rhythms leads to a veritable destruction of the capacity of the immune system, not to eliminate, but to keep emerging tumor cells under non-proliferation control. Malignancy is simply the obvious outcome of chronic alteration or absence of hormonal rhythms which strictly control the maturation and the activity of the thymo-lymphatic, immune system. Dilman's vision is thus here confirmed and extended. This approach allows now to proceed to cancer prevention with a simple and efficient monitoring of those physiologic hormone values which must be maintained and express precisely the existence of a central "pineal life clock" related to reproductive and immune functions and to the pineal program of aging.
Alternative therapy approaches are also suggested for advanced, non curable and metastatic cancer by using a novel method for xenogeneic (between different species) bone marrow transplantation.

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ABSTRACT

Aging-Reversing Properties of Thyrotropin Releasing Hormone (TRH)

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Work in our laboratory has shown the remarkable and varied effects of TRH in the rapid reversal of aging-related changes and alterations in old rodents. It was also demonstrated that these restoring effects of TRH were not exerted via the thyroid gland, with the obvious increase of synthesis or secretion of thyroid hormones, but depended on a newly found and rather unexpected direct activity of TRH. We suggested that the tripeptide TRH, thanks to its ubiquitous localization in nature and its high concentration in key tissues such as the pineal gland, the pancreatic insulin-producing beta cells and the anterior hypothalamic area, represents a vehicle for most fundamental energy-regulating and hormone-synchronizing activities.

In fact, the restoring effects of TRH could be seen in all models used, such as aging, immunodeficient animals, virus-infected and stressed mice, hypothalamus lesioned mice and in particular in old animals with typical adiposity and progressive decay of neuroendocrine, immune and hormonal functions. TRH associated to melatonin normalizes lipid metabolism and prolongs longevity in aging mice. All this previous work prompted us to study the effects of short-term, acute administration of TRH or its chronic oral administration, on organs, tissues and aging-related metabolic and hormonal markers, in order to acquire more knowledge on effects, dosage and timing of administration according to its circadian cyclicity. In addition, we wanted to verify its anti-aging effects on two most fundamental functions, namely gonadal- reproductive and kidney-urinary.

The results demonstrate that both a short-term, acute or a chronic, long-term oral administration of TRH to old, aging mice, results into positive changes and rapid correction to more juvenile levels of most typical aging-related hormonal and metabolic alterations.

Remarkably, 4-month oral treatment with TRH maintains testes function in aging mice. As hinted by the significant increase of testes weight, TRH taken from the drinking water produces a maintenance and/or reconstitution of testes structure and function as shown by active proliferation and formation of mature spermatogonia and intensive spermatogenesis in the follicles. Apparently TRH greatly enhances the final maturation process of spermatogonia to spermatozoa.

4-month oral treatment with TRH protects the kidneys from amylod and hyalin infiltration of both tubuli and glomeruli, which is typical of aging mice. In fact, massive deposits of amyloid and hyalin material are clearly infiltrating the shrunken glomeruli of untreated mice with loss of filtration capacity, while hardly present in TRH-treated mice. Massive hyalin degeneration can also be observed in the tubular vessels of the untreated control mice.

The extensive and repeated experiments with parenteral and oral administration of TRH show a most remarkable aging-delaying and apparently even aging-reversing effects of the neuropeptide TRH. Again, similarly to melatonin, we are confronted with an anti-aging agent with a broad spectrum of activities which must be necessarily linked to a most fundamental role in the regulation of metabolic and hormonal functions.

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ABSTRACT

Morphogenetic and immunoregulatory role of endoplasmic reticulum resident heat shock protein GP96

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Heat shock proteins (HSPs) are phylogenetically conserved proteins, present in all prokaryotes and eukaryotes that are involved in various physiological and pathological processes. According to their function and size, or cellular localization, they are classified into major classes (small HSPs, HSP40, 60, 70, 90, and 110 families) and several members of a family. Gp96 (known also as glucose-regulated protein 94) is the endoplasmic reticulum (ER)-resident protein belonging to the HSP90 family. It is upregulated in response to glucose starvation and other stressful stimuli that disrupt protein synthesis in the ER, acting as a molecular chaperon involved in the correction of unfolded proteins, in the activation of proteasome-dependent ER-associated degradation of the misfolded proteins and in activation of protein translation that modulate the polypeptide traffic into the ER. In addition, it has been implicated in antigen presentation and MHC class I and II upregulation, in the activation and maturation of dendritic cells and proinflammatory cytokine secretion, as well as in chaperoning of Toll-like receptors, acting as a "danger signal" to the innate and adaptive immunity. Moreover, owing to its specific function in Ca2+ homeostasis and in the insulin-IGF/signaling pathways it was proposed that gp96 participates in mechanisms that are critical for cell growth, differentiation and responses to ER stress.

To underline some aspects of these functions, in this survey we will present the data showing the expression of gp96 in the conditions of: 1) normal growth (liver regeneration after partial hepatectomy, syngeneic pregnancy, fetal organogenesis), 2) stress and ageing and 3) autoimmunity (chronic relapsing experimental autoimmune encephalomyelitis; CR-EAE). Tissue expression of gp96 protein and mRNA was estimated in the liver, thymus and spleen and the data were correlated with phenotype and cytotoxicity of hepatic and splenic mononuclear lymphatic cells against the NKT and NK-sensitive targets. In the model of CR-EAE gp96 expression in the brain was correlated with the intensity of clinical symptoms.

The data have shown that gp96 is highly upregulated in fastly proliferating and remodeling tissues (in regenerating liver, at the fetoplacental barrier, during fetal organogenesis), as well as in healing tissues after autoimmune attack (in the brain and spinal cord during the remission phases of EAE). Enhanced level of gp96 expression was also found in the thymus of aged and stress-exposed mice. Moreover, the kinetic studies made in the model of liver regeneration showed that gp96 upregulation was followed by maturation of dendritic cells, accumulation of $CD3^{intermediate}/NK1.1^{+}/CD69^{+}$cells in the liver and $CD4^{+}CD25^{+}Fox3^{+}$ cells in the liver and thymus, as well as by augmentation of NKT and NK-mediated cytotoxicity in the liver and in the spleen.

The data imply that during the disturbance of morphostasis gp96 may serve as a natural adjuvant for chaperoning antigenic self peptides into the immune surveillance pathways, resulting in activation of autoreactive NKT, which in cooperation with Treg cells participate in more or less successful reestablishment of self tolerance (Supported by grant 0621341-1337 from Croatian Ministry of Science).

ABSTRACT

Non-receptor and receptor mediated oxidative stress in murine cerebellum neurons and neuroblastoma both accompanied by phosphorylation of MAP (ERK 1/2) kinase

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Primary culture of murine cerebellum neurons (1) and neuroblastoma N-18 (2)were used to induce oxidative stress resulting in accumulation of reactive oxygen species (ROS) and activation of ERK1/2. Short-term incubation (15 min) of cerebellum neurons with homocysteine (HC) or N-methyl-D-aspartate (NMDA) induces phosphorylation of ERK1/2 thus providing partial activation of the enzyme. Exposure of the cells with hydrogen peroxide (H_2O_2) results to the same effect but its time dependence develops slowly with the time of maximal activation at 5 min of exposure. Inhibitors of NMDA receptors, MK-801 (which prevents function of receptor operated channel) or D-AP5 (which competes with the ligand for specific binding site) both prevented activation of cells by HC or NMDA but not affect H_2O_2 action.
Neuroblastoma cells demonstrated similar features being activated both by receptor mediated or receptor independent modes.
Another receptor dependent way of stimulation of oxidative stress is exposure of cells to ouabain. This cardiac glycoside under low concentration (10 nM) induces ROS accumulation and substantial stimulation of ERK 1/2, activation being started after 10 min of incubation.
Neuropeptide carnosine (5 mM) added to the cells 2 hr before oxidative stress prevents ROS accumulation and activation of ERK 1/2, thus suggesting an ability of carnosine to regulate early response gene expression.
Because ERK1/2 kinase plays a key role in function of early response genes the model used is a useful approach to characterize an effect of a number of natural and synthetic anti-cancer drugs on the expression of the early response genes.

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ABSTRACT

From Calories to molecules.
The role of carbohydrates and AGEs in atherosclerosis

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From Calories to molecules

The human body is a vital organization of introduced from the outside molecules. You inherit and transmit DNA molecules, and not Joule-Calories. The human body accumulates, stores and uses chemical energy (ATP); it does not use thermal energy for mechanical, osmotic, chemical or electrical labour.

The primary biological parameter is an organism's oxygen consumption and carbon dioxide production, and not the introduced by the daily diet Joule- Calories.

It is necessary to move from food Joule-Calories to nutrients molecules, actually used by the cells after the digestion of ingested food and the absorption of individual nutrients molecules contained in the ingested food itself (glucose, amino-acids, fatty acids, vitamins, minerals, water). The "molecular quality", i.e. the molecular different nutritional composition, affects the metabolism, the individual hormonal profile, without a real correlation with the different foods' Joule-Calories. Moreover, some of the nutrients molecules (such as vitamins, minerals and nutraceutical molecules) do not provide any Joule-Calorie.

The food Joule Calories tables provide just an approximate idea about the food actual energy content. It is not acceptable to consider equal the heat generated by the oxidation of individual foods in a thermodynamically closed system (as a calorimeter with respect to chemical energy), to the metabolic heat (body temperature) that the same foods can generate inside the human cells.

The Joule-Calories measure the heat produced in a thermodynamically closed system by the oxidation of a food in its entirety. The human body is a biological thermodynamically open system. The chemical energy which is stored or which is released depends on the actual use of the nutrients molecules, absorbed from the gut and carried by the blood cells. It is not related to food in its entirety, but to what remains after the digestion and intestine absorption of the food. The different biological, metabolic, hormonal subjectivity generates and uses chemical energy (ATP) and thermal energy (metabolic heat - body temperature) in a different manner in different organisms. The food Joule-Calories tables provide a rough idea on the actual energy content of food. Joules-Calories are an artefact with no real scientific value in the physio-pathological and clinical approach to a human body. There is no correspondence between the tabular Joule-Calories, listed in the nutrition labels, and their actual physiological role generated inside the human body. The variables that can influence and affect the chemical energy contained in foods are numerous:

- Subjective coefficient of digestibility, intestinal absorption of ingested food;
- Nutritional subjectivity (age, sex, body composition: fat mass, lean muscle mass);
- Metabolic efficiency of the nutrient cell unit (capillary - extracellular matrix - connective tissue disease with collagen protein glycation - metabolically active cell);
- Specific dynamic action of food from food-induced thermogenesis (DIT, Diet Induced Thermogenesis);
- Oxygen availability and consumption at the cellular level;
- Hormonal profile and action on the cell membrane hormone receptors;
- Pathological clinical profile, hepatic functional status;
- The daily nutritional overall model and the food handling: food production, food technology.

It 's more important to check the metabolic efficiency (oxygen consumption/carbon dioxide production) than the daily calculation of Joule-Calories.
Joule-Calories exist only outside the human body. The metabolic capacity to oxidize, to accumulate, to mobilize the chemical energy is individual. The human body uses and accumulates chemical energy (ATP), and it does not use thermal energy for function and labour.
The metabolic heat (body temperature) is generated in brown adipocytes only by the oxidation of saturated fatty acids. The other body cells use chemical energy: glucose and fatty acids oxidation for mechanical, osmotic, chemical, electrical labour.
The Respiratory Quotient (RQ) is an index of individual metabolic efficiency:
QR >1, lipogenesis condition with passage of the carbohydrates to lipids;
QR: <0.7, glycogenesis and ketogenesis condition.
The daily intake of dietary carbohydrates actually absorbed influences the individual metabolic efficiency, rather than the daily calculation of the Joule-Calories (lithogenesis / glycogenesis / ketogenesis / glucose level / insulin secretion / insulin resistance condition, AGEs - Advanced Glycation Endproducts - formation).
The carbohydrates daily intake is a primary factor in the atherosclerosis genesis, aging process related to the AGEs formation and to the pathology of connective tissue.

The role of carbohydrates and AGEs in atherosclerosis
The Advanced Glycation Endproducts (AGEs) formation is an important biochemical abnormality accompanying diabetes mellitus and, likely, inflammation in general. Here we summarize and discuss recent studies indicating that the AGEs' effects on vessel wall homeostasis may account for the rapidly progressive atherosclerosis associated with diabetes.
Driven by hyperglycaemia and oxidant stress, AGEs form to a greatly accelerated degree in diabetes. Within the vessel wall, collagen-linked AGEs may "trap" plasma proteins, quench nitric oxide activity and interact with specific receptors to modulate a large number of cellular properties. On plasma low density lipoproteins (LDL), AGEs initiate oxidative reactions that promote the oxidized LDL formation. The interaction of AGEs with endothelial, as well as with other cells accumulating within the atherosclerotic plaque (such as mononuclear phagocytes and smooth muscle cells), provides a mechanism to augment vascular dysfunction. Specifically, the interaction of AGEs with vessel wall component increases vascular permeability, the expression of procoagulant activity and the generation of reactive oxygen species, resulting in increased endothelial expression of endothelial leukocyte adhesion molecules. AGEs potently modulate initiating steps in atherogenesis involving blood-vessel wall interactions, triggering an inflammatory-proliferative process and, furthermore, critically contribute to propagation of inflammation and vascular perturbation in established disease. Thus, a better understanding of the biochemical mechanisms by which AGEs contribute to such processes in the vessel wall could be relevant to devise preventive and therapeutic strategies for atherosclerosis.

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ABSTRACT

Metabolites that induce neurodegeneration as therapeutic targets

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Alzheimer's disease (AD) is a complex disorder with pathological changes noted years before development of dementia. The most popular hypothesis for AD is that amyloid β protein (Aβ) aggregated into a toxic form that leads to accumulation of the microtubule-associated protein tau (MAPT) in neurons. These lesions lead to loss of synaptic terminals, dysfunction and ultimately death of neurons. The theory is supported by the neurotoxicity of Aβ aggregates and by familial AD (FAD) mutations that misprocess Aβ precursor (APP), deposit plaques and tangles and induce dementia in humans. Interestingly, we find that APP is highly expressed in the eyes and Aβ is efficiently secreted into the vitreous and aqueous humors making the eye a target for neurodegeneration by this pathway like the brain. We have observed that several key metabolic pathways influence amyloid levels and may therefore be responsible for AD pathogenesis in humans. These pathways include isoprenoids that form intermediates and branches in the cholesterol-biosynthesis pathway and homocysteine, which is an intermediate in the once-carbon cycle of methionine metabolism. Interestingly, cholesterol and homocysteine have been identified as AD risk factors. Moreover, AD and several retinal degeneration syndromes share the same risk factors and may therefore share pathways of pathogenesis. Our studies suggest mechanisms of action by these key pathways that may suggest methods for prevention and treatment of these dreadful diseases.

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ABSTRACT

The quest continues: Stromboli cocktail V: aging, cancer and longevity

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1. The latest scientific and clinical reports from this conference will be evaluated to "separate the wheat from the chaff" . . . i.e., good data vs. anecdotes. Thus the famous (infamous) Stromboli Cocktail (references 1 and 2) will be brought up to date.

2. Longevity/statistics will be reviewed: why do the most scientifically advanced countries have such low (comparatively) life expectancies? Scientific knowledge expands exponentially each decade, while there has been *no* significant advance in our knowledge of government, economics, politics, anti-corruption, etc. since the dawn of history.

3. What can we expect in the future? Will the human species outlive the cockroaches? Can we expect to get closer to that theoretical asymptote of 120 years of human life? Will the ceiling ever be lifted?

4. Among the dismal realities of today's world one happy thought: We thank Walter Pierpaoli for his heroic efforts to put together a fifth Stromboli Conference!

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ABSTRACT

Physiological significance of the pineal gland and its hormone melatonin

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The mammalian pineal gland is a neuroendocrine transducer that is an integral part of the brain. Through the nocturnally elevated synthesis and release of the neurohormone melatonin, the pineal gland codes and disseminates information on circadian time, providing a link between the outside world and biochemical and physiological internal demands of the body. Addressing molecular details behind rhythmic signaling in the mammalian pineal gland and mechanisms of decoding the melatonin message of time are of general interest to better understand the organization of the circadian system (1). This holds particularly true for the human, as melatonin has subtle influences on the circadian system (phase-shifting the activity of the master clock in the hypothalamic suprachiasmatic nucleus [SCN]; maternal-fetal communication during pregnancy), and as chronobiological dysfunctions in (wo-)man are often associated with alterations in melatonin synthesis. The severe circadian misalignments, present in the elderly (demented) patient, but also in individuals, affected by Alzheimer Disease, the Smith-Magenis-Syndrome, Autism Spectrum Disorder, and Sleep Phase disorders, are all accompanied by impaired melatonin synthesis. Recent advances in understanding signaling dynamics of the human pineal gland has already fostered significantly to counteract chronobiological dysfunctions through a proper restoration of the nocturnal melatonin surge.

While the conservation of pineal melatonin synthesis despite evolutionary pressure proves its importance, remarkable species-specific differences exist in its regulation, which are only poorly linked to the activity pattern of an animal (nocturnal *versus* diurnal). In most rodents, with the notable exception of *Octodon degus*, the activity of the rate-limiting enzyme for melatonin synthesis, the Arylalkylamine N-acetyltransferase (AA-NAT), is regulated via a transcriptional gating mechanism (1). For unknown, perhaps evolutionary reasons, the post-translational regulation of AA-NAT is representative for melatonin dynamics in taxonomic groups outside rodents. In the human pineal gland, protein-protein interactions and nucleo-cytoplasmic shuttling gain increasing importance, indicating a novel twist in molecular dynamics of pineal neuroendocrine cells (1).

Decoding the melatonin message in target tissues and cells requires the presence of high affinity receptors for the pineal hormone (MTs). The evolutionary highly conserved presence of MTs is known for long in the SCN and in the hypophyseal pars tuberalis (PT). While the susceptibility of the SCN oscillator to melatonin is only limited, it was shown that through heterologous sensitization of the adenylyl-cyclase in cells of the hypophyseal pars tuberalis (PT) during nighttime, the pineal hormone enables adenosine to induce cAMP-sensitive genes, thereby initiating a time-decoding clockwork that drives endocrine function (2). An exciting observation is the presence of MTs in the mammalian hippocampus, since mechanisms of memory formation are clearly day-time-dependent (3). Within efforts to decipher these temporal gating mechanisms, we could recently demonstrate that the circadian system is involved in the timing of hippocampal mnemonic processes (4), and that the neurohormone melatonin, disseminating circadian time cues through an elevated nighttime release, affects dynamics of the expression of trans-activating clock genes in the hippocampus, to shape daytime-dependent memory processes in the mouse.

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ABSTRACT

Beneficial effect of chronic melatonin treatment on several physiological parameters of old male and female Wistar rats

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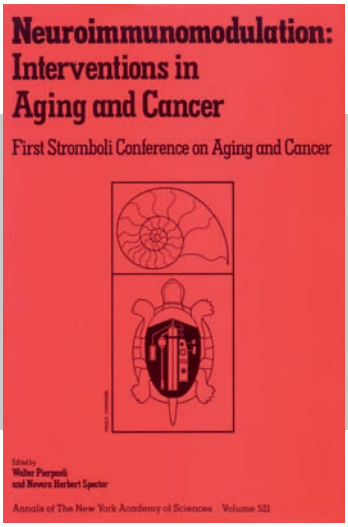
Aging induces changes in several organs and tissues, such as the central nervous system, immune system, liver and bone and this process might be due to oxidative damage caused by free radicals and inflammatory mediators. Melatonin is a hormone with well-known antioxidant properties. In this study the effect of melatonin administration on age-induced alterations in hepatocytes, skin, central nervous system immune system and bone are presented.. Twenty-two-month old male and female Wistar rats were used as experimental model and were analysed intact or castrated, untreated or after the chronic administration of 1mg/ Kg / day of melatonin in the drinking water for 10 weeks. At the end of the treatment the different parameters were investigated. In hepatocytes aging induced a significant increase in lipid peroxydation, nitric oxide, carbon monoxide and cyclic guanosyl-monophosphate, as well as a reduction in ATP content when compared to young animals. An increase in inflammation related parameters such as TNF alfa, NFkB, IL 1, IL 2 and IL 6 as well as a reduction in anti-inflammatory parameters such as IL 4 and IL 10 were also detected. An increase was seen in cytosolic citochrome C whereas a reduction was evident in mitochondrial content with age. Melatonin administration significantly ameliorated all these age-related changes in males and females. In the skin a reduction of epidermal thickness together with a marked increase of the hypodermis with great fat accumulation was observed in old rats, together with an increase of nucleosomes and LPO and a reduction in bcl2 levels in cultured keratinocytes. Melatonin treatment was able to reduce the fat content of the hypodermis and to increase bcl2 and reduce nucleosomes and LPO in skin cells in both sexes. In the central nervous system aging is associated to memory and cognitive alterations. In this study, the number of neurons in the hilus of the dentate gyrus has been assessed in male and female Wistar rats between 3 and 24 months of age, using the optical fractionator method. Male rats had more neurons than females at all the ages studied. Significant neuronal loss was observed in both sexes between 22 and 24 months of age. When treated with melatonin for 10 weeks, 22 month-old male and female rats showed the same descent in neurones than old animals treated with saline but increased neurogenesis as detected by BrDU staining. A reduction of nucleosomes and an increase in bcl2 was also observed in brain homogenates. These findings indicate that melatonin is neuroprotective to a certain extend in old male and female animals.
The impairment of the immune system with aging, or "immunosenescence", appears to contribute to the increased morbidity and mortality of the aged subjects. Moreover, T cell functions and NK activity seem to be the immune responses most affected by aging. In addition, the immune system has different level of efficiency in males and females. In the present work the changes between 2 and 24 months in lymphocyte chemotaxis, T lymphoproliferative response to the mitogen ConA, IL-2 release and NK activity of cells from axillary nodes and spleen of male and female rats have been studied. The same functions have been also determined in aging females ovariectomized at 12months of age which represents a model of menopause in rats. An age related decrease has been found in all investigated functions, with slightly different evolutions depending on the immune organ and gender considered. In general, values obtained in females are higher than those found in males, but ovariectomy decreased the immune responses. Data obtained show a certain degree of immunosenecence taking place with age in rats, with males being less immunocompetent than intact age mat-

ched females but showing a similar immune response than ovariectomized animals.
Conclusion: Melatonin administration could exert beneficial effects against age-induced changes in various physiological parameters in old male and female Wistar rats.



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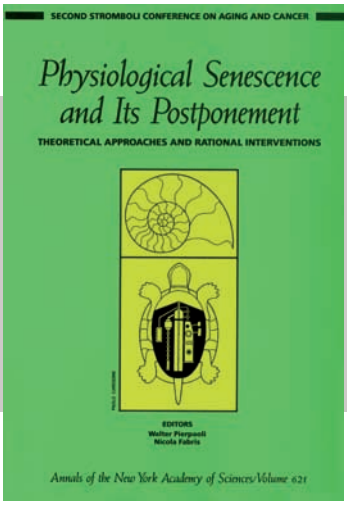

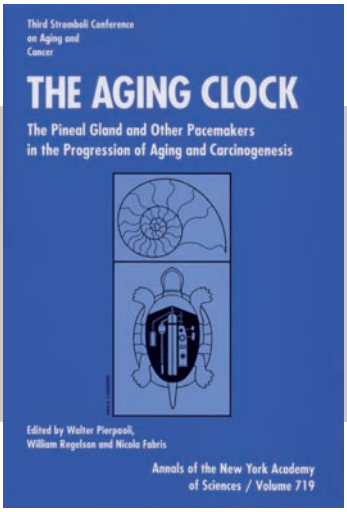

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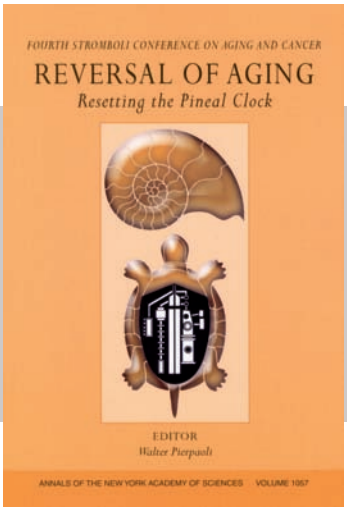

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