THE ADIPOKINOME AND THE INFLAMMATORY RESPONSE – NOT ENOUGH OXYGEN?

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Adipose tissue is a major endocrine organ, with white adipocytes releasing >50 different signaling proteins. These 'adipokines' are highly diverse in structure and function, with a number being directly linked to immunity and the inflammatory response. The synthesis and release of inflammatory adipokines rises markedly as adipose tissue mass expands in obesity (with the exception of adiponectin which has an anti-inflammatory action), and the tissue contributes to the chronic mild inflammation characterizing the disorder. Although the inflammatory response in adipose tissue is considered to underlie the development of the metabolic syndrome and other obesity-associated diseases, its mechanistic basis is unknown. We have, however, recently proposed that it could reflect a response to hypoxia as tissue mass expands, large adipocytes becoming hypoxic as their distance from the vasculature increases, the inflammatory response serving to stimulate blood flow and vascular development. We have used two different approaches to investigating the effects of hypoxia on adipokine expression in human adipocytes - a 'candidate gene' strategy and PCR arrays. The effect of hypoxia, induced by incubation under low (1%) oxygen tension, on the expression and secretion of a series of inflammation-related adipokines has been examined. Hypoxia induced a rapid and substantial increase in the hypoxia-sensitive transcription factor, HIF-1α, and led to a reduction in adiponectin and haptoglobin mRNA levels; adiponectin secretion also decreased. In contrast, low 0_2 tension resulted in substantial increases in FIAF/angiopoietin-like protein 4, IL-6, leptin, MIF, PAI-1 and VEGF mRNA levels. The secretion of IL-6, leptin, MIF, and VEGF from the adipocytes was also stimulated by exposure to 1% O_2. Similar results were obtained when the adipocytes were incubated with $CoCl_2$, suggesting that HIF-1α is directly implicated in the transmission of the effects of hypoxia on adipokine production. In a microarray approach, PCR arrays (Superarray) for 84 genes in the hypoxia signaling pathway were employed. Application of the arrays to human adipocytes incubated in 1% O_2 showed that expression of 12 genes was upregulated by hypoxia while 9 genes were downregulated. The genes altered by hypoxia in the candidate gene study were also changed with the arrays. The arrays showed, however, that the expression of one gene – metallothionein-3 (MT3) - was dramatically upregulated in hypoxia (>600-fold increase in mRNA level). The induction of MT3 expression with low O_2 was confirmed by RT-PCR and real-time PCR. MT3 (also known as growth inhibitory factor), may act as a protectant against hypoxia-induced cell damage and might modulate adipogenesis. Hypoxia also affects other components of adipocyte function; we have recently found that the expression of the GLUT-1, GLUT-3 and GLUT-5 facilitative glucose transporter genes is upregulated by hypoxia in human adipocytes and GLUT-1 protein is increased. Importantly, the increase in transporter protein is linked to functional changes in that the uptake of 2-deoxy glucose was markedly stimulated under hypoxic conditions. This suggests that glucose utilisation and insulin responsiveness in adipocytes may be dysregulated by hypoxia. It is concluded that hypoxia induces extensive metabolic changes in adipocytes, and the need to adapt to a low O_2 tension may be a central influence on adipose tissue function. Hypoxia is likely to affect not only adipocytes, but also the macrophages and other cell types within adipose tissue. We gratefully acknowledge funding from the BBSRC (UK).

ADIPOBIOLOGY OF NERVE GROWTH FACTOR IN STRESSED AND DIABETIC RODENTS

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Nerve growth factor (NGF) is a signalling polypeptide produced by a number of different cells of mammals, man included. There is emerging evidence indicating that NGF is present also in the adipose tissue, but its possible role remains poorly investigated. We have recently reported that NGF, BDNF and leptin levels in the bloodstream, and in brain and immune cells underwent through significant changes in metabolic syndrome patients (*Prog Brain Res* 2004; 146: 279-289) and during stressful and diabetic conditions (*Neurosci Lett* 2007; 426: 39-44; *Arch Ital Biol* 2007; 145: 87-97). In the present study, we investigated whether these conditions may alter NGF presence in white subcutaneous and abdominal and brown subscapular adipose tissue, and for further understanding the possible role of adipose-derived NGF, we monitored the distribution of mast cells, a cell type known to be source of and target for NGF. Type 1 diabetes mellitus was induced in adult rats by streptozotocin treatment, and stress was induced in adult male mice by aggressive behavior due to social isolation. NGF was measured with immunoenzymatic assay and mast cell number and distribution; evaluated in serial histological sections of the adipose tissues stained with toluidine blue. The results of our study revealed that both stress and diabetes influence the presence of NGF and mast cells in adipose tissue. We also found that these experimental conditions induced mast cell degranulation, suggestive of NGF release from these cells. Altogether, a possible role of NGF in both stressful and diabetic conditions requires further adipocentric evaluations. This may contribute to the research in adipobiology of neurotrophic factors, particularly NGF, BDNF, CDNF, and metallothioneins (*Med Sci Monit* 2003; 9: HY19-21).
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ANIMAL MODELS OF OBESITY: IMPLICATIONS FOR *HOMO OBESUS*

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Many routes lead to transition from healthy to obese phenotype. Obesity is a multifactorial, low-grade chronic inflammatory disease of energy, cardiovascular and metabolic dysbalance. Hence *Homo obesus* (man the obese) is at high risk of multiple health problems. The prevalence of obesity has increased significantly over the past 25 years and it becomes a leading global health problem, affecting, for example, more than 30 % of adults in the United States with health care costs at 70-100 billion dollars a year as well as reduction in life expectancy by 5-20 years (*JAMA* 2006; 295: 1549-1555). Hence the urgent need to develop strategies to prevent and treat obesity and related cardiometabolic and other diseases is emerged. Animal models are of great importance for studying obesity-related phenomena including pathogenesis, physiologic mechanisms of food intake and energy expenditure, cardiometabolic, liver and other complications, also antiobesity drug development. In our studies, we focused on the pathogenesis of monosodium glutamate-induced obesity. In effect, the results of such studies may contribute to a better understanding of the mechanisms leading to *H. obesus* and, consequently, help for retransition to *H. sanus* (man the healthy).

CELL BIOLOGY OF HUMAN ADIPOGENESIS

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The process of adipogenesis is of great importance for the body's fat formation and deposition, and its study may contribute to a better understanding of the pathogenesis of cardiometabolic disorders including atherosclerosis, hypertension, obesity, type 2 diabetes, and the metabolic syndrome. It has been repeatedly studied *in vitro*. However, given that 3T3-L1 are of an embryonic origin, it is not clear to what extent they represent the adipogenesis in white adipose tissue. On the other hand, most of the *in vivo* investigations are on animal material and only few concern human adipose tissue. Using histochemical, enzymehistochemical, immunohistochemical and electron microscopical analyses, we follow the developmental steps of human subcutaneous adipogenesis *in situ*. The results show that it starts at 6th week of gestation, which is much earlier period than that pointed by other authors (*Early Hum Dev* 1984; 10: 1-11, *ibid* 1992; 28: 79-88). The differentiating human embryonal adipose cells possess specific features as accumulation of lipid droplets; positive activity for the lipogenic enzymes, especially lipoprotein lipase; positive expression of leptin and S-100. These characteristics can be accepted as early and decisive criteria of adipogenesis. Being not typical for the other cells present in the embryonal subcutis, they help to distinguish the earliest preadipocyte as well as its origin, supporting the hypothesis that adipocytes may directly originate from mesenchymal cells via own progenitors, apart from fibroblasts and vascular cells. During early human embryogenesis, leptin acts as an important hormonal factor regulating adipocyte growth and development. Further studies are required to molecularly dissect the puzzle of human adipogenesis.

NEURAL EXPRESSION OF THE FREE FATTY ACID RECEPTOR GPR40

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The G-protein coupled receptor 40 (GRP40) is a transmembrane receptor for free fatty acids, and is known for its relation to insulin secretion in the pancreas. Recent studies demonstrated that spatial memory and hippocampal long-term potentiation of rodents and cognitive function of humans are improved by a dietary supplementation of with arachidonic and/or docosahexaenoic acids, which are possible ligands for GPR40. While free fatty acid effects on the brain might be related to GPR40 activation, the role of GPR40 in the central nervous system (CNS) is at present not known. Here we studied expression and distribution of GPR40 in CNS of adult monkeys by immunoblotting and immunohistochemstry. Immunoblotting analysis showed a band of approximately 31 kD consistent with the size of GPR40 protein. GPR40 immunoreactivity of was observed in the nuclei and/or perikarya of a wide variety of neurons including neurons in the cerebral cortex, hippocampus, amygdala, hypothalamus, cerebellum, and spinal cord. We also studied the expression of GPR40 in the progenitor cell niche of the adult monkey hippocampus under normal and postischemic conditions. Confocal analysis of immunostained sections revealed GPR40 immunoreactivity in neural progenitors, immature neurons, astrocytes and endothelial cells of the subgranular zone (SGZ) of the dentate gyrus, a well-known neurogenic niche within the adult brain. Immunoblotting analysis showed that the GPR40 protein increased significantly in the second week after global cerebral ischemia as compared to the control. This was compatible with the postischemic increment of GPR40-positive cells in SGZ as detected by immunohistochemistry. Taken together with our previous findings of SGZ progenitor cell upregulation in the second postischemic week, the presented in this study data suggest that certain free fatty acids may act via GPR40 to regulate adult hippocampal neurogenesis after ischemia in monkeys. Our results provide a morphological basis for clarifying the role of GPR40 in the adult primate CNS.

OBESITY AND DIABETES: THE GUT-FAT-BRAIN AXIS

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Obesity represents the single most important contributor to type 2 diabetes mellitus (T2DM) risk, with adipose tissue (AT) currently perceived as an important site of overlapping metabolic and immune function. Within this, AT is also recognised as an endocrine organ, with the ability to have adverse effects on other organs due, in part, to adipokines, which directly influence the brain, liver, heart, and skeletal muscle. Furthermore, the recognition that AT may have an inflammatory role, as adipocytes contain many components of the innate immune pathway, offers further possibilities for relating obesity with chronic subclinical inflammation. In addition to this, it is clear that the functionality of AT, affected by fat distribution, age, gender, menopausal status and disease state, alters many metabolic pathways and can give a better understanding as to the importance of human AT within the context of health and disease. Further, there is clear cross talk between the gut, fat and brain. Our studies show the effect of ghrelin on AT secretion of leptin, NPY and CGRP. Also, serum/CSF studies highlighting that adipokines besides leptin may also cross the blood brain barrier with potential effects on satiety. The relationships between organ cross talk are complex and our recent studies have explored the role of gut-derived bacterial endotoxin, lipopolysaccharide (LPS), as a source of inflammation in disease states. Such studies have therefore ascertained whether LPS derived from the human gastrointestinal tract, may contribute directly to systemic inflammation and thus the pathogenesis of T2DM and/or Fatty liver disease (FLD). Analysis of serum bacterial endotoxin has shown significantly higher levels in T2DM patients compared with controls, and correlated positively with fasting insulin in both groups. Serum endotoxin was also noted to correlate positively with the pro-inflammatory cytokine, TNF-α, in the T2DM subjects. In addition, endotoxin levels were significantly higher in patients with FLD compared with non-diabetic subjects, whilst FLD alone produced comparable endotoxin levels to T2DM. As these studies indicated a gut-derived mediator for subclinical inflammation, and that hyperinsulinaemia may alter gut permeability to increase endotoxin load. Our studies have also shown that the innate immune pathway in human AT may provide a mechanism for LPS to mediate an inflammatory response via two pathways, NFκB and c-Jun kinase. Regulation occurs via a positive feed-forward mechanism producing adipokines, whilst the release of the anti-inflammatory adipokine, adiponectin, is reduced. These studies have thus far highlighted the intracellular pathways involved in metabolic disease, focussing on the need to look beyond cells or individual cellular systems to understanding the interaction between organs. Research, such as this will help define appropriate therapeutic intervention and drug targets for future therapy directed at AT.

OXIDATIVE STRESS AND ENDOTHELIAL (DYS)FUNCTION: THERAPEUTIC INTERVENTIONS WITH ANTIOXIDANTS

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The consequences of endothelial dysfunction represents a leading cause of death in western countries, as well as in Serbia. Though medical and social impact of this problem is increased, precise pathogenic mechanisms, possible therapeutic interventions and prevention are not clarified. It is well known that patients with increased low-density lipoproteins (LDL) fraction of total cholesterol possess high risk for possible coronary vascular event or stroke, what "accused" LDL

as very atherogenic molecule. However, LDL *per se* is not so atherogenic, as its oxidative modification, that is, oxLDL, delivered by damaged vascular wall. Vascular cell components, including macrophages, and oxidative stress are included in these pathogenic events. OxLDL is recognized by specific macrophage receptors, which internalized OxLDL and thus transformed macrophages into foam cell. We tried to connect our basic experiments in isolated heart with some clinical events where oxidative stress is involved. One part of our basic investigation was to assess the effects of vitamin C and folic acid on coronary flow (CF) and nitrite outflow (NO) alone or under inhibition of nitric oxide synthase (NOS) in isolated rat heart. The hearts of male Wistar albino rats (n=12, 8 week old, BW 80-200 g) were perfused according to Langendorff technique at constant perfusion pressure conditions (CPP, 40-120 cm H_2O). The experiments were performed during control conditions, in the presence of (i) vitamin C (100 μM) or vitamin C plus L-NAME (30 μM), and (ii) folic acid (100 μM) or folic acid plus L-NAME. The results showed that applied vitamins have different effects on isolated rat heart and opposite interaction with NOS-NO system. On the other hand, the aim of our clinical study was to examine parameters of oxidative stress and its response on different types of supplementation in top sportsmen. The testing was made in 43 top-level competitors in rowing (n=13), cycling (n=10) and taekwondo sport (n=20). All sportsmen were selected for the national teams according to the selection criteria. Different type of supplementation at all sportsmen has not statistically significant difference in dynamic of parameters of oxidative stress at rowers and cyclists in dependence of applied therapy, while in taekwondo existed statistically significant difference in concentration of thiobarbituric acid reactive substances, which suggest us that the type of sport and training activity (anaerobic compared to aerobic) affects oxidative stress, as well as on its dynamic in sternous exercise. Further studies may bring more light into the role of endothelial (dys)function and its possible interactive play with adipose (dys)function (Tonchev *et al*, this Symposium) in health and disease. Supported by Ministry of Science and Environmental Protection, Republic of Serbia (Number 145014).

PREDICTIVE PHARMACOGENOMICS: EXAMPLES FROM DRUG METABOLISM AND TOXICITY

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Pharmacogenomics is a new scientific approach serving to identify some genetic differences in human body in order to develop and tailor new drugs. The practical aim is to develop real "individual" pharmacotherapy by maximizing drug efficacy and minimizing drug toxicity. That needs better knowledge of individual's as well as of drug metabolic "profile". Here some methodological as well as practical examples will be given from the last achievements in genetic differences of drug metabolizing enzymes system and the resulting differences in drug effects and toxicity. Pharmaceuticals and nutraceuticals will be more personalized in the future. Slight genetic differences - sometimes as small as a change in a single base pair - can affect the way an individual metabolizes drugs. Pharmacogenomics will identify the patient population most likely to benefit from a given medication. Personalized medicine will replace the traditional trial-and-error practice of medicine.

ROLE OF REACTIVE OXYGEN SPECIES AND EXTRACELLULAR SIGNAL-REGULATED KINASES (ERK) IN LEPTIN-INDUCED HYPERTENSION

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We investigated if extracellular signal-regulated kinases (ERK) and oxidative stress are involved in the pathogenesis of arterial hypertension induced by chronic leptin administration in the rat. Leptin was administered at a dose of 0.25 mg/kg twice daily s.c. for 4 or 8 days. Leptin increased blood pressure (BP) since 3rd day of the experiment. Superoxide dismutase (SOD) mimetic, tempol, normalized BP in leptin-treated rats on days 6, 7 and 8, whereas ERK inhibitor, PD98059, exerted a hypotensive effect on days 3 through 6. Leptin increased ERK phosphorylation in renal and aortic tissues more markedly after 4 than after 8 days. In addition, leptin reduced urinary Na^+ excretion and increased renal Na^+, K^+-ATPase activity, and these effects were abolished on days 4 and 8 by PD98059 and tempol, respectively. The levels of nitric oxide (NO) metabolites and cGMP were reduced in animals receiving leptin for 8 but not for 4 days. Markers of oxidative stress (H_2O_2 and lipid peroxidation products) were elevated to a greater extent after 4 than after 8 days of leptin treatment. In contrast, nitrotyrosine, a marker of protein nitration by peroxynitrite, was higher in animals receiving leptin for 8 days. NADPH oxidase inhibitor, apocynin, prevented leptin's effect on blood pressure, ERK, Na^+, K^+-ATPase/Na^+ excretion and NO formation at all time points. SOD and glutathione peroxidase (GPx) activities in renal and aortic tissues were reduced in group treated with leptin for 8 days. These data indicate that (i) ERK, activated by oxidative stress, are involved only in early phase of leptin-induced BP elevation, (ii) later phase of leptin-induced hypertension is characterized by excessive NO inactivation by superoxide, and (iii) time-dependent shift from ERK to O_2^--NO dependent mechanism may be associated with reduced SOD/GPx ratio, which favors formation of O_2^- instead of H_2O_2.

ADIPOTOPOGRAPHY: TOFI *VERSUS* TOTI, OR A HIDDEN *HOMO OBESUS*

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In humans, white adipose tissue is partitioned into a few large depots, including visceral and subcutaneous location, and many small depots associated with heart, blood vessels, lymph nodes, ovaries, eyes, kidneys, adrenal glands, also located in liver, skeletal muscles and mammary glands. Recently, it is increasingly known that adipose tissue is an endocrine organ producing more than 100 types of biologically active proteins (adipokines). Accordingly, *Homo obesus* is currently viewed as a disorder triggering the pathogenesis of a variety of cardiometabolic, liver, ovary, lung, and mental (e.g. Alzheimer's disease) disorders (*Curr Pharm Des* 2007; 13: 2176-2179). Adipotopography (fat mapping) is an emerging subfield of adipobiology dealing with localization and amount of adipose tissue in the human's body. Thus people may express TOFI, TOTI or other phenotypes (Table).

Table. *Adipotopography (fat mapping): variations+*

TOFI**	thin outside, fat inside
TOTI*****	thin outside, thin inside
FOFI*	fat outside, fat inside
FOTI***	fat outside, thin inside

+ The number of asterisks indicates quality of cardiometabolic health, as related to adipose tissue. Hence, stay TOTI!

TOFI (Thin Outside, Fat Inside) was described by Dr Jimmy Bell, head of the Molecular Imaging Group at Hammersmith Hospital, London, UK. We dubbed that a hidden phenotype of *H. obesus*. It can be visualized by using current imaging technologies such as echography, computed tomography, magnetic resonance imaging, and proton magnetic resonance spectroscopy. A predictive message of adipotopography is that "being thin does not automatically mean you are not fat." The concept of TOFI holds that small adipose depots, when enlarged and activated (by inflammatory, overnutritional or other stimuli), may exert disease-promoting actions over adipose tissue-associated organ(s). Thus, the traditional diagnostic significance of BMI, as well as other anthropometric criteria (waist and hip circumference alike), should be re-evaluated in obesity and related diseases. Importantly, dieting is enough to keep one being thin outside (TO), whereas physical activity prevents the accumulation of internal fat, thus one being thin inside (TI), hence TOTI. In conclusion, TOFI is a Trojan Horse inside the human's body, a pathological phenomenon, whereas TOTI is a healthy adipose phenotype. Briefly, slim or obese, get your fat map.

TUNICA ADIPOSA: FROM ENDOTHELIAL TO ADIPOSE DYSFUNCTION IN CARDIOMETABOLIC DISEASE

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A long standing paradigm holds that the vascular wall consists of three coats: *tunica intima*, *t. media,* and *t. adventitia*. In cardiometabolic diseases such as atherosclerosis, hypertension, obesity, diabetes and the metabolic syndrome, endothelial and adventitial dysfunctions are widely studied. However, a paradigm shift comes of age: adipose tissue can express not only metabolic, but also secretory phenotype, particularly in the adipobiology of disease. We focus here on adventitia and periadventitial adipose tissue (PAAT) of human coronary arteries obtained from autopsies and during surgery, and conceptualize that PAAT may indeed be the forth, outermost vascular coat, hence, *t. adiposa*. By analogy with "endothelial dysfunction", we introduce the term "adipose dysfunction". Importantly, PAAT as well as epicardial adipose tissue produce various adipokines and other factors exerting protective (adiponectin, IL-10, IL-1Ra, NGF, metallothioneins, NO) and pathological (TNF-α, IL-1,-6,-18, PAI-1, MCP-1, ROS) actions. Altogether, our "friend-and-foe" hypothesis of *t. adiposa* may further prompt research efforts in basic, translational and clinical vascular adipobiology. Keeping in mind that we should no longer, as hitherto, cut *t. adiposa* from the artery wall, but keep it attached and in place, and subject to thorough examination, "no-touch harvesting technique" in coronary artery bypass surgery being a clinical example of such an "adipoprotective" approach. Likewise, imaging methods such as echocardiography and MRI are becoming useful tools in clinical evaluation of cardiovascular adipose tissue. Our ongoing cell culture studies may shed further light into this matter of adipobiology.

Dedicated to the memory of our big friend, Dr Ivan S. Stankulov (1944-2007).