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Adipose Tissue and Skeletal Muscle Plasticity in Obesity and Metabolic Disease

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1. Introduction

Obesity and lack of physical activity are two major factors contributing considerably to the pathogenesis of many chronic diseases so prevalent in contemporary human population. Adipose tissue and skeletal muscle are therefore the primary organs one would immediately suggest to target in an attempt to battle metabolic disease progression. Fine tuning of the physiological processes within the two organs have a large potential to modulate (i) energy balance, (ii) lipid storage-utilization efficiency as well as (iii) central and peripheral actions in the brain, gastrointestinal system or liver which are integrated by the endocrine activity of the two energy balance maintaining tissues.

2. Adipose tissue in metabolic health and disease

Despite the fact that the primary role of adipose tissue is an effective lipid storage and timely regulation of its release and that these processes could, in a simplified adipocentric view, be the primary determinants of the dyslipidemia and metabolic disease progression, adipose tissue has a broad range of other regulatory functions exerted *via* its autocrine, paracrine and endocrine actions. Adipose tissue secretory products, "adipokines", could modulate food intake, energy expenditure, or tissue oxidative capacity (Trayhurn et al. 1998; Ukropec et al. 2001; Ahima & Lazar 2008; Henry & Clarke 2008; Friedman 2011). In addition, adipose tissue dynamically changes its structure (*tissue remodeling, lipid composition*), function (*lipid storage & lipolysis*) as well as endocrine action in response to different physiological (*fasting / refeeding, exercise, microgravity*) and pathophysiological (*obesity, prediabetes, diabetes, cachexia, lipodystrophy, growth hormone deficiency*) conditions (Ukropec et al. 2008; Itoh et al. 2011; Pietilainen et al. 2011). It is important to understand that adipose tissue is a mixture of very different cell-types. Apart from approximately 50% of mature lipid-laden adipocytes it contains various stromal cells including preadipocytes, endothelial cells, fibroblasts, pluripotent stem cells and immune cells which substantially influence its function (Bjorntorp 1974; Sethi & Vidal-Puig 2007; Divoux & Clement 2011). Extreme enlargement of the fat cell size, such as we have recently observed in individuals with growth hormone deficiency, is perhaps the best early marker of the obesity related - metabolic disease development (Ukropec et al. 2008a) (Fig. 1.). Adipose tissue with enlarged adipocytes, expressing markers of the local tissue microhypoxia but not responding to it

properly and attracting large amount of activated immunocompetent cells, has recently been termed "pathogenic adipose tissue" (Bays et al. 2008; Ukropec et al. 2008b).
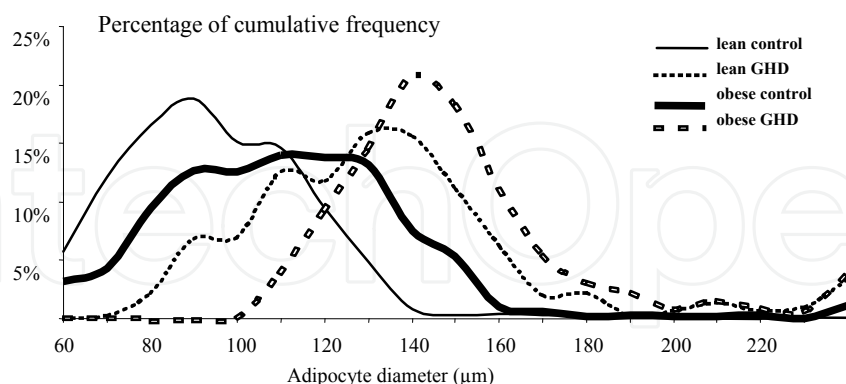

Fig. 1. Fat cell size in obesity and in growth hormone deficiency (GHD), percentage of cumulative frequency (Y axis), (Ukropec et al. 2008a).

The tissue damage due to overwhelming adipocytes with lipids, largely exceeding their lipid storage capacity, changes the adipokine secretory profile and leads to uncontrolled release of a large amount of lipids into circulation while the capacity of the adipose tissue adaptive remodeling is compromised. This is followed by the accumulation of lipids in tissues not designed for the lipid storage such as liver, skeletal muscle, pancreatic beta cells or lung which largely interferes with their physiological functions and accelerates the development of metabolic disease (Bays et al. 2008; Foster et al. 2010; Unger et al. 2010). Limited expandability of the adipose tissue seems to determine individual propensity to the development of metabolic disease (Arner, P. et al. 2011). Adaptive expansion of the adipose tissue is enabled by combination of adipocyte hypertrophy and hyperplasia. Expansion of adipose tissue requires quite extensive tissue remodeling, in order to maintain adequate energy and oxygen supply, active neuronal network as well as integrity and functional properties of cellular membranes (Itoh et al. 2011; Pietilainen et al. 2011). Broader knowledge of the fat cell life-cycle dynamics is critical for our understanding the pathophysiological mechanisms limiting adipose tissue hyperplastic expansion. In 2008, Arner's group analyzed the adipocyte turnover by detecting the genomic DNA incorporation of atmospheric ^{14}C derived from above-ground nuclear bomb tests in period between 1955 and 1963. This work revealed that approximately 10% of fat cells are renewed per year at all adult ages and levels of BMI and that neither adipocyte death nor generation rate is altered in early onset obesity. It seemed that the steady production of adipocytes in adults results in a stable size of the constantly turning over adipocyte population (Spalding et al. 2008). More recent work by these authors examining morphology of the subcutaneous adipose tissue from 764 individuals with broad range of BMI (18-60 kg.m[2]) defines hyperplasia and hypertrophy as a difference between measured adipocyte volume and volume predicted by the curve-like fit, for adipocyte volume and body fat mass (Fig. 2.). In this analysis occurrence of hyperplasia or hypertrophy correlated with fasting plasma insulin and insulin sensitivity. In addition, total adipocyte number was greatest in individuals with pronounced hyperplasia, and smallest in those with pronounced hypertrophy. The absolute number of new adipocytes generated each year was 70% lower in patients with hypertrophy than with hyperplasia. Whereas the relative death rate (~ 10% per year) or mean age of adipocytes (~ 10 years) was not correlated with adipocyte morphology (Arner, E. et al. 2010).
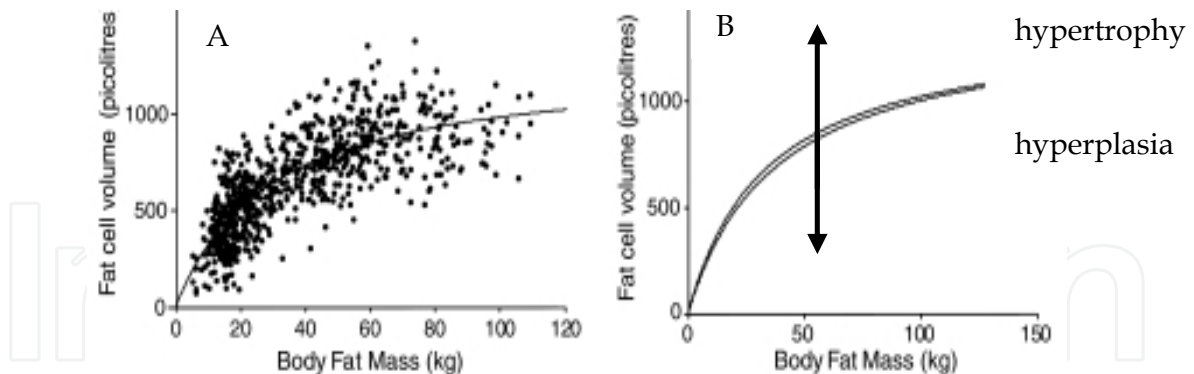
Fig. 2. (A) Graph depicts large variability in adipose tissue morphology in individuals with identical body fat mass (764 subjects). (B) Level of hyperplasia is represented by adequately lowered morphology value while hypertrophy is associated with parallel increase in morphology value defined as a difference between measured and expected adipocyte volume given by the curve-like fit , for given body fat mass (Arner, E. et al. 2010).

Insulin sensitivity could therefore govern adipose tissue morphology towards beneficial hyperplastic state at the population level. Conversely, defects in insulin action are interconnected with the hypertrophic adipocytes, and higher risk of lipid flooding the nonadipose tissues. Absolute numbers of adipocytes as well as their capacity to expand and store lipids are quite difficult to modulate. Morbid obesity and lipodystrophy represent the two medical conditions associated with excessive hypertriglyceridemia, hepatic steatosis, and disordered muscle glucose metabolism, due to defected ability of adipose tissue to store lipids or the selective loss of adipose tissue respectively. Activation of adipogenic programme by PPARγ agonists or chronic leptin treatment improves insulin-stimulated hepatic and peripheral glucose metabolism in obese and lipodystrophic patients respectively (Petersen et al. 2002; Rieusset et al. 2002; Van Gaal et al. 2003). Adipogenesis is necessary to increase the adipose tissue cellularity (hyperplastic adaptive change) and lipid storage capacity; it is largely dependent on the signal transducers and activators of transcription (STAT) pathway. In brief, transcription factors C/EBPα, C/EBPβ, and PPARγ control adipogenesis by regulating STAT5B and STAT5A. Regulation of PPARγ-STAT5 by C/EBPβ signaling seems to be the crucial adipogenesis - initiating cascade of the various adipogenic genes (Jung et al. 2011). Activation of adipogenic program should be paralleled with the extracellular matrix remodeling. As mentioned above, adipocytes are embedded in a unique extracellular matrix which main function is to provide mechanical support, in addition to participating in a variety of signaling events. Extracellular matrix requires remodeling to accommodate growing adipocytes in the expanding adipose tissue. We have recently participated in the research by Christian Wolfrum's laboratory investigating regulatory processes related to adipose tissue hyperplasia. In this work, the transcription factor retinoid-related orphan receptor γ (RORγ) was identified as an important regulator of adipocyte development through regulation of its newly identified target gene matrix metallopeptidase-3. RORγ might serve as a novel predictor for the risk of metabolic complications in obesity as well as a pharmaceutical target for the treatment of obesity-associated diseases (Meissburger et al. 2011).

Khan et al., recently proposed that "adipose tissue fibrosis" is a hallmark of metabolically challenged adipocytes. Authors observed that the absence of collagen VI, the highly enriched extracellular matrix component of adipose tissue, results in the uninhibited expansion of individual adipocytes, which is paradoxically associated with substantial improvements in whole-body energy homeostasis, both with high-fat diet exposure and in the ob/ob background. Weakening the extracellular scaffold of adipocytes seems to enable their stress-free expansion during states of positive energy balance, which is consequently associated with an improved inflammatory profile (Khan et al. 2009). Further support to the notion that metabolic deregulation is rather due to lipid-leakage than the adipocyte hypertrophy *per se* comes from the experiment where mice lacking leptin were made to overexpress adiponectin. This led to the modest increase in circulating levels of full-length adiponectin and to subsequent normalization of glucose and insulin levels, dramatic improvement of glucose tolerance and positive effect on serum triglyceride levels. Adiponectin in fact completely rescued the diabetic phenotype in ob/ob mice. These mice displayed increased expression of PPARγ target genes and a reduction in macrophage infiltration in adipose tissue and systemic inflammation. Adiponectin expressing ob/ob mice, however, were morbidly obese, with significantly higher levels of adiposity and adipocyte hypertrophy than their ob/ob littermates. Adiponectin seems to act as a peripheral "starvation" signal promoting the storage of triglycerides preferentially in adipose tissue. As a consequence, reduced triglyceride levels in the liver and muscle convey improved systemic insulin sensitivity despite adipocyte hypertrophy (Kim et al. 2007).

2.1 Specificities of subcutaneous and visceral adipose tissue

In contrast to visceral adipose tissue, which is often blamed from inducing detrimental metabolic effects, subcutaneous adipose tissue has the potential to benefit lipid and glucose metabolism. It has been repeatedly shown that differences in regional body fat distribution determine the propensity for the development of obesity related metabolic complications (Tchernof 2007). Accumulation of fat in the visceral region (mesentery, omentum, retroperitoneum), that in fact corresponds to central obesity (determined by increased waist circumference) is associated with cardiovascular disease and type 2 diabetes, independently on overall obesity (Wajchenberg 2000; Hamdy et al. 2006; Pischon et al. 2008). The amount of visceral fat increases with age in both genders but man in general have greater visceral adiposity than women (Wajchenberg 2000). Consistent with this notion, removal of visceral adipose tissue (omentectomy) decreases glucose and insulin levels in humans (Thorne et al. 2002). By contrast peripheral obesity – increased subcutaneous adipose tissue mass, mainly in the region of buttock and thighs seem to be associated with improved insulin sensitivity and lower risk for type 2 diabetes mellitus (Snijder et al. 2003; Koska et al. 2008). One possible explanation for the detrimental effect of visceral fat accumulation comes from its unfortunate anatomical location (Arner, P. 1998; Bergman et al. 2006), but second theory based on adipose tissue transplantation experiments blames rather the tissue internal properties such as unfavorable secretory profile (Matsuzawa et al. 1999).

Adipose tissue transplantation experiments have been primarily used as a tool to study physiology for human reconstructive surgery, but they provide important information on differences between visceral and subcutaneous adipose tissue which opens the vision of the adipose tissue or adipose tissue derived stem cells transplantation for the treatment of obesity and metabolic disorders.

2.2 Brown adipose tissue in human physiology

Humans and other mammals have two types of adipose tissue that contribute to control of the whole body energy metabolism. The above discussed white adipose tissue, "the bad guy" associated with obesity, is necessary for energy storage. Brown adipose, "the good guy", contains a lots of mitochondria and is ready to burn energy to generate heat in response to cold or dietary intake, keeping the body warm and slim (Cannon & Nedergaard 2004). Until recently, physiologically relevant amount of brown fat was only found in newborns. However, accumulating evidence indicates that adult humans – or at least significant portion of us retain physiologically relevant amount of brown fat (van Marken Lichtenbelt et al. 2009; Vijgen et al. 2011; Virtanen & Nuutila 2011). This provides an exciting possibility to precisely regulate the adaptive thermogenic process in humans, which could dissipate energy and lower the obesity related metabolic burden. Brown adipose tissue activity in humans was determined with the aid of ^{18}F-fluorodeoxyglucose positron-emission tomography and computing tomography mainly in the supraclavicular region of cold-exposed individuals. Importantly, specimens of the adipose tissue from the supraclavicular region of adult humans with active brown adipose tissue were positive for UCP1 protein (Fig. 3.) (van Marken Lichtenbelt et al. 2009; Zingaretti et al. 2009). Vision of translating this knowledge into the clinical practice is quite reachable (Nedergaard & Cannon 2010; Tseng et al. 2010). Clinical importance could be significant, despite the fact that the volume of active brown adipose tissue tends to be lower in the overweight or obese than in the lean individuals (van Marken Lichtenbelt et al. 2009), and that it decreases with age (Cypess et al. 2009). Interestingly, applying the personalized cooling protocol for maximal nonshivering conditions to morbidly obese individuals could still increase brown adipose tissue activity (Vijgen et al. 2011).
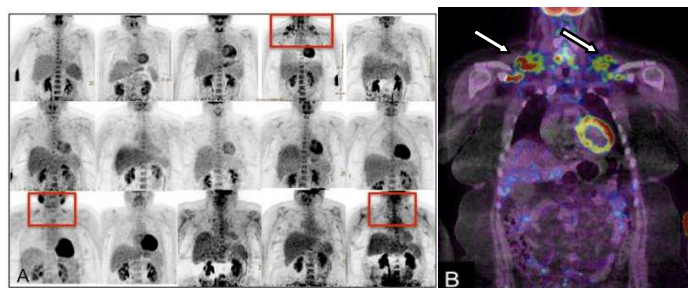

Fig. 3. Metabolically activated brown adipose tissue in supraclavicular region (arrows, B) in morbidly obese individuals after personalized cooling protocol (Vijgen et al. 2011).

2.3 Metabolic activation of the white adipose tissue

It has recently been shown that brown adipocytes and muscle cells share the common origin and in this respect they are quite distinct from white adipocytes (Tseng et al. 2008; Seale & Lazar 2009). The question remains, what is the origin of "brown fat-like white (brite) " adipocytes containing UCP1 which could be induced in white fat depots under certain pohysiological (cold exposure) (Fig. 4.) or pharmacological (activation of SNS, agonists of PPARγ) conditions (Granneman et al. 2005; Li et al. 2005; Ukropec et al. 2006). Nedegaard`s laboratory had recently reported that chronic treatment with the PPARγ agonist rosiglitazone promotes not only the expression of PGC1α and mitochondriogenesis but also a catecholamine – inducible UCP1 gene expression in a significant subset of the white adipocytes, giving them the genuine, thermogenic capacity.
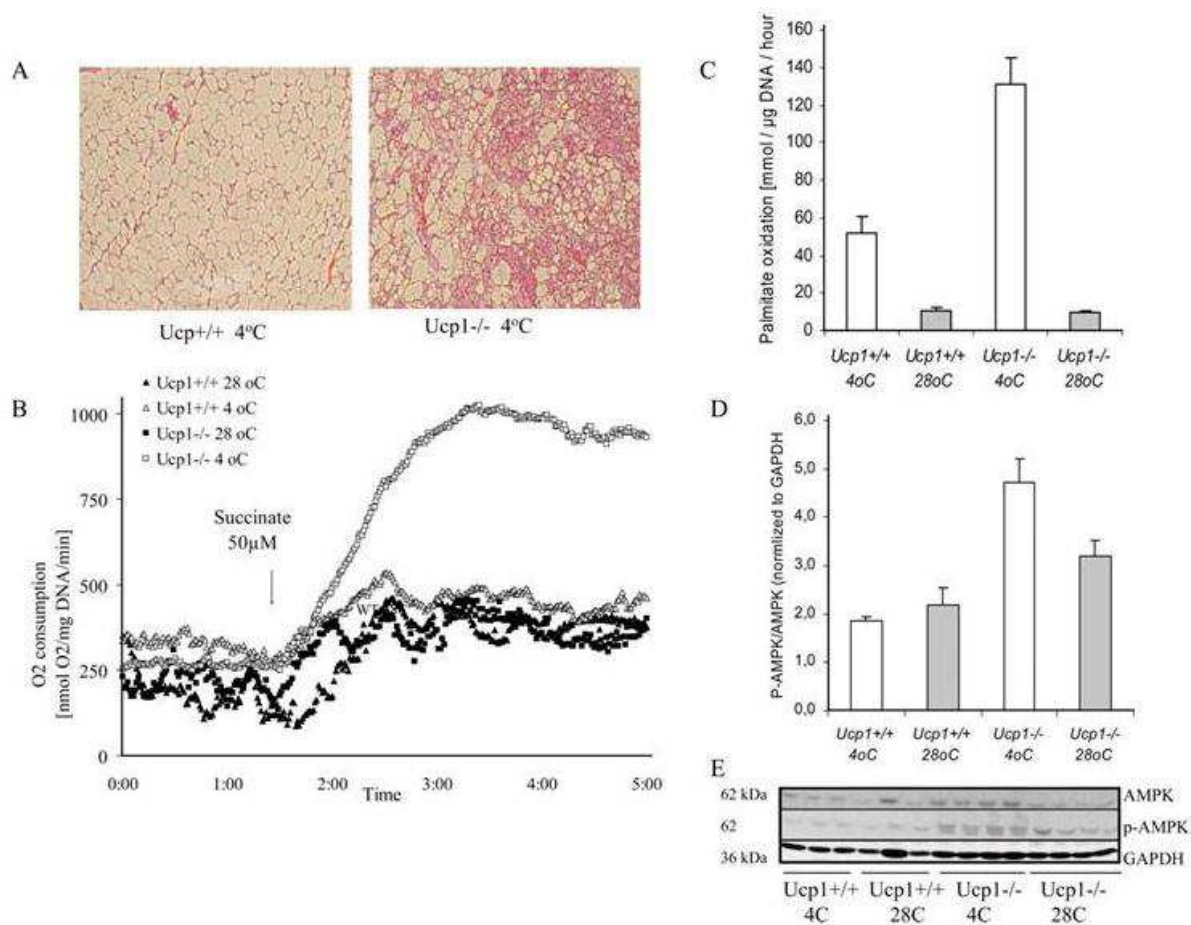
Fig. 4. Metabolically activated "brite adipocytes" as found in inguinal white adipose tissue of mice lacking the UCP1-thermogenesis after gradual exposure to cold.
(**A**) histomorphology, (**B**) O_2 consumption by oxymetry, (**C**) adipose tissue *ex vivo* palmitate oxidation, (**D&E**) evidence for AMPK activation (Ukropec et al. 2006).

In collaboration with laboratory of dr. Kvatnansky we have recently observed that catecholamines, important regulators of lipolysis in adipose tissue, could be produced within adipocytes. Adipocytes isolated from mesenteric adipose tissue expressed genes encoding the catecholamine biosynthetic enzymes and produced catecholamines *de novo*. Administration of tyrosine hydroxylase inhibitor, alpha-methyl-p-tyrosine, significantly reduced concentration of catecholamines in isolated adipocytes *in vitro* (Fig. 5.). We therefore hypothesized that the sympathetic innervation of adipose tissue is not the only source of catecholamines and that adipocyte-derived catecholamines could dynamically modulate metabolic or thermogenic properties of the white adipose tissue perhaps by enhancing "brite adipocyte" function (Vargovic et al. 2011).

3. Adipocentric view on the pathophysiology of metabolic disease

The prevalence of obesity and its consequent pathologies in modern society is of serious health concern. Although the expansion of adipose tissue mass during pathological obesity is in itself not a grave problem, rather it is the ensuing pathologies resultant of this state, including development of hypertension, type 2 diabetes and cardiac myopathies, that impacts peoples lives and health services worldwide.

Clearly not all obese individuals develop metabolic and cardiovascular complications; here we discuss several regulatory mechanisms representing a base for the strategies to prevent metabolic disease development.
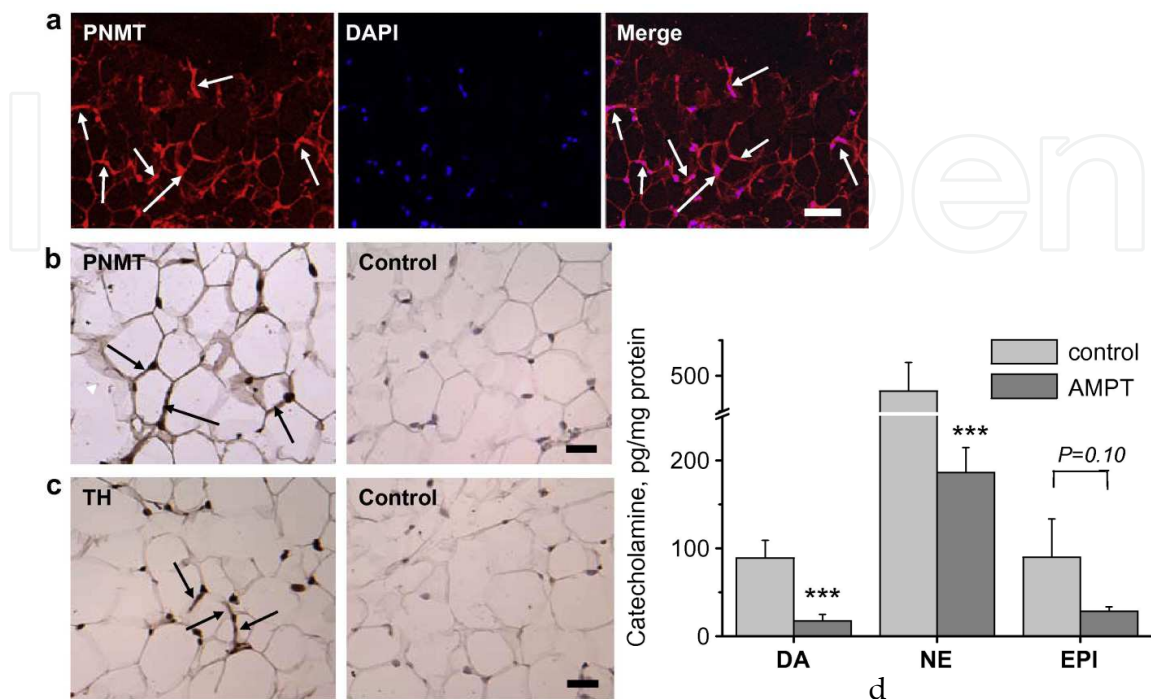

Fig. 5. Adipocytes have internal catecholamine production capacity. Adipose tissue contains mRNA and proteins specific for tyrosine hydroxylase (TH) and phenylethanolamine N-methyltransferase PNMT as shown on histological sections probed with specific PNMT (**a,b**) and TH (**c**) antibodies, scale bar: 20 μm. (**d**) Adipocytes freshly isolated from mesenteric adipose tissue produce dopamine (DA), norepinephrine (NE) and epinephrine (EPI) into the media. Production of catecholamines is largely inhibited by addition of alpha-methyl-p-tyrosine (AMPT) – competitive inhibitor of TH activity (Vargovic et al. 2011).

3.1 Hypoxia

Hypothesis that adipose tissue populated by large adipocytes contains the local microhypoxia suffering areas, which has a profound effect on the tissue metabolic and inflammatory phenotype, has been largely accepted. Hypoxia is one of the major triggers strongly inhibiting adipocyte differentiation. Tissue hypoxia in obesity is associated with the defects in the nutrient and oxygen supply into the tissue, related to a defective blood flow regulation which might be perpetuated by the increased fat cell size (Yun et al. 2002). This is happening in spite of the almost unlimited capacity of adipose tissue to expand in a non-transformed form, which is a very unique property of adipose tissue that cannot be seen in any other organ. To accomplish this adipose tissue requires potent mechanisms to remodel, acutely and chronically, as it can rapidly reach the diffusional limit of oxygen; molecular response to hypoxia is therefore an early determinant that limits healthy adipose tissue expansion. Proper expansion requires a highly coordinated response among many different cell types, including endothelial precursor cells, immune cells, and preadipocytes (Sun et al. 2011). It has also been demonstrated that mitochondrial oxidative apparatus is essential for the white fat adipocyte differentiation (De Pauw et al. 2009). Beside their key role in ATP

production, mitochondria constitute the primary source of reactive oxygen species (ROS), which have a great potential to influence the tissue plasticity.

ROS are not only considered a negative factors contributing to degenerative processes and ageing, but also a physiological signal molecules participating in the oxygen sensing mechanisms (Chandel & Budinger 2007). Mitochondrial ROS production influences the size of the white adipocytes, and ROS are in fact antiadipogenic signaling molecules triggering the hypoxia-dependent inhibition of adipocyte differentiation (Carriere et al. 2004). In addition, decreased oxygen availability stimulates the programming of cellular metabolism towards increased glycolysis and fatty acid and triacylglyceride synthesis (Halperin et al. 1969; Kinnula et al. 1978). Hypoxia-inducible factor (HIF), dimers composed of HIF1α, HIF2α or HIF3α (collectively HIFα) and HIF1β/ARNT subunits, play a key role in the coordination of these metabolic adaptations (Trayhurn et al. 2008; Krishnan et al. 2009). HIFα subunits are constitutively expressed but degraded under normoxia due to prolyl hydroxylase activity, which marks them for recognition by the von Hippel-Lindau (VHL) tumor suppressor protein pVHL, that acts as part of an E3 ubiquitin ligase complex to target HIFα subunit for proteasomal degradation. Loss of pVHL function or hypoxia leads to accumulation of HIFα, dimerization with HIFα/ARNT and the activation of numerous hypoxia-inducible genes (Krek 2000; Semenza 2001). Previous work by Krek`s laboratory provided the seminal observation that hypoxia activated pVHL and HIF1α oxygen sensing system affects normal physiological function of heart and pancreatic beta cells by triggering the changes in the glucose and fatty acid metabolism (Zehetner et al. 2008; Krishnan et al. 2009). Interestingly, hypoxia present in atherosclerotic lesions contributes to the pro-inflammatory lipid-loaded foam cells formation, as it decreases expression of enzymes involved in β-oxidation and increases expression of enzymes related to fatty acid synthesis and lipid droplet formation. The aforementioned processes possibly stimulate progression of the atherosclerotic plaque formation (Bostrom et al. 2007). Finally, tissue hypoxia largely modulates adipocytokine production and possibly contributes to the adipose tissue inflammation in obesity (Hosogai et al. 2007; Wang et al. 2007; Ukropec et al. 2008).

3.2 Inflammation – Macrophage, adipocyte and preadipocyte plasticity

Chronic low level of inflammation present in the "pathogenic" adipose tissue has been found to have adverse effects on the adipose tissue physiological functions contributing thus to the metabolic disease. It has been shown that increase in both body fat mass and adipocyte cell size are directly related to the number of macrophages found in the adipose tissue (Wellen & Hotamisligil 2005; Weisberg et al. 2006; Goossens 2008). A net pro-inflammatory response of the adipose tissue may result from adipose tissue secretion of pro-inflammatory factors; adipose tissue secretion of factors that stimulate other tissues to produce inflammatory factors; and decreased production of anti-inflammatory factors. Although the contribution of specific cell types to inflammation is uncertain, evidence is mounting that implicates adipose tissue macrophages as the significant contributor to inflammation in insulin resistant adipose tissue (Kanda et al. 2006; Neels & Olefsky 2006). There are controversial reports related to the importance of the CC chemokine ligand 2 (CCL2, monocyte chemoattractant protein-1) for the macrophage-recruitment and activation in obesity (Kamei et al. 2006; Inouye et al. 2007). Interestingly CCL2 has also been proposed to affect metabolism independently of its macrophage-recruiting capabilities (Inouye et al. 2007). There is also preliminary data indicating that the tissue infiltration by macrophages

depends upon the expression of osteopontin, an extracellular matrix protein and pro-inflammatory cytokine which promotes the monocyte chemotaxis and cell motility. Mice exposed to a high-fat diet exhibited increased plasma osteopontin level, and elevated expression of osteopontin in macrophages recruited into adipose tissue. In addition, obese mice lacking osteopontin displayed improved insulin sensitivity in the absence of an effect on the diet-induced obesity, body composition or energy expenditure. These mice further demonstrated decreased macrophage infiltration into adipose tissue, which may reflect both impaired macrophage motility and attenuated monocyte recruitment by stromal vascular cells. Finally, obese osteopontin-deficient mice exhibited decreased markers of inflammation, both in adipose tissue and systemically (Nomiyama et al. 2007).

Adipose tissue resident macrophages show significant heterogeneity in their properties and activation state, reflecting the local metabolic and immune microenvironment (Gordon & Taylor 2005). Different stimuli activate macrophages to express distinct patterns of chemokines, surface markers and enzymes that ultimately generate the diversity of macrophage function seen in inflammatory and non-inflammatory settings. It has recently been proposed that adipose tissue macrophages, which accumulate with obesity and are implicated in insulin resistance switch their phenotype from one of an alternatively activated (M2) to pro-inflammatory (M1) cells (Lumeng et al. 2007). Characteristic features of the IFN-γ induced pro-inflammatory (M1) macrophages include enhanced MHC class II expression, but distinctive up-regulation of i-NOS. Alternative activation of macrophages (M2) is strongly associated with extracellular parasitic infections, allergy, humoral immunity, and fibrosis. It is characterized by up-regulation of the endocytic lecithin-like receptors and arginase rather than i-NOS (Gordon 2007). Therefore, the alternatively activated (M2) macrophages seem to have high capacity for the tissue remodeling and repair.

It had been recently proposed that PPARγ is required for maturation of alternatively activated macrophages (M2), which could also participate to its insulin sensitizing effect (Odegaard et al. 2007). Disruption of PPARγ in myeloid cells impaired alternative macrophage activation and predisposed to the development of diet-induced obesity, insulin resistance, and glucose intolerance. This might be related to the concomitant down-regulation of oxidative phosphorylation gene expression in skeletal muscle and liver (Odegaard et al. 2007). Phenotype of macrophages in the pathogenic-hypoxic adipose tissue might also be regulated by HIF-1 since the functional loss of HIF-1α resulted in a dramatic reduction of the intracellular ATP stores in macrophages to approximately 15-20%, most likely due to the inhibition of the HIF-1α regulated glycolytic energy generation (Cramer & Johnson 2003; Cramer et al. 2003). It could be hypothesized that resident alternatively activated macrophages have a beneficial role in regulating nutrient homeostasis and suggest that macrophage polarization towards the alternative state might be a useful strategy for treating type 2 diabetes, by modulating adipose tissue phenotype.

Fatty acid binding proteins (FABPs), which are common to adipocytes and macrophages, could also play an important role in metabolic and inflammatory disease, and might therefore represent desirable therapeutic targets for metabolic syndrome (Erbay et al. 2007). Macrophage-derived foam cells express the adipocyte fatty acid-binding protein (FABP) aP2 that plays an important role in regulating the development of insulin resistance in obesity. It has been shown that macrophages deficient in aP2 display alterations in the inflammatory cytokine production. Through its distinct actions in adipocytes and macrophages, aP2 links

together the features of the metabolic syndrome including insulin resistance, obesity, inflammation, and atherosclerosis (Linton & Fazio 2003).

3.3 Phospholipid membrane composition

In the last decades, free radical processes delineated an interdisciplinary field linking chemistry to biology and medicine. Free radical mechanisms became of importance as molecular basis of physiological and pathological conditions. Lipids, in particular unsaturated fatty acids, are susceptible to free radical attack. The reactivity of the double bond toward free radicals is well known; in particular the reversible addition of radical species to this functionality determines the cis-trans double bond isomerization. Since the prevalent geometry displayed by unsaturated fatty acids in eukaryotes is cis, the occurrence of the cis-trans isomerization by free radicals corresponds to the loss of an important structural information linked to biological activity (Ferreri & Chatgilialoglu 2009). Formation of trans isomers of unsaturated fatty acid in biological membranes can have important meaning and consequences connected to radical stress associated with nutritional overload and mitochondrial defects. It might, together with changes in membrane lipid composition (Pietilainen et al. 2011), substantially modulate lipid membrane biophysical characteristics such as thickness, fluidity, protein lateral diffusion capacity, permeability to small molecules in expanding adipocytes and contribute thus to the development of metabolic disease in obesity.

3.4 Pollutants and metabolic health

Physical inactivity and unhealthy diet are well recognized environmental influences largely increasing the risk for metabolic disease development. Recent advances in detecting the presence of various persistent organic pollutants in the surrounding world as well as within our bodies, prompted us to evaluate its possible role in pathogenesis of different endocrine and metabolic pathological states (Langer et al. 2003; Langer et al. 2007; Langer 2010; Langer et al. 2010; Ukropec et al. 2010; Langer et al. 2011).

A heavily polluted area of Eastern Slovakia was targeted by the PCBrisk cross-sectional survey to search for possible links between environmental pollution and both prediabetes and diabetes. Associations of serum levels of five persistent organic pollutants (POPs), namely polychlorinated biphenyls (PCBs), 2,2'-bis(4-chlorophenyl)-1,1-dichloroethylene (p,p'-DDE), 2,2'-bis(4-chlorophenyl)-1,1,1-trichloro-ethane (p,p'-DDT), hexachlorobenzene (HCB) and beta-hexachlorocyclohexane (β-HCH), with prediabetes and diabetes were investigated in 2,047 adults. Prevalence of prediabetes and diabetes increased in a dose-dependent manner, with individuals in upper quintiles of individual POPs showing striking increases in prevalence of prediabetes (Fig. 6.) Interestingly, unlike PCBs, DDT and DDE, increased levels of HCB and β-HCH seemed not to be associated with increased prevalence of diabetes (Ukropec et al. 2010). Cumulative effect of all five persistent organic pollutants (sum of orders) more than tripled the prevalence of prediabetes while that of diabetes was increased more than six times as compared to the referent quintile composed of individuals with lowest levels of pollutants in serum. We as well as the others have clearly shown that increasing serum concentrations of individual persistent organic pollutants considerably increased prevalence of prediabetes and diabetes in a dose-dependent manner. Interaction of industrial and agricultural pollutants in increasing prevalence of prediabetes or diabetes

is likely (Hong et al. 2010; Ukropec et al. 2010; Howard & Lee 2011; Lee, D. H. et al. 2011; Lee, D. H. et al. 2011; Lee, H. K. 2011).
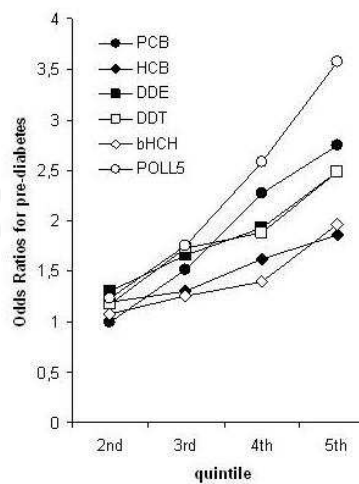

Fig. 6. The prevalence of prediabetes increases with increased circulating levels of PCBs (sum 15 congeners of polychlorinated biphenyls); DDE (2,2'-bis(4-chlorophenyl)-1,1-dichloroethylene); DDT (2,2'-bis(4-chlorophenyl)-1,1,1-trichloro-ethane); HCB (hexachlorobenzene) and b-HCH (beta-hexachlorocyclohexane); POLL5 represents the sum of orders for all 5 pollutants. Odds ratios were adjusted for age, gender and BMI.

4. Skeletal muscle in metabolic health and disease

Skeletal muscle represents a large mass of tissue, and its primary function is to use energy, though quite inefficiently, to enable us the 3D life, voluntary positioning and moving our bodies in a surrounding space. This makes an active muscle to be the most effective energy burner. In addition to obvious metabolic consequences, regular exercise activates central reward mechanisms and makes us happy (Figure 7.) (Sher 1998; Boecker et al. 2008).
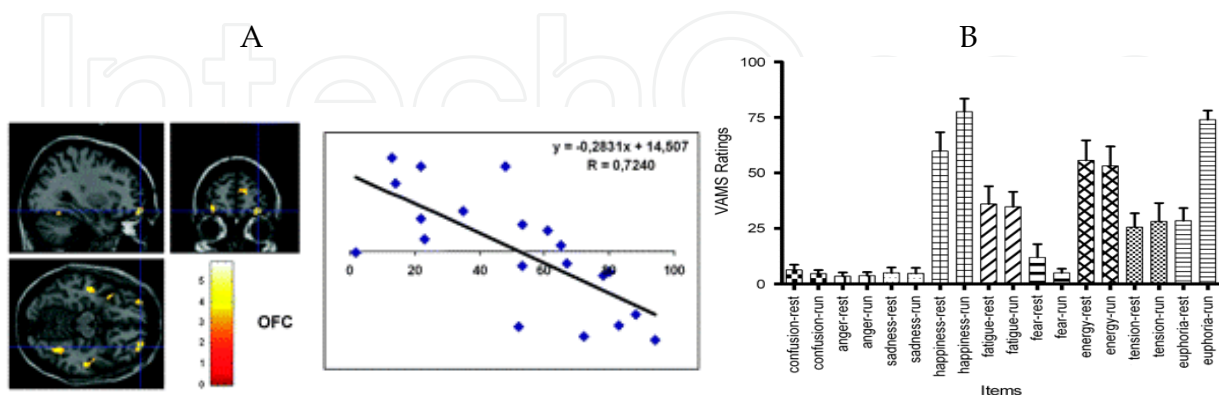

Fig. 7. Correlation of opidergic ligand 6-O-(2-[18F]fluoroethyl)-6-O-desmethyldiprenorphine binding in right orbitofrontal cortex (OFC) with the visual analog mood scale (for euphoria) in runners (**A**) and effect of exercise on the individual's mood expressed in the visual analog mood scale (**B**) (Boecker et al. 2008).

More importantly, inadequate physical activity, associated with defects in mitochondrial function and changes in ultrastructure as well as muscle endocrine properties, largely contributes to the imbalance between energy intake and energy expenditure and is tightly associated with many chronic metabolic and cardiovascular diseases (Bluher & Zimmer 2010; Pedersen 2011). Physical activity is a key factor to bring individuals living in a modern society with plenty of palatable food choices to energy balance. The mechanisms that tie muscle activity to health are unclear. Generation of "exercise pill" targeting organ systems involved in facultative thermogenesis had been envisaged (Himms-Hagen 2004). And results of studies aimed at identifying the endocrine properties of exercising muscle are encouraging our thinking in this respect. In our recent study we observed on the sample of 71 individuals with a broad range of BMI that overweight and obesity is associated with decreased physical activity. This might be not so surprising. But low physical activity level was also associated with decreased insulin sensitivity, increased fat cell size and expanded visceral adiposity all independent on BMI (Fig. 8.). In addition, the basic metabolic rate was positively and respiratory quotient negatively associated with the duration of the daily physical activity representing thus a direct link between physical activity and major determinants of energy homeostasis (Ukropcova et al., unpublished observations).
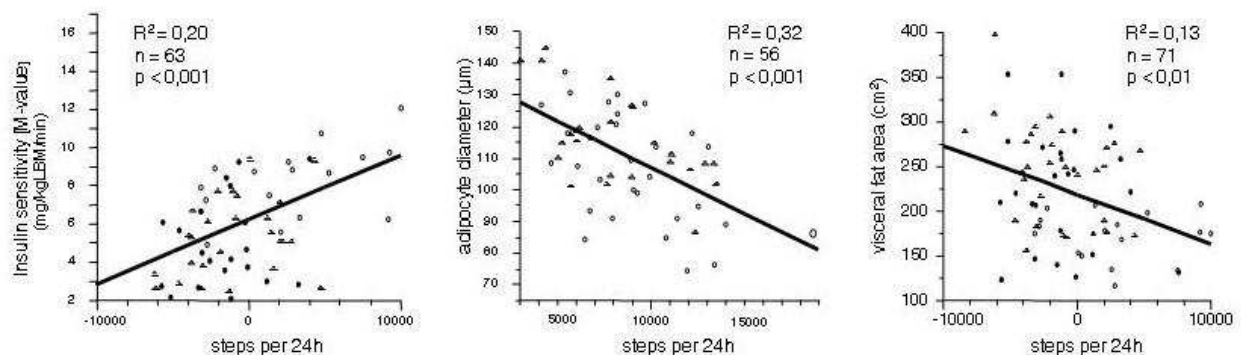

Fig. 8. Free-living ambulatory activity (number of steps in 24h) correlates with insulin sensitivity, modulates adipocyte diameter as well as visceral adiposity (Ukropcova et al., unpublished observations).

This complements the previous observations by others indicating that inactivity initiates unique cellular processes that are qualitatively different from the exercise responses. Inactivity physiology studies are beginning to raise a new concern with potentially major clinical and public health significance. Sedentary lifestyle threatens our society. The average nonexercising person may become even more metabolically unfit in the coming years if they sit too much and thereby lower the normally high volume of intermittent nonexercise physical activity in everyday life (Fig. 8) (Hamilton et al. 2007; Levine et al. 2008). Dynamic interrelations of skeletal muscle and adipose tissue during exercise are necessary to support muscle performance. This requires precise spacio-temporal management of the adipose tissue metabolic flux. The transcriptional coactivator PGC1α has recently been shown to regulate several exercise-associated aspects of muscle function. There is mounting evidence suggesting that this transcription factor controls muscle plasticity, suppresses a broad inflammatory response and integrates many beneficial effects of exercise on metabolic health (Handschin & Spiegelman 2008).

4.1 Exercise and skeletal muscle endocrinology

The recent identification of skeletal muscle as an endocrine organ that produces and releases biologically active substances, "myokines", expands our knowledge on how the endocrine, immune and nervous systems contribute to the maintenance of homeostasis, especially when energy demands are increased (Pedersen & Febbraio 2008). To date, only a few muscle cell-secreted proteins with auto-, para-, or endocrine functions have been identified. It could be hypothesized that skeletal muscle releases a large number of biologically active substances which participate to cell-to-cell and organ-to-organ cross-talk. It also has to be noted that specific biological functions of known myokines are very incompletely understood.

Certain myokines, such as calprotectin (Mortensen et al. 2008), IL15 (Nielsen & Pedersen 2007) and IL6 (Jonsdottir et al. 2000), are acutely induced by muscle contraction but might not necessarily be increased in response to muscle training (Pedersen & Febbraio 2008; Haugen et al. 2010). Exercise training involves multiple adaptations including increased pre-exercise skeletal muscle glycogen content (Kirwan et al. 1990), enhanced activity of key enzymes involved in β-oxidation (Schantz 1986), increased sensitivity of adipose tissue to epinephrine-induced lipolysis (Crampes et al. 1986), and increased muscle capacity to oxidize fat (Holloszy & Booth 1976; Phillips et al. 1996). It could therefore be hypothesized that secretory activity of muscle subjected to inadequate physical activity would be qualitatively and quantitatively distinct from that of the trained athlete, and that it could simply be regulated by e.g. the glycogen level (Keller et al. 2001; Steensberg et al. 2001), reactive oxygen species production (Kosmidou et al. 2002; Steensberg et al. 2007) or by modulating biological availability of various forms of lipids (Peter et al. 2009), such as found in obesity.

Previous reports indicate that calprotectin, IL6 and IL15 might contribute to homeostatic control of glucose and lipid metabolism (Van Hall et al. 2003; Febbraio et al. 2004). In addition, fibroblast growth factor-21 (FGF-21), the potent metabolic regulator, shown to improve glucose metabolism and insulin sensitivity in animal models, had recently been found to be expressed and secreted *in vitro* from murine muscle cells and *in vivo* from human muscle in response to insulin stimulation (hyperinsulinemic-euglycemic clamp) (Hojman et al. 2009). Follistatin-like 1 (Fstl-1) is another myokine whose functional significance in physiological and pathological processes is incompletely understood. Preliminary evidence indicates that Fstl-1 promotes endothelial cell function and stimulates revascularization in response to ischemic insult through its ability to activate Akt-eNOS signaling in muscle (Ouchi et al. 2008). Interleukin-8 is a CXC family chemokine increased in human muscle in response to concentric exercise (Akerstrom et al. 2005), which has also been shown to have angiogenic actions associated with activation of CXCR2 receptors in the human microvascular endothelial cells (Bek et al. 2002; Frydelund-Larsen et al. 2007). Recent report by Drevon's laboratory describes interleukin-7 as a novel myokine affecting myogenesis *in vitro* in human primary muscle cells. Interleukin-7 is up-regulated by exercise training in male individuals undergoing a strength training program (Haugen et al. 2010).

4.2 Mitochondrial biogenesis in skeletal muscle – Energetic remodeling of muscle phenotype in obesity, insulin resistance and exercise

Mitochondria are energy power plants of the cells, believed to have evolved over billions of years from invading prokaryotic oxygen utilizing "quite energizing" eubacterium to early eucaryotic cells, giving the life on earth new energy spark (Lanza & Nair 2010). Their

structure and function is orchestrated by a strict coordination of nuclear and mitochondrial genome. Of ~1.000 mitochondrial proteins, only 13 are encoded by the mitochondrial genome, remaining proteins are translated from nuclear genome and transported across the inner mitochondrial membrane (Lanza & Nair 2010). Mitochondria cover majority of energetic needs of cells by coupling substrate oxidation with ATP formation, the process known as oxidative phosphorylation. This process also generates reactive oxygen species (ROS). It has been estimated that 0.2 – 2% of oxygen taken up by the cell is converted into ROS (Harper et al. 2004). Mechanisms for detoxifying the ROS are quite well developed in a eukaryotic cell which is another reason for their long lasting partnership with "dangerous" mitochondria. Sustained excessive production may accumulate amount of ROS exceeding the antioxidant capacity of the specific cell, eventually leading to cell damage and death (Harman 1956). During recent years, mitochondria , though not only those found in skeletal muscle, were put on the spot as organelles involved in aging and associated chronic civilization diseases such as Alzheimer's disease (Reddy 2009), some forms of cancer, obesity and type 2 diabetes (Johannsen & Ravussin 2009).

4.2.1 Mitochondria in obesity, insulin resistance and type 2 diabetes

Recent evidence indicates that insulin resistance in skeletal muscle might develop due to the reduced capacity of mitochondria to oxidize lipids (Bjorntorp et al. 1967; Kelley et al. 2002; Petersen et al. 2004; Ukropcova et al. 2007) and reduced capacity for insulin-stimulated ATP-synthesis (Petersen et al. 2005). Obese individuals and subjects with type 2 diabetes are characterized also by reduced adiponectin signaling (Kern et al. 2003; Civitarese et al. 2004; Rasmussen et al. 2006), lower rates of fasting lipid utilization and impaired switch to carbohydrate oxidation in response to insulin (Kelley et al. 1999; Kelley & Mandarino 2000; Ukropcova et al. 2005; Ukropcova et al. 2007). Recent studies using microarray expression analysis reported a decrease in the expression of genes involved in mitochondrial biogenesis in skeletal muscle of individuals with insulin resistance (Patti et al. 2003) and T2D (Mootha et al. 2003). Further studies in insulin resistant subjects and individuals with type 2 diabetes have shown reduced mitochondrial content, lower electron transport chain activity in total mitochondria and in intramyofibrilar and subsarcolemal mitochondrial fractions (Kelley et al. 2002; Ritov et al. 2005). Taken together, these data support the hypothesis that insulin resistance in human skeletal muscle arises from lowering mitochondrial number and functional capacity. Another hypothesis challenges this paradigm; it is supported by observations that increased fatty acid availability is associated with increased mitochondrial fat oxidation. However, mitochondrial overload with energy rich substrates highlights the pathophysiological role of ROS and that of products of incomplete mitochondrial oxidation rather than simple lowering of mitochondrial functional capacity (Koves et al. 2008; Holloszy 2009). The importance of mitochondria for energy homeostasis makes this organelle an exciting target for investigation and better understanding to regulation of mitochondrial biogenesis and function would help us to understand its putative role in the pathogenesis of obesity and insulin resistance.

4.2.2 Exercise and ageing keep constant battle for healthy mitochondria

Exercise is one of the two physiological stimuli known to increase production of new mitochondria and to improve mitochondrial efficiency. In our work, we have shown that caloric restriction, the only officially acknowledged physiological stimulus demonstrated to

prolong lifespan, is also inducing mitochondrial biogenesis in human skeletal muscle (Civitarese et al. 2007). Many scientists are on a quest, pursuing the vision of exercise mimicking pill, capable of induction of mitochondrial biogenesis *in vivo*. „Exercise in a pill" (another option would be a pill mimicking caloric restriction) is by many considered a putatively great tool to combat obesity and civilization diseases. However, healthy lifestyle intervention, with sufficient physical activity and matching caloric intake still proves to be the most natural and effective way how to stay fit, healthy and with increased chances to live up to be a hundred.

4.2.3 Adipose tissue and skeletal muscle interplay

Our organism can be viewed as a very complex society of tissues that need to communicate with one another in order to maintain metabolic health. Tissue cross-talk plays the central role in the regulation of food intake, energy expenditure, oxidative capacity, adaptation to changes in physical activity, nutritional status etc. As mentioned above, adipose tissue (as well as many other tissues in our body) is (are) a (the) source of many biologically active substances with autocrine, paracrine and endocrine activities, exerting effects over many different neighboring as well as distant tissues and organs.

Adiponectin is the most studied adipocytokine which is in relatively high quantities secreted from adipose tissue into the bloodstream. Adiponectin has very positive effects on our metabolic health as it activates glucose and fatty acid metabolism and improves insulin sensitivity. Adiponectin levels are inversely correlated with body fat mass and positively with insulin sensitivity (Hara et al. 2005) and it also displays anti-atherogenic and anti-inflammatory effects (Antoniades et al. 2009). This hormone was first characterized in mice as a transcript overexpressed in preadipocytes (precursors of fat cells) differentiating into adipocytes. The human homologue was identified as the most abundant transcript in adipose tissue. Contrary to expectations and despite being produced in adipose tissue, adiponectin was found to be decreased in obesity. The gene was localized to chromosome 3p27, a region highlighted as affecting genetic susceptibility to T2D and obesity. Supplementation by differing forms of adiponectin was able to improve insulin control, blood glucose and triglyceride levels in mouse models. The question remains what are the mechanisms underlying positive effects of adiponectin on metabolism?

The molecular mechanisms leading to mitochondrial dysfunction in obesity and T2D remain largely unknown. Bergeron et al (Bergeron et al. 2001) demonstrated that activation of cAMP-activated protein kinase (AMPK) increases both mitochondrial biogenesis and oxidative capacity in skeletal muscle of rodents. In animal models of T2D, the activation of AMPK by adiponectin increases muscle and hepatic fat oxidation and improves insulin sensitivity (Yamauchi et al. 2001). Studies in obese and diabetic rhesus monkey demonstrate that plasma adiponectin level declines in the early phases of obesity and in parallel to the progressive development of insulin resistance (Hotta et al. 2001). Furthermore, circulating plasma adiponectin levels and the expression of both adiponectin receptors are reduced in subjects with a family history of diabetes (Civitarese et al. 2004), while prospective studies in Pima Indians show that high concentrations of adiponectin is protective against the development of T2D (Lindsay et al. 2002). Collectively, these data define a pathway in skeletal muscle by which adiponectin contributes to energy homeostasis by modulating mitochondrial number and function (Civitarese et al. 2006). Early defects in the secretion of adiponectin or in adiponectin signaling might contribute to the lower mitochondrial content

and/or function in the prediabetic state. Interestingly and in accordance with our results, it has been recently demonstrated that an adiponectin-like molecule, a recombinant globular domain of adiponectin (rgAd110-244), has a significant therapeutic potential to treat insulin resistance in mice fed a high fat diet for 3 months (Sulpice et al. 2009). This makes adiponectin derivatives a promising new treatment for T2D.

It appears that adiponectin is also produced by skeletal muscle and that globular adiponectin is capable of inducing the differentiation and fusion of muscle cells in vitro (Fiaschi et al. 2009). Mimicking of pro-inflammatory settings or exposure to oxidative stress strongly increases the production of adiponectin from differentiating primary muscle cells. These data suggest a novel function of adiponectin, coordinating the myogenic differentiation program.

4.2.4 Mitochondrial biogenesis in muscle cells – Lipids and exercise

Fatty acids are known to be the ligands of various transcription factors involved in the regulation of metabolism and mitochondrial biogenesis (Gilde & Van Bilsen 2003). It has been shown previously that fatty acids as well as a diet with an increased fat content is capable of inducing mitochondrial biogenesis both in vitro and in vivo (Watt et al. 2006; Hancock et al. 2008). In our work, we have tested the effect of chronic, 4-day long exposure to palmitate on metabolic phenotypes of human primary skeletal muscle cells. We observed an increase in number of active mitochondria as measured by incorporation of mitotracker (fluorescencent dye selectively activated within respiring mitochondria) as well as increased expression of genes involved in mitochondrial biogenesis, increase in the capacity for fatty acid oxidation (Ukropcova et al. 2005, Ukropcova et al, unpublished observation). At this moment we can only speculate on the mechanisms behind this oxidation boosting effect of palmitate. However, it has been shown that fatty acids are capable of activating AMP activated protein kinase (AMPK) in skeletal muscle (Watt et al. 2006). AMPK signaling is activated in energy deficit states and it primarily saves the cell by inducing *de novo* mitochondrial biogenesis. It cooperates with transcription factor PGC1α, overexpression of which has been demonstrated to enhance both lipid oxidation and synthesis (Espinoza et al. 2010). Another possibility is that palmitate is a ligand for the transcription factors involved in the regulation of cell´s oxidative capacity, such as PPARδ (Gilde & Van Bilsen 2003). Animal (Hancock et al. 2008) as well as clinical studies (Bajaj et al. 2007) also support the role of fatty acids for PGC1α regulation at the level of gene expression. We and others have indicated that saturated fatty acids (e.g. palmitate) contribute to the regulation of metabolism by self-promoting their utilization *via* increased oxidative capacity of the skeletal muscle cell.

In addition, dynamic interrelations of skeletal muscle and adipose tissue during exercise are necessary to support muscle performance and adipose tissue energy fluxes management. The transcriptional coactivator PGC1α has also been shown to regulate several exercise-associated aspects of muscle function. It could be hypothesized that this protein controls muscle plasticity, suppresses a broad inflammatory response and mediates the beneficial effects of exercise on metabolic health (Handschin and Spiegelman 2008).

4.2.5 Caloric restriction induces mitochondrial biogenesis in skeletal muscle

Caloric restriction is a non-genetic manipulation that results in the lifespan extension of many different species, from yeasts to dogs, and even primates, and it is accompanied by

delayed onset of chronic civilization diseases (Ball et al. 1947; Anderson et al. 2009). There are also hints that people who eat a calorie-restricted diet might live longer than those who overeat. People living in Okinawa, Japan, have a lower energy intake than the rest of the Japanese population and an extremely long life span (Willcox et al. 2007). In addition, calorie-restricted diets beneficially affect several biomarkers of aging, including decreased insulin sensitivity. Based on combined favorable changes in lipid and blood pressure, caloric restriction with or without exercise induces weight loss and favorably reduces risk for cardiovascular disease even in healthy non-obese individuals (Lefevre et al. 2009) and ameliorates the age-related loss of muscle mass, sarcopenia, in a variety a species (Marzetti et al. 2009). But how might caloric restriction slow aging? Some of the theories behind the lifespan extending effect of caloric restriction include (i) decreased oxidative damage, (ii) altered glucose utilization, (iii) increased insulin sensitivity, (iv) neuroendocrine changes and (v) enhanced stress responsiveness (Allard et al. 2009). Reduction of oxidative damage to proteins, lipids, and DNA is one of the leading theories, although the underlying mechanisms of this process are unclear. Cellular nutrient sensing systems seem to mediate many of the metabolic responses to caloric restriction, including the regulation of free radical production and oxidative stress. Mitochondria are the major consumers of cellular oxygen (~85%) and the predominant production site of free radicals, a by-product of oxidative phosphorylation. Studies in mammals have shown that caloric restriction reduces the generation of free radicals by mitochondria, in parallel to reductions in mitochondrial proton leak and whole-body energy expenditure. Paradoxically, caloric restriction induces mitochondrial proliferation in rodents (Lanza & Nair 2010), and either lowers (Handschin & Spiegelman 2008) or does not affect mitochondrial oxygen consumption (Lanza & Nair 2010). Low mitochondrial content seems to contribute to increased ROS production. When mitochondrial mass is reduced, mitochondria have increased "workload," leading to higher membrane potential and increased ROS production (Handschin & Spiegelman 2008; Lanza & Nair 2009; Lanza & Nair 2010). It has also been demonstrated that caloric restriction is strongly associated with an increased level and activation of sirtuins, namely the Sir2 histone deacetylase and its mammalian ortholog Sirt1. Sirtuins are members of the silent information regulator 2 (Sir2) family, a family of Class III histone/protein deacetylases. The enzymatic activity of most sirtuins has been shown to be dependent on nicotinamide dinucleotide, suggesting that the activity of these enzymes is dependent on the nutritive state of the organism (Allard et al. 2009). Specific Sirt1 activation mimics low energy levels and protects against diet-induced metabolic disorders by enhancing fat oxidation (Feige et al. 2008). PGC1α is a transcriptional coactivator playing a pivotal role in the regulation of mitochondrial biogenesis, which is known to be induced in response to exercise and caloric restriction (Fig. 8.). Research strongly supports the health benefits of exercise in humans of all ages. Increased exercise in the absence of other behavioral changes prevents the onset of many chronic diseases (Elbekai & El-Kadi 2005).

In our study we showed that short-term caloric deficit (caloric restriction with or without exercise) coordinately up-regulated the expression of genes involved in mitochondrial biogenesis in skeletal muscle resulting in increased mitochondrial content, improved whole body energy efficiency, and decreased DNA fragmentation in non-obese humans (Civitarese et al. 2007). Our results suggest that caloric restriction induces biogenesis of "efficient" mitochondria as an adaptive mechanism, which in turn lowers oxidative stress.
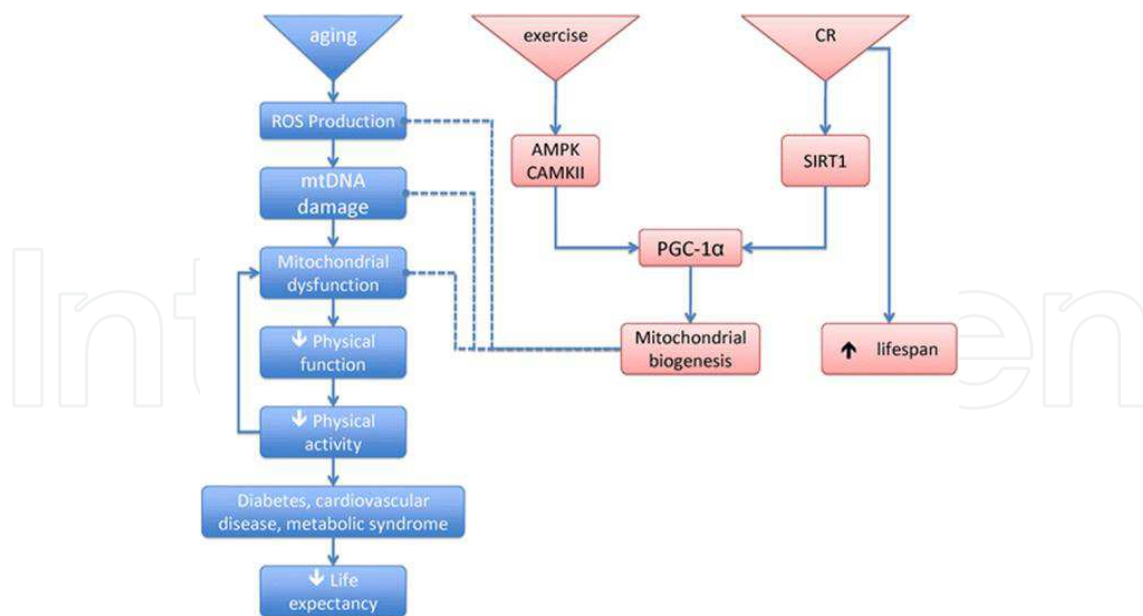
Fig. 9. The free radical theory of aging posits that a senescent phenotype is induced by accumulation of oxidative damage resulting from reactive oxygen species. Exercise and caloric restriction (CR) are two interventions that induce mitochondrial biogenesis through PGC-1α. Although exercise and CR increase average life expectancy by protecting against age-related comorbidities, only CR has been shown to increase maximal life span; an effect that seems to require the activation of sirtuins (Lanza & Nair 2010).
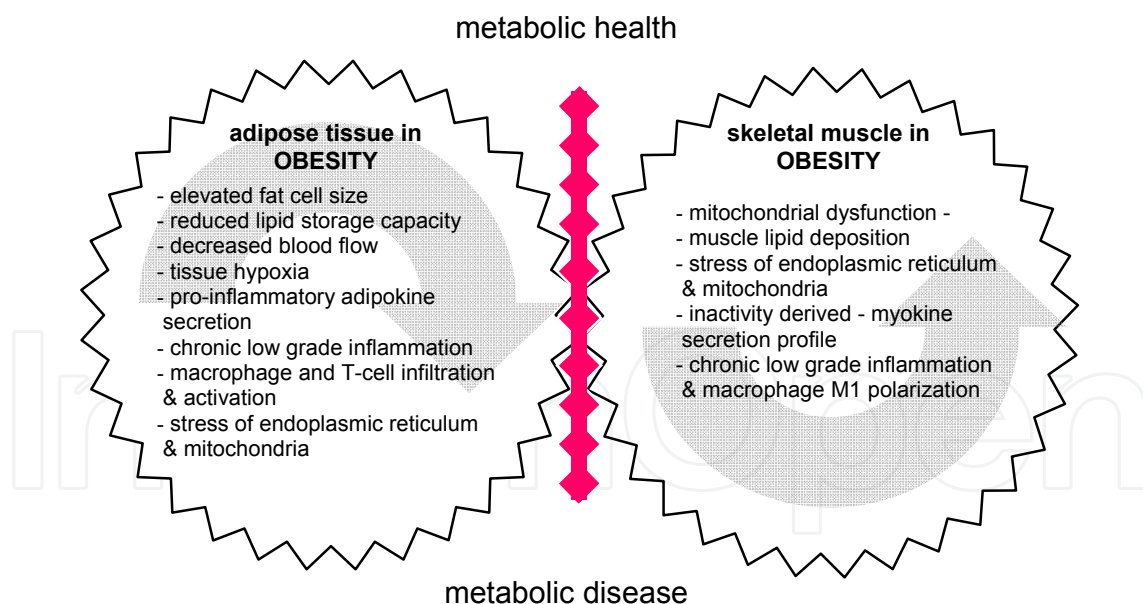

Fig. 10. Determinants of metabolic health and disease (Ukropec et al. 2008)

5. Conclusion

Ability of tissues to adapt morphologically and functionally to different physiological situations determines the overall metabolic health. Increased adipose tissue mass but mainly adipocyte lipid overload is responsible for the "pathogenic" adipose tissue phenotype. This

phenotype, characteristic by extra-large unilocular adipocytes, further promotes tissue hypoxia and development of chronic persistent inflammation and metabolic stress. Pathogenic modification of the adipocyte modulates its metabolic, secretory and immunologic function leading to the development of metabolic disease (Fig. 10.). Inactive skeletal muscle, overloaded with fat could also contribute to metabolic imbalance by switching the fiber type towards less oxidative (less insulin sensitive) fibers, by lack of anti-inflammatory and insulin-sensitizing myokine production as well as by chronic inflammation associated with mitochondrial stress and stress of endoplasmic reticulum (Fig. 10.). Our environment greatly modifies our metabolic health by means of dietary influences and exercise activity which together with pathologies associated with hyperlipidemia, chronic systemic hypoxia and tissue inflammation determines adipose tissue and skeletal muscle metabolic and secretory phenotype and subsequently our metabolic health.

It is generally accepted that regular physical activity prevents metabolic and cardiovascular disease development, and supports healthy aging. Skeletal muscle has been shown to produce and secrete several bioactive factors (hormones) termed "myokines". Different spectra of myokines originating from either active "trained" or inactive "sedentary" skeletal muscles elicit distinct adaptive changes in immune system, metabolic balance and processes of cellular growth and differentiation in order to maintain the whole body homeostasis. This requires extensive communication of skeletal muscle with many different cells and organs but the nature of mechanisms that tie muscle activity to metabolic health is not completely understood. It seems to be essential (i) to identify myokines differentially expressed and secreted from muscle cells derived from healthy and obese individuals, and individuals with type 2 diabetes; to (ii) determine basic principles of the muscle cross-communication with adipocytes (differentiation) and endothelial cells (angiogenesis) in fostering tissue plasticity necessary for adaptation to obesity and type 2 diabetes; and (iii) to discover novel myokines and to investigate their physiological significance in cell culture models and *in vivo* in genetically modified animal models as well as in humans. Myokines may be involved in mediating the health beneficial effects of exercise and play important roles in the protection against chronic diseases associated with low-grade inflammation, insulin resistance, hyperlipidemia, such as cardiovascular disease, type-2-diabetes, and cancer. Extension of the knowledge on the mechanisms whereby regular exercise offers protection against chronic diseases in combination with clinical research serves as a foundation for the development of public health guidelines with regard to exercise. Moreover, identification of new myokines and understanding basic principles and mechanisms of their action will potentially provide pharmacological targets for the treatment of metabolic and cardiovascular disorders.

6. Acknowledgement

7. References

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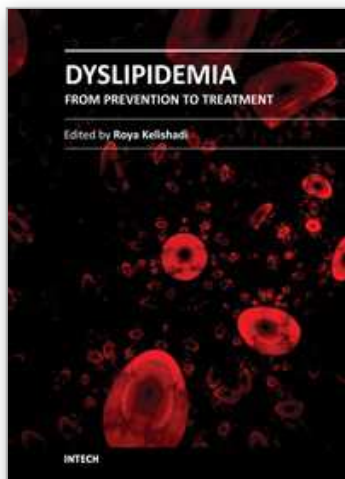
Dyslipidemia - From Prevention to Treatment
Edited by Prof. Roya Kelishadi

Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

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