kPNI
Europäische Gesellschaft für klinische
Psycho-Neuro-Immunologie

# Globesity – the obesity pandemic

*By: Leo Pruimboom, Ass. prof. University of Girona*

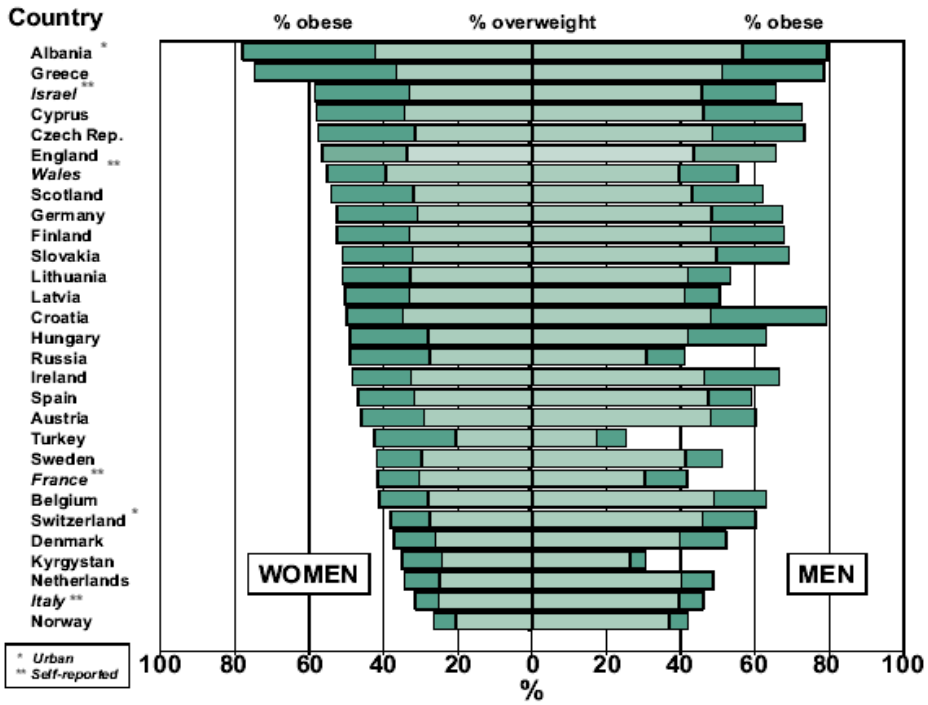
## Introduction

The global increase in obesity, along with the associated adverse health consequences, has heightened interest in the fundamental causes of excessive weight gain. Attributing obesity to "gluttony and sloth", or blaming the obese for overeating and limited physical activity, oversimplifies a complex problem, since substantial differences in metabolic efficiency between lean and obese people have been decisively demonstrated. The underlying physiological basis for these differences has remained poorly understood. Inflammatory susceptibility, social role, adverse early life experiences, low birth weight, genetic polymorphisms, conditional factors, chronic stress, brain damage, the use of non-caloric sweeteners and changes in thermogenesis are factors which have all been related to weight gain and pathological obesity. Homeothermy and thermogenesis are hardly ever taken into account. The energetic requirements of homeothermy, the maintenance of a constant core temperature in the face of widely divergent external temperatures, accounts for a major portion of daily energy expenditure. Changes in body temperature are associated with significant changes in metabolic rate. These facts raise the interesting possibility that differences in core temperature may play a role in the pathophysiology of obesity.

Not only the fact that the prevalence of obesity has increased has to be considered; one of the more surprising features of adipose tissue described over the past 10 years is that adipose tissue in general, and adipocytes in particular, have the potential to be a rich source of a vast array of secretory proteins. Since infiltrating immune cells (most notably monocytes) are known to have a profound effect on adipocytes, interest in the stromal fraction of adipose tissue has increased considerably. These stromal components consist of fibroblast-like preadipocytes, endothelial cells, vascular smooth muscle cells, neurons, and immune cells. The macro-etiological factors of weight gain and the micro-characteristics of adipose tissue interact, producing an "obese phenotype", or, in more layman's terms, an overweight individual. Within a clinical setting, only people with inflammatory activity of adipose tissue can be considered a risk group for the development of cardiovascular disorders, diabetes, depression and auto-immune diseases.
Therefore, this seminar text will analyse the important differences between the "metabolically healthy obese phenotype" and the "metabolically unhealthy obese phenotype".

The world has seen an unprecedented increase in the prevalence of overweight and obesity in recent decades, as global shifts in diet and lifestyle cause ever more people to have a positive energy balance. The World Health Organisation's latest projections indicate that in 2005, approximately 1.6 billion adults worldwide were overweight (BMI≥25 kg/m2) and at least 400 million were obese (BMI≥30 kg/m2), numbers which are projected to reach 2.3 billion and 700 million by 2015. Figure 1 shows the current obesity levels in Europe. The idea that stopping the obese from overeating and stimulating them to be physically active solves their problem has not led to a decrease in the number of obese people; neither has it succeeded in stopping the secular increase in prevalence of the inflammatory obese phenotype. Since obesity is a global problem with huge health and economic consequences, not only for our generation but also for future ones, we should look for more subtle explanations that could help solve it.

Figure 1: Obesity levels in Europe




Source: International Obesity Task Force

Figure 1 The obesity epidemic in Europe

**The energy balance equation**
*Energy intake = energy output + storage*

Energy intake refers to ingested calories; storage refers to change in bodyweight, largely produced by fat. In the Quebec Overfeeding Twin Study, intake was controlled and physical activity was limited. However, storage (weight gain) varied considerably, demonstrating that differences in metabolic efficiency result from changes that are independent of physical activity.

Energy output is the most complex of the components in the energy balance equation and varies considerably among individuals. In sedentary people, a rough approximation of the major compartments of energy expenditure is as follows: Resting (or "basal") Metabolic Rate (RMR) accounts for approximately 80% of energy output. About two thirds of RMR is for maintenance of homeothermy (warm-bloodedness), about one third is to maintain cellular integrity, ionic gradients, protein turnover, and the like. Resting metabolic rate is largely regulated by thyroid hormones, with a minor contribution from the sympathetic nervous system. Resting metabolic rate differs by as much as 600 kcal/d for a 70-kg man. Physical activity (exercise) accounts for about 10% in truly sedentary humans; in addition to intentional activity, this category includes non-purposeful movements such as fidgeting, which may differ among lean and obese individuals, as well as upright posture.

The remaining 10% is frequently referred to as thermogenesis, meaning heat production that is unrelated to physical activity. This component is regulated by the sympathetic nervous system and includes "non-shivering thermogenesis" in response to cold exposure and "diet-induced thermogenesis" in response to dietary intake. These are "adaptive" or "facultative" forms of thermogenesis in that they mediate specific physiological functions. Although disputed in the past, evidence for adaptive thermogenesis in humans has now been

convincingly established.
It should be emphasized that, for non-sedentary individuals, the activity component may be much greater than 10% of total energy expenditure. Evidence has been obtained indicating that the combination of activity plus adaptive thermogenesis accounts for about 44% of total energy expenditure on average, meaning that RMR would constitute about 56% of total energy expenditure in normally active humans, as compared to 80% in the truly sedentary. Thus, thermogenesis in sedentary humans accounts for a large part of their energy expenditure. Thermogenesis depends on the level of thermo-stress, starting at an environmental temperature below 22°C. As modern humans live a thermoneutral life (thanks to clothes and heated housing), thermogenesis is unnecessary. Absence of thermogenesis reduces sympathetic triggering of so-called brown adipose tissue (BAT), inducing apoptotic cell death of brown adipocytes and loss of optimal diet-induced thermogenesis (100% dependent on BAT activity). In more popular terms: if you don't use it, you lose it. At rest, sedentary people have reduced energy expenditure and therefore run a higher risk of weight increase. This process seems to be a staple for secular increase of bodyweight worldwide, making BAT a focal point for scientific research into obesity and human health in general.

**Brown adipose tissue and its role in body weight maintenance**
Updating the energy equation – the influence of BAT (figure 2, Lidell, M. E. & Enerbäck, S. *Nat. Rev. Endocrinol.*13 April 2010).

*Energy intake = physical energy expenditure + normothermia + diet-induced thermogenesis + cold-induced thermogenesis + need for ATP at rest*

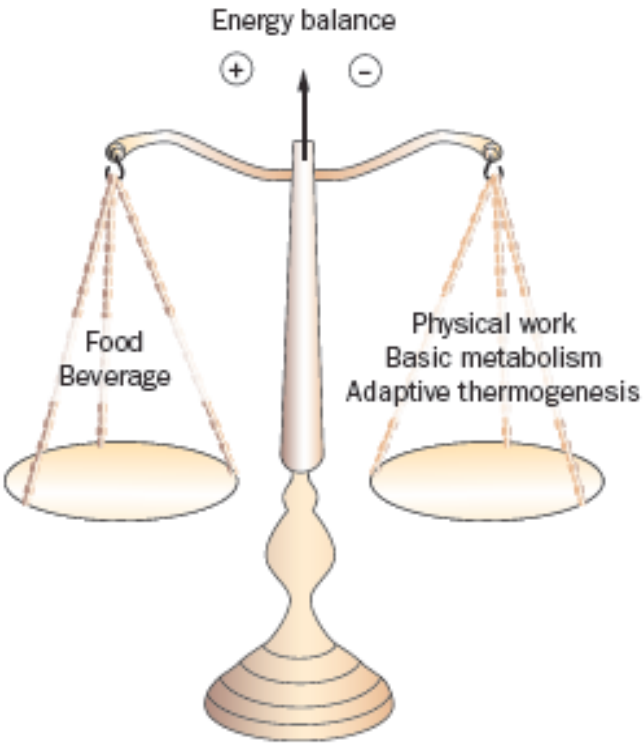



Figure 2 A more appropriate energy balance; cold- and diet-induced thermogenesis as part of energy output (Lidell 2010)

The function of brown adipose tissue is to transfer energy from food into heat; physiologically, both the heat produced and the resulting decrease in metabolic efficiency can be of significance. Both the acute activity of the tissue, i.e., the heat production, and the recruitment process in the tissue (that results in a higher thermogenic capacity) are under the control of norepinephrine released by sympathetic nerves.

In thermoregulatory thermogenesis, brown adipose tissue is essential for classical non-shivering thermogenesis (this phenomenon does not exist in the absence of functional brown adipose tissue), as well as for the cold acclimation recruited norepinephrine-induced thermogenesis.
Heat production from brown adipose tissue is activated whenever the organism is in need of extra heat, e.g., postnatally, when entering a febrile state and during arousal from hibernation. The rate of thermogenesis is centrally controlled by a pathway initiated in the hypothalamus.

Food intake as such also results in activation of brown adipose tissue; a series of diets, apparently all characterized by being low in protein, result in a leptin-dependent recruitment of the tissue. This metaboloregulatory thermogenesis is also under hypothalamic control. When the tissue is active, high amounts of lipids and glucose are combusted in the tissue. The development of brown adipose tissue with its characteristic protein, uncoupling protein-1 (UCP1), probably played a decisive role in the evolutionary success of mammals, as its thermogenesis enhances neonatal survival and allows for an active life, even in cold environments.

The role of brown adipose tissue in diet-induced thermogenesis (DIT) has recently been determined by the group of Jan Nedergaard and Barbara Cannon (Feldman 2008). Diets high in fat and those high in protein should increase DIT by at least 10%. Absence of DIT has been seen in animals and humans lacking BAT and UCP-1 expression, making them susceptible for weight gain and obesity.

People that have high levels of UCP-1 and BAT use 200 kcal/meal if the meal is high in protein. High protein meals increase DIT by 100% compared to carbohydrate-rich meals (figure 3, Johnston 2002). HCD are therefore obesogenic whereas diets high in protein protects against obesity and the inflammatory phenotype.

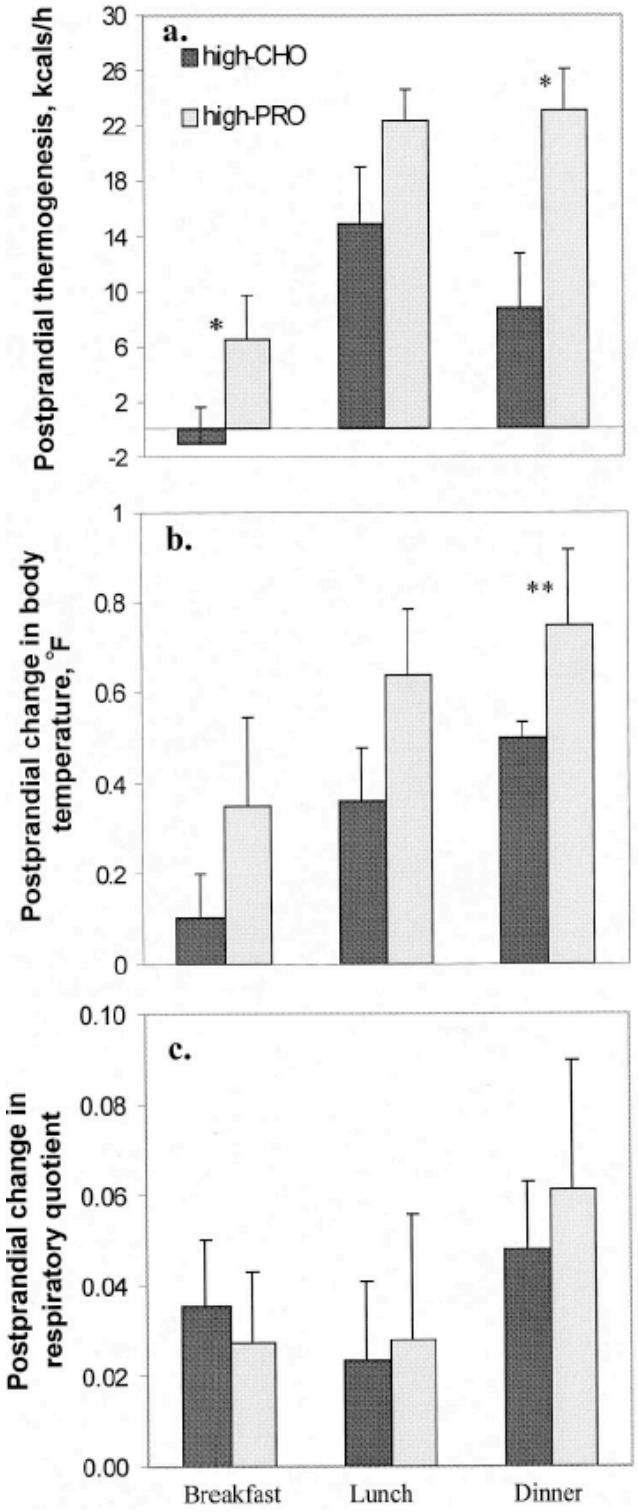



Figure 3. (a) Postprandial thermogenesis (calculated as the difference between post-meal REE and the baseline, fasting REE), (b) postprandial change in body temperature, and (c) postprandial change in respiratory quotient in young, healthy women after ingestion of high-protein meals *vs.* high-carbohydrate meals. Values are reported as the mean _SEM; * denotes significant difference between diets at the meal indicated (*p* _ 0.05); **denotes a trend for

difference between diets at the meal indicated ($p$ _ 0.082).

Protein-induced thermogenesis is probably caused by the fact that proteins cannot be stored, while fat and glucose can (Westerterp 2004). The direct necessity for metabolisation following protein intake induces UCP-1 activation and increases BAT activity.

Figure 4 Shows the three pathways of energy input – energy output after food intake.

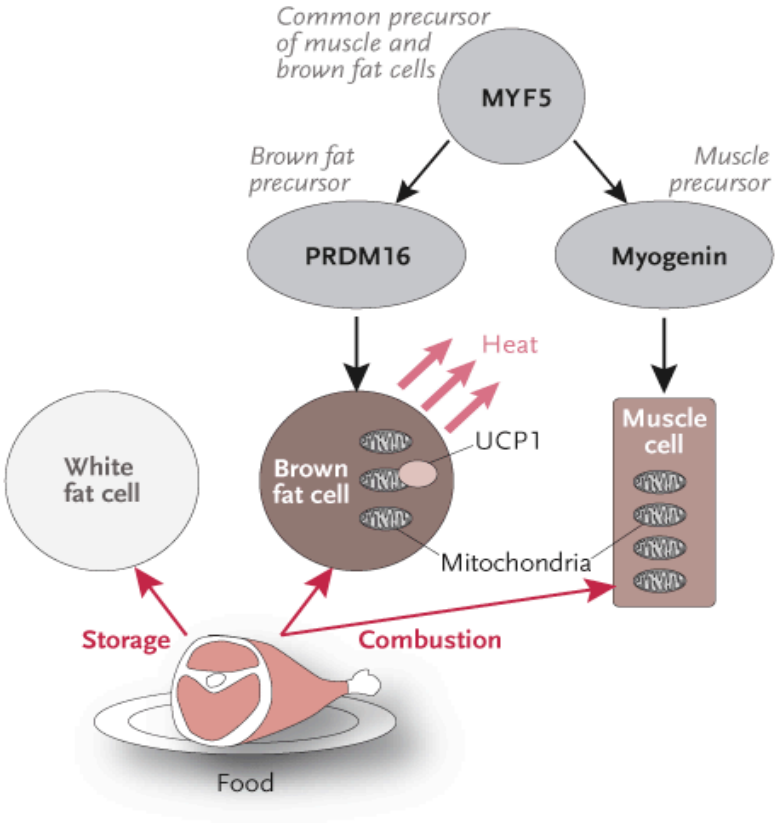



Figure 4 The triple pathway of energy use following food intake. UCP-1-activity in brown adipose tissue is responsible for the use of (excess) free fatty acids and (excess) glucose in the production of body heat (source: http://api.ning.com/files/96cp-gEfiEp8ORQR2KvYikxhvKxvoROOTwsn4ndiqz6KeaV*ihGHbnDOmMGFfm0TZTRXSkbA-ACKip8A4FLqVQVElEAZc41a/brownfat_figure.gif)

UCP-1 activation in BAT seems to be essential for adaptability in the current energy-abundant environment.

Figure 5 shows the relationship between activated and recruited BAT. The consequence of BAT atrophy and its decreased rate of activity leads to a decreased energy output and, consequently, weight gain and a possibly inflammatory obese phenotype (Cannon 2004). It should be concluded that strategies for activating BAT and its essential protein UCP-1 can be of great importance in combating the ever-increasing incidence of obesity and related diseases such as cardiovascular disorders, type 2 diabetes, metabolic syndrome, depression, auto-immune diseases and several types of cancer.

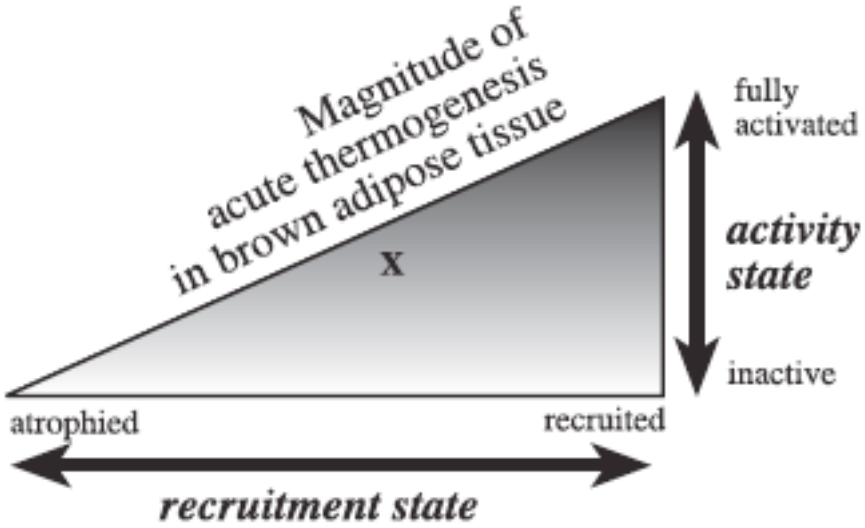



Figure 5 The interaction between presence and activity in Brown Adipose Tissue. BAT could be the "hidden factor" in the secular increase in obesity (Cannon 2004)

Human evolution has been characterized by the adaptability to, sometimes severe, temperature changes. Homo sapiens has populated parts of the world such as Siberia, northern Norway and Alaska, all of which exhibit very low temperatures. Our adaptability to low temperatures is probably based on the evolutionary maintenance of BAT in adult humans (Zingarrety 2009).

Figure 6 shows the need for heat production in environments cooler than thermoneutrality Cannon 2004). Cold treatment should therefore be considered a valuable intervention for obese people (van Marken 2009). Note that cold treatment only seems to be effective when the whole body is cooled and not when cold is only locally applied (Jansky 2006).

Cold-induced activation of BAT takes place within minutes/hours, while BAT recruitment therapy needs at least months of whole body cooling treatment (Bartness 2007). The optimal cooling temperature is around 12°C, until shivering thermogenesis is induced. Long-term treatment produces a timely retarded shivering thermogenesis which means that BAT has been recruited and activated (Bartness 2007).

BAT activation through cold and diet can increase energy output by 30 – 40%, which is an average of 200 – 350 kcal. This amount is substantial enough to be capable of maintaining body weight in an energy abundant environment in which people tend to eat too much and show a lack of physical activity.

Susan Segerstrom showed that 1°C of adaptive thermogenesis (in a cold environment) can produce an extra loss of 250 kcal (Segerstrom 2007). The most effective nutrients and herbs increasing diet-induced thermogenesis are proteins (with special emphasis on the amino acid L-tyrosine, capsaicin (cayenne), green tea, coffee, DHA, arachidonic acid, piperin (black pepper), curcumin (curcuma) and Euodia fruit (Sneddon 2009, Belza 2007, Diepvens 2007, Westerterp 2004, Johnston 2002, Arai 2002, Kobayashi 2000).

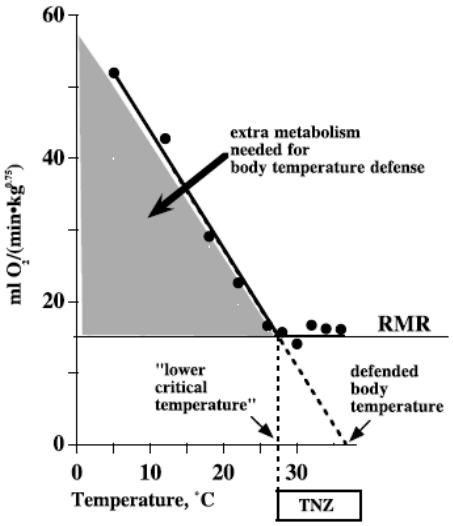



Figure 6 Environmental temperatures below the critical temperature induce activity of additional thermogenesis by BAT (Cannon 2004).

A placebo-controlled trial showed a significant effect on body weight, reduction in total fat and white fat through activation of additional thermogenesis by means of a so-called bioactive combination of supplements (Belza 2007, table 1).

| *Ingredient* | *Daily dosage* |
|---|---|
| Green tea extract | 1500 mg (whereof 376 mg catechins) |
| L-Tyrosine | 1218 mg |
| Caffeine | 302 mg (whereof 150 mg from green tea and 152 mg anhydrous caffeine) |
| Cayenne[a] | 450 mg (whereof 1.2 mg capsaicin or 240.000 scoville heat units) |
| Calcium carbonate | 3890 mg (whereof 2000 mg elementary calcium) |

Table 1 The bioactive combination used in a placebo-controlled trial (Belza 2007) during 8 successive weeks

Figure 7 shows the possible pathway by which this combination could activate BAT. Sympathetic innervation by noradrenalin triggers BAT uncoupled protein 1 activation. Capsaicin stimulates tyrosine hydroxylase which converts the precursor amino acid L-tyrosine into noradrenalin.
Catechins from green tea inhibit the breakdown of NA by blocking the phase II enzyme catechol-O-methyltransferase (COMT), whereas caffeine decreases the production of AMP and ATP, increasing heat-production and consumption of free fatty acids and glucose by BAT.

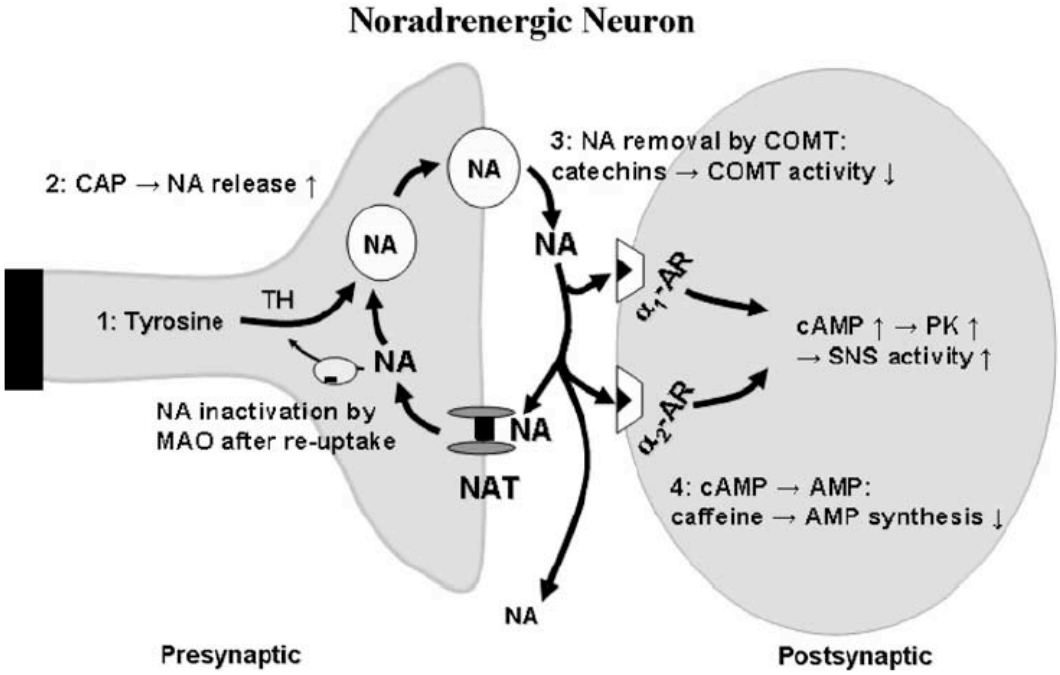



Figure 7 The working mechanism of the use of a so-called bioactive combination of L-tyrosine, green tea, caffeine and capsaicin. See the text for an explanation (Belza 2007).

Overall, it can be stated that the presence and activation of BAT are essential for maintaining body weight and an optimal fat percentage in humans. Activation is normally induced by cold, exercise and nutritional composition. Deiodinase II (DIDII), the enzyme responsible for converting T4 into T3, plays a crucial role in diet- and cold-induced thermogenesis.
Lack of DIDII due to selenium and/or iodine deficiency can lead to decreased BAT activation and loss of BAT (Celi 2009, figure 8). BAT was discovered in adults only a few years ago.

Scientific evidence makes it very plausible that the presence and activation of BAT has been driven by the evolutionary pressure of cold environments and high protein intake in early hominoids. Currently, human beings are living a "Star Trek" life with high carbohydrate intake, thermoneutrality, low-protein diets often deficient in micronutrients.
Absence of BAT makes people susceptible to weight gain and the inflammatory phenotype. Figure 9 recapitulates the latter two consequences of BAT atrophy in humans (van Marken 2009).

If normothermia and thermogenesis are reduced, people gain more weight than expected. Rapid increase in body weight is related to storage of abdominal subcutaneous, visceral and ectopic white fat. It are these three locations which seem to be responsible for the development of the metabolically unhealthy obese phenotype through several pathways, including tissue hypoxia, release of pro-inflammatory adipocytokines, fibrosis, insulin resistance and catecholamine resistance.

The next chapter will treat the scientific evidence related to the metabolically healthy and unhealthy obese phenotypes and provides possible solutions for people who have developed the inflammatory pathological obese phenotype leading to CVD, metabolic syndrome, depression and auto-immune diseases.

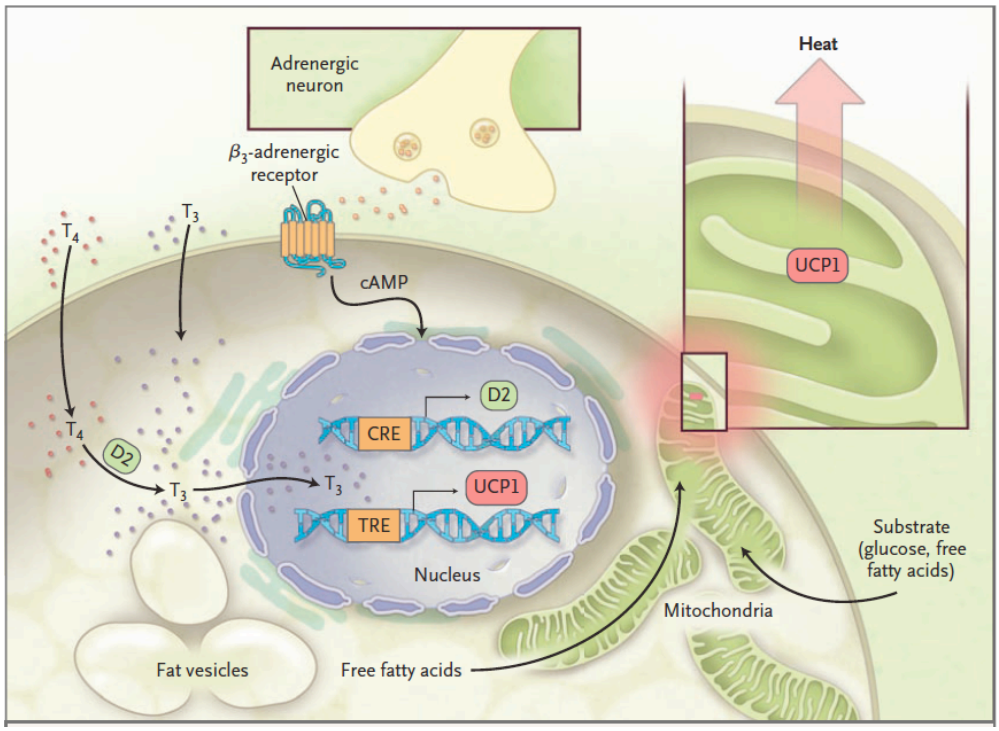



Figure 8 The activation of uncoupled protein 1 by T3, which is produced in the brown adipocyte itself through conversion of T4 by deiodinase II (D2), which needs selenium and iodine for co-enzymatic activation (Celi 2009).

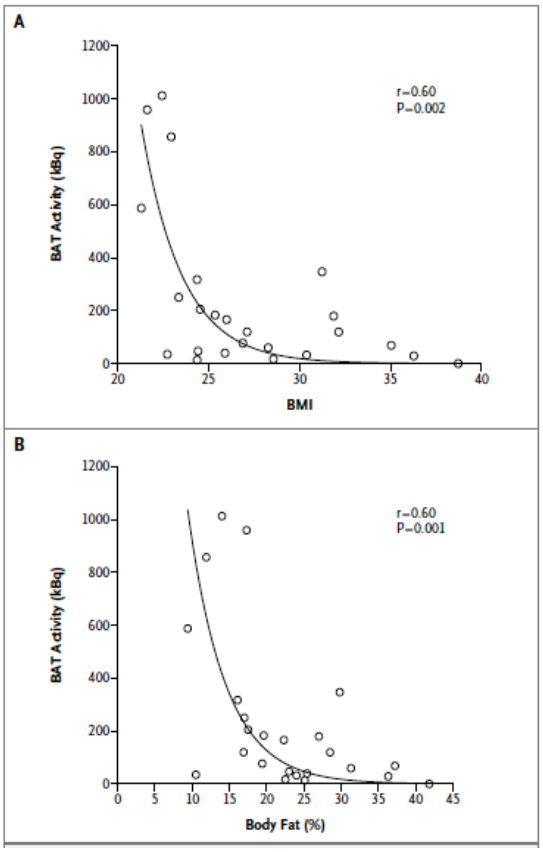


Figure 9 The relationship between BAT, body mass index (panel a) and total body fat (panel b). Note that both interactions are exponentially related (van Marken 2009).

**Healthy versus pathological obesity**

Obesity is a potent risk factor for metabolic and cardiovascular disease at the population level. However, at the level of the individual patient, correlations between body mass index and cardiovascular disease are not always straightforward, due, in part, to differences among adipose tissue depots with respect to the overall rate of adipocyte dysfunction, local degree of inflammation, and tissue vascularisation. Adipose tissue is a heterogeneous mix of adipocytes, stromal preadipocytes, immune cells, and endothelium. Combined, adipose tissue functions as a complex endocrine organ, secreting a host of factors collectively referred to as adipokines. The adipocyte "secretome" consists of molecules that have direct metabolic relevance to those with effects unrelated to metabolism. These include the highly adipocyte specific proteins adiponectin and leptin, the inflammatory chemokine TNF-alpha and an array of interleukins, angiogenic and vascoactive molecules such as VEGF and angiotensin II. The relative abundance of each adipokine potentially dictates the effects of adipose tissue as a whole. Adipose tissue develops in several distinct anatomical depots within the body, and the differential expansion of these depots is of great importance. Expansion of visceral or abdominal white adipose tissue (WAT) has been most strongly correlated to insulin resistance and cardiovascular disease in humans and animals. Conversely, expansion of subcutaneous WAT does not appear to have the same negative systemic consequences on metabolism.

At the other end of the spectrum is the condition of lipodystrophy wherein the dramatic loss of adipose tissue triggers a high degree of insulin resistance and signs of other metabolic dysregulation similar to visceral WAT expansion.
The importance of maintaining at least remnants of WAT was demonstrated by injecting adipocyte progenitors into the residual adipose depots of lipodystrophic mice: the depots expanded and the systemic metabolic profile was properly restored (Rutkowski 2009). Brown adipose tissue (BAT) falls within an entirely different metabolic category due to its primary function in generating body heat in infants and rodents. BAT is rich in mitochondria, highly vascularised, and because it affords none of the ill effects of visceral WAT, serves as an ideal paradigm for "good" adipose tissue (see above).

Combined, these disparities in the metabolic effects of distinct fat deposits not only dispel the generalized notion that adipose tissue exerts negative metabolic consequences under all conditions, but begs the question as to what distinguishes these individual depots with respect to their ability to expand. Recent results suggest that the balance between angiogenesis and hypoxia has a significant impact on the modulation of "good" versus "bad" tissue expansion, thereby implicating the local microvasculature as a key modulator of the systemic impact of adipose depots.
"Good" fat seems to be characterized by free expansion, small adipocytes and succeeded angiogenesis, whereas "bad" fat is poor in oxygen, lacks total neoangiogenesis and consists of big adipocytes embedded in a rigid fibrotic tissue
(figure 10, Rutkowski 2009, Khan 2009, Atti 2008, Scherer 2005, Rajal 2003).

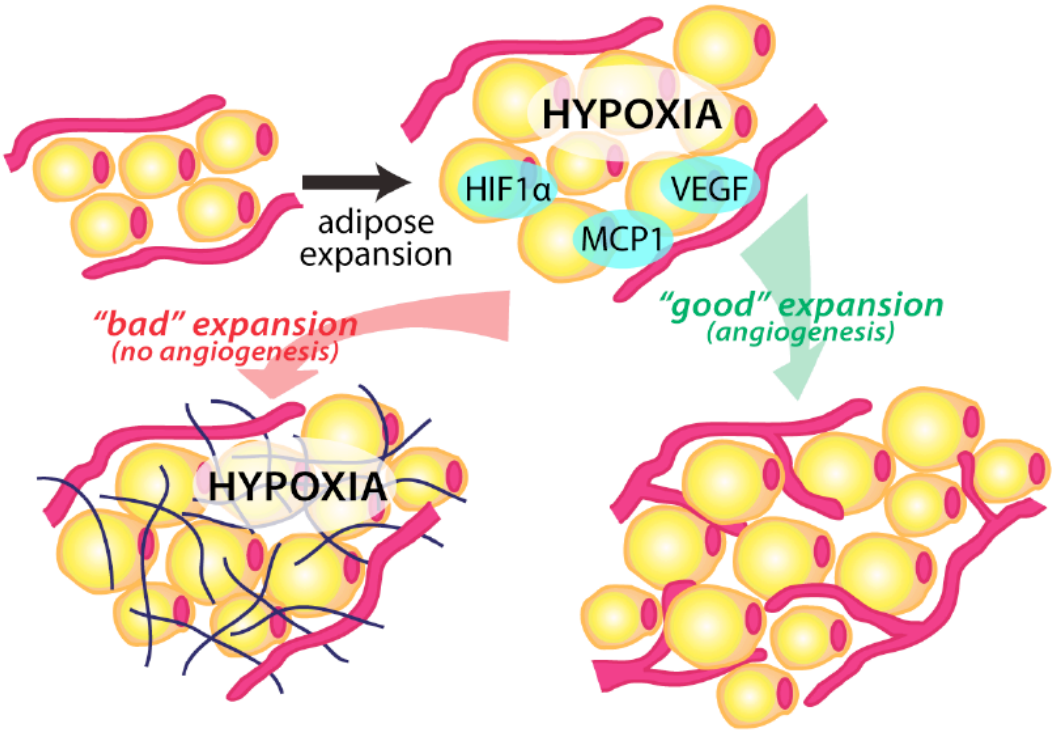



Figure 10 The difference between good and bad fat. Hypoxia seems to be the crucial factor (Rutkowski 2009)

**The healthy obese phenotype**

As yet, there is no uniform definition for obesity phenotypes. Healthy vs. pathological obesity has been defined based on levels of insulin resistance as well as on clustering of cardiometabolic risk factors, including components of metabolic syndrome, diabetes, and inflammation. Despite these varying definitions, the literature routinely demonstrates a high prevalence of healthy obese individuals. Defining healthy obesity solely on insulin sensitivity, Stefan et al. (Stefan 2008) have recently shown in a German population that 24.4% of obese participants were healthy rather than at-risk, despite the fact that participants were required to have a family history of diabetes and a previous diagnosis of impaired glucose tolerance or gestational diabetes.

Analyses done by the group of Rachel Widman (Widman 2009) using nationally representative data from the adult US population, defining healthy obesity as no more than one of six common cardiometabolic risk factors/diabetes [elevated blood pressure, elevated triglyceride, C-reactive protein, Homeostasis Model Assessment insulin resistance, or glucose levels/diabetes, or decreased HDL levels], indicated that 35.4% of obese US adult women and 29.2% of obese US adult men possessed the healthy obesity phenotype. Recalculating the prevalence of healthy obesity using more stringent criteria (BMI_30 kg/m2 but possessing none of the six cardiometabolic risk factors and conditions assessed), 16.6% of obese adults were still categorized as healthy obese.

Potential mechanistic determinants of healthy vs. at-risk obesity are related to the location and micro-structural differences between “healthy” and “unhealthy” fatty tissue. In addition to being a reservoir for energy, white adipose tissue is now recognized as an endocrine organ that releases a number of inflammatory cytokines and expresses receptors for traditional endocrine hormones.

As the epidemiology of healthy obesity still remains largely unstudied, its underlying mechanistic determinants seem to be related to expression of hypoxia inducible factor and its transcribed genes responsible for neoangiogenesis and the production of collagen tissue (Khan 2009).

Further possible factors are given by the role of a number of potential candidate hormones and pathophysiologic processes that are likely to play a role in allowing certain obese individuals to maintain a healthy cardiometabolic profile including adiponectin, leptin and resistin (Rajala 2003). Recent data, though limited, suggest that the characteristics of adipose tissue, including where it is located, its metabolic activity, and its histological characteristics, rather than the total amount of adipose tissue, may be of greater relevance and may partially determine cardiometabolic health among obese individuals.

Healthy fat locations seem to be peripheral subcutaneous fat and brown fat located at cervical, sternal and subclavicular level (Landsberg 2009, Scherer 2005, Haney 2002). Abdominal, visceral, ectopic and hyperactive omental fat should be considered possible pathological locations of pro-inflammatory fatty tissue contributing to the pandemic inflammatory obese phenotype.

People with a healthy obese phenotype can be healthy for more than 30 years although they show body mass indexes of over 30 and a total fat mass of 40%. This phenotype is further characterized by the equal distribution of fat on the body (arms and legs included and not only the torso) with so-called "fluffy" (or soft) fatty tissue.

**The pathological inflammatory obese phenotype**

Insulin resistance (IR) and the resulting elevated plasma levels of insulin have been related to metabolic syndrome and susceptibility to non-communicative inflammatory diseases such as CVD and depression (Hemmingsen 2009, Aminot 2004). Insulin itself is anti-inflammatory through several pathways, including inhibition of the universal inflammatory transcription factor nucleus factor kappa B (NfkB) and the increased uptake by insulin sensitive tissues of free fatty acids and glucose (figure 11, Dandone 2009, Chaudhuri 2004).

The key question is: Does insulin resistance constitute the inflammatory obese phenotype? Evidence for this is contradictory and inconsistent. In Pima Indians, the most insulin sensitive individuals turned out to exhibit a greater tendency towards weight gain than the most insulin resistant ones and low insulin levels were better predictors of weight gain.
Hyperinsulinemia accompanying insulin resistance can possibly arrest weight gain rather than promote it by increased sympathetic nervous system activity and postprandial thermogenesis. Mice with fat-specific disruption of the insulin receptor have reduced obesity. Contradicting this, other mechanisms have been suggested by which insulin resistance may facilitate fat storage.

Insulin exerts an antilipolytic effect in adipocytes and presumably this effect is relatively well-preserved in an otherwise insulin resistant state. Loss of neuronal insulin-leptin signalling can stimulate weight gain, but this mainly occurs through hyperphagia rather than metabolic frugality. The basic tenet of the hypothesis that insulin resistance contributes to a thrifty metabolism leading to energy storage is not unanimously supported.
A number of molecular mechanisms are now known by which adipocytes actively modulate insulin resistance. Surgical removal of fat rapidly reverses insulin resistance. Weight loss can prevent progression from impaired glucose tolerance to type 2 diabetes. The prevalence of obesity and IRS have rapidly increased and it is more logical to assume that increased obesity owing to increased energy intake has resulted into increase in insulin resistance (Watve 2007).

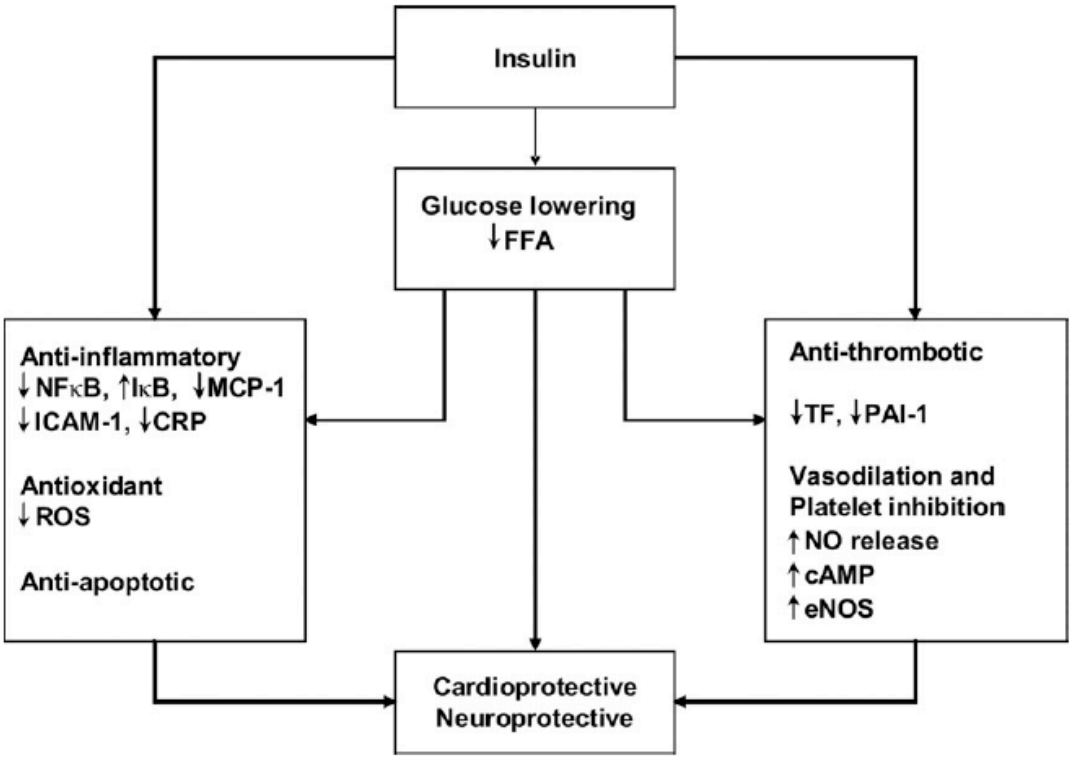



Figure 11 The anti-inflammatory, antiapoptotic, cardioprotective, and neuroprotective effects of insulin have been demonstrated both in humans and in animal models.

The vasodilatory, reactive oxygen species (ROS)-suppressive, antiplatelet, antithrombotic,and profibrinolytic effects have been demonstrated in humans.

ACS _ acute coronary syndromes;
cAMP _ cyclic adenosine monophosphate;
CRP _ C-reactive protein;
eNOS _ endothelial nitric oxide synthase;
FFA _ free fatty acid;
ICAM _ intracellular adhesion molecule;
IKB _ intracellular kappa B;
MCP _ monocyte chemoattractant protein;
NF_B _ nuclear factor-kappa B;
NO _ nitric oxide;
PAI _ plasminogen activator inhibitor;
TF _ tissue factor.

Higher insulin levels are probably adaptive when people suffer from insulin resistance, producing activation of the noradrenergic pathway in BAT (thermogenesis, Reaven 1996), overruling resistance levels (Hemminger 2009) and producing a shift towards the conservation of insulin function on non-insulin dependent tissues such as the brain and the pancreas which use insulin as a growth factor (Belsare 2010, Watve 2008, Watve 2007).

Figure 12 shows the adaptive functional shift towards insulin independent organs when dependent organs and tissues (such as muscle and subcutaneous fat) develop insulin resistance.

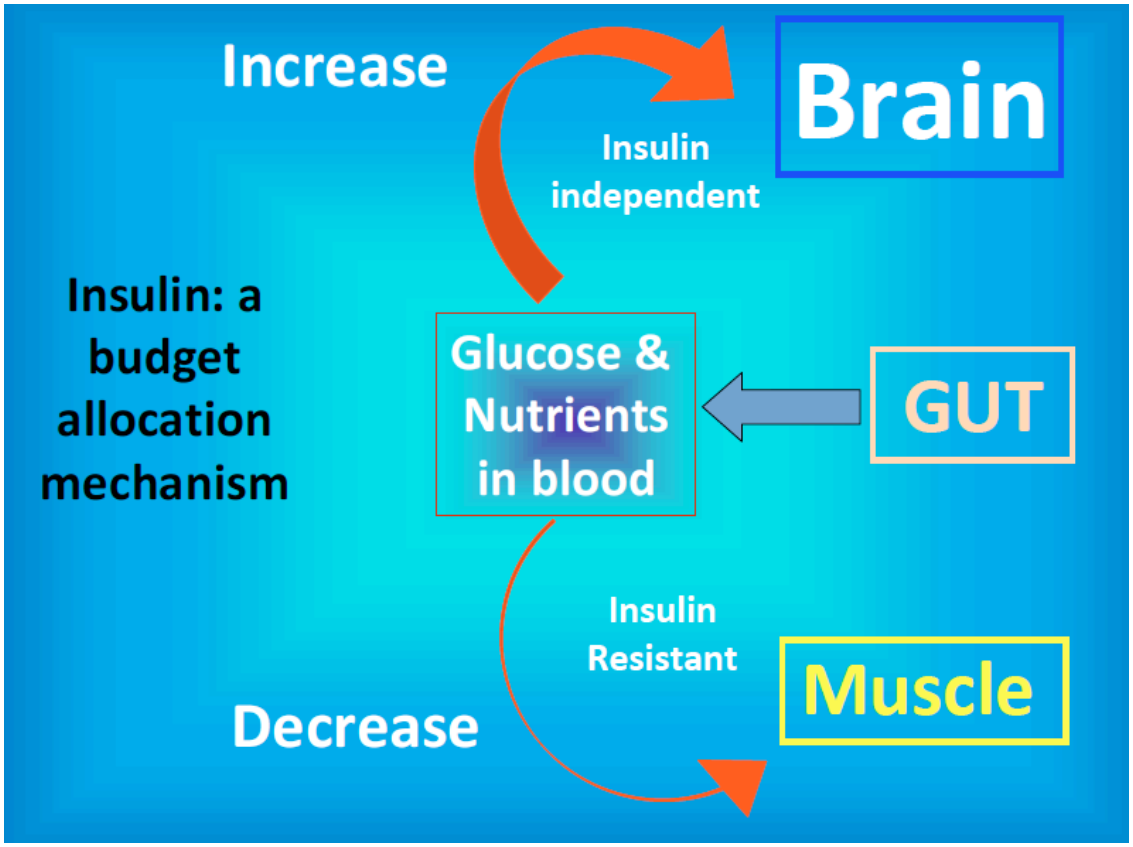



Figure 12 The shift from muscle to brain in insulin-resistant people; this shift can be considered adaptive as brain tissue (and other insulin independent organs such as the pancreas) is more important than muscle in a person with a typically sedentary life-style.

The exocrine pancreas is responsible for the production of digestive enzymes including proteases, lipases and amylases. These enzymes facilitate the uptake of macronutrients in the duodenum and the upper part of the small gut. Exocrine pancreatic tissue is independent of insulin (it does not need insulin to transport glucose) and uses insulin as a growth hormone. This function is essential for pancreatic conservation and therefore guaranteed by gap junctions between endocrine beta cells and the enzyme-producing acinar cells, the so-called islet-acinar portal system (Czako 2009, Pap 2004).

Damage to exocrine cells is inevitable because of partial activation of cell damaging proteases and lipases within the pancreas itself. To promote repair, insulin transport to the exocrine pancreas is therefore essential (Lam 1999). A recent review about the overall function of the islet-acinar portal system by Barreto et al (Barreto 2010) shows evidence that this system, maintained by a gap junction (figure 13), is atrophic in people suffering from metabolic syndrome, DM type II, hypertension and other inflammatory disorders.

The endocrine pancreas excretes all of its substrates into the portal vein. Therefore, the first organ to register possible damage to the islet-acinar system is the liver. The present author's explanation for this connection (the exocrine pancreas – liver connection) is the need to inform the liver about possible damage to the gap junctions between acinar and islet cells. Absence of these junctions impedes the repairing capability of insulin and could produce an exocrine pancreatic insufficiency syndrome. EPI can lead to significant loss of energy uptake by the gut and produce multiple organ disorder, failure and possibly death.

Molecules from the damaged pancreas together with an increase in free insulin are sensed by hepatocytes. Insulin resistance of the liver should be considered adaptive, enabling increase in arterial insulin levels, facilitating the reparation of acinar cells through insulin uptake from the pancreatic arteries as compensation for the lack of intra-pancreatic insulin transport (Pruimboom in prep.).

The development of IR in people with a positive energy balance should be considered adaptive and driven by evolution. Insulin availability to insulin independent organs, such as the brain and the pancreas, is more important than the glucose uptake in muscle in further sedentary people. Treating people with the inflammatory obese phenotype should therefore start with pancreas-repairing interventions, including pancreatic enzymes, zinc and probiotics (Pruimboom 2010). Treating IR starts when the typical EPI signs disappear with special emphasis on steatorrhea (Dominguez-Muñoz 2007).

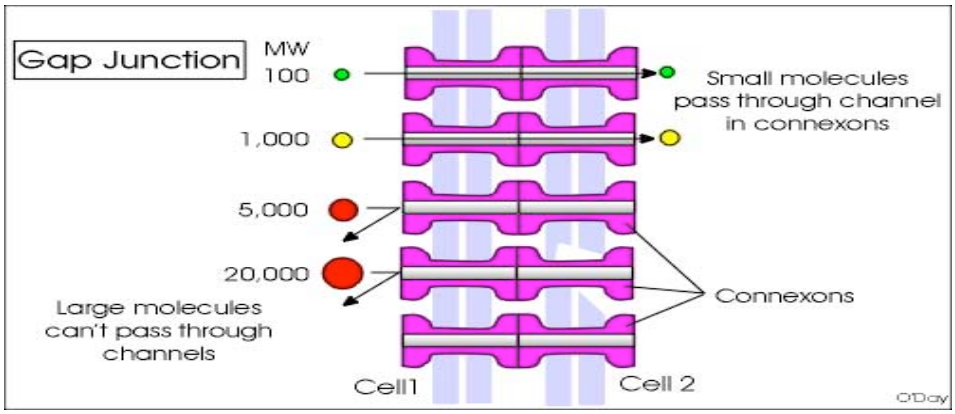



Figure 13 A gap junction as example of the islet-acinar portal system

It seems that the healthy obese phenotype and the pathological obese phenotype differ in the capability of producing and activating BAT, store fat at more or less pathological locations, metabolic efficiency and, not yet reviewed, the social role of the affected person.

The next chapter will treat the microstructural difference between healthy and pathological fat. The interaction between macro- and microstructural differences gives rise to the development of a treatment which could help to reduce this global problem.

**The difference between healthy and pathological white adipose tissue**

Overweight people can be divided in slow weight gain individuals and so-called "yo-yo individuals" (Schaar 2010). Fast weight gain has been related to increased susceptibility for the development of metabolic syndrome and inflammatory disorders (Demerath 2009), whereas slow weight increase seems to be benign, at least the first decades (Rasouli 2008, Scherer 2005). Slow weight gain enables adipocytes to proliferate and expand freely while fast adipocyte expansion could produce a hypoxia-susceptible type of fat (Khan 2009, Halberg 2009, Pasarica 2009). Free expanding adipocytes do not or hardly suffer from oxygen deficiency, while fast expanding tissue, including fat, tends to suffer from hypoxia and the necessity of activating the hypoxia-induced transcription factor 1 (HIF1, Khan 2009, Trayhurn 2007, Hosogai 2007, Ye 2007).

The half-life of HIF1 usually does not exceed a 5 minute period whereas HIF1 activity in inflammatory fat tissue can show an increased half-life of up to 60 minutes (Halberg 2009). HIF1 activates a wide array of genes involved in wound healing, including neoangiogenesis, cell proliferation/differentiation and collagen production. Adipocytes, which are part of the

adipose tissue, are normally embedded in a network of collagen (otherwise cells would be "floating"). The type of collagen is dependent on the type of enzyme activated by HIF1.

The normal wound-healing and tissue-expanding reaction will show higher levels of hyaluron-synthetase than lysyl oxidase. Long-term activation of HIF1 augments the production of lysyl oxidase, an enzyme responsible for deep tissue cross-linking and the subsequent type VI, very rigid, collagen (Halberg 2009, Khan 2009, Henegar 2007).

Figure 14 shows the difference between freely expanding "healthy" adipocytes and the pathological phenotype (Halberg 2009). The healthy phenotype is characterized by free expansion, few and little adipocytes, completed neoangiogenesis, high oxygen efficiency and low inflammatory activity.

The huge adipocytes go with the pathological phenotype, which is further characterized by a higher amount, and poor circulation of rigid collagen, high inflammatory activity and loss of PPAR sensibility. This last fact makes adipocytes less sensible to PPAR interventions (such as metformin or omega 3), making the person more vulnerable to pathological influences.

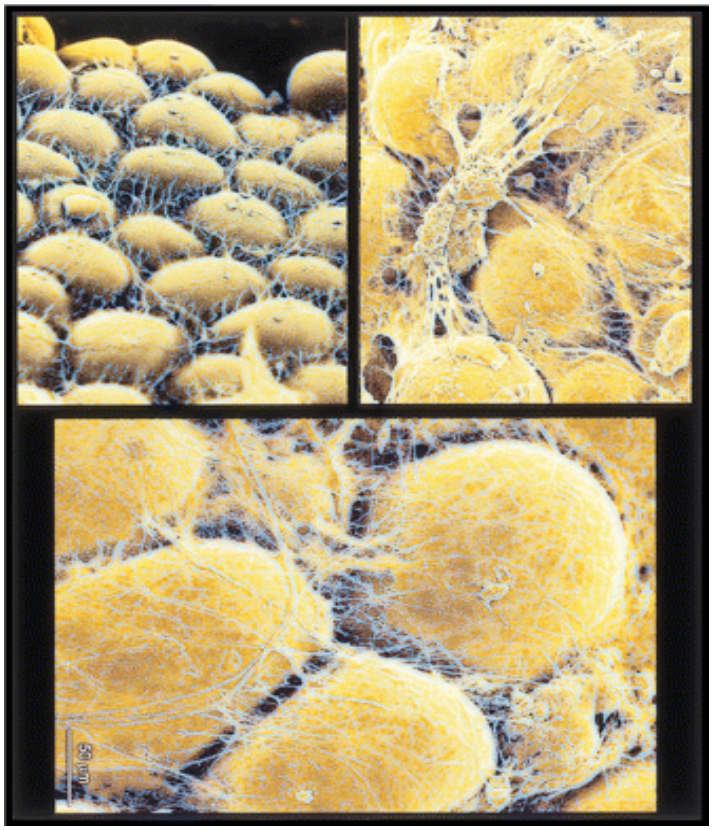


Figure 14 Healthy (upper left) versus inflammatory (upper right and below) fatty acid tissue (explanation see text)

The fast expansion of hypoxic adipocytes without a completed neoangiogenesis augments the danger of necrotic cell death in the centre of the fatty tissue plaque. The danger signals leaking from the necrotic cells attract macrophages which start to produce pro-inflammatory cytokines attracting other cells (such as neutrophils) to the now inflamed tissue. The infiltrating innate immune cells will consequently produce cytotoxic substances, damaging even more adipocytes, producing a "teufelskreiss".
It is probably this sequence of processes which makes a human being susceptible to the development of an inflammatory obese phenotype and non-communicative diseases such

as CVD, diabetes type II, depression and auto-immune disorders.

Figure 15 shows a schematic overview of the described process.

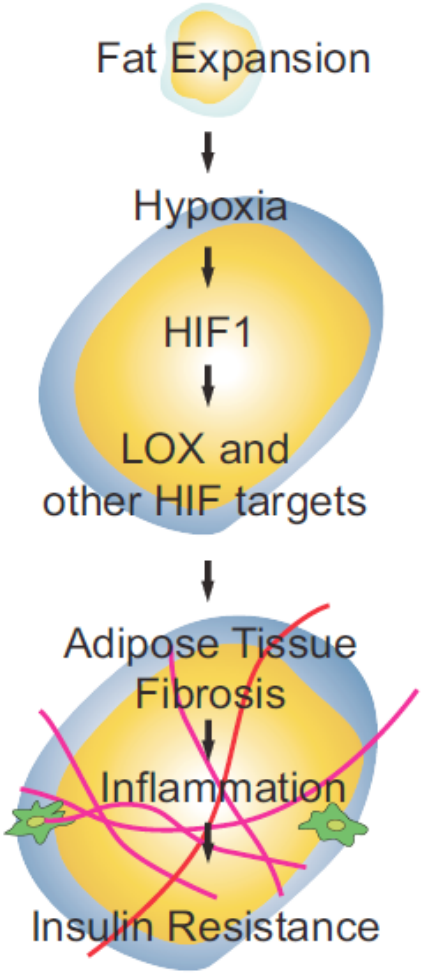



Figure 15 The process of producing inflammatory, insulin-resistant adipose tissue causing the pathological obese phenotype to develop

The amount of cytokine produced by central adipose tissue increases the central gradient to such an extent that peripheral wound healing usually is disturbed – this is a typical destiny for pathologically obese people (Watve 2007). Wound healing should follow a certain time- and event-specific sequence (Broughton 2006). Wound healing disorders could therefore be used as possible biomarkers of the inflammatory phenotype.

HIF1 and its target genes are all copper dependent and so is lysyl oxidase(Bie 2007). HIF1 can be switched off through upregulation of adiponectin (an anti-inflammatory adipocytokine)and molybdenum (a copper antagonist, Yance 2006) in the form of tetrahydromolybdate. The adiponectin-gene is a peroxysome proliferator-activator receptor gamma (PPARγ) target and can be stimulated by PPARγ ligands. Interesting candidates are vitamin D, vitamin A and the omega-3 fatty acid DHA (Sertznig 2010, Straus 2007). A notable fact is that for treatment purposes, a high dose of up to 12 grams of DHA is needed (Calder 2001).

It can be concluded that, in stead of insulin, *long-term insulin resistance* is the basic

mechanism leading to the inflammatory phenotype typical in obese people suffering from cardiovascular disorders, type 2 diabetes, depression and auto-immune diseases. Treatment of the inflammatory phenotype should be based upon improving insulin sensitivity (but not before pancreatic function is restored!).

Intervention candidates are metformin (proximate medicine) while substances such as omega-3 fatty acids (Masterton 2010), probiotics (Esposito 2009, Solga 2008), sylimarin (Velussi 1997), curcumin (Aggarwal 2010), allium sativum (Kodai 2009), momordica charantia (Hui 2008), resveratrol (Esker 2009) and zinc (Hashemipour 2009) have been proven to be effective natural interventions for people suffering from IR and its consequences.

**The consequences of the inflammatory obese phenotype**
The known consequences of the inflammatory obese phenotype are:

- Cardiovascular disorders
- Depression and other mental diseases
- Metabolic syndrome and type 2 diabetes
- Auto-immune diseases
- Some cancers

On the basis of these pathologies, a late (but not yet too late) diagnosis of inflammatory obesity can be made. Subliminal disorders which could be used as valid biomarkers of inflammation are:

- Acne
- Polycystic ovary syndrome
- Myopia
- Gout and pseudo-gout
- Skin tags
- Hyperpigmentation
- Alopecia
- Acanthosis nigricans
- Obstructive sleep apnea
- Paradontosis
- Hypertrophy of prostate and uterus
- Secular increase of body length

These are the pandemic disorders that turn inflammatory obesity and its consequences into a major global health problem. Together, they constitute what can be called '***A globesity pandemic'.***

**Conclusion**
The incidence of obesity is increasing throughout the world, producing severe health and economic problems, not only in developed countries but also in developing ones. Early preventive interventions are necessary to diminish the impact of sedentary life styles characterised by overabundant food intake (figure 16, Handschin 2008). Nevertheless, not all sedentary people with high energy intake develop obesity and even less of them develop *inflammatory* obesity.

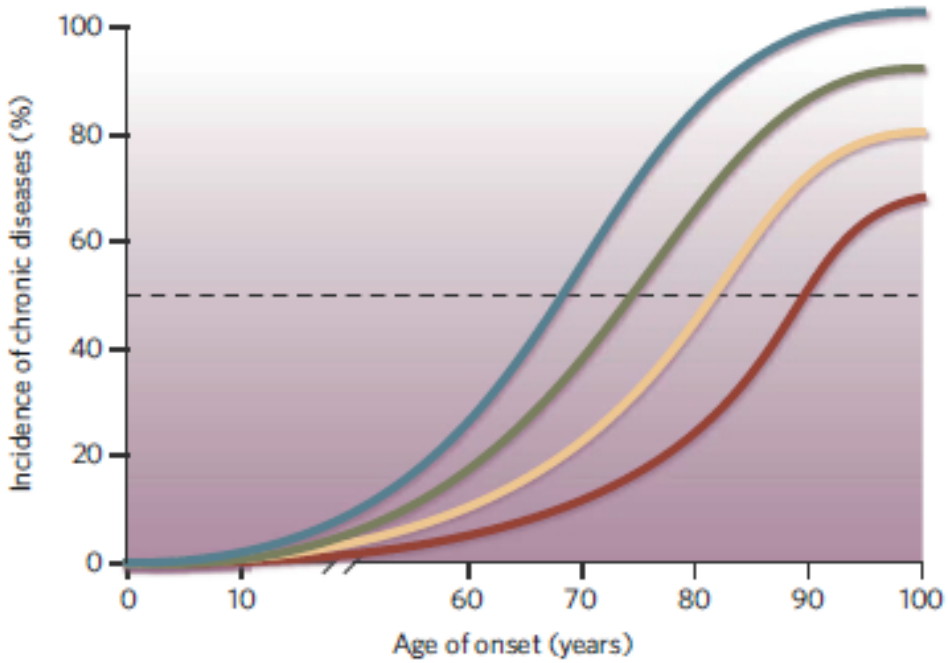



Figure 16 The onset of chronic disease depends on the start of the sedentary life-style (Handschin 2008).

Factors such as diet- and cold-induced thermogenesis seem to play an essential role in maintaining body weight and overall health. The modern human being lives a thermoneutral life and consumes a carbohydrate-rich diet. Both factors reduce energy output and make people more susceptible to obesity and inflammation. Further factors such as micronutrient deficiency (Eaton 2002) and early-life adverse experiences (ACE series) do also exert their influence.

Watve and colleagues give a new explanation for the development of obesity in people – a shift from soldier to diplomat induced IR, which had to be adaptive when nutrient intake depended on proteins and fats (Watve 2007). If this is true, social identity could drive us towards an even more obese phenotype – a phenotype highly susceptible to inflammation through the actual high carbohydrate diet having rapid body weight increasing effects. A behavioural return to a lifestyle a little bit more resembling that of hunter/gatherers could direct fat storage to the skin with the immune system following suit. Central inflammatory processes would diminish, wound healing would improve and behaviour normalized:

***'To restore health we have to go back to the future'***

**Literature**

1. Adams AE, Kelly OM, Porter RK. Absence of mitochondrial uncoupling protein 1 affects apoptosis in thymocytes, thymocyte/T-cell profile and peripheral T-cell number. BBA - Bioenergetics (2010), doi: 10.1016/j.bbabio.2010.04.016.
2. Aggarwal BB. Targeting Inflammation-Induced Obesity and Metabolic Diseases by Curcumin and Other Nutraceuticals. Annu. Rev. Nutr. 2010. 30:173–99.
3. Aminot-Gilchrist DV, Anderson HDI. Insulin resistance–associated cardiovascular disease: potential benefits of conjugated linoleic acid. Am J Clin Nutr 2004;79(suppl):1159S– 63S.
4. Arai S. Global view on functional foods: Asian perspectives. British Journal of Nutrition (2002), 88, Suppl. 2, S139–S143.
5. Attie AD, Scherer PE. Adipocyte metabolism and obesity. J. Lipid Res. 2009. 50: S395-S399.
6. Avena NM, Rada P, Hoebel BG. Evidence for sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav Rev. 2008 ; 32(1): 20–39.
7. Baak MA van. Meal-induced activation of the sympathetic nervous system and its cardiovascular and thermogenic effects in man. Physiology & Behavior 94 (2008) 178–186.
8. Barreto SG, Carati CJ, Toouli J, Saccone GTP. The islet-acinar axis of the pancreas: more than just insulin. Am J Physiol Gastrointest Liver Physiol 299: G10–G22, 2010.
9. Belsare PV, Watve MG, Ghaskadbi SS, Bhat DS, Yajnik CS, Jog M. Metabolic syndrome: Aggression control mechanisms gone out of control. Medical Hypotheses 74 (2010) 578–589.
10. Belza A, Frandsen E, Kondrup J. Body fat loss achieved by stimulation of thermogenesis by a combination of bioactive food ingredients: a placebo-controlled, double-blind 8-week intervention in obese subjects. International Journal of Obesity (2007) 31, 121–130.
11. Belza A, Gille MB, Schultz John S, Kondrup J. The □-adrenergic antagonist propranolol partly abolishes thermogenic response to bioactive food ingredients. Metabolism Clinical and Experimental 58 (2009) 1137–1144.
12. Berg F, Gustafson U, Andersson L. The Uncoupling Protein 1 Gene (UCP1) Is Disrupted in the Pig Lineage: A Genetic Explanation for Poor Thermoregulation in Piglets. PLoS Genet. 2006 Aug 18;2(8):e129.
13. Blaak EE, Hul G, Verdich C, Stich V, Martinez JA, Petersen M, Feskens EFM, Patel K, Oppert JM, Barbe P, Toubru S, Polak J, Anderson I, Astrup A, Macdonald I, Langin D, Sørensen T, Saris WH, NUGENOB Consortium. Impaired Fat-induced Thermogenesis in Obese Subjects: The NUGENOB Study. Obesity. 2007;15:653-663.
14. Boyd Eaton S, Strassman BI, Nesse RM, Neel JV, Ewald PW, Williams GC, Weder AB, Eaton III SB, Lindeberg S, Konner MJ, Mysterud I, Cordain L. Evolutionary Health Promotion. Preventive Medicine 34, 109-118 (2002).
15. Bray GA, Bellanger T. Epidemiology, Trends, and Morbidities of Obesity and the Metabolic Syndrome. Endocrine, vol. 29, no. 1, 109–117, February 2006.
16. Canoy D, Buchan I. Challenges in obesity epidemiology. Obesity reviews 8 (Suppl. 1), 1–11, 2007.
17. Celi FS, Brown Adipose Tissue - When It Pays to Be Inefficient. N engl j med 360;15, April 2009.
18. Cha SH, Fukushima A, Sakuma K, Kagawa Y. Chronic Docosahexaenoic Acid Intake Enhances Expression of the Gene for Uncoupling Protein 3 and Affects Pleiotropic mRNA Levels in Skeletal Muscle of Aged C57BL/6NJcl Mice. J Nutr. 2001 Oct;131(10):2636-42.

19. Chaudhuri A, Janicke D, Wilson MF, Tripathy D, Garg R, Bandyopadhyay A,Calieri J, Hoffmeyer D, Syed T, Ghanim H, Aljada A, Dandona P. Anti-Inflammatory and Profibrinolytic Effect of Insulin in Acute ST-Segment–Elevation Myocardial Infarction. Circulation 2004;109;849-854.
20. Dandona P, Chaudhuri A, Ghanim H, Mohanty P. Insulin as an Anti-Inflammatory and Antiatherogenic Modulator. J Am Coll Cardiol 2009;53:S14–20.
21. Del Mar Gonzalez-Barroso M, Ricquier D, Cassard-Doulcier AM. The human uncoupling protein-1 gene (UCP1): present status and perspectives in obesity research. Obesity reviews (2000) 1, 61–72.
22. Diepvens K, Westerterp KR, Westerterp-Plantenga MS. Obesity and thermogenesis related to the consumption of caffeine, ephedrine, capsaicin, and green tea. Am J Physiol Regul Integr Comp Physiol 292: R77–R85, 2007.
23. Feldmann HM, Golozoubova V, Cannon B, Nedergaard J. UCP1 Ablation Induces Obesity and Abolishes Diet-Induced Thermogenesis in Mice Exempt from Thermal Stress by Living at Thermoneutrality. Cell Metabolism 9, 203–209, February 4, 2009.
24. Frederich RC, Lollmann B, Hamann A, Napolitano-Rosen A, Kahn BB, Lowell BB, Flier JS. Expression of ob mRNA and its Encoded Protein in Rodents - Impact of Nutrition and Obesity. J. Clin. Invest. Volume 96, September 1995, 1658-1663.
25. Gong DW, He Y, Karas M, Reitman M. Uncoupling Protein-3 Is a Mediator of Thermogenesis Regulated by Thyroid Hormone, b3-Adrenergic Agonists, and Leptin. The Journal of Biological Chemistry Vol. 272, No. 39, Issue of September 26, pp 24129-24132, 1997.
26. Halton TL, Hu FB. The Effects of High Protein Diets on Thermogenesis, Satiety and Weight Loss: A Critical Review. Journal of the American College of Nutrition, Vol. 23, No. 5, 373–385 (2004).
27. Handschin C, Spiegelman BM. The role of exercise and PGC1□ in inflammation and chronic disease. Nature | Vol 454 | 24 July 2008, 463-9.
28. Hany TF, Gharehpapagh E, Kamel EM, Buck A, Himms-Hagen J, Schulthess GK von. Brown adipose tissue: a factor to consider in symmetrical tracer uptake in the neck and upper chest region. Eur J Nucl Med (2002) 29:1393–1398.
29. Hayden MR, Patel K, Habibi J, Gupta D, Tekwani SS, Whaley-Connell A, Sowers JR. Attenuation of Endocrine-Exocrine Pancreatic Communication in Type 2 Diabetes: Pancreatic Extracellular Matrix Ultrastructural Abnormalities. J Cardiometab Syndr. 2008 ; 3(4): 234–243.
30. Hemmingsen B, Lund SS, Wetterslev J, Vaag A. Oral hypoglycaemic agents, insulin resistance and cardiovascular disease in patients with type 2 diabetes. European Journal of Endocrinology 161 1–9.
31. Henegar C, Tordjman J, Achard V, Lacasa D, Cremer I, Guerre-Millo M, Poitou C, Basdevant A, Stich V, Viguerie N, Langin D, Bedossa P, Zucker JD, Clement K. Adipose tissue transcriptomic signature highlights the pathological relevance of extracellular matrix in human obesity. Genome Biology 2008, 9:R14.
32. Huang H, Song TJ, Li X, Hu L, He Q, Liu M, Lane MD, Tang QQ. BMP signaling pathway is required for commitment of C3H10T1/2 pluripotent stem cells to the adipocyte lineage. Proc Natl Acad Sci U S A. 2009 Aug 4;106(31):12670-5.
33. Inokuma KI, Ogura-Okamatsu Y, Toda C, Kimura K, Yamashita H, Saito M. Uncoupling Protein 1 Is Necessary for Norepinephrine-Induced Glucose Utilization in Brown Adipose Tissue. Diabetes 2005 May;54(5):1385-91.
34. Jakus PB, Sandor A, Janaky T, Farkas V. Cooperation between BAT and WAT of rats in thermogenesis in response to cold, and the mechanism of glycogen accumulation in BAT during reacclimation. J Lipid Res. 2008 Feb;49(2):332-9.
35. Janský L, Matoušková E, Vávra V, Vybíral S, Janský P, Jandová D, Kní□ková, Kunc P. Thermal, Cardiac and Adrenergic Responses to Repeated Local Cooling. Physiol. Res. 55: 543-549, 2006.

36. Johnston CS, Day CS, Swan PD. Postprandial Thermogenesis Is Increased 100% on a High-Protein, Low-Fat Diet versus a High-Carbohydrate, Low-Fat Diet in Healthy, Young Women. Journal of the American College of Nutrition, Vol. 21, No. 1, 55–61 (2002).
37. Joo JI, Kim DH, Choi JW, Yun JW. Proteomic Analysis for Antiobesity Potential of Capsaicin on White Adipose Tissue in Rats Fed with a High Fat Diet. Journal of Proteome Research 2010, 9, 2977–2987.
38. Keller MP, Attie AD. Physiological Insights Gained from Gene Expression Analysis in Obesity and Diabetes. Annu. Rev. Nutr. 2010.30:341-364.
39. Khan T, Muise ES, Iyengar P, Wang ZV, Chandalia M, Abate N, Zhang BB, Bonaldo P, Chua S, Schere PE. Metabolic Dysregulation and Adipose Tissue Fibrosis: Role of Collagen VI.Molecular and Cellular Biology, Mar. 2009, pp. 1575–1591 Vol. 29, No. 6.
40. Kobayashi Y, Nakano Y, Kizaki M, Hoshikuma K, Yokoo Y, Kamiya T. Capsaicin-Like Anti-Obese Activities of Evodiamine from Fruits of *Evodia rutaecarpa,* a Vanilloid Receptor Agonist. Planta Med 67 (2001) 628-633.
41. Kozak LP, Anunciado-Koza R. UCP1: its involvement and utility in obesity. Int J Obes (Lond). 2008 December ; 32(Suppl 7): S32–S38.
42. Kuji I, Imabayashi E, Minagawa A, Matsuda AMH, Miyauchi T. Brown adipose tissue demonstrating intense FDG uptake in a patient with mediastinal pheochromocytoma. Ann Nucl Med (2008) 22:231–235.
43. Landsberg L, Young JB, Leonard WR, Linsenmeier RA, Turek FW. Is obesity associated with lower body temperatures? Core temperature: a forgotten variable in energy balance. Metabolism Clinical and Experimental 58 (2009) 871–876.
44. Madsen L, Pedersen LM, Haukaas Lillefosse H, Fjære E, Bronstad I, Hao Q, Petersen RK, Hallenborg P, Ma T, De Matteis R, Araujo P, Mercader J, Bonet ML, Hansen JB, Cannon B, Nedergaard J, Wang J, Cinti S, Voshol P, Døskeland SO, Kristiansen K. UCP1 Induction during Recruitment of Brown Adipocytes in White Adipose Tissue Is Dependent on Cyclooxygenase Activity. PLoS One. 2010 Jun 30;5(6):e11391.
45. Marken Lichtenbelt WD van, Vanhommerig JW, Smulders NM, Drossaerts JMAFL, Kemerink GJ, Bouvy ND, Schrauwen P, Teule GJJ. Cold-Activated Brown Adipose Tissue in Healthy Men. N Engl J Med 2009; 360:1500-1508.
46. Menzaghi C, Scherer PE, Ercolino T, Trischitta V, Di Paola R, Berg AH, Doria A, Warram JH. A Haplotype at the Adiponectin Locus Is Associated With Obesity and Other Features of the Insulin Resistance Syndrome. Diabetes. 2002 Jul;51(7):2306-12.
47. Migrone G, Rosa G, Greco AV, Manco M, Vega N, Hesselink MK, Castagneto M, Schrauwen P, Vidal H. Decreased Uncoupling Protein Expression and Intramyocytic Triglyceride Depletion in Formerly Obese Subjects. Obes Res. 2003 May;11(5):632-40.
48. Moira AP de, Power C, Li L.Changing Influences on Childhood Obesity: A Study of 2 Generations of the 1958 British Birth Cohort. Am J Epidemiol 2010;171:1289–1298.
49. Muis MJ, Bots ML, Grobbee DE, Stolk RP. Insulin treatment and cardiovascular disease; friend or foe? A point of view. Diabetic Medicine, 22, 118-126, 2004.
50. Muoio DM. Metabolism and Vascular Fatty Acid Transport. N Engl J Med 2010; 363:291-293.
51. Murakami M, Kamiya Y, Morimura T, Araki O, Imamura M, Ogiwara T, Mizuma H, Mori M. Thyrotropin Receptors in Brown Adipose Tissue: Thyrotropin Stimulates Type II Iodothyronine Deiodinase and Uncoupling Protein-1 in Brown Adipocytes. Endocrinology 2001 142: 1195-1201.
52. Pruimboom L. Globesity; the obesity pandemia.
53. Rajala MW, Scherer PE. Minireview: The Adipocyte—At the Crossroads of Energy Homeostasis, Inflammation, and Atherosclerosis. Endocrinology. 2003 Sep;144(9):3765-73.
54. Reaven GM, Lithell H, Landsberg L. Hypertension and Associated Metabolic Abnormalities - The Role of Insulin Resistance and the Sympathoadrenal System. N Engl J Med 1996; 334:374-382.

55. Rousset S, Alves-Guerra MC, Mozo J, Miroux B, Cassard-Doulcier AM, Bouillaud F, Ricquier D. The biology of mitochondrial uncoupling proteins. Diabetes. 2004 Feb;53 Suppl 1:S130-5.
56. Rutkowski JM, Davis KE, Scherer PE. Mechanisms of Obesity and Related Pathologies: The Macro- and Microcirculation of Adipose Tissue. FEBS J. 2009 October ; 276(20): 5738–5746.
57. Ryu JW, Kim MS, Kim CH, Song KH, Park JY, Lee JD, Kim JB, Lee KU. DHEA administration increases brown fat uncoupling protein 1 levels in obese OLETF rats. Biochemical and Biophysical Research Communications 303 (2003) 726–731.
58. Schaar B, Moos-Thiele C, Platen P. Effects of Exercise, Diet, and a Combination of Exercise and Diet in Overweight and Obese Adults – A Meta-Analysis of the Data. The Open Sports Medicine Journal, 2010, *4*, 17-28.
59. Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. Diabetes. 2006 Jun;55(6):1537-45.
60. Sikora E, Scapagnini G, Barbagallo M. Curcumin, inflammation, ageing and age-related diseases. Immun Ageing. 2010 Jan 17;7(1):1.
61. Sneddon AA, Rayner DV, Mitchell SE, Bashir S, Ha JH, Wahle KW, Morris AC, Williams LM. Dietary Supplementation with Conjugated Linoleic Acid Plus n-3 Polyunsaturated Fatty Acid Increases Food Intake and Brown Adipose Tissue in Rats. Nutrients 2009, 1, 178-196.
62. Straus DS, Glass CK. Anti-inflammatory actions of PPAR ligands: new insights on cellular and molecular mechanisms. Trends Immunol. 2007 Dec;28(12):551-8.
63. Timmons JA, Pedersen BK. The Importance of Brown Adipose Tissue. N Engl J Med 2009; 361:415-421.
64. Trayhurn P, Wang B, Wood IS. HIF-1  protein rather than mRNA as a marker of hypoxia in adipose tissue in obesity: focus on "Inflammation is associated with a decrease of lipogenic factors in omental fat in women," by Poulain-Godefroy et al. Am J Physiol Regulatory Integrative Comp Physiol, October 1, 2008; 295 (4): R1098-R1098.
65. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto NJ, Enerbäck S, Nuutila P. Functional Brown Adipose Tissue in Healthy Adults. N Engl J Med 2009;360:1518-25.
66. Watve M, Mandani S. Why serum chemokine levels are raised in insulin resistance syndrome: An immune reversal hypothesis. Current Science Vol. 95, No. 2, 25 July 2008, pp. 171-4.
67. Watve M. Behavioral origins of metabolic syndrome disorders. Nature Precedings : doi:10.1038/npre.2010.4833.1 : Posted 29 Aug 2010.
68. Watve M. Ecological correlates of wildlife diseases. Nature Precedings : doi:10.1038/npre.2010.4834.1 : Posted 29 Aug 2010.
69. Watve MG, Yajnik CS. Evolutionary origins of insulin resistance: a behavioral switch hypothesis. BMC Evol Biol. 2007 Apr 17;7:61.
70. Westerterp KR. Diet induced thermogenesis. Nutr Metab (Lond). 2004 Aug 18;1(1):5.
71. Wildman RP, Mackey RH, Bostom A, Thompson T, Sutton-Tyrrell K. Measures of Obesity Are Associated With Vascular Stiffness in Young and Older Adults. Hypertension. 2003 Oct;42(4):468-73. Epub 2003 Sep 2.
72. Wildman RP. Healthy obesity. Current Opinion in Clinical Nutrition and Metabolic Care 2009, 12:438–443.
73. Wolf G. Brown adipose tissue: the molecular mechanism of its formation. Nutrition Reviews Vol. 67(3):167-171.
74. Wu Y. Overweight and obesity in China - The once lean giant has a weight problem that is increasing rapidly. BMJ VOLUME 333 19 AUGUST 2006;362-3.
75. Yance DR jr, Sagar SM, Targeting Angiogenesis With Integrative Cancer Therapies, Integrative Cancer Therapies 5(1); 2006 pp. 9-29.
76. York DA, Al-Baker I. Effect of corticotropin on brown adipose tissue mitochondrial GDP binding in obese rats. Biochem. J. (1984) 223, 263-266.

77. Zingaretti MC, Crosta F, Vitali A, Guerrieri M, Frontini A, Cannon B, Nedergaard J, Cinti S. The presence of UCP1 demonstrates that metabolically active adipose tissue in the neck of adult humans truly represents brown adipose tissue. FASEB J. 2009 Sep;23(9):3113-20.