EXACTA Adipose tissue—more than just fat

Obesity and obesity-related diseases have turned into a major global health risk. This is no longer restricted to highly developed countries and has reached epidemic degrees in many regions. A diversity of metabolic and inflammatory pathophysiological phenotypes can be related to obesity, which represent a burden for healthcare and insurance systems, but particularly to affected people. Our understanding of adipose tissue is no longer limited to its role in energy storage, but also includes knowledge about complex endocrine and immune interactions and involvement in the mechanical and thermal protection of the body. Therefore the discussion about energy intake and weight gain cannot be reduced to society’s body images and the treatment of obese patients should deviate from the focus on certain body mass index (BMI) levels. Recently there have been many studies aiming to gain more detailed insight into the complex relations between adipose tissue along with metabolic and inflammatory pathophysiological phenotypes. Adipose tissue is known to influence diverse metabolic parameters. A precise understanding of these effects is necessary to comprehend specific needs of obese patients. A number of articles addressing basic mechanisms related to obesity have recently appeared in Acta physiologica.

One area of clinical relevance for obese patients is the immune system. Duan et al recapitulate the connections between a high fat diet and diseases. Amongst these connections, the impact of a high fat diet on the immune system is one aspect. For instance they cite Turnbaugh et al and Le Chatelier et al, whose studies suggest an association of the gut microbial composition with adiposity and inflammation. Alterations in the gut microbiota and direct effects of free fatty acids on intestinal cells may be the first triggers for an upregulation of proinflammatory cytokines and adipokines. Duan et al relate a number of studies to each other that describe an upregulation of proinflammatory mediators in different tissues due to the elevation of circulating free fatty acids. Overall this leads to systemic low-grade inflammation, which then can lead to chronic diseases and certain types of cancer. For more details, please see the review by Duan et al on this topic. Another example is the activation of purinergic receptors in adipose tissue, which leads to the release of ATP through the pannexin-1 pore. ATP release is sensitive to glucose and insulin and correlates with increased cell metabolism, induces Ca$^{2+}$ signalling and lipolysis in adipocytes and promotes macrophage migration. Deregulation of the described ATP signalling can contribute to adipose tissue inflammation.

In search for possible obesity treatments, Decara et al explored potential new targets to tweak energy availability and/or expenditure. To regulate pathways of lipid and cholesterol metabolism, two receptors (GLP-1R and β3-AR) were found to mediate signalling in the control of mass and feeding behaviour via co-administrated agonists (liraglutide and CL316243). Those substances were able to potentiate an overall negative energy balance and to increase plasma levels of insulin and the pro-inflammatory interleukin-6 in male rats. Such a more negative energy balance goes along with a reduction in weight gain, fat/non-fat mass ratio and liver fat content and can influence the metabolic regulation of lipids and cholesterol. The research of Decara et al suggests the application of treatment with both agonists within obesity therapies.

It has become clear that in obesity not only adipose tissue itself is affected. The research of Chunchai et al focuses on the relation between obesity and metabolic and inflammatory brain pathologies. Their recent study monitors the influence of testosterone on obesity-induced metabolic disturbance, cognitive function as determined by the Morris Water maze test, glial morphological changes, increased hippocampal oxidative stress and cell apoptosis in hippocampus and cortex in rats. The authors investigated animals under high fat diet with bilateral-orchiectomy and their sham operated controls. Interestingly, under high fat diet a cognitive decline in obesity was aggravated by testosterone deprivation. The underlying mechanism might be related to oxidative stress and glial apoptosis.

Behaviour, influencing food intake as well as physical activity, is a key determinant in the development of obesity. The arcuate nucleus in the hypothalamus, together with anorexigenic POMC (pro-opiomelanocortin) neurons are key players in appetite suppression. Dysregulation of signalling pathways of hypothalamic and peripheral tissues leads to a dysfunctional regulation of energy intake. In this context Gao et al did show that adipocyte derived extracellular vesicles can enter...
hypothalamic anorexigenic neurons in the brain. They contain MALAT1 (metastasis-associated lung adenocarcinoma transcript-1), which acts as a competitive endogeneous RNA and activates the mTOR (mammalian target of rapamycin) signalling downregulating POMC protein expression.

Genetic variations may lead to tremendous changes in metabolic responses. Mutations in the non-selective monovalent cation channel TRPM5 have been associated with type II diabetes and metabolic syndrome. In addition, CD36 - a mediator for fatty acid uptake in skeletal muscle was identified as a link between obesity and skeletal muscle redox homeostasis and muscle regeneration. When Verpoorten et al fed mice with a high-fat diet, the CD36 deficient group occurred to be protected from weight-gain in comparison to the wild-type mice. But perturbed satellite cell function in this group also did provoke negative effects on muscle homeostasis and regeneration.

One major obesity-related metabolic disorder is diabetes mellitus type 2. Uncontrolled diabetes leads to serious damage due to chronic hyperglycaemia and can cause blindness, kidney failure, heart attacks, stroke and lower limb amputation. With hundreds of million people suffering from their inability to regulate their blood sugar, it is of major interest to understand the molecular mechanisms and find possible treatment targets behind obesity and diabetes. When Axelrod et al supervised 10 adults who changed from a sedentary routine to one that included five aerobic exercise trainings per week, they documented an alteration in the expression of mitochondrial fusion and fission proteins in their skeletal muscle. They were able to show that in addition to improved skeletal muscle mitochondrial volume, number and density, regular exercise training can promote a more fused, tubular network, which may contribute to insulin sensitivity and substrate utilization. Kristensen et al also showed that skeletal mitochondrial function and skeletal muscle lipid storage differ in their quality between lean and obese subjects. They demonstrate that alterations in the structure of muscle mitochondrial network and in the quality of skeletal muscle lipid droplets go along with gastric bypass surgery-induced weight loss and insulin resistance remission. Although findings on white adipose tissue oxygenation in humans with obesity are conflicting, in a group of 26 obese patients Lund et al did show that gastric bypass surgery-induced weight loss did provoke corresponding changes in mitochondrial respiratory capacity and increase in insulin sensitivity. Just very recently Makrecka-Kuka et al summarized mitochondrial dysfunction in association with altered metabolic function in the diabetic heart.

Glucagon and insulin are two major hormones balancing glucose utilization, production, and its uptake from blood into adipose as well as muscle tissue. The trans membrane protein GLUT4 is a main insulin-sensitive transporter responsible for glucose uptake. Recently, GLUT12 has gained attention as a promising new target for the treatment of insulin resistance. It was previously shown by Purcell et al that transgenic GLUT12-overexpressing mice show increased insulin sensitivity mediated by an increased glucose clearance rate in insulin-responsive tissues. In a recent study Gil-Iturbe et al describe GLUT12 as a leptin, adiponectin and insulin responsive receptor that plays a role in the modulation of glucose absorption. In this study the authors investigated the uptake of radiolabelled sugars into cells as well as GLUT12 expression under different levels of leptin and adiponectin and other conditions such as hypoxia in cell culture experiments. Interestingly, the same stimuli produce opposite effects on GLUT12 and GLUT4 expression. For example, hypoxia upregulates GLUT12 and downregulates GLUT4.

In addition to pathological adipocyte phenotypes, other obesity related factors can contribute to pathological phenotypes. Those clinically relevant outcomes are for example: sleep apnoea-induced intermittent hypoxia, effects on endothelial cell calcium signalling and alterations in renal sympathetic nerve activity. There are also studies that predict a relation between obesity and the risk to develop cancer.

Nowadays, adipose tissue is not only understood as a fat storage that releases free fatty acids, but as a complex endocrine organ that influences hormone balance, metabolic regulation and inflammatory levels, to name just a few. Although the regulatory effects of adipose tissue on oxidative stress, insulin resistance and inflammation are not fully understood (for more reviews see Ref. there are many hints due to relations that lead to a complex clinical picture of obese patients (see also Ref. ). In order to enable obese patients to maintain a long-term high life-quality, the here listed studies are only a few that aim to understand the manifold courses of affects that are triggered by adipose tissue dysfunction.

**CONFLICT OF INTEREST**

The author declares no financial or other conflict of interest that might bias this article.

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