Summary of Ph.D. thesis

Interaction between adipocytes and immune cells in pathogenesis of obesity related pro-inflammatory state of adipose tissue

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<tr>
<td>AT:</td>
<td>adipose tissue</td>
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<tr>
<td>BAs:</td>
<td>bile acids</td>
</tr>
<tr>
<td>ER:</td>
<td>endoplasmic reticulum</td>
</tr>
<tr>
<td>ERS:</td>
<td>endoplasmic reticulum stress</td>
</tr>
<tr>
<td>FA:</td>
<td>fatty acids</td>
</tr>
<tr>
<td>FXR:</td>
<td>farnesoid X receptor</td>
</tr>
<tr>
<td>HFM:</td>
<td>high fat meal</td>
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<tr>
<td>IL8:</td>
<td>interleukin 8</td>
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<tr>
<td>IR:</td>
<td>insulin resistance</td>
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<tr>
<td>LCD:</td>
<td>low calorie diet</td>
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<tr>
<td>MCP1:</td>
<td>monocyte chemoattractant protein 1</td>
</tr>
<tr>
<td>mRNA:</td>
<td>messenger ribonucleoid acid</td>
</tr>
<tr>
<td>PBMC:</td>
<td>peripheral mononuclear cells</td>
</tr>
<tr>
<td>PPARγ</td>
<td>peroxisome proliferator-activated receptor gamma</td>
</tr>
<tr>
<td>sGAT:</td>
<td>subcutaneous gluteal adipose tissue</td>
</tr>
<tr>
<td>SVF:</td>
<td>stroma-vascular fraction</td>
</tr>
<tr>
<td>T2DM:</td>
<td>type 2 diabetes mellitus</td>
</tr>
<tr>
<td>TGR5:</td>
<td>G protein bile acid coupled receptor 1</td>
</tr>
<tr>
<td>TNFα:</td>
<td>tumor necrosis factor alpha</td>
</tr>
<tr>
<td>TUDCA:</td>
<td>tauroursodeoxycholic acid</td>
</tr>
<tr>
<td>UDCA:</td>
<td>ursodeoxycholic acid</td>
</tr>
<tr>
<td>UPR:</td>
<td>unfolded protein response</td>
</tr>
<tr>
<td>VLCD:</td>
<td>very low calorie diet</td>
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<tr>
<td>WM:</td>
<td>weight maintenance</td>
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INTRODUCTION

1.1 Obesity
Obesity is characterized by an excessive accumulation of adipose tissue (AT). Development this state is an important risk factor for a number of medical conditions including diabetes, cardiovascular disease, hypertension, fatty liver disease that contribute to the morbidity and mortality. Therefore, there is a great need for obesity prevention or treatment. In present, three major strategies exists for treatment of obesity: lifestyle modification, medical therapies and bariatric surgery. Deciphering of exact effects of dietary intervention on AT is a goal of many studies including those that are the basis of this PhD thesis.

1.2 Adipose tissue
AT is a specialized, highly innervated and vascularised organ that consists from adipocytes and cells of stroma-vascular fraction (SVF) (preadipocytes, endothelial, immune cells and others). It can expand by increasing the size of pre-existing adipocytes (hypertrophy) or by generating new small adipocytes (hyperplasia). While increased adipocyte size correlates with poorer metabolic parameters, AT dysfunction, inflammation and adipocyte death, similar relationship between hyperplastic AT and adverse metabolic outcomes was not documented. Differentiation of preadipocytes/ability of AT to expand by hyperplasia is impaired in obesity and one of the goals of this thesis was to study the effect of weight loss on differentiation capacity of adipose precursors.

1.2.1 Adipose tissue depots
AT is a multi-depot organ located primarily in three major anatomical areas – 1. subcutaneous, 2. intra-abdominal fat depots associated with internal organ and 3. numerous small AT depots with specialized function related to the neighboring tissue. The regional distribution of body fat is an important determinant of health complications: increased visceral adiposity is associated e.g. with insulin resistance (IR), type 2 diabetes mellitus (T2DM), hypertension and with other comorbidities. On the other hand, increased amounts of AT in the gluteofemoral region is associated with improved insulin sensitivity and lower risk of developing T2DM in comparison to central obesity. Only few studies tried to decipher the basis of the protective character of subcutaneous
gluteal adipose tissue (sGAT); different uptake and release of nonesterified fatty acids (FA) in the subcutaneous abdominal AT when compared to sGAT \(^8\) or higher activity of lipoprotein lipase (LPL) \(^9\) suggestive of a higher capacity of sGAT for lipid accumulation could be candidates underlying cause. However, reasons of the phenomenon have still not been fully elucidated and are solved in this PhD thesis.

### 1.2.2 Adipose tissue as an endocrine organ

The whole AT is an active metabolic tissue that secretes metabolically important hormones, cytokines and chemokines. Those of them produced specifically by adipocytes are called ‘adipokines’ \(^10\), cytokines and chemokines are produced by both, adipocytes and cells of SVF. AT products have multiple effect on the organism and some of them also contribute to IR and cardiovascular complications associated with obesity \(^11\).

The best known adipokines are leptin and adiponectin. Cytokines produced by AT (by both adipocytes and SVF cells), can be divided into 3 groups: the first group is based on pro-inflammatory cytokines like tumor necrosis factor alpha (TNFα), interleukin 6 (IL6), macrophage migration inhibitory factor (MIF), interleukin 1 beta (IL1β) and transforming growth factor β1 (TGFβ1) \(^12\). The second group contains anti-inflammatory cytokines including interleukin 10 (IL10), interleukin 1 receptor antagonist (IL1RA) and interferon β (IFNβ). The third group are chemokines recruiting immune cells like monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 2 (MIP2), interleukin 8 (IL8) \(^13\) and others. The importance of cytokines lay in their direct effect on cellular metabolism as shown i.e. for TNFα that directly decreases insulin sensitivity and increases lipolysis in adipocytes \(^14\).

### 1.2.3 Inflammation

In obesity, circulating levels of inflammation markers, i.e. pro-inflammatory cytokines and acute phase proteins (haptoglobin and C-reactive protein: CRP) are substantially increased and this chronic state is defined as so called low-grade inflammation that may be causal in the development of IR and the other disorders associated with obesity \(^15\). It has been shown that the source of these inflammatory molecules are hypertrophied adipocytes and mainly immune cells (macrophages and lymphocytes) infiltrated into obese AT \(^16\).

### 1.3 Endoplasmic reticulum stress

One of the mechanisms which can contribute to the development of IR during obesity is a dysfunction of endoplasmic reticulum (ER) referred to as endoplasmic reticulum stress (ERS) \(^53\). The ER is an organelle responsible for
the trafficking, synthesis and maturation of proteins. Conditions that challenge ER function lead to an adaptive response system known as the unfolded protein response (UPR). The UPR pathway is mediated by three proximal transmembrane proteins: the first branch of UPR is represented by an activation of protein kinase RNA-like endoplasmic reticulum kinase (PERK), the second UPR branch is represented by an activated inositol requiring enzyme 1 (IRE1). The last branch of UPR consists of activating transcription factor (ATF) 6; All of them lead to the transcription activation of chaperones able to alleviate ERS.

1.4 Chemical chaperones
ERS plays an important role in the development of IR as well as inflammation. An experimental approach exists to resolve ERS and to support the ER folding machinery by providing exogenous low molecular weight compounds – chemical chaperones – that inhibit the formation of misfolded structures or aggregates. The short chain fatty acid derivative 4-phenylbutyrate (PBA) and the tertiary bile acids (BAs) have been shown to have chaperone-like activity. Regarding the chaperone activity of BAs, the most data concern animal studies, clinical data are insufficient. Therefore one of the aims of this PhD thesis was to determine the effect of BAs on ERS in human adipocytes and blood cells.

1.4.1 Bile acids
BAs are the end products of cholesterol catabolism. In addition to their critical roles in lipid and vitamin absorption, they are ligands for many receptors as well and thus play very important role in intracellular signaling. The best known nuclear receptor of BAs, farnesoid X receptor (FXR) was found to be highly expressed in the liver, intestine, kidney and adrenal glands. Signaling through this receptor has pleiotropic effect including the regulation of liver regeneration, hepatic inflammation or carcinogenesis and moreover, as proved in mice model, FXR may control AT biology as well.

The total G protein-coupled receptor (GPCR) family comprises over 800 receptors and the most studied member of this group (in relation to BAs) is G protein bile acid coupled receptor 1 (TGR5). The expression of TGR5 was detected in gallbladder epithelium, in the intestine, human monocytes and in brown AT. The beneficial effect of TGR5 activation revealed in brown AT is mediates thorough increased energy expenditure what can prevent obesity and T2DM development.
AIMS OF THE THESIS

This PhD thesis is divided into two parts according to the character of treatments: long term dietary interventions are summarized in the first part and two cross sectional studies are solved in the second part.

Specific aims therefore were:

Part I (studies evaluating the effects of long term dietary interventions)

❖ To compare the expression profile of inflammatory markers (cytokines and macrophage markers) between subcutaneous abdominal and gluteal AT in basal state and during the dietary intervention.

❖ To compare the secretory profiles and the adipogenic capacities of adipose cells derived from AT before and after weight loss.

Part II (studies focused on ERS and chemical chaperons)

❖ To determine whether chemical chaperones, ursodeoxycholic acid (UDCA) and its taurine conjugate, tauroursodeoxycholic acid (TUDCA), are able to suppress the stress of endoplasmic reticulum in adipose cells. To analyze effects of these BAs on human preadipocytes and differentiated adipocytes derived from paired samples of subcutaneous abdominal and gluteal AT.

❖ To determine whether inflammation induced by consumption of high fat meal is linked with stress of endoplasmic reticulum and whether UDCA is able to modified/prevent the formation of inflammation state and stress of endoplasmic reticulum in vivo.
RESULTS

List of publications

Part I

1. Expression of inflammation-related genes in gluteal and abdominal subcutaneous adipose tissue during weight-reducing dietary intervention in obese women
Lucia Mališová, Lenka Rossmeislová, Zuzana Kováčová, Jana Kračmerová, Michaela Tencerová, Dominique Langin, Michaela Šiklová-Vitková and Vladimír Štich
Physiological Research, 2014, March, 63(1): 73-82 IF: 1.5

2. Weight loss improves the adipogenic capacity of human preadipocytes and modulates their secretory profile
Lenka Rossmeislová, Lucia Mališová, Jana Kračmerová, Michaela Tencerová, Zuzana Kováčová, Michal Koc, Michaela Šiklová-Vitková, Nathalie Viquerie, Dominique Langin, and Vladimír Štich

Part II

3. Ursodeoxycholic Acid but not tauroursodeoxycholic Acid inhibits proliferation and differentiation of human subcutaneous adipocytes
Lucia Mališová, Zuzana Kováčová, Michal Koc, Jana Kračmerová, Vladimír Štich, Lenka Rossmeislová
Plos One, 2013, December, 8(12):e82086 IF: 3.7

4. Postprandial inflammation is not associated with endoplasmic reticulum stress in PBMC from healthy lean men
Jana Kračmerová, Eva Czudková, Michal Koc, Lucia Mališová, Michaela Šiklová, Vladimír Štich and Lenka Rossmeislová
British Journal of Nutrition, 2014, April, in press IF: 3.3
COMENTS TO THE RESULTS AND DISCUSSION

The first part of this thesis contains two clinical studies that were performed to examine the effects of diet-induced weight loss on inflammation status of gluteal AT in comparison with abdominal AT (part 1, study 1) as well as differentiation and secretory capacity of adipocytes (part 1, study 2). In the second part, two cross-sectional studies were designed to reveal 3. the effect of BAs on AT cells (part 2, study 3) and 4. to examine the relationship between ERS and postprandial inflammation in blood cells (part 2, study 4).

**Part I**

Body fat distribution is an important determinant of cardiovascular and metabolic diseases. The adverse effect of upper body fat accumulation and protective role of the lower body fat accumulation has been confirmed in many studies, although reasons of metabolic differences between these two depots have not been fully elucidated. Therefore, in the first study we examined if different clinical impact of gluteal and abdominal AT could be explained by lower pro-inflammatory profile of gluteal AT.

14 pre-menopausal women underwent 6 months lasted-dietary intervention consisting from 3 periods: low calorie diet (LCD), very low calorie diet (VLCD) followed by weight maintenance (WM) phase. Paired samples of gluteal and abdominal subcutaneous AT were acquired by needle biopsy and messenger ribonucleic acid (mRNA) of cytokines and macrophage markers, as markers of inflammatory status of AT, were further analyzed by real-time polymerase chain reaction (RT PCR).

Both, gluteal and abdominal, AT were analyzed before and during the whole calorie restriction. Contrary to the work of Evans et al. that reported higher expression of inflammatory genes in subcutaneous gluteal AT compared to abdominal AT, we reported no major differences in gene expression of pro-inflammatory markers between both depots in basal state. Discrepancies between our and Evans’s study could be based on differences in subjects recruited in the two studies: our study included only obese white women in contrast with mixed group of lean and obese black and white South African women examined in the study of Evans et al. Analysis of inflammation-related markers between both depots during dietary interventions revealed differences only in the pattern of 3 cytokines in gluteal compared to abdominal AT. The differential response of these markers might be linked to different response of gluteal AT (when compared to abdominal AT) to one of the upstream regulators of pro-inflammatory cytokine production, endocannabinoid system, as described in the study of Bennetzen et al. Moreover, similarly to
our previous study we observed enhancement of gene expression of macrophage markers in both depots during VLCD phase of diet what could be explained by enhanced FA release from adipocytes, as a possible trigger of macrophage activation and infiltration mediated by toll like receptor (TLR) 4 signaling.

To sum up, this study was focused on the comparison of inflammatory status of two depots before, during and after the weight loss. The data showed that weight loss induced by 6 months lasted dietary intervention leads to the similar changes in gene expression of pro-inflammatory markers in both subcutaneous abdominal AT and subcutaneous gluteal AT. Moreover, there were no major differences in gene expression in basal state between both examined depots.

The second study was focused on investigation of the effect of diet induced weight loss on adipocyte characteristics. Therefore, 23 obese, pre-menopausal women were included into 5-6 months lasting 2 phases dietary intervention: 3 moths’ LCD and consequently 3 months of WM. Adipocytes characteristics were examined in vitro: cell cultures were derived from adipose precursors acquired by needle biopsy in abdominal region before and after dietary intervention.

One of goals of this study was to compare the differentiation capacity of preadipocytes acquired from obese women before and after weight loss. As confirmed by quantification of lipid accumulation and gene expression analysis, the adipogenic potential of preadipocytes increased after weight loss as has been shown earlier in rat models. Lipogenesis that is essential for adipocytes maturation is down-regulated in obese patients but our study showed that adipocytes derived after the weight loss exhibited higher expression of key lipogenic enzymes. Moreover, the expression of osteogenic factor runt-related transcription factor 2 (RUNX2) was lower in preadipocytes after weight loss. This suggests that weight loss inhibits alternative lineage programs (e.g., osteogenesis) and favors the adipogenic differentiation.

The second aim of this study was the estimation of secretory capacity of adipocytes: levels of MCP1 or IL8 that increased with obesity, decreased after dietary intervention. Production of one of the insulin-sensitizing adiponectin was significantly enhanced in in vitro differentiated adipocytes derived from AT after weight loss.

Taken together, we determined that weight loss increased adipogenic capacity of preadipocytes and shifts their secretion profile to less pro-inflammatory state.
Stress of endoplasmic reticulum is one of the molecular triggers of adipocyte dysfunction and chronic low-grade inflammation accompanying obesity. It can be alleviated by chemical chaperons – BAs. Therefore, the third study was designed to study in vitro effects of UDCA and TUDCA on human preadipocytes and adipocytes derived from subcutaneous abdominal and gluteal AT obtained from 10 pre-menopausal obese women. Stress of endoplasmic reticulum, proliferation and differentiation of adipocytes as well as their inflammatory statuses were estimated. We revealed that UDCA, not TUDCA, have strong anti-proliferative effects what is in line with data of studies of Krishna-Subramanian et al. (2012) and Peiró-Jordán et al. (2012), that confirmed anti-proliferative potential of UDCA in carcinoma and normal intestinal cells.

Similar effect was observed in the case of differentiation: the effect of UDCA on adipocyte differentiation was striking inhibitory, as confirmed both, as oil red O staining of neutral lipids as the expression of key adipogenic markers. The mechanism through which UDCA acts is probably dependent on the sustained extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) phosphorylation which has been implicated in phosphorylation and consequently inhibition of master adipogenic regulator peroxisome proliferator-activated receptor gamma (PPARγ). The chaperone like properties indicated BAs as a potential therapy of obesity-related comorbidities. However, we could not confirm this beneficial effect of BAs in human adipocytes as neither of them was able to alleviate acute ERS induced by tunicamycin in these cells; none from 3 pathways of ERS was decreased as documented on the expression levels of X-box binding protein 1 (XBP1), heat shock protein A5 (HSPA5) and activating transcription factor (ATF) 4. Indeed, in support of our observation in human adipocytes, in vivo treatment of obese subjects with TUDCA did not alter the expression of ER chaperones in AT. This might be caused by low expression of BAs transporters in most extrahepatic tissues including AT.

Finally, we tested whether both BAs are able to reduce the pro-inflammatory status of adipocytes and thus eventually to decrease attraction of monocytes/macrophages into AT. Quite contrary, UDCA strongly up-regulated mRNA levels of chemokine and cytokines without activation of nuclear factor κ beta (NFκB) pathway as was confirmed previously.

To summarize, the effect of both BAs on adipocytes and its precursors are comparable in cells from both examined depots. But the effect of individual BAs was different: not only proliferation of preadipocytes but also...
differentiation of adipocytes was inhibited specifically by UDCA but not by TUDCA.

The fourth study was focused on the investigation of molecular triggers that lead to postprandial inflammation. Few studies have been shown that treatment of cells with saturated FA and high level of glucose is accompanied by ERS development and ERS-associated inflammation may be alleviated by chemical chaperons. Therefore, 10 healthy men were recruited to observation of postprandial inflammation in vivo in two-one day studies. The participants were given lactose (placebo-lactose) or ursodeoxycholic acid (URSOSAN) and consequently high fat meal (HFM) containing high content of lipids and sugars to induce postprandial inflammation. Fluorescence-activated cell sorting (FACS) analysis of cell surface markers and gene expression analysis of inflammatory cytokines in peripheral blood mononuclear cells (PBMC) separated into two populations of immune cells, monocytes and leukocytes, was performed. We observed that HFM is able to induce postprandial inflammation; absolute number of all measured cell, granulocytes, monocytes and leukocytes and mRNA levels of pro-inflammatory cytokines increased regardless of treatment to placebo or URSOSAN. Moreover, postprandial inflammation was accompanied by elevated level of CD11c, a marker of monocyte activation. To determine whether postprandial inflammation could be triggered by enhanced ERS, we analysed ERS markers representing all 3 arms of UPR. Following HFM challenge, mRNA expression of majority of ERS markers was not altered in PBMC. Thus, the classic activation of UPR does not seem to be the driver of postprandial inflammation. Due to the fact that HFM was not able to induce ERS, the effect of UDCA was negligible.

In conclusion, HFM-induced inflammation detectable on the level of gene expression in PBMC was not associated with elevated ERS and could not be prevent by UDCA.
CONCLUSIONS

This thesis was focused on the analysis of the effect of weight loss and of modulation of ERS on the pro-inflammatory status and other characteristics of AT. In addition, the link between ERS and postprandial inflammation was studied in blood cells. Two prospective dietary studies and two studies with pharmacological intervention were included into the thesis to fulfil aims of this thesis.

- Different clinical impact of subcutaneous gluteal and abdominal adipose tissue is not associated with differences in the inflammatory state of the respective adipose tissue: profile of mRNA expression of inflammation-related genes was not different in gluteal compared to abdominal adipose tissue in basal state or in response to dietary intervention.

- Weight loss induced by calorie restriction shifted the cytokine secretion profile of differentiated adipocytes in vitro towards a less pro-inflammatory one and improved preadipocyte adipogenic capacities.

- Neither ursodeoxycholic, nor tauroursodeoxycholic acid, the potential chaperones of stress of endoplasmic reticulum, were able to suppress the stress of endoplasmic reticulum in human adipose cells. Ursodeoxycholic acid negatively affected both proliferation and differentiation of adipose cells.

- Postprandial inflammation induced by consumption of high fat meal was not linked with the stress of endoplasmic reticulum in blood cells. Accordingly, chemical chaperone, ursodeoxycholic acid, was not able to prevent the postprandial inflammation in vivo.
SUMMARY

Obesity is considered to be a worldwide epidemic disease characterized by an accumulation of AT. Increased adiposity can perturb normal metabolic functions and lead to the development of diseases like insulin resistance and other metabolic disorders. A large amount of clinical studies have been shown that changes in inflammatory signaling in adipose tissue cells, increased infiltration of immune cells into AT as well as stress of endoplasmic reticulum belong to the key molecular steps leading to the development of metabolic disturbances associated with this disease.

Adverse metabolic effects of AT accumulation can be diminished by calorie restriction resulting in weight loss. In addition, stress of endoplasmic reticulum could be alleviated by chemical chaperones including bile acids. These two approaches for the treatment of obesity or the obesity-associated disturbances were basis for this PhD thesis.

In the first part of this work, we studied inflammation status of gluteal in comparison with abdominal AT and differentiation and secretory capacity of adipocytes after weight loss in obese patients. We revealed that inflammatory profile of gluteal AT, estimated by mRNA level of macrophages and cytokines as markers of inflammatory status of the body, did not explain the different clinical impact of subcutaneous abdominal and gluteal AT. We proved that weight loss is associated with an improvement of adipogenic capacity of preadipocytes in obese women as well as with change of the inflammatory status of adipocytes from more to less pro-inflammatory profile.

The second part of this PhD study consists from two cross-sectional clinical studies focused on the determination of the role of stress of endoplasmic reticulum and bile acids in AT and blood cells exposed to different experimental conditions.

We investigated effects of ursodeoxycholic acid (UDCA) and tauroursodeoxycholic acid (TUDCA) on preadipocytes and adipocytes derived from human AT of obese patients. Our results demonstrate that from two studied bile acids, only UDCA, is able to influence physiology of AT cells and neither from two tested bile acids were able to suppress the stress of endoplasmic reticulum.

Except for the excess of AT, also food intake is accompanied by transiently elevated concentrations of inflammatory markers in the bloodstream, so-called postprandial inflammation. We hypothesised that stress of endoplasmic reticulum could be one of the possible triggers of postprandial inflammation.
However, our results showed that postprandial inflammation was not accompanied by the stress of endoplasmic reticulum and was not preventable by UDCA.

To sum up, results of this thesis contributed to the understanding of the impact of weight loss and chemical chaperones on the molecular characteristics of AT. At the same time, the outcomes of the thesis stressed the need of further investigation of the individual AT depots, role of bile acids in human AT physiology and triggers of postprandial inflammation.
SUHRN

Obezita je považovaná za ochorenie svetového epidemiologického významu. Je charakterizovaná hromadením tukového tkaniva (TT), ktoré sa spája so zhoršením normálnej metabolickej funkcie tohto tkaniva. Veľké množstvo klinických štúdií poukazuje na obezitou vyvolané zmeny v zápalovej signalizácii, zvýšenej infiltrácií imunitných buniek do tukového tkaniva, či stres endoplazmatického retikula ktoré sú možnými molekulárnymi pričinami vedúcimi k vzniku inzulinovej rezistencie a iných metastických chorôb asociovaných s obezitou.
Zhoršenú metabolickú funkciu TT môže zlepšiť kalorická restrikcia. A chemické šaperóny, akými sú žlčové kyseliny, modulujú stres endoplazmatického retikula. Spomínané dva prístupy liečby obezity a ochorení asociovaných s obezitou sa stali podkladom pre túto prácu.

V prvej časti tejto práce sme študovali pro-zápalový stav gluteálneho TT v porovnaní k abdominálnemu TT, ako aj diferenciačné a sekrečné vlastnosti adipocytov po úbytku váhy u obéznych pacientov. V prvej štúdií sme zistili, že zápalový profil gluteálneho TT, hodnotený pomocou mRNA hladín makrofágov a cytokínov, nevysvetľuje rozdiel klinického dopadu podkožného a gluteálneho TT v tele. Ďalej bolo dokázané, že úbytok hmotnosti ide ruka v ruke so zlepšenou schopnosťou preadipocytov diferencovať, ako aj znižením ich pro-zápalového profilu.

Druhá časť tejto práce pozostáva z dvoch prierezových klinických štúdií zameraných na determináciu účinku žlčových kyselín na preadipocyty a adipocyty. Hodnotili sme účinok ursodeoxycholovej (UDCA) a tauoursodeoxycholovej kyseliny na preadipocyty a adipocyty zo TT obéznych pacientov. Naše výsledky demonštrujú, že z dvoch testovaných žlčových kyselín, jedine UDCA je schopná ovplyvniť fyziológiu buniek TT, avšak žiadna z týchto dvoch kyselín nebola schopná potlačiť stres endoplazmatického retikula.

Nelén prebytok TT, ale a príjem potravy sprevádza prechodne zvýšená koncentrácia zápalových markrov v krvnom riečisku za vzniku postprandiálneho zápalu. Pretože presné molekulárne mechanizmy spúšťajúce postprandiálny zápal nie sú úplne známe, predpokladali sme že stres endoplazmatického retikula by mohol byť možným spúšťačom tohto stavu. Naše výsledky však naznačujú, že postprandiálny zápal nie je asociovaný so vznikom stresu endoplazmatického retikula, a preto UDCA bola v týchto podmienkach neúčinná.
Na záver, výsledky tejto práce prispeli k pochopeniu dopadu úbytku hmotnosti a vplyvu chemických šaperónov na molekulárne charakteristiky TT. Zároveň, výstupy tejto práce poukazujú na potreby ďalšieho skúmania jednotlivých dep TT, úloh žlčových kyselín vo fyziológií ľudského TT a spúšťačov postprandiálneho zápalu.
ANNECES

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