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Summary of Ph.D. thesis

Regulation of adiponectin and its isoforms production in human obesity

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INTRODUCTION

Obesity is a multifactorial disorder influenced by genetic and environmental factors with increasing incidence worldwide at an alarming rate. Obesity is characterized as a low-grade inflammatory state accompanied by insulin resistance which can actually develop into a broad clinical complications. The development of obesity-related complications closely relate with dysfuncion of adipose tissue caused by abnormal fat accumulation leading to the peripheral insulin resistance and metabolic disruption of insulin sensitive organs (e.g. muscle, liver) subsequently inducing whole body insulin resistance. Seeking for the culprits of insulin resistance and obesity-related disorders many possible inductors or contributors disturbing body energy homeostasis has been revealed.

Two theories are emerging that provide a molecular understanding of obesity-related insulin resistance [1]. First, enduring nutritional overload causes a failure of effective metabolic buffering in adipose tissue through well-controlled release and uptake of free fatty acids on demand. Overnutrition results in exhaustion of the adipocytes storage capability concomitant with overflow of fatty acids to other organs, such as liver and muscle. This improper fatty acids accumulation negatively impacts the normal metabolic functions and affects the sensitivity of these organs to insulin action. The second hypothesis, and not mutually exclusive to the first one, suggests that caloric excess causes a remodeling of adipose tissue with increased macrophage content, changes of tissue cellularity, and dysregulation of the adipocytes function with a variety of stresses (hypoxia, oxidative stress, stress of endoplasmatic reticulum (ER)) and inflammatory processes within adipose tissue [2]. Expansive adipose tissue triggers qualitative and/or quantitative changes in adipokine production with variable effects on lipid synthesis, lipolysis, insulin action, adipogenesis and the overall adipocyte metabolism. Dysregulation of adipokines production by adipose tissue, with the shift to the production of a proinflammatory, atherogenic, and diabetogenic adipokine pattern, is supposed to be one of the major culprits of metabolic disorders and chronic low-grade inflammatory state occuring in obesity [3]. Higher levels of proinflammatory adipokines may modulate insulin sensitivity and lead to both local and systemic insulin resistance. In contrast to many other adipokines, levels of adiponectin has

been proved to be reduced in a number of obese and insulin resistant states [4-6] and weight loss and/or improvement of insulin sensitivity might increase adiponectin expression or plasma levels [7-10]. Series of clinical and experimental studies have reported that adiponectin functions as an anti-atherogenic, antiinflammatory and anti-diabetic adipocytokine, and protects against obesity-related cardiovascular and metabolic diseases. Environmental factors, such as overnutrition and physical inactivity and/or genetic factors can lead to low plasma adiponectin level (hypoadiponectinaemia) (Figure 1.). Further, impairement of adiponectin has been demonstrated in relation to obesity-related metabolic disturbances (dislipidemia, hypertension, metabolic syndrome, diabetes, atherosclerosis). However, it is unrevealed yet whether decreased adiponectin production is a cause or a consequence of the dysregulated metabolic state [11].

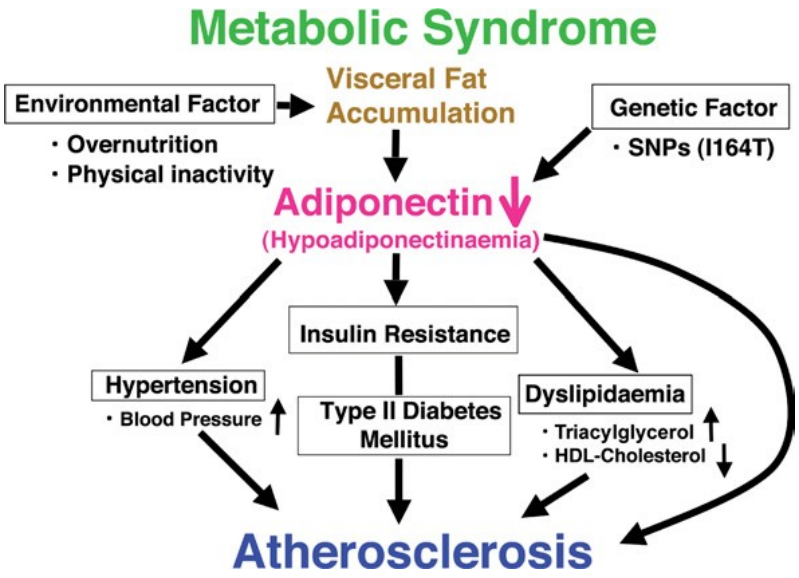

Figure 1. Adiponectin in the metabolic syndrome and related disturbances (Okamoto, 2006, Clinical Science, 110:267–278).

Adiponectin is present intracellularly and in the circulation in various homomultimeric complexes [12, 13]. It is synthesized as a single polypeptide which is assembled in the ER into different molecular weight isoforms. The basic adiponectin isoform consists of low molecular weight (LMW) trimers which are formed throughout noncovalent interactions within the collagenous domains in a triple helix. The oxidizing environment within the lumen of the ER favours disulfide bond formation through which trimers can associate into middle

molecular weight (MMW) hexamers and high molecular weight (HMW) multimers composed of 12-18 monomers [14, 15]. Particular isoforms are suggested to be affected selectively in obese, insulin-resistant or diabetic patients [16, 17] and weight reduction and/or treatment with thiazolidinedions might reverse its levels, targeting preferencialy the HMW form [18]. The mechanism causing the decrement of adiponectin levels and its particular isoforms in obesity is of interest particularly when considering its positive pleiotropic effects in the body. The process of the protein secretion might be critical especially since multimeric proteins and selective regulations in the secretion pathway might be expected. It is known that weight loss in most cases leads to the improvement of clinical parameters and overall heath. Although, the involvement of adiponectin in the weight loss-induced improvement of whole body insulin sensitivity is still not clear.

Therefore, looking for the regulations that could contribute to lower levels of adiponectin in obesity and especially for dysregulations of particular adiponectin isoforms could help to understand the physiological impact of this protein and could contribute to alleviating obesity related deteriorations of metabolic state.

AIMS OF THE THESIS

The general aim of my research in frame of my PhD study was to investigate the regulation of the production of adipose tissue derived proteins in obesity with special focus on adiponectin and its isoforms; to examine the relation of its impaired production with the state of obesity and insulin resistance; to observe changes induced by non-pharmacological weight loss directed interventions achieved by caloric restriction in different groups of subjects; and to reveal possible role and depot specific regulations of adiponectin production in obesity.

The particular goals were:

- Examine the impact of weight-reducing dietary interventions on the levels of adiponectin and adiponectin isoforms in circulation of obese people;

- Investigate relationship between the diet-induced modifications of insulin resistance and those of adiponectin isoforms;

- Investigate the changes of adiponectin and adiponectin isoforms secretion in human adipose tissue during the caloric restriction-induced weight loss;

- Compare adiponectin and adiponectin isoforms production in subcutaneous versus visceral adipose tissue and investigate the impact of obesity on the adiponectin isoforms production in these two fat depot.

RESULTS

LIST OF PUBLICATIONS:

1. An increase in plasma adiponectin multimeric complexes follows hypocaloric diet-induced weight loss in obese and overweight pre-menopausal women.
Polak J, Kovacova Z, Jacek M, Klimcakova E, Kovacikova M, Vitkova M, Kuda O, Sebela M, Samcova E, Stich V.
Clinical Science (Lond), **2007**, 112(11):557-565.
IF 4.613

2. Total adiponectin and adiponectin multimeric complexes in relation to weight loss-induced improvements in insulin sensitivity in obese women: the NUGENOB study.
Polak J, Kovacova Z, Holst C, Verdich C, Astrup A, Blaak E, Patel K, Oppert J M, Langin D, Martinez J A, Sørensen T I A and Stich V.
European Journal of Endocrinology, **2008**, 158: 533–541.
IF 3.482

3. Secretion of adiponectin multimeric complexes from adipose tissue explants is not modified by very low calorie diet.
Kovacova Z, Vitkova M, Kovacikova M, Klimcakova E, Bajzova M, Hnevkovska Z, Rossmeislova L, Stich V, Langin D, Polak J.
European Journal of Endocrinology **2009,** 160(4):585-592.
IF 3.482

4. The impact of obesity on secretion of adiponectin multimeric isoforms differs in visceral and subcutaneous adipose tissue
Zuzana Kovacova, Michaela Tencerova, Balbine Roussel, Zuzana Wedellova, Lenka Rossmeislova, Dominique Langin, Jan Polak and Vladimir Stich.
Accepted for publication in *International Journal of Obesity.*
IF 5.125

COMMENTS ON THE ORIGINAL PAPERS:

Three longitudinal dietary studies were designed to examine the effects of diet-induced weight loss on metabolic improvements in relation to adiponectin and specificaly to the multimeric isoforms of adiponectin and one cross-sectional study to examine the contribution of different fat depots (SAT and VAT) in the regulation of adiponectin isoform production.

In the first study, we examinated if diet-induced changes in body weight and insulin sensitivity are associated with changes in the quantity of adiponectin multimeric complexes.

20 pre-menopausal women with the BMI classified as overweight or obese were recruited. All subjects underwent 12 weeks of low caloric diet (LCD) resulting in significant loss of weight and improvement of whole-body insulin sensitivity. Similarly, parameters of lipid and glucose metabolism improved following the diet.

Our study showed that LCD induced an increase in plasma levels of all the adiponectin multimeric complexes (HMW, MMW and LMW) with the biggest increase of the LMW isoforms. To understand the physiological relationship and involvement of adiponectin isoforms in diet-induced improvement of the metabolic parameters, the correlations between adiponectin multimeric complexes and biochemical and anthropometrical indices have been performed. HMW isoform has shown to have an important role in the regulation of insulin sensitivity. Our data proved a close association of the HMW isoform with fasting glucose levels, however, no associations between the HOMA (homeostasis model assessment) index with any of the adiponectin multimeric complexes have been detected. Moreover, the HMW adiponectin was negatively associated with WHR (waist/hip ratio) and diet-induced changes in the HMW form negatively related with changes in the percentage of fat mass suggesting its impairment with central body fat mass expansion.

To summarize, our study showed that moderate weight loss induced by 3 months hypocaloric diet led to an increase in the amounts of HMW, MMW and LMW adiponectin multimeric complexes in plasma. No direct relationships between the diet-induced changes in individual adiponectin complexes and parameters of insulin sensitivity were found.

In the second study, we investigated whether diet-induced changes in insulin sensitivity relate with plasma adiponectin levels and changes of adiponectin multimeric isoforms. Therefore, we performed a retrospective study with focus on a well defined groups of obese subject undergoing 10-week low-caloric low-fat diet. The selection of the two groups (called

as ‘responders’ and ‘non-responders’) was based on the evaluation of the highest and lowest reduction of HOMA index of the participants after the diet-induced weight loss. Both responders and non-responders, achieved comparable reduction of body weight and fat mass and did not differ in other anthropometric or metabolic parameters before and after weight loss (body weight, fat mass, BMI, waist circumference, fasting plasma glucose, FFAs) except of insulin levels and plasma triglycerides. Our data showed that total plasma adiponectin levels did not change in consequence of the diet-induced weight loss in both group, however both groups had significant lower levels of total adiponectin as compared to the lean group. Strong negative associations between total plasma adiponectin and indices of insulin sensitivity (HOMA index and fasting insulin levels) were found in the entire obese group at the beginning of the diet. The quantity of all three studied isoforms of adiponectin (HMW, MMW, and LMW) was not different between the responders and non-responders following the diet. In our study, neither the quantity of the HMW isoform nor the HMW/total adiponectin ratio was different between obese responders and non-responders at baseline or following the diet. The only diet induced changes were for the LMW form in a group of non-responders. Among the analyzed multimeric complexes, a negative association between the LMW and MMW forms and baseline fasting insulin levels and between HOMA index and the MMW forms were observed.

Despite the expected associations between adiponectin and parameters of insulin sensitivity due to suggested insulin sensitizing effects of adiponectin, the results of our study have not supported the role of adiponectin or its particular isoforms in diet-induced whole body insulin sensitivity improvement. Therefore, factors other than adiponectin presumably mediate the major improvements of the weight loss-induced insulin sensitivity changes.

In the third study, we investigated the effect of 8-weeks of a weight reducing very low-calorie diet (VLCD) on the distribution of adiponectin isoforms in plasma and on their secretion by intact adipose tissue explants from obese subjects. 20 obese subjects underwent eight weeks of VLCD leading to an average weight loss of 11kg and significant improvement of parameters of lipid and carbohydrate metabolism. At baseline and at the end of the dietary intervention, a needle biopsy of SAT was performed and tissue samples were subsequently used for cultivation in culture media that were afterwards used for an assessment of adiponectin multimeric isoform profiles. The quantity of isoforms was determined by a novel ELISA system based on the selective measurements of human adiponectin multimers using a specific protease digestions directed to particular multimers disruption. Semiquantitative

Western blot was also used for the determinantion of the relative representation of particular isoforms in relation to total adiponectin. The effect of the VLCD diet on adiponectin multimers was examined also in plasma and the pattern of multimers was compared with that secreted by adipose tissue explants. We found that the profile of adiponectin isoforms secreted by adipose tissue explants differs from the profile in plasma. We have not observed any changes in total adiponectin or in the isoforms of adiponectin after weight loss in plasma or in secretions. Also the ratio of HMW to total adiponectin was not different before and after the diet both in plasma and in secreted media of the explants.

To summarize, our data shows that 8 weeks of intense dietary intervention does not induce changes in secretion and plasma levels of adiponectin multimeric isoforms. Total or HMW adiponectin alone are not major determinants of diet-induced improvement in insulin sensitivity. Additionally, we found that HMW is the major form that is released by adipose tissue and the profile of circulating adiponectin isoforms is different from the profile released by adipose tissue. The secretion pathway and post-secretion events influencing the adipose tissue – blood adiponectin delivery remains unclear and the factors behind adipose tissue that might have a role in the regulation of adiponectin complex distribution.

The fourth study was designed to study the contribution of two main human adipose tissue depots – SAT and VAT on the secretion of adiponectin and its multimeric isoforms and the impact of obesity.

In line with the studies of the role of different fat depots in pathophysiology of obesity-related disturbances, we hypothesized that the production of total adiponectin and its isoforms may be affected by depot-related manner. To analyze the effect of obesity on impairment of adiponectin production and possible impact on the particular multimeric isoforms we included 23 subjects undergoing abdominal surgery and divided them into two groups based on BMI: non-obese and obese. Paired samples of adipose tissue were obtained from every subject and used for determination of adiponectin secretion. The adiponectin isoforms were determined using the well-established native Western blot analyses that enabled us to establish all three isoforms of adiponectin and provided reliable data on the proportions of adiponectin isoforms. Quantity of total adiponectin was measured by standard ELISA method.

The two groups differed significantly in anthropometric and metabolic variables like insulin, HOMA index and parameters of lipid metabolism (HDL cholesterol, triglycerides). Further, lower levels of total plasma adiponectin were found in the obese group. When looking at the distribution of adiponectin isoforms in plasma, no differences in the adiponectin isoforms

were proved between the two groups. However, the profile of adiponectin isoforms secreted by the two depots differed and the ratio of HMW/total adiponectin secreted into the conditioned media was higher in VAT than in SAT explants in the group of non-obese and this significant difference was diminished in the obese group (Figure 2). The release of total adiponectin varies between depots, although only SAT total adiponectin production seems to be affected by obesity state. The quantity of total adiponectin secreted into conditioned media was lower in SAT in obese when compared to non-obese and no significant difference was observed for VAT production. Comparison of the adiponectin isoform profiles secreted by fat tissue and the profile in plasma showed substantial difference (Figure 2.). In both, culture media of SAT and VAT explants, the most abundant isoform was the HMW confirming the previous data and proving that HMW is the predominant form secreted from adipose tissue *in vitro*.

This study proved that depot-specific regulations in adiponectin production especially in the complex distribution might exist and fat tissue dysregulation in obesity might affect the composition and release of adiponectin and its particular isoforms.

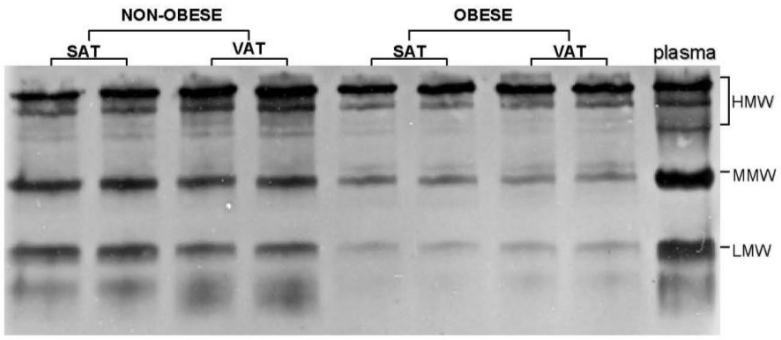

Figure 2. A representative Western blot of adiponectin multimeric complexes in culture media from SAT and VAT explants of non-obese and obese people, and a representative plasma sample.

CONCLUSIONS

The aim of the presented set of studies was to investigate the role of adiponectin and its isoforms in pathogenesis of insulin resistance. It was based on recent findings providing evidence of differetial metabolic effects of the individual isoforms of adiponectin. We examined in prospective and cross-sectional studies association between insulin sensitivity and plasma levels and adipose tissue secretion rate of adiponectin and its isoforms.

- 3 months low calorie diet that resulted in a reduction of body weight by 7.4% and improvements of metabolic parameters and insulin sensitivity increased the amounts of adiponectin multimeric isoforms in plasma. No direct relationships between the diet-induced changes in adiponectin and individual adiponectin complexes in respect to parameters of insulin sensitivity were found.

- In a next prospective dietary study we used a different approach and compared the diet-induced changes in adiponectin and its isoforms in two groups of subjects with markedly different diet-induced responses of insulin sensitivity. There were no differences in the diet-induced changes of adiponectin and its isoforms between "responders" and "non-responders". Thus, the study did not bring evidence – similarly to the previous one – of a role of adiponectin isoforms in the diet-induced modification of insulin sensitivity.

- As plasma levels of adiponectin isoforms need not necessarily reflect their actual secretion from adipocytes we paid attention, in the next study, to the diet-induced changes of secretion of adiponectin and its isoforms in explants of subcutaneous adipose tissue obtained during the dietary intervention. No diet-induced changes in the profile of secreted adiponectin isoforms were detected. However, a clear difference between the profile secreted from adipose tissue and that in the circulation was found.

- In the last study we paid attention to differences in the secretion of adiponectin and its isoforms between SAT and VAT and demonstrated that obesity is associated with

lower secretion of total adiponectin in SAT and, in a fat depot-related manner, with alternations in the profile of secreted adiponectin multimeric isoforms. Extending the results of the previous study, we found, that the profile of adiponectin isoforms secreted by both, SAT and VAT, is different from that in the circulation. The latter finding warrants further studies on the regulation of adiponectin transport between adipose tissue and circulation.

SUMMARY

It is apparent that the imbalance in energy intake and expenditure coming hand-to-hand with the „westernisation“ of our lifestyle leads to an elevated number of overweight and obese individuals that are commonly in a greater risk of developing chronic complications (e.g. insulin resistance, type 2 diabetes and cardiovascular diseases) with increased mortality.

The development of obesity-related complications closely relate with dysfunction of adipose tissue leading to the peripheral insulin resistance and metabolic disruption of insulin sensitive organs (e.g. muscle, liver) subsequently inducing whole body insulin resistance. Since adipose tissue is the biggest endocrine organ in the human body producing many hormones influencing functions of adipose tissue itself or other organs, alteration of their spectrum has been revealed as one of the possible inductors or contributors disturbing body energy homeostasis. Adipose tissue serves as a major site for storage of surplus nutritions, however, long-term positive energy imbalance and high dose calorie intake lead not only to expansion of fat mass but mainly to the pathological changes of the tissue. In states of obesity, adipose tissue is under constant metabolic stress, resulting in the activation of the stress and inflammatory response. It leads to the remodeling of adipose tissue with increased macrophage accumulation, the important source of proinflammatory cytokines in adipose tissue. Abnormal release of cytokines, adipokines and FFAs, that act in a paracrine or autocrine fashion amplify the proinflammatory state within adipose tissue and cause local insulin resistance. Increased fat load increases adipocyte cell size that leads to a shift in the pattern of secreted adipokines as a result of dysregulated adipocyte metabolism. This might have different pathological consequences regarding location of the fat tissue. A number of products secreted by adipose tissue (e.g. adipokines, fatty acids) are affected in a depot-related manner. In fact, differences in protein production or gene expression of many adipocytokines were demonstrated in VAT when compared to SAT. Adiponectin stands out among multiple adipokines due to its most abundant expression in adipose tissue, high plasma levels, its pleiotripoc beneficial effects not only in metabolism and its unusual negative correlation with fat mass and obesity-related complications. Adiponectin has been suggested to play an important role in pathogenesis of obesity-related complications, e.g. insulin resistance and T2DM. Therefore, adiponectin and its regulation has attracted an enormous attention and has become a promising target in treating of obesity-related disorders. Two main thearapeutic approaches might be applied to manipulate a protein levels, namely, administration of the recombinant protein, or

augmentation of its endogenous production. The production of recombinant adiponectin has met number of difficulties due to its complicated multimeric but biologically important structure. Because of this and adiponectin relatively high plasma levels [113] the effort to improve adiponectin endogenous production and to increase its plasma levels by pharmacological or non-pharmacological approaches has became more attractive field of preclinical research. Many pharmacological drugs (e.g. TZDs, statins) have been proved to manipulate adiponectin production at different levels (mRNA expression, post-translational processing or secretion process). Next approach is to treat obesity itself and in consequence to normalize adiponectin levels. The typical strategies for obesity treatment are divided into 3 categories: non-pharmacological (diet and increased physical activity), pharmacological (anti-obesity drug treatment) and surgical (e.g. gastric banding). Caloric restriction-induced weight loss is a powerful and effective tool to improve metabolic parameters and insulin sensitivity and the possibility of increasing adiponectin levels promoted by dietary interventions has attracted increased attention and has been also one of the goals of our studies in frame of this work.

In our studies we focused particularly on the adiponectin isoforms regulation in relation to molecular adaptations of human adipose tissue by dietary interventions. With respect to the secretory activity of adipose tissue we investigated possible mechanisms influencing the profile of adiponectin isoforms expressed in obesity. Based on our results and results of many other studies it seems that production of adiponectin and the increase of its levels in circulation might be effectively achieved by lifestyle modifications, however, relatively large weight reduction is needed. Our study comparing the secretion of adiponectin by the two main adipose tissue depots (SAT and VAT) revealed that adiponectin isoform profile differs between depots with regard to obesity state. Therefore, differential metabolism and functions of the fat depots might play a role in adiponectin regulation and suggest one of the possible mechanisms affecting adiponectin isoform expression in obesity. Further investigations of adiponectin regulation, particularly the isoforms processing, are needed to understand mechanism of its deterioration in obesity and to be able to reveal novel approaches of increasing adiponectin levels in obesity-related disorders.

SÚHRN

Je zjavné, že nerovnováha medzi energetickým príjmom a výdajom prichádza ruka v ruke s "westernizáciou" nášho životného štýlu, čo vedie postupne k zvýšenému počtu osôb s nadváhou a obezitou, ktorí majú podstatne vyššie riziko vzniku chronických komplikácií (ako npr. inzulínová rezistencia, diabetes mellitus 2. typu, kardiovaskulárne ochorenia). Vznik týchto komplikácií úzko súvisí s dysfunkciou tukového tkaniva, ktorá vedie k periférnej inzulínovej rezistencii a metabolickým poruchám inzulín senzitívnych orgánov (napr. svaly, pečeň) a následne môže dojsť k vzniku centrálnej inzulínovej rezistencii. Vzhľadom k tomu, že tukové tkanivo je najväčší endokrinný orgán v tele a produkuje veľa hormónov, ktoré ovplyvňujú funkcie tukového tkaniva samotného ako aj iných orgánov, zmeny v ich produkcii je jedným z možných induktorov či prispievateľov k narušeniu energetickej homeostázy.

Tukové tkanivo je prednostným miestom skladovania prebytkov živín, avšak dlhodobá pozitívna energetická nerovnováha a vysoký kalórický príjem vedú nielen k expanzii tukového tkaniva, ale hlavne k jeho patologickým zmenám. V stave obezity, tukové tkanivo je pod neustálym metabolickým stresom, čo vedie k aktivácii zápalových reakcií. Dochádza k prestavbe tukového tkaniva so zvýšenou akumuláciu makrofágov - dôležitý zdroj prozápalových cytokínov v tukovom tkanive. Abnormálne uvoľňovanie adipokínov a voľných mastných kyselín, ktoré pôsobia parakrinne alebo autokrinne, umocňujú prozápalový stav tukového tkaniva a spôsobujú lokálnu inzulínovú rezistenciu. Zvýšené ukladanie tukov súvisí so zmenou velkosti adipocytov, čo može ovplyvniť produkciu niektorých adipokínov ako výsledok dysregulácie metabolizmu adipocytov. Boli preukázané rozdiely v produkcii adipokínov medzi jednotlivými depotmi tukového tkaniva (napr. subkutánny (SAT) versus viscerálny (VAT)) a patologické dôsledky abnormálneho metabolizmu tukového tkaniva sa líšia vzhľadom k jeho umiestneniu v rámci tela.

Adiponektin vyniká medzi adipokínmi ako najhojnejší produkt exprimovaný tukovým tkanivom, sú známe jeho široké pleiotropné účinky nielen v metabolizme, má vysoké hladiny v plazme a preukazuje neobvyklú negatívnu koreláciu s množstvom tuku a obezitou. Adiponektin sa ukazuje ako dôležitý faktor v patogenéze komplikácií spojených s obezitou, ako napr. inzulínová rezistencia a diabetes. Preto sa adiponektinu a jeho regulácii venuje

značná pozornosť a stal sa potencionálnym cieľom pri liečbe ochorení spojených s obezitou. Dva hlavné terapeutické prístupy môžu byť použité pre manipuláciu zastúpenia proteínov, a to; podávanie rekombinantného proteínu, alebo zvyšovanie jeho endogénnej produkcie. Produkcia rekombinantného adiponektinu sa stretla s radou problémov kvôli jeho komplikovanej multimérnej, ale biologicky dôležitej štruktúre. Rovnako, relatívne vysoké plazmatické hladiny adiponektínu viedli k presmerovaniu úsilia na zlepšenie endogénnej produkcie adiponektinu a zvýšenie jeho plazmatických hladín farmakologickými či nefarmakologickými prístupmi. Viacero liekov pužívaných při liečbe diabetu alebo hypertenzie (napr. TZDs, statíny) preukázalo efekt na produkciu adiponektínu na rôznych úrovniach (mRNA, post-translačné modifikácie alebo sekrečný proces). Ďalším prístupom je liečba obezity samotnej a v dôsledku toho normalizácia hladiny adiponektínu.

Základné prístupy na liečbu obezity sú rozdelené do 3 hlavných kategórií: nefarmakologická (diéta a zvýšenie fyzickej aktivity), farmakologická (liečivá) a chirurgická (napr. bandáž žalúdka) liečba. Obmedzenie príjmu kalórií je účinný prístup k zlepšeniu metabolických parametrov a citlivosti na inzulín, a možnosť zvýšenia hladín adiponektínu pomocou diétnych intervencií priťahuje čoraz väčšiu pozornosť a bol jedným z hlavných cieľov nášho štúdia.

V našich klinických štúdiách sme sa zamerali predovšetkým na reguláciu izoforiem adiponektínu vo vzťahu k molekulárnym adaptáciam ľudského tukového tkaniva po diétnych intervenciách. Vzhľadom na sekrečnú aktivitu tukového tkaniva sme sledovali možné mechanizmy ovplyvňujúce profil izoforiem adiponektinu a vplyv obezity. Na základe našich výsledkov a výsledkov ďalších štúdií sa zdá, že produkcia adiponektinu a zvýšenie jeho hladín v cirkulácii by mohlo byť účinne dosiahnutelné zmenou životného štýlu, avšak výrazné zníženie telesnej hmotnosti sa zdá byť kritickým faktorom. Naša štúdia porovnávajúca sekréciu adiponektinu dvoch hlavných depot tukového tkaniva (SAT a VAT) ukázala, že profil izoforiem adiponektinu sa líši v jednotlivých depotoch s ohľadom na stav obezity. Preto rozdielny metabolizmus a funkcie tukového tkaniva v závislosti na lokalizaciu v rámci tela hrá rolu v regulácii adiponektinu a ukazuje sa ako jeden z možných mechanizmov ovplyvňujúci expresiu izoforiem adiponektinu v obezite.

Ďalšie skúmanie regulácie adiponektinu, najmä jeho izoforiem, je potrebné na pochopenie mechanizmu jeho zníženej tvorby v obezite a aby bolo možné hladať nové prístupy k zvýšeniu hladiny adiponektinu pri poruchách spojených s obezitou.

ANEX

Macrophage gene expression is related to obesity and the metabolic syndrome in human subcutaneous fat as well as in visceral fat

Klimcakova E, Roussel B, Kovacova Z, Kovacikova M, Siklova-Vitkova M, Combes M, Hejnova J, Decaunes P, Maoret JJ, Vedral T, Viguerie N, Bourlier V, Bouloumié A, Stich V, Langin D.

Diabetologia. 2011 Apr;54(4):876-87.

IF 6.973

Worsening of Obesity and Metabolic Status Yields Similar Molecular Adaptations in Human Subcutaneous and Visceral Adipose Tissue: Decreased Metabolism and Increased Immune Response

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