ENDOCRINE AND METABOLIC EFFECTS OF ADIPOSE TISSUE IN CHILDREN AND ADOLESCENTS

ENDOKRINA IN PRESNOVNA FUNKCIJA MAŠČOBNEGA TKIVA PRI OTROCIH IN MLADOSTNIKIH

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Received/Prispelo: Nov 6, 2014
Accepted/Sprejeto: Jan 14, 2015

Review article/Pregledni znanstveni članek

ABSTRACT

Adipose tissue is implicated in many endocrine and metabolic processes. Leptin was among the first identified adipose-secreted factors, which act in an auto-, para- and endocrine manner. Since leptin, many other adipose tissue factors were determined, some primarily secreted from the adipocytes, some from other cells of the adipose tissue.
So-called adipokines are not only involved in obesity and its complications, as are insulin resistance, type 2 diabetes and other components of the metabolic syndrome, but also in growth, reproduction, bone metabolism, immune response, cancer development and many other important biological processes. Research in the field of adipokines has revealed new insights into the physiological and pathophysiologal processes and opened new therapeutic possibilities. In the present article, a special emphasis is devoted to research in children and adolescents.

Keywords:
adipose tissue, obesity, endocrinology, adipokine, metabolic syndrome, child

IZVLEČEK

Maščobno tkivo ima vlogo pri številnih endokrinih in presnovnih procesih. Lepin je bil med prvimi odkritimi dejavniki iz maščobnega tkiva, ki delujejo avto-, para- in endokrino. Od opredelitve leptina so odkrili še številne druge dejavnike, od katerih se nekateri izločajo iz maščobnih celic, nekateri pa iz drugih celic maščobnega tkiva.
Tako imenovani adipokini niso povezani le z debelostjo in njenimi zapleti, kot so rezistenca proti inzulinu, sladkorna bolezen tipa 2 in druge komponente metabolnega sindroma, temveč tudi z rastjo, razmnoževanjem, presnovo kosti, imunskim odzivom, razvojem rakavih bolezni in mnogimi drugimi pomembnimi biološkimi procesi. Raziskave na področju adipokinov so opredelile nove fiziološke in patofiziološke procese in odprle nove možnosti zdravljenja. V tem prispevku poseben poudarek namenjamo raziskavam pri otrocih in mladostnikih.

Ključne besede:
maščobno tkivo, debelost, endokrinologija, adipokini, metabolni sindrom, otroci

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1 BACKGROUND

Adipose tissue was long considered to be an energy storage tissue only. Adipocytes store energy in the form of triglycerides when there is an excess of energy, and release it when energy is needed. By studying genetically obese and diabetic mice (ob/ob, db/db), it was determined that factors released from adipocytes are able to communicate with distant tissues and influence their function. Leptin was the first cytokine with such function to be determined. Since leptin, several additional factors with endocrine functions were determined. Some - as leptin and adiponectin - are released from the fat cells exclusively, whilst others are also released from others cells of the adipose tissue (macrophages, fibrocytes, endothelial cell), and other organs (liver, bone) (1, 2).

In the manuscript, we will discuss the role of the selected adipokines in obesity, and the development of components of metabolic syndrome, with an emphasis on their role in children and adolescents.

2 LEPTIN

The discovery of leptin caused a paradigm shift in the way adipose tissue is perceived. It is no longer regarded as an energy storage organ only, but also as an important endocrine organ with important effects on body metabolism. Leptin levels are increased in adipose tissue and circulation in human obese subjects, including children and adolescents (3-5). Mutations in the leptin gene or its receptor are associated with human morbid and early obesity (2, 6). Its levels are correlated with body mass index (BMI) and fat store content. They are decreased in subjects with decreased fat mass, such as lipodystrophy and anorexia (7, 8). Following weight loss, leptin levels decrease in both adults and children (9, 10). Leptin levels are higher in subcutaneous that visceral adipose tissue. They are higher in females as compared to males, and this dimorphism is present already in children (5). A mechanism described behind this dimorphism is the suppressive effect of androgens on leptin expression in adipocytes (11).

Central nervous system (CNS) leptin effects - particularly at the level of hypothalamus - are associated with energy homeostasis. Following secretion of leptin from fat stores into circulation, it is transported across the blood-brain barrier to CNS, where it stimulates processes that result in decreased food intake and increased energy consumption. In common obesity leptin resistance at the level of CNS, is a mechanism explaining continued energy intake despite severely increased circulating leptin levels (12).

In addition to CNS, leptin receptors are also present in peripheral tissues, where leptin decreases fat stores in the skeletal muscle and liver by stimulating fatty acid oxidation and glucose uptake. Peripheral leptin resistance (particularly in skeletal muscle) is also linked to insulin resistance (IR) in obesity (13, 14), and to the development of nonalcoholic fatty liver disease and metabolic syndrome in children (15, 16).

Besides its effects on energy homeostasis, leptin has several other important endocrine functions. The lack of leptins action at the level of CNS, is also associated with reduced reproductive function (6). Leptin is implicated in the regulation of immunologic and inflammatory processes (17). At the level of the bone, leptin has a dual and opposing role. On one hand, it stimulates osteoblasts, bone mineralization and growth, while, on the other hand, it suppresses bone development (18, 19). It has also been implicated in tumorigenesis, as leptin receptors can be found in certain cancer cells, possibly enabling leptin to stimulate growth of these cells under certain conditions (20).

Leptin has been successfully used in the therapy of leptin deficient subjects ameliorating hyperphagia, extreme obesity, hypogonadism and impaired cell immunity (6). Leptin is able to induce puberty in hypogonadotropic hypogonadism due to leptin deficiency, and to reduce liver steatosis associated with obesity due to leptin-deficiency (21, 22). In polygenic obesity, leptin therapy was not as successful, probably due to leptin resistance being the main feature in this condition (12). It could, however, be potentially used in subjects following weight loss. In these subjects, a decrease in fat content leads to decreased leptin levels and decreased energy expenditure, possibly preventing further weight loss or enabling a regain of lost weight. By administration of leptin at this stage, one could prevent a regain of weight in these subjects (23). In addition, leptin mimetics have been proposed to overcome leptin resistance, and co-administration of amylin with leptin was shown to positively modify leptin signalling (24).

3 ADIPONECTIN

Adiponectin is expressed in the mature adipocyte and is secreted into blood circulation, where it is present in 3 main oligomeric forms, high molecular weight (HMW) form being linked with most of the effects on peripheral tissues (25).

In contrast to leptin, and indeed most of the other adipokines, adiponectin blood levels are not increased, but decreased in obesity, including in children (26). There is a strong negative correlation between plasma adiponectin levels with body fat mass (27). Following weight loss, adiponectin levels increase in both adults and children (26, 28). The anti-obesity effect is associated

with the ability of adiponectin to increase body's energy expenditure and to decrease differentiation of adipocytes in experimental animals (29).

Adiponectin is, similarly to leptin, secreted in a gender dimorphic fashion, with circulating levels being higher in women than in men. Although stimulation of adipocytes with human male serum leads to a decrease in the expression of adiponectin, increasing concentrations of testosterone or estradiol do not influence either adiponectin mRNA expression or secretion, implicating, to date, unidentified serum gender specific factors (30).
In the peripheral tissues, adiponectin's actions are mediated through adiponectin receptor 1 or 2 (AdipoR1, AdipoR2). In skeletal muscles, adiponectin acts mainly through AdipoR1 and through AdipoR2 in the liver. Variations in the expression levels of these receptors at the level of the peripheral tissues, are in addition to circulating levels associated with adiponectin's effects (31).

Adiponectin acts as an insulin sensitizer in both experimental animals and humans. Insulin sensitising mechanism is linked to a reduction of hepatic gluconeogenesis and an increase of muscle glucose transport (32). Low levels of adiponectin, especially HMW form, are associated with the development of IR, type 2 diabetes (T2D), components of the metabolic syndrome and cardiovascular disease (33-35). This link is also present in children and adolescents (36, 37). Certain single nucleotide polymorphisms (SNP) in the adiponectin gene are associated with low adiponectin levels and T2D (38, 39). On the other hand, increased adiponectin levels are associated with the reduced risk of T2D (40), and therapy with insulin sensitizing drugs thiazolidinediones increases adiponectin (primarily HMW) levels (41). In children, lifestyle modifications also result in a beneficial increase in adiponectin levels, accompanied by increased insulin sensitivity (26).

Adiponectin has also anti-inflammatory and anti-oxidant properties. It inhibits tumor necrosis factor (TNF), alpha and superoxide radical generation in endothelial cells, and TNFalpha generation in adipose tissue (42). Low levels of adiponectin are also associated with nonalcoholic steatohepatitis independent of IR (43). In addition, low levels of adiponectin are linked to an increased risk of malignancies (44).

4 VISFATIN

Previously known as pre-B cell colony enhancing factor, visfatin is a controversial adipokine, whose levels were shown to be either increased, normal or decreased in adult human obesity (45-48). In children and adolescents, circulating visfatin levels and SNPs in visfatin gene were also inconsistently linked to obesity determined by BMI or waist circumference (49-51). Furthermore, it is controversial whether visfatin is predominantly expressed in human visceral or subcutaneous adipose tissue (45, 52, 53).

Visfatin binds to insulin receptor and was suggested to have insulin-like effects (52). It was determined to be a nicotinamide phosphoribosyltransferase implicated in promoting insulin secretion upon glucose stimulation (54, 55). Circulating visfatin levels are increased by hyperglycaemia in mouse models of T2D and in humans with type 1 diabetes (T1D) and T2D (52, 56). Again, these results were not confirmed in all studies, and SNPs in visfatin gene are not linked to T2D (54). In obese children, visfatin levels do not differ between those with and without IR (51). On the other hand, in children visfatin gene, SNPs are linked to higher visfatin levels, components of metabolic syndrome and low grade inflammation (51).

A decrease in body weight - following bariatric surgery - and exercise in T1D subjects lowers visfatin levels (47, 57). Treatment with insulin sensitizing drug rosiglitazone in humans does not lower visfatin levels (58).

Visfatin is implicated in the pathogenesis of chronic conditions, as are atherosclerosis and cardiovascular diseases (59). It is suggested to be a proinflammatory cytokine. As obesity is a state of chronic low-grade inflammation, this could be the common mechanism explaining some of the reported results; still, visfatin's role in obesity and its complications need to be further addressed.

5 RESISTIN

Although resistin is also expressed in adipocytes, the main source of resistin in humans are macrophages (60). Structurally, resistin is very similar to adiponectin including the formation of higher-order oligomerisation structures. In contrast to adiponectin, however, low-molecular structures are more physiologically active (61). Increased resistin levels were determined in human obesity in both adults and children, and a SNP in the resistin promoter is associated with obesity (62-65). More specifically, circulating levels of resistin were, in particular, associated with body fat mass in children (66). In animal obesity models, increased resistin levels are linked to IR, and resistin was described as a possible link between obesity and the development of T2D (67). Decreasing resistin levels or blocking its action, is linked to improved insulin sensitivity and glucose metabolism (67, 68). In humans, controversial results on the role of resistin in the development of IR, T2D and metabolic syndrome are described (63, 64, 69). Increased circulating levels are also reported in T1D subjects (70). A SNP in resistin promoter is, in addition to obesity, also associated with T2D (71).

Resistin is also linked with states of inflammation including low-grade inflammation in obesity (72, 73). Similarly as for visfatin, resistin's role in the development of obesity and its complications needs to be further addressed.

6 RETINOL BINDING PROTEIN 4 (RBP4)

Increased circulating and adipose tissue RBP4 levels are linked to obesity and visceral fat mass content (74, 75). Several studies, however, found no correlation between circulating RBP4 levels, the level of obesity, and the amount and distribution of adipose tissue (76-78).

RBP4 is suggested to be involved in early processes of atherosclerosis and cardiovascular diseases (79, 80). Circulating and adipose tissue RBP4 levels are associated with IR and T2D in both adults and in children and adolescents (81-83). RBP4 levels also correlate with other components of the metabolic syndrome (84-86). They decrease with lifestyle interventions - reduction of weight, increased exercise - in adults, children and adolescents (76, 87, 88). The associations between RBP4 levels and the development of obesity and its complications, such as IR, impaired glucose tolerance, T2D and certain components of the metabolic syndrome, have, however, not been found consistently in both adults and children (77, 78, 89-92).

Obesity is a state of low-grade inflammation. Several adipokines have been shown to be regulated by inflammatory factors (93). We therefore studied RBP4 expression in human adipocytes exposed to inflammatory milieu (culture media from activated machrophages), or selected proinflammatory cytokines interleukin 1 beta (IL-1beta) and TNFalpha, and determined that RBP4 expression in adipose tissue was consistently decreased in a proinflammatory environment (94). These results link inflammation and altered expression of RBP4 in adipose tissue, even though it seems that changes in RBP4 expression in adipose tissue are not directly related to the changes in circulating RBP4 levels that often precede the development of systemic IR (94, 95).

The levels of circulating RBP4 seem to be regulated in a sex-dependent manner. Males, including adolescents, showed higher levels of RBP4 compared to females (78, 96-99). Also, women with increased androgen levels had in increase in circulating RBP4 (78, 96-99). This sexual dimorphism was, however, not demonstrated in all studies (75, 100-102). Two classic adipokines, leptin and adiponectin, are regulated in a sex-dependent manner. In contrast to RBP4, their levels are lower in males compared to females, and further studies demonstrated that the male sex hormone testosterone inhibited the expression of leptin and adiponectin in adipocytes (11, 103).

We therefore decided to further explore the gender specific regulation of RBP4 expression in human adipocytes. As a model system, we used the human Simpson-Golabi-Behmel syndrome (SGBS) cell strain. These cells are characterized by a high capacity for adipogenic differentiation, and therefore provide a suitable cell system to study human adipocyte biology (104).

Effects of gender specific serum factors on RBP4 expression in human SGBS adipocytes were investigated. We collected serum samples from 10 healthy non-obese females (estradiol 89.99 pg/ml, testosteron 0.37 ng/ml, leptin 16.0 ng/ml) and 10 healthy non-obese males BMI- and age-matched volunteers (estradiol 34.58 pg/ml, testosterone 4.18 ng/ml, leptin 2.2 ng/ml). After pooling these samples, we added them to adipocyte cultures at a concentration of 10 % (vol/vol). As a control experiment, we first studied the expression of adiponectin. As expected from earlier studies, male serum was more efficient in downregulating adiponectin mRNA than female serum (Figure 1A) (30). Likewise, both female and male serum suppressed RBP4 mRNA expression, with male serum showing a significantly stronger inhibitory effect than female serum (Figure 1B). These results are in accordance with the data obtained from male and female adipose tissue explants, where significantly higher mRNA expression was determined in female adipose tissue when compared to male (100).

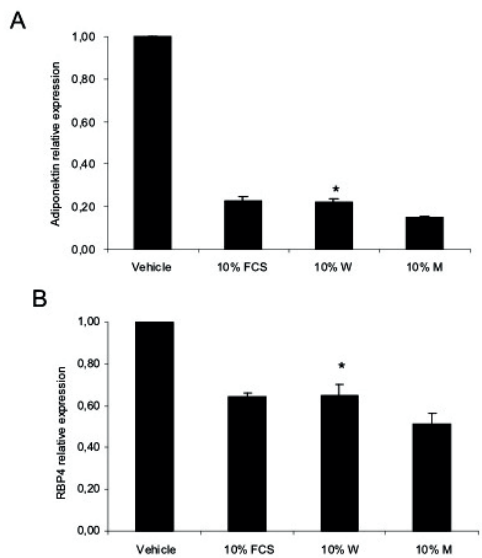

Figure 1A, 1B. Effects of pooled 10 % female (F) or male (M) serum on adiponectin (A) and retinol binding protein 4 (B) mRNA expression in SGBS adipocytes.

mRNA expression ratios were determined by qRT-PCR, using succinate dehydrogenase as a reference. Data are presented as mean ± SEM of 3 or more independent experiments, and are normalized to the expression or secretion in the vehicle (1% ethanol) treated samples. *p < 0.05 when compared to the vehicle.

7 CHEMERIN

Adipose tissue and liver are the main sources of chemerin, a chemo-attractant protein that acts through chemokine like receptor 1 (CMKLR1), which is located to adipocytes, endothelial cells and inflammatory cells (e.g. dendritic cells and macrophages). Chemerin is implicated in the process of adipogenesis, and its higher levels are associated with obesity, especially visceral, in both adults and children (105, 106). Interestingly, higher levels were determined in vitamin D deficient obese children, compared to vitamin D non-deficient obese children (107). Dysregulation of chemerin is associated with several metabolic abnormalities, such as increased blood pressure and total cholesterol, decreased HDL cholesterol, prediabetic state of IR and T2D (105). Chemerin levels positively correlate with leptin and negatively with adiponektin levels (108). In children, higher levels are associated with low-grade inflammation and endothelium dysfunction, as determined by markers of endothelial activation intercellular adhesion molecule-1 (ICAM-1) and E-selectin (109).

8 CONCLUSIONS

Adipose tissue is regarded an important endocrine tissue. Dysregulation of factors secreted from the adipose tissue – so-called adipokines – is not linked only to obesity and its complications, but has also important effects on bone metabolism, reproduction, immunity, cancer development, etc.

Several adipokines are considered biomarkers of patho-physiological states, in particular those linked to obesity. Some are still considered controversial due to inconsistent experimental results, and will have to be further studied in larger and well-controlled studies. In the future, disease-specific arrays of adipokines will possibly be used to determine, with higher specify and sensitivity, those at a significant risk of selected disease, or they will be used as monitoring tools to evaluate the efficacy of treatment. Of importance, noninvasive methods that will enable us to determine the origin of studied adipokines (e.g. visceral vs. subcutaneous adipose tissue) will bring the role of adipokines, as biomarkers, to a new and a higher level.

In addition, it is possible that the manipulation of the expression or actions of selected adipokines will be used therapeutically in the future. To this effect, leptin was the first adipokine used therapeutically in states of leptin deficiency (e.g. congenital leptin deficiency or certain lypodystrophies). As adipokines have increasingly important endocrine and metabolic effect also in non-obesity associated states, it is probable that adipokine therapy will also be used in non-obesity relates states. Delivery of therapeutic adipokine to a specific tissue, possibly with the use of combination therapy, would be of special benefit.

CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

FUNDING

This study was supported by the Slovenian National Research Agency grants P3-0343, J3-6798 and J3-6804.

ETHICAL APPROVAL

Not required.

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