CELL VOLUME - ROLE IN OBESITY AND ITS MAINTENANCE MINIREVIEW

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ZAPREMINA ĆELIJE I NJENA ULOGA U NASTANKU I ODRŽAVANJU GOJAZNOSTI

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ABSTRACT

Keeping volume within certain limits is a prerequisite for cell integrity and proper function. The defense against excess cell swelling is accomplished also by a reduction of the intracellular osmolarity by synthesis of osmotically less active macromolecules from their specific subunits (proteosynthesis and lipogenesis). At the same time proteolysis and lipolysis is inhibited. Conversely, cell shrinkage stimulates lipolysis, degradation of proteins to amino acids, degradation of glycogen to glucosephosphate and simultaneously protein, lipid and glycogen synthesis is inibited. The degradation products are osmotically more active than the macromolecules and their breakdown generates cellular osmolarity resulting in water entry into cells. Recently new interesting view of ***chronic*** *changes of the cell volume and its role in model of body weight loss and regain in obesity is considered; secretion profile of adipocytes is related to their size. Decrease of body weight is constituted by the drop of fat in adipocytes, they consequently shrink. Surrounding extracellular matrix has to adjust to traction forces. To ascertain a sufficient supply of glucose and fat for re-storage, adipocytes change their pattern of secreted adipokines altering the total body metabolism and promoting energy intake. Shrunken adipocytes show insulin resistance, whereas glucose uptake is facilitated in osmotically swollen adipocytes. Compensating mechanism in patients on very-low calorie diet during weight maintenance period includes increase in water content of adipose tissue correlating with increase of insulin sensitivity. Consideration of participation these mechanisms might bring new insight into understanding of obesity pathophysiology and treatment.*

Key words: chronic change of cell volume, obesity, adipokines, insulin

SAŽETAK

Održavanje volumena ćelije u okviru određenih granica je preduslov za očuvanje njenog integriteta i adekvatno funkcionisanje. Sprečavanje preteranog bubrenja ćelije se, između ostalog, postiže smanjenjem intracelularne osmolarnosti, sintezom osmotski manje aktivnih makromolekula iz njihovih specifičnih subjedinica (proteosinteza i lipogeneza). Istovremeno, procesi lipolize i proteolize su inhibisani. Nasuprot tome, smežuravanje ćelije podstiče lipolizu, razgradnju proteina do amino-kiselina, i razgradnju glikogena u glukozofosfate, dok su sinteza proteina, lipida i glikogena inhibisani. Produkti razgradnje su osmotski aktivniji u odnosu na makromolekule, a njihova dalja degradacija povećava ćelijsku osmolarnost, što rezultuje ulaskom vode u ćeliju. Nedavno je razmotreno novo, zanimljivo gledište na hroničnе promene ćelijskog volumena i njenu ulogu u modelu gubitka telesne težine i ponovne gojaznosti - sekretorni potencijal adipocita je povezan sa njihovom veličinom. Smanjenje telesne težine je bazirano na redukciji količine masti u adipocitima i njihovom sledstvenom smežuravanju. Okolni ekstracelularni matriks mora da se prilagodi trakcionim silama. Da bi obezbedili dovoljne količine glukoze i masti za ponovno skladištenje, adipociti menjaju način sekrecije adipokina, a time i ukupan metabolizam organizma, stimulišući unos energije. Smežurani adipociti pokazuju insulinsku rezistenciju, dok osmotski nabubreli lakše preuzimaju glukozu. Kompenzacijski mehanizam kod pacijenata sa veoma niskim kalorijskim unosom, tokom perioda održavanja telesne težine, obuhvata porast sadržaja vode u masnom tkivu, što je povezano sa povećanjem osetljivosti na insulin. Uzimanje u obzir ovih mehanizama može doneti novi uvid u razumevanju patofiziologije i lečenja gojaznosti.

Ključne reči: *hronične promene ćelijskog volumena, gojaznost, adipokini, insulin*

ABBREVIATION

ECM – extracellular matrix

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Keeping volume within certain limits is a prerequisite for cell integrity and proper function. Protective mechanisms should have to develop in early forms of life. A variety of organisms and cell types spanning all taxonomic groups are exposed to osmotic stresses. Phylogenetically divergent organisms employ uniquely adapted mechanisms of cell volume regulation proceeding by highly conserved physiological processes[1]. Most of the acute cell reactions to volume changes are aiming at the reestablishment of initial volume status. To drive water flux, which finally accomplishes cell volume adjustment, cells produce an osmotic difference between the intra- and extracellular spaces by inducing osmolyte transport. The defense against excess cell swelling is accomplished by a reduction of the intracellular osmolarity by release of inorganic and organic osmolytes from the cell and by synthesis of osmotically less active macromolecules from their specific subunits (proteosynthesis and lipogenesis[2-6]). At the same time proteolysis and lipolysis is inhibited. Consequently water leaves the cells, their size and shape return to regular values. Conversely, acute cell shrinkage stimulates the degradation of lipids, proteins to amino acids and glycogen to glucosephosphate and inhibits lipid, protein and glycogen synthesis[6]. The degradation products are osmotically more active than the macromolecules and their breakdown generates cellular osmolarity resulting in water entry.

In higher organisms cell volume response to osmotic challenge is integrated into a signal transduction network regulating various cell functions including gene expression, cell proliferation, apoptosis, migration, metabolism, secretion of hormones and mechanism of their effect [6-10]. Very interesting is powerful effect of cell swelling to induce exocytosis of material in intracellular secretory vesicles[8-10]. This mechanism induces secretion of peptide and protein hormones and enzymes. Considering that endocrine secretion is normally under delicate control leading to the release of appropriate amount of hormone in response to endogenous secretagogues or specific stimuli, swelling-induced exocytosis represents stimulus relatively independent from hormonal regulation.

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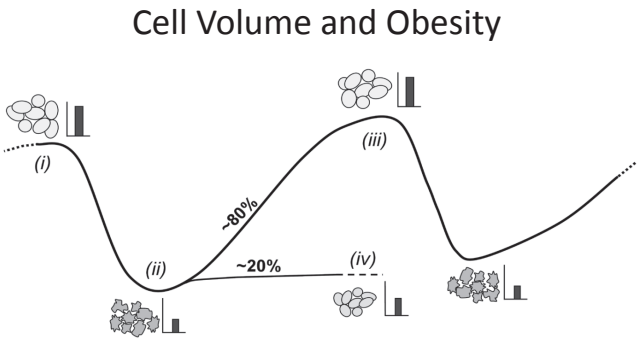
Cell volume returns to original values after moderate osmotic challenge within minutes[10]. While acute changes of cell volume are well known to be integrated into a signal transduction network affecting various functions, impact of chronic changes of cell volume on cellular functions have been rarely investigated. Recent article of Edwin Mariman[11] brings new interesting view on the mechanism involved in body weight loss and regain in obese patients: in this biological model long lasting cellular volume changes are considered. Chronic changes of the volume[11,12] and lipid content of adipocytes and their impact on secretion of adipokines (Fig. 1) play a pivotal role. Obese people have large adipocytes; a decrease of body weight after calory restriction is constituted by the release of fat from adipocytes, they consequently shrink. According to model of Mariman[11, 13] their surrounding extracellular matrix (ECM) has to be adjusted and reconstructed as well (Fig. 1). For the construction of new collagen fibers, collagen proteins have to be synthesized and modified, which is an energy-demanding process. Under conditions of calorie restriction during weight loss, such energy is not available. As a consequence, the adaptation of the ECM cannot keep up with that of the cell and stress will build up between the ECM and the cell due to traction forces inducing a cut down on the further release of fat - cellular stress results in increased resistance against releasing fat. Secretion of adipokines changes. The adipocytes under normal conditions secrete numerous peptide hormones that regulate the metabolic activity of other peripheral tissues but also influence the energy intake[14]. By changing the adipokine profile, adipocytes can manipulate the eating behavior of their host. In fact, Skurk et al showed that the secretion profile is related to adipocyte size[15] suggesting that during weight loss and shrinkage of cells, adipocytes will automatically change their adipokine secretion profile. Leptin is one of those hormones that play a role in signaling the fat content of the body to the brain. Its plasma levels are associated to the amount of fat mass[16]. If the stored fat content is sufficient, it is signaled by leptin to the brain and as a consequence appetite is repressed. The production of leptin[16] is directly and adiponectin undirectly proportional to adipocytes size. Consequently during weight loss their levels change allowing the feeling of hunger. Interestingly, during weight loss plasma leptin levels drop far beyond what would be expected from the amount of lost fat mass. Typically, a 15-20% loss of fat mass is accom-



E.C.M. Mariman: An adipobiological model for weight regain after weight loss. Adipobiology, 3; 9-16, 2011

Figure 1. Adipobiology of weight cycling. The weight cycling is shown by the solid line. Obese people have large adipocytes and high plasma levels of leptin as shown by the bar (i). Upon weight loss adipocytes shrink and accumulate cell stress. Leptin levels are reduced by 40-60% (ii). The changed adipokine profile induces eating behavior and up to 80% of people return to the original weight or go beyond it. Leptin levels rise again dramatically (iii). Twenty percentage of people or more succeed in maintaining a lower weight with a reduced leptin level (iv). The others start on their next round of weight loss and attempt of weight maintenance (iii). From Mariman, Adipobiology 2011;3:9-16 with permission.

panied by a reduction of 40-60% in leptin[11]. This signals a state of leptin deficiency in the brain[17]. Eventual increase of energy intake by the host supplying sufficient glucose and fat promotes storage of triglycerides and return to the original volume with relieve from cell stress. In addition to leptin, also other adipokines may help promote energy flux towards the stressed adipocytes. For the host this would mean that after weight loss there is increased risks for weight regain originating from the cellular stress of the adipocytes. A biological model for weight regain after weight loss[11, 18] is based on the behavior of shrinken adipocytes, accumulation of structural stress and change of adipokines secretion.

INSULIN RESISTANCE

As recently reviewed, acute cell volume changes induced in adipocytes by an application of a hypertonic or a hypotonic solution alter some of their fundamental physiological functions: glucose uptake and metabolism[19]. Osmotically shrunken adipocytes show insulin resistance, which is a characteristic of type 2 diabetes mellitus and metabolic syndrome, whereas glucose uptake is facilitated in osmotically swollen adipocytes[19]. Cell swelling induced by insulin mediates some of its effects in hepatocytes[20] including proteosynthesis. Uptake of water by the shrunken cells to compensate in part for the lost adipocyte volume[18] seems to be very effective solution. Laaksonen et al.[21] observed that the water content of adipose tissue of obese men and women significantly increased after 9 weeks on a very-low-calorie diet and further increased during a 1 year weight maintenance period. Moreover, at various time points during the follow up, increase in subcutaneous adipose tissue water content correlated with increase in insulin sensitivity. Although the authors assume that the increased water content is due to increase in blood flow and blood volume, improved glucose uptake suggests that adipocytes accumulated water to compensate decreased volume. Indeed, one of the consistent metabolic feature of adipocytes in obese/overweight subjects after weight loss and a short period of weight maintenance is an improved glucose uptake capacity[22].

CONCLUSION

Release of fat from adipocytes results in the decrease of their volume. This is connected with the change of spectrum of secreted adipokines, traction stress between extracellular matrix and shrunken adipocytes and insulin resistance. Successful maintenance of lower body weight is accompanying by increase of water in adipose tissue connected with increase of insulin sensitivity. Consideration of the role of cell volume changes in the obesity may contribute to better understanding of its pathophysiology and bring novel approach in treatment.

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