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Alteration of local adipose tissue trace element homeostasis as a possible mechanism of obesity-related insulin resistance

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ABSTRACT

The mechanisms of association between obesity and the related metabolic disturbances in general and insulin resistance in particular are extensively studied. Taking into account a key role of adipose tissue insulin resistance in the development of systemic obesity-related insulin resistance, the estimation of mechanisms linking increased adiposity and impaired insulin signaling in adipocytes will allow to develop novel prophylactic and therapeutic approaches to treatment of these states. A number of trace elements like chromium, zinc, and vanadium have been shown to take part in insulin signaling via various mechanisms. Taking into account a key role of adipocyte in systemic carbohydrate homeostasis it can be asked if trace element homeostasis in adipose tissue may influence regulatory mechanisms of glucose metabolism. We hypothesize that caloric excess through currently unknown mechanisms results in decreased chromium, vanadium, and zinc content in adipocytes. Decreased content of trace elements in the adipose tissue causes impairment of intra-adipocyte insulin signaling subsequently leading to adipose tissue insulin resistance. The latter significantly contributes to systemic insulin resistance and further metabolic disruption in obesity. It is also possible that decreased adipose tissue trace element content is associated with dysregulation of insulin-sensitizing and proinflammatory adipokines also leading to insulin resistance. We hypothesize that insulin resistance and adipokine dysbalance increase the severity of obesity subsequently aggravating alteration of adipose tissue trace element balance. Single indications of high relative adipose tissue trace element content, decreased Cr, V, and Zn content in obese adipose tissue, and tight association between fat tissue chromium, vanadium, and zinc levels and metabolic parameters in obesity may be useful for hypothesis validation. If our hypothesis will be confirmed by later studies, adipose tissue chromium, vanadium, and zinc content may be used as a prognostic biomarker of metabolic disturbances in obesity. Hypothetically, development and approbation of drugs increasing adipose tissue chromium, vanadium, and zinc content may help to achieve better metabolic control in obesity and obesity-related insulin resistance. However, stronger basis is required to prove our hypothesis. In particular, future studies should investigate the influence of obesity severity of adipose tissue trace element content, estimate the association between adipose tissue metals and metabolic parameters, and highlight the mechanisms involved in these changes. Both in vivo and in vitro studies are required to support the hypothesis.

Introduction

Obesity is a modern biomedical problem [1] involving more than 500 million persons worldwide in 2008 [2]. It is proposed that the number of overweight and obese subjects will reach 2.3 billion and 700 million, respectively, in 2015 [3]. Obesity is classically defined as an excessive development of adipose tissue in the body [4]. At the same time, this expansion is accompanied by impaired adipose tissue functions and low-grade inflammation [5]. Due to its complex pathogenesis, obesity is tightly associated with a number of metabolic disturbances like hypertension, dyslipidemia, and systemic insulin resistance [6], altogether clustered into

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"metabolic syndrome" [7]. The presence of metabolic syndrome is associated with increased cardiovascular morbidity and mortality [8] as well as all-cause mortality [9].

The mechanisms of association between obesity and the related metabolic disturbances in general and insulin resistance in particular are extensively studied. It has been proposed that adipose tissue insulin resistance plays one of the key roles in the development of systemic insulin resistant. A number of theories for association between obesity and insulin resistance have been proposed. In particular, it has been shown that obese adipose tissue is characterized by release of non-esterified fatty acids (NEFA) into the bloodstream [10]. NEFA increase cellular diacylglycerol levels [11] finally leading to serine (Ser(307)) phosphorylation of the insulin receptor substrate (IRS) 1 [12]. Such modification of IRS results in inability of the molecules to activate phosphatidylinositol-3-kinase and impaired insulin signaling [13]. Low-grade inflammation in obesity is characterized by excessive production of proinflammatory cytokines and decreased secretion of anti-inflammatory adipokines (adiponectin) in adipose tissue [14]. Obesity induced c-Jun N-terminal kinase activation results in IRS-1 serine phosphorylation at sites (Ser302 and Ser307) negatively affecting downstream insulin signaling [15]. It has been also shown that TNFα suppresses tyrosine phosphorylation of insulin receptor and its substrates [16]. Finally, adipose tissue secretes adiponectin, an adipokine possessing insulin sensitizing properties [17] and obesity-related adipose tissue endocrine dysfunction is characterized by decreased adiponectin production resulting in impaired insulin sensitivity [18]. The association between adipose tissue dysfunction and insulin resistance is also supported by a large body of data indicating a key role of adipocytes in glucose metabolism [19]. Both adipose tissue and muscles perform insulin-dependent glucose uptake. However, alteration of insulin-dependent glucose transport in adipose tissue, but not in muscles has a significant effect on systemic glucose tolerance [20]. At the same time, the search for potential mechanisms linking obesity and insulin resistance still continues [21]. Taking into account a key role of adipose tissue insulin resistance in the development of systemic insulin resistant in obesity [22], the estimation of mechanisms linking obesity and adipose tissue insulin resistance will allow to develop novel prophylactic and therapeutic approaches to treatment of these states.

Trace elements in insulin signaling

Trace elements play a vital role in maintenance of a healthy state via participation in a large number of cellular processes [23]. The main role of essential trace elements in the living cell is associated with its role as a cofactor for enzymes, regulators of enzyme activity, and regulation of redox homeostasis [24]. A growing body of data indicates that certain trace elements play a significant role in regulation of carbohydrate metabolism [25]. The most convincing data were obtained on chromium, vanadium and zinc. Despite the similar total effect on carbohydrate metabolism, the mechanisms of hypoglycemic action of these metals are distinct. In particular, it has been shown that chromium increases membrane fluidity [26], insulin receptor tyrosine kinase activity [27,28], enhances Glut 4 translocation [29], and up-regulates mRNA levels of Glut 4, insulin receptor, glycogen synthase and uncoupling protein 3 [30]. Vanadium possesses inhibitory action on phosphotyrosine phosphatases [31] associated with regulation of cellular redox environment [32], activates insulin receptor kinase [33], increases protein tyrosine phosphorylation [34], and enhances Glut 4 translocation [35]. At the same time, earlier studies have indicated that zinc activates phosphatidylinositol-3-kinase, protein kinase B, and increases insulin receptor β-subunit phosphorylation [36] through suppression of protein tyrosine phosphatases [37].

Moreover, the results of experimental and clinical studies demonstrate a protective effect of trace element supplementation on insulin resistance. In particular, chromium picolinate has been shown to improve metabolic parameters and insulin sensitivity in human [38,39] and laboratory rats [40,41]. A number of vanadium compounds also increase tissue insulin sensitivity both in clinical [42–44] and experimental [45,46] studies. Zinc supplementation was shown to decrease blood glucose, improve insulin sensitivity in obese and diabetic patients [47–49] and animal models [50,51].

Along with affecting insulin-mediated pathways, chromium [52–54], and zinc [55–57] also decrease inflammation that is known to play a significant role in obesity and insulin resistance development [58]. Therefore, a significant interplay between trace elements and insulin resistance exist.

Hypothesis

Multiple studies have indicated that obesity is associated with alteration of trace element homeostasis in the organism. In particular, a decrease in chromium, vanadium and zinc content in scalp hair, urine, whole blood, plasma, and serum of obese and diabetic subjects has been demonstrated [59–62]. However, insufficient attention was given to investigation of adipose tissue trace element balance in obesity both in clinical and experimental studies. Taking into account a key role of adipocyte in systemic carbohydrate homeostasis it can be asked if trace element homeostasis in adipose tissue may influence regulatory mechanisms of glucose metabolism.

We hypothesize that caloric excess through currently unknown mechanisms result in decreased chromium, vanadium, and zinc content in adipocytes. Decreased content of trace elements in the adipose tissue causes impairment of intra-adipocyte insulin signaling subsequently leading to adipose tissue insulin resistance. The latter significantly contributes to systemic insulin resistance and further metabolic disruption in obesity. It is also possible that decreased adipose tissue trace element content is associated with dysregulation of insulin-sensitizing and proinflammatory adipokines also leading to insulin resistance. We hypothesize that insulin resistance and adipokine dysbalance increase the severity of obesity subsequently aggravating alteration of adipose tissue trace element balance (see Fig. 1).

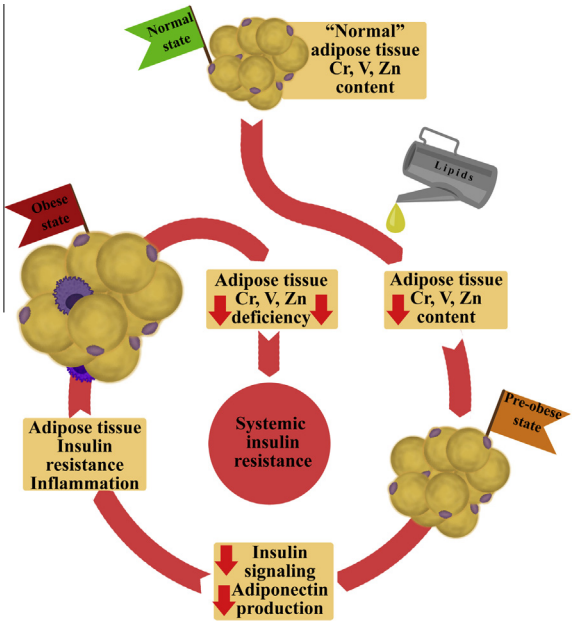

Fig. 1. A hypothetical role of impaired adipose tissue trace element content in development of obesity-associated insulin resistance.