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Short Communication

Portal and peripheral cortisol levels in obese humans

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Abstract

Aims/hypothesis. Excess total body and visceral fat has been associated with insulin resistance, diabetes and the metabolic syndrome. Excess glucocorticoids produce both central obesity and diabetes. However, systemic glucocorticoid levels are normal in typical Type 2 diabetes and persons with idiopathic obesity. Glucocorticoids can be produced locally through the enzyme 11β hydroxysteroid dehydrogenase type 1 (11β HSD-1). Transgenic mice with selective overexpression in adipose tissue of 11β HSD-1 to levels seen in humans develop visceral obesity, hyperlipidaemia and insulin-resistant diabetes associated with a 2.7-fold increase in corticosterone levels in portal compared to peripheral circulation. To examine whether the liver is exposed to higher levels of glucocorticoids, which may undergo metabolic degradation prior to measurement in the systemic circulation, we assessed concentrations of cortisol in the portal and peripheral circulation in morbidly obese humans.

Methods. Portal and peripheral blood samples were obtained simultaneously from six morbidly obese humans with and without diabetes during bariatric abdominal surgery. The samples were assessed for serum cortisol to determine whether an increase in the portal to peripheral circulation is found in obese humans. Insulin, which undergoes metabolic clearance in the liver, and thyroxin (free T_4), which does not, were also assessed.

Results. Levels of serum cortisol (698.8±200.4 vs 696.3±232.4 nmol/l, portal vs peripheral, p=0.9) and free T_4 (22.0±7.8 vs 20.6±8.1 pmol/l, portal vs peripheral, p=0.3) were not significantly different in portal compared to peripheral circulation. Portal insulins were significantly higher than peripheral levels (466.7±302.9 vs 78.5±50.9 pmol/l, portal vs peripheral, p=0.03).

Conclusions/interpretation. These observations suggest that in morbidly obese humans the liver is not exposed to excess glucocorticoids.

Keywords Cortisol · Human · 11β Hydroxysteroid dehydrogenase · Obesity · Portal blood

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Abbreviations: 11β HSD, 11β hydroxysteroid dehydrogenases · 11β HSD-1, 11β hydroxysteroid dehydrogenase type 1 · T_4, thyroxin

Introduction

Diabetes and obesity are increasing in prevalence at epidemic rates in the United States and worldwide. Fat distribution is an important determinant of the extent of metabolic abnormalities associated with obesity. Thus a disproportionate accumulation of visceral fat carries greater risk of insulin resistance, diabetes, hypertension, dyslipidaemia and cardiovascular disease. The metabolic activity of visceral fat differs from that of peripheral fat [1].

Cushing's syndrome, a state of glucocorticoid excess, is associated with central obesity, insulin resistance and diabetes, all of which improve with the treatment of hypercortisolism. Moreover, glucocorticoids have been shown to play a regulatory role in adipose stromal cell differentiation and function [2], suggesting glucocorticoids may influence fat distribution and therefore explain many features of the metabolic syndrome. However, circulating glucocorticoid concentrations in people with idiopathic obesity or Type 2 diabetes are usually found to be normal [3, 4]. The enzymes 11β hydroxysteroid dehydrogenases (11β HSD) catalyse the interconversion of inactive 11-keto steroids into active glucocorticoids (cortisone to cortisol in humans, and 11-dehydrocorticosterone to corticosterone in rodents) and are important in the regulation of intracellular glucocorticoid concentrations [5]. Two isoforms of 11β HSD (types 1 and 2) have been identified. In human adipose tissue 11β HSD-1 is expressed at higher levels in visceral than in subcutaneous fat [6], which could provide a mechanism for higher levels of cortisol synthesis in human omental adipocytes.

The role of the 11β HSD-1 enzyme in human disease is incompletely understood. Levels of 11β HSD-1 mRNA correlate with functional enzyme activity, and 11β HSD-1 mRNA is expressed in adipocytes, stroma and vessel walls in human subcutaneous and omental tissues obtained at biopsy [6, 7, 8]. Although the enzyme localisation does not differ between lean and obese subjects, mRNA levels were found to be higher in the adipose but not in stromal tissue from obese persons [9]. Furthermore, 11β HSD-1 activity correlates with measures of adiposity and insulin resistance in Caucasian and Pima Indian ethnic groups [8]. However, transcriptional up-regulation of 11β HSD-1 mRNA in adipose tissue was not found to be associated with conventional in vivo measurements of urinary cortisol metabolites [7]. These findings suggest that increased levels or activity of the enzyme 11β HSD-1 play a role in mediating local glucocorticoid excess.

Recently, transgenic mice selectively overexpressing 11β HSD-1 in adipocytes to levels seen in humans have been shown to have visceral obesity, insulin resistance and diabetes, dyslipidaemia and significant elevations of corticosterone in adipose tissue and portal blood (corticosterone portal levels 63% higher than peripheral circulation levels) [10]. We hypothesised that increased activity of 11β HSD-1 in omental adipose tissue could generate raised portal cortisol levels in humans with obesity; these raised levels would not be reflected by measurement of systemic cortisol assessment due to metabolism in the liver. To date the relationship between systemic and portal cortisol levels and idiopathic obesity in humans is unknown.

Subjects and methods

The protocol was approved by the Human Subject Committee at the Beth Israel Deaconess Medical Center and the Joslin Diabetes Center, and informed consent was obtained from all participants. Six morbidly obese subjects with and without diabetes, who had been scheduled for bariatric surgery, were recruited for the study. All subjects had normal liver function tests and were not known to have Cushing's syndrome. After an overnight fast prior to surgery, a catheter for withdrawal of peripheral blood samples was placed in the dorsum of the hand and kept patent by normal saline. After general anaesthesia, the surgeon obtained a portal vein blood sample using a winged 21-guage needle. Blood was withdrawn simultaneously from the portal and peripheral catheters. All subjects were haemodynamically stable during the time of blood sampling. Blood samples were obtained between 08.00 and 10.00 hours. In addition to cortisol levels, blood samples were also obtained for insulin and free thyroxin (T_4), both selected as substances that differentially undergo clearance in the liver.

Serum cortisol levels were determined using a Chemiluminescent Immunoassay (Bayer, Tarrytown, N.Y., USA). Both serum insulin and free T_4 were analysed using radioimmunoassays (Diagnostic System Laboratories, Webster, Tex., USA).

Data are expressed as means ± SD and were analysed using a two-tailed paired Student's *t* test. Statistical significance was at a *p* value of less than 0.05. Sample size was determined to show at least half the change seen in portal cortisol levels in the transgenic mice model overexpressing 11β HSD-1 in adipocytes [10].

Results

Subject characteristics included: (i) age (38.7±10.5 years); (ii) sex (three men, three women); (iii) weight (152.0±19.5 kg; BMI 53±3 kg/m^2); and (iv) HbA_1c (7.5±2.6%). Three subjects had diabetes including one with Type 1 diabetes. One of the Type 2 diabetic subjects was on insulin, metformin and pioglitazone, the other was without medical therapy.

Peripheral and portal vein values of cortisol, free T_4 and insulin are shown in Fig. 1. There was no significant difference in the portal and peripheral cortisol levels (698.8±200.4 vs 696.3±232.4 nmol/l, portal vs peripheral, p=0.9). Similarly free T_4 (22.0±7.8 vs 20.6±8.1 pmol/l, portal vs peripheral, p=0.3), which was measured as a negative control, showed no significant difference between portal and peripheral levels. Portal insulin levels were significantly elevated when compared to peripheral levels as previously demonstrated [11], serving as a positive control (466.6±302.9 vs 78.5±50.9 pmol/l, portal vs peripheral, p=0.03). This was despite a smaller gradient for the one Type 1 diabetic subject receiving exogenous insulin.

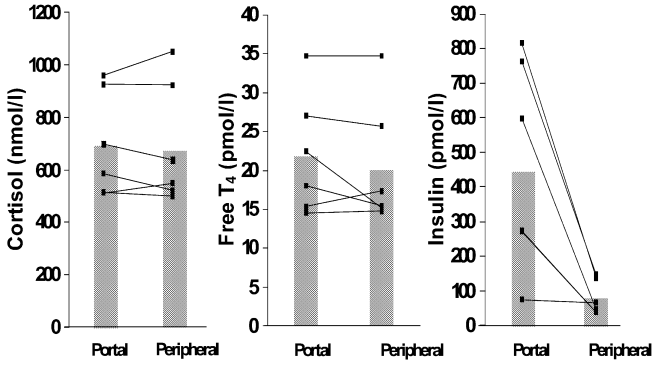

Fig. 1. Portal and peripheral concentrations of cortisol (p=NS), free thyroxin (T_4) (p=NS) and insulin (p=0.03). Lines: individual data; bars: mean data

Discussion

Although there are many phenotypic similarities between syndromes of glucocorticoid excess and syndromes of insulin resistance, serum or urinary cortisol levels are not overtly elevated in persons with prevalent forms of obesity, diabetes or insulin resistance [3, 4]. Glucocorticoid hormone action is important in the regulation of adipose tissue differentiation, function and distribution [2]. The enzyme 11β HSD-1 preferentially converts inactive cortisone to hormonally active cortisol. Enzyme levels are higher in adipose tissue from visceral than in tissue from peripheral depots [8]. Transgenic disruption of 11β HSD-1 attenuates glucocorticoid action and increases insulin sensitivity [12]. Selective overexpression of 11β HSD-1 in adipose tissues of rodents causes the metabolic syndrome phenotype, and mice with increased expression of 11β HSD-1 have higher portal cortisol levels and an increased risk of developing visceral obesity and diabetes [10]. Therefore, we sought to determine if cortisol levels are elevated in the circulation draining the omental fat, but were unable to demonstrate such a gradient.

It is possible that a portal and peripheral gradient may be measurable in persons with isolated central obesity but may not be evident in our study population with morbid generalised obesity. Although all subjects were haemodynamically stable at the time of blood sampling, during surgical stress adrenal source cortisol levels could increase, thereby diminishing the portal to peripheral cortisol ratios. Furthermore, local paracrine or intracellular effects of cortisol could result from increased 11β HSD-1 activity in omental adipose tissues without measurable increases in the portal circulation. Indeed, 11β HSD-1 may amplify glucocorticoid action in a tissue-specific, pre-receptor mechanism [5].

Pharmacological inhibition of 11β HSD-1 may clarify the role of the enzyme in the metabolic syndrome and may prove a useful therapeutic target for treatment of diabetes and the metabolic syndrome [13, 14, 15]. An active constituent of liquorice, glycyrrhetinic acid, and its hemisuccinate derivative carbenoxolone are potent inhibitors of the 11β HSD enzymes. Although non-selective inhibition of the 11β HSD isoforms is associated with clinically limiting adverse effects including increasing blood pressure, carbenoxolone can, by inhibiting hepatic 11β-reductase, reduce intrahepatic cortisol concentrations, and has been demonstrated in healthy and diabetic humans to increase hepatic insulin sensitivity and decrease glucose production with little effect on peripheral insulin sensitivity [16, 17]. Unfortunately, in the Zucker rat this agent has been shown to inhibit 11β HSD-1 activity in liver, but not in adipose tissue or skeletal muscle [18], and inhibition of the enzyme in adipose tissue may be necessary for full effectiveness.

In summary, in cells in vitro and in rodents in vivo the 11β HSD-1 enzyme has been demonstrated to play an important role in the metabolic syndrome. The demonstration of its significance in vivo in humans will require additional investigation.

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