Title

Adiponectin and negative mood in healthy premenopausal and postmenopausal women.

Journal

Hormones and behavior, 58(5)

ISSN

0018-506X

Authors

Adam, Tanja
Schamarek, Imke
Springer, Elizabeth A
et al.

Publication Date

2010-11-01

DOI

10.1016/j.yhbeh.2010.05.006

Peer reviewed

Hormones and Behavior 58 (2010) 699–704

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Adiponectin and negative mood in healthy premenopausal and postmenopausal women

Tanja Adam [a], Imke Schamarek [b], Elizabeth A. Springer [b], Peter J. Havel [c], Elissa E. Epel [b,*]

[a] Department of Preventive Medicine, University of Southern California, 2250 Alcazar Street, CSC 213, Los Angeles, CA 90033, USA
[b] Department of Psychiatry, University of California, Box 0848, 3333 California Street, San Francisco, CA 94143, USA
[c] Department of Nutrition, University of California, 3426 Meyer Hall, Davis, CA 95616, USA

ARTICLE INFO

Article history:
Received 7 January 2010
Revised 7 May 2010
Accepted 9 May 2010
Available online 17 May 2010

Keywords:
Adiposity
Adiponectin
Mood
Stress
Catecholamines

ABSTRACT

Negative mood and stress are associated with cardiovascular and metabolic disease. There are likely many physiological mechanisms underlying the poor health outcomes. The relationship of psychological states (negative mood, life stress, and stress-responsive hormones) and adiponectin, an adipokine that promotes insulin sensitivity, was investigated in two separate studies. The two groups of participants included 52 healthy, premenopausal women, and 63 postmenopausal women with a range of stress levels. The relationship between adiponectin and psychological state (perceived stress and negative mood) was examined cross-sectionally in both groups of participants, but also prospectively (1 year later) in the group of postmenopausal women.
In premenopausal women, negative mood and nocturnal urinary epinephrine were significantly related to adiponectin, independent of BMI. In postmenopausal women, negative mood was not associated with adiponectin cross-sectionally, but negative mood was a significant predictor for lower levels of adiponectin 1 year later, independent of initial adiponectin concentrations and changes in body mass index. Lastly, having a depressive disorder was related to lower adiponectin. As adiponectin levels are associated with insulin resistance, obesity, and diabetes mellitus, these findings suggest there may be an adiponectin-mediated pathway explaining in part how negative mood affects metabolic health. Mechanistic studies are needed to explore this potential relationship further.

Introduction

Eighty percent of adults, women more than men, report at least some stress in their lives (Adam and Epel, 2007). Given the well known relationship between stress arousal and energy regulation, the Metabolic Syndrome falls into the realm of stress-related disorders (Chrousos, 2000b). While the hypothalamus and the brain stem represent the central control stations of stress regulation, the hypothalamic–pituitary–adrenal (HPA) axis together with the efferent sympathetic/adrenomedullary system are the peripheral limbs, vital for survival in stressful situations (Habib et al., 2001; Tsigos and Chrousos, 2002). These systems not only regulate the stress response, but also play an important role for energy metabolism. Excess cortisol secretion due to chronic stressors including job strain (Vitaliano et al., 2002)) and increased sympathoadrenal activity (Brunner et al., 2002) are associated with visceral obesity and other features of the metabolic syndrome (Rosmond, 2005).

Adipose tissue is no longer considered an inert tissue devoted to energy storage, but is now recognized as an endocrine organ secreting a variety of biologically active components (Kwon et al., 2005). These secretory products from the adipocyte, labeled as "adipokines," include leptin, resistin and adiponectin (Flier, 1995, 2001). Adiponectin, the gene product of the adipose gene transcript 1 (*apM1*), is a protein that is exclusively and abundantly expressed in white adipose tissue (Fantuzzi, 2005)—the larger the adipocyte the lower the adiponectin production (Swarbrick and Havel, 2008). Low adiponectin concentrations are associated with insulin resistance, metabolic disease (Stefan et al., 2002; Weyer et al., 2001), and earlier mortality (Poehls et al., 2009). In the attempt to understand how stress arousal may impact obesity-related disease risk, adiponectin may be of particularly interest. The promoter region of apM1 contains consensus sequences for glucocorticoid receptor binding and may be influenced by environmental fluctuations such as chronic stress (Fernandez-Real et al., 2003), possibly contributing to the adverse effects of stress on metabolic parameters such as insulin sensitivity (Chrousos, 2000b). Indeed, reduced apM1 gene expression and reduced adiponectin plasma levels are associated with obesity and type 2 diabetes mellitus in humans (Kern et al., 2003; Kwon et al., 2005; Weyer et al., 2001). It has been shown that exogenous glucocorticoid administration decreases adiponectin concentrations transiently in human subjects (Fallo et al., 2004). In rodents, beta adrenergic agonists reduced adiponectin in both adipose tissue and blood, suggesting that

* Corresponding author. Department of Psychiatry, University of California, 3333 California Street, Suite 465, San Francisco, CA 94143-0848, USA. Fax: +1 415 476 7744.
E-mail address: eepel@lppi.ucsf (E.E. Epel).

0018-506X/$ – see front matter © 2010 Published by Elsevier Inc.
doi:10.1016/j.yhbeh.2010.05.006

catecholamines may also play a regulatory inhibitory role (Delporte et al., 2002).

A stress-responsive hormone that has been shown to potentially regulate adipose tissue mass is dehydroepiandrosterone (DHEA) (Karbowska and Kochan, 2005). DHEA_S is the major circulating steroid in humans and is almost exclusively secreted by the cortex of the adrenal gland (Wolf and Kirschbaum, 1999). It is a precursor hormone for several bio-active sex steroids such as estradiol and testosterone (Parker, 1991). DHEA and its sulfate ester (DHEA_S) have fat reducing properties at least in males, and may function as an anti-obesity agent in various models of obesity (Hansen et al., 1997; Kajita et al., 2003; Karbowska and Kochan, 2005). The relevance of animal models for human DHEA-S research is uncertain, since rodents have no or very little DHEA-S. DHEA concentrations decline with age (Orentreich et al., 1984) and stress (Wolf and Kirschbaum, 1999) and low DHEA has been associated with various disorders such as insulin resistance, type 2 diabetes and atherosclerosis in males (Herrington et al., 1990; Yamaguchi et al., 1998). Emerging evidence shows that DHEA's protective properties may be mediated in part by an up-regulation of adiponectin gene expression and an increase in adiponectin secretion from adipose tissue (Karbowska and Kochan, 2005). It has been hypothesized that adiponectin mediates the relationship between psychopathology and obesity (Yilmaz, 2008), and one study found a relationship between lower adiponectin in depressed compared to non-depressed men and women (Leo et al., 2006).

To our knowledge no research has explored the relationship between stress, mood, stress hormones and adiponectin. Therefore the aim of the present study was to examine the relationship between adiponectin, psychological stress and mood, in younger (Study 1) and older (Study 2) women, as well as stress-related hormones (available in Study 1).

Methods

Participants

Study 1: Premenopausal women

Fifty-two healthy, premenopausal women (all mothers), aged between 20 and 50 years, were recruited through their child's health care professional in clinics in Bay Area hospitals, or by public posting. The women were admitted to a General Clinical Research Center (GCRC) for a study on caregiving and health, during the first 7 days of the follicular phase, if not on oral contraceptives. Women taking oral contraceptives came to the GCRC during placebo days.

To capture a range of stress levels, the sample included both mothers of chronically ill children and a control group of mothers with healthy children. All women had at least one biological child. Forty-one mothers had children with a chronic disorder (such as neurological, a gastrointestinal disorder, or a pervasive development disorder), and 21 had healthy children. The study protocol was approved by the Institutional Review Board of the University of California, San Francisco. Written, informed consent was obtained from all participants The participants were free of any acute or chronic health condition by self-report, with the exception of controlled hypertension ($n=2$) and controlled hypothyroidism ($n=1$). Participants did not consume more than seven alcoholic beverages per week, or exercise more than one hour a day. They refrained from alcohol the day before the study. The measures collected are listed below.

Study 2: Postmenopausal women

A second sample comprised 63 healthy, postmenopausal women aged between 51 and 79, who also were recruited in the Bay Area of California through flyers in the community, newspaper advertisements and an Internet homepage (Craigslist). This mainly white sample (80.9%) also included one Black, one Hispanic/Latina and seven Asian women. Similarly to the first sample, a wide range of stress levels was captured by including women giving care to a relative diagnosed with dementia as well as non-caregiving women.

Exclusion criteria were similar as in Study 1, and included the presence of major medical conditions such as heart disease, cancer or diabetes, use of medications containing agents known to affect stress hormone levels and regular smoking. The study protocol was approved by the Institutional Review Board of the University of California, San Francisco. Written, informed consent was obtained from all participants. We were able to obtain the same battery of measures from a subsample of these women ($n=25$) 1 year later for prospective data analysis.

Psychological assessments (Study 1 and Study 2)

Perceived stress levels were assessed by means of the Perceived Stress Scale (PSS) (Cohen et al., 1983). The PSS is a 10-item scale that measures the degree to which situations in an individual's life are appraised as stressful.

Subjective Positive and negative affect was measured with the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988). Positive affect refers to positive states such as enthusiastic, active, attentive, strong or alert and negative affect refers to a general dimension of subjective distress, encompassing a variety of aversive mood states such as anger, contempt, disgust, fear and nervousness. In addition, a SCID interview was conducted for women in Study 2, by trained interviewers to assess major depression and dysthymia.

Anthropometric data

In both studies, weight was measured using a balance beam scale, and height was measured with a stadiometer. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. In Study 2, trunk fat was measured at baseline and 12 months later using a Holographic DEXA-Scan at the UCSF CTSI clinic.

Stress-responsive hormones (Study 1 only)

A 12 h nocturnal urine sample (20:00 h to 08:00 h) was collected from a subsample of 52 participants and assayed for stress hormones (free urinary cortisol, epinephrine, and norepinephrine) and creatinine. The selection of the subsample was based on the amount or urine collected. Participants who had collection volumes less than 300 ml ($n=4$) were determined to have incomplete collections and their urinary hormone values were excluded from analyses, as done in other studies with 12 h urine collections (Greendale et al., 1999). Urine samples were kept in a cooler with ample ice blocks for the duration of the collection. Samples were picked up immediately the next morning. Aliquots were frozen at −80 °C until analysis.

Urinary epinephrine and norepinephrine were assayed with kits provided by American Laboratory Products Company (Alpco), Windham, NH. The sensitivity was 0.33 and 1.33 ng/ml, respectively, for epinephrine and norepinephrine. For epinephrine the intra- and interassay coefficients of variation (CV's) were 7.2 and 15.4%, respectively. For norepinephrine, the intra- and interassay CV's were 10.2 and 15.0%, respectively. Cortisol was measured by a radioimmunoassay. The sensitivity of the method is 10 nml. Intra- and interassay CV's were 9.3 and 5.4%, respectively. Creatinine was measured spectrophotometrically by the Jaffe reaction at 490 nm after extraction of the samples with ethyl ether to remove interfering substances.

Blood sample collection and processing

Study 1

Blood sampling took place at Oakland Children's Hospital Pediatric Clinical Research Center. Participants fasted for 10 h, starting from dinner the previous night. At 0800 in the morning subjects had a fasting blood draw. Blood samples were centrifuged, aliquoted and

stored in polypropylene vials at −80 °C until analysis. Samples were assayed for adiponectin (μg/ml) and DHEA_S (ng/ml).

DHEA_S concentrations were measured by Enzyme Immuno Assay (EIA), and free testosterone by 125I-based radio immune assays (RIA) with kits obtained from Diagnostic Systems Laboratories, Inc. (DSL, Webster, TX) (Miller et al., 2004).

Plasma adiponectin concentrations were measured using a radioimmunoassay for human adiponectin (Millipore, MA) at the UC Davis lab of Dr. Peter Havel. The assay utilizes 125I-labeled adiponectin and an anti-adiponectin rabbit antiserum to measure adiponectin concentrations by the double antibody/PEG technique. Standards over the range of 1–200 ng/ml were prepared using recombinant human adiponectin. All plasma samples were diluted 1:200 yielding an effective range of 0.2–40 μg/ml. The intra-assay and interassay coefficients of variation of adiponectin concentrations in this laboratory in the range of 3–25 μg/ml are 5.1–7.2% and 9.1–12.1%, respectively. Adiponectin levels are relatively stable during the daytime (Swarbrick and Havel, 2008).

Study 2

Blood draws took place at the CTSI General Clinical Research Center at the University of California, San Francisco. Participants fasted for 8 h starting from midnight and with the actual fasting blood draw being performed at 8 o' clock in the morning. Blood samples were centrifuged, aliquoted and stored in polypropylene vials at −20 °C until analysis. Adiponectin was assayed in Dr. Havel's lab, as in Study 1 above.

Statistical analysis for both studies

Statistical analysis was performed with SPSS software (version 15.0, SPSS Inc., Chicago, IL, USA). Results are reported as mean values ± standard errors (SE). Differences between caregivers and non-caregivers were assessed by analysis of variance (ANOVA). Adiponectin data of Study 2 were not normally distributed and were therefore log-transformed.

Zero-order Spearman correlation coefficients were used to assess associations between plasma adiponectin with psychological and hormonal variables.

Partial correlations were conducted to control for BMI and age. Oral contraceptives, smoking, and age were tested as potential covariates and since they were not related to adiponectin they were not included. In the longitudinal analysis (Study 2) we controlled for change in BMI from baseline to 12 month follow up as well as plasma adiponectin level at baseline. A p value of <0.05, two tailed, was considered significant.

For Study 2, we performed a hierarchical linear regression to assess the contribution of negative mood to adiponectin at 12 months above and beyond baseline adiponectin, and change in BMI from baseline to 12 months. We entered baseline adiponectin and change in BMI in step 1, and negative mood in step 2. To adjust for the skewed distribution of adiponectin, we performed natural logarithmic transformations.

Results

Study 1

Fifty-two premenopausal women with complete data were included in the statistical analysis, with age ranging from 19 to 50 years (M age = 38.16, SD = 6.24; M BMI = 26.71, SD = 6.73). As expected, adiponectin was correlated with BMI ($r = -0.40$, $p = 0.001$). Therefore correlations are shown as raw and adjusted for BMI and age (Table 1). In this cross-sectional approach negative mood was inversely correlated with plasma adiponectin, independent of BMI ($r = 0$–0.30, $p < 0.05$). As demonstrated in Fig. 1, plasma adiponectin levels were consistently low for women with the strongest negative mood ratings. In contrast to women with high negative mood ratings, women with the lowest negative mood ratings show a greater range of adiponectin levels.

Table 1
Pearson correlations between adiponectin and stress-related variables in premenopausal women (Study 1).

	Zero-order correlations	Partial correlations (adjusted for age and BMI. Additionally, for urinary hormones, adjusted for creatinine)
Psychological state		
Negative mood ($n = 56$)	**−0.40***	**−0.29***
Positive mood ($n = 56$)	0.07	0.11
Perceived stress ($n = 60$)	−0.07	−0.23
Hormones		
Urinary epinephrine (mg/ng) ($n = 38$)	**−0.34***	**−0.42***
Urinary cortisol (nml) ($n = 38$)	−0.06	0.06
Urinary norepinephrine (mg/ng) ($n = 37$)	−0.24	−0.23
Serum DHEA_S (ng/ml) ($n = 61$)	**−0.26***	**−0.25***

* $p < 0.05$ (two-tailed).

Adiponectin was also significantly and inversely related to nocturnal urinary epinephrine ($r = 0$–0.46, $p \leq 0.005$; Fig. 2) independent of BMI, and to serum DHEA-S ($r = -0.27$, $p < 0.005$), an inverse, and a non-significantly correlation with norepinephrine. Adiponectin was not associated with perception of life stress or urinary cortisol. Adiponectin was not related to positive affect. Positive affect, however, was negatively related to perceived stress.

Study 2

Forty-eight postmenopausal women had complete data and were included in statistical analysis. They had an age range between 51 and 79 years (M age 61.87, SD = 6.51). Their mean BMI was 26.72 (SD = 5.49). Postmenopausal women reported significantly less negative mood compared to premenopausal women (M negative mood = 8.8, SD = 9.4 vs. M negative mood = 19.2, SD = 10.9, respectively, $p < 0.05$). The two groups also had significantly different baseline adiponectin concentrations (M adiponectin = 7.2, SD = 3.2 ng/ml for premenopausal vs. M adiponectin = 13.2, SD = 5.2 ng/ml in postmenopausal women). BMI was not significantly different between groups (M BMI = 26, SD = 6.7 in premenopausal vs. M BMI = 24, SD = 5.3 in postmenopausal women).

As expected, adiponectin was inversely, but not significantly related to BMI ($r = -0.24$, $p = 0.083$). In postmenopausal women, the cross-sectional association between adiponectin and mood was not significant ($r = 0.04$, $p = 0.78$). However, prospectively there was a

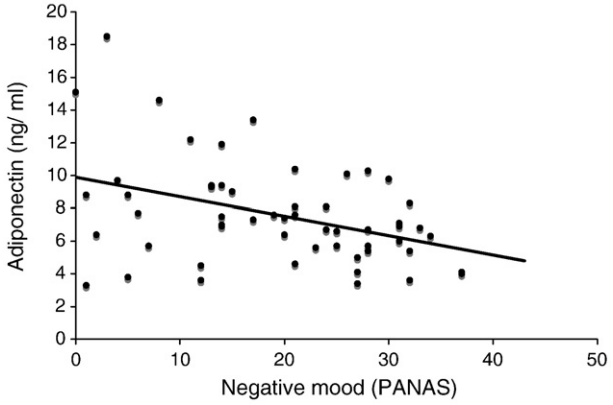

Fig. 1. Scatterplot of cross-sectional association between negative mood and plasma adiponectin levels (Study 1). $p < 0.05$.

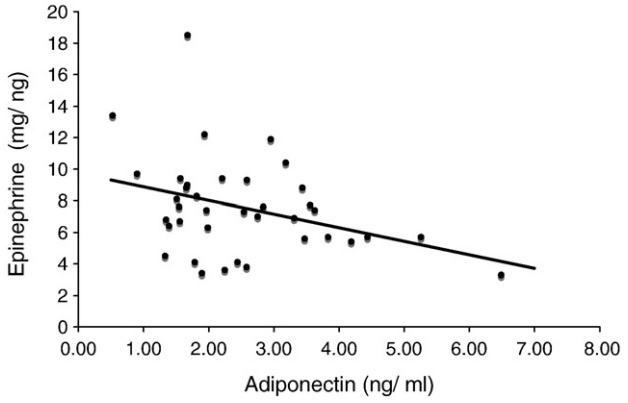

Fig. 2. Scatterplot of relation between adiponectin and urinary epinephrine (Study 1). $p<0.05$.

significant inverse relationship between negative mood at baseline and plasma adiponectin levels obtained in the follow up sample ($n=28$) 12 months later, adjusting for change in BMI as well as baseline age and adiponectin concentrations (partial $r=-0.48$, $p=0.002$), showing women with high negative mood at baseline have decreases in adiponectin 1 year later.

In a 3 step hierarchical linear regression, baseline adiponectin accounted for 87% variance in step 1, BMI change for an additional 2% in step 2, and in the last step, negative mood accounted for an additional 4.7% of the variance in adiponectin 1 year later ($T=-4.5$, $p=0.001$).

It is remarkable that decreases in adiponectin were independent of changes in body fat. It is reasonable that negative mood might decrease adiponectin through increasing not just total fat but in particular abdominal fat, since larger abdominal fat cells produce less adiponectin. Therefore, we also tested this relationship while controlling for abdominal fat changes, as measured by a DEXA scan (using trunk fat). This inverse relationship between negative mood scores at baseline and adiponectin changes at 12 month follow up, remained significant even after controlling for change in trunk fat from baseline to 12 months ($r=-0.46$, $p=0.002$).

Lastly, as a secondary analysis, we also analyzed the relation between depression category at baseline, as assessed by the SCID, and adiponectin. There were 8 women with current depression, and 2 with dysthymia, which were not enough to analyze separately, so we combined these women into one group. We tested whether adiponectin was different by group, adjusting for BMI. At baseline, women with a depressive disorder (depression or dysthymia, $n=10$) had significantly lower adiponectin than the group without a depressive diagnosis (M adiponectin = 9.96, SD = 1.5 vs. 14.0, SD = 0.73, $F(2,53)=5.6$, $p<0.02$). A year later, both groups had decreased with similar magnitude, by 1 ug/dl.

Discussion

We found that adiponectin may be responsive to negative mood and adrenergic tone, at least in terms of nocturnal epinephrine levels. There is converging evidence that negative affect and stress create susceptibility to physical illness, such as to the common cold, cardiovascular disease and premature mortality (Brummett et al., 2001; Cohen et al., 1991; Stewart-Brown, 1998). Underlying mechanisms such as chronic inflammation (Chrousos, 2000a) and cortisol dysregulation contribute to metabolic disease (Chrousos, 2000a), but other pathways, such as changes metabolic peptides, have not yet been well elucidated.

In a cross-sectional approach, premenopausal women scoring highest on a scale that measures subjective negative affect show the lowest plasma adiponectin concentrations, controlling for BMI. Having low levels of negative mood, however, was not related to higher adiponectin but rather to a wide range of adiponectin concentrations. Similarly, in both studies, there was no association between positive mood with higher adiponectin. These findings suggest specificity for high levels of negative mood as one factor potentially influencing adiponectin level in humans. In the study of elderly women, surprisingly, negative mood was not associated with adiponectin. However, we also had measured diagnoses of depressive disorders (current major depression or dysthymia). This index of more severe negative mood—having a depressive disorder—was associated with significantly lower levels of adiponectin. This supports earlier findings linking major depression to lower adiponectin, when comparing 32 participants with depression to controls (Leo et al., 2006).

To further address the question of temporal sequencing, we analyzed data of a sub-sample of elderly women over 1 year, and found a significant negative correlation between negative mood at baseline and lower plasma adiponectin levels 1 year later, covarying baseline adiponectin. This relationship was independent of changes in BMI, age or trunk fat.

Although the study was not designed to compare effects of stress and depression, it is notable that neither measure of stress—objective stress, as measured by caregiver group, and perceived stress—were related to adiponectin, whereas both measures of negative affect (negative mood as measured by the PANAS, and having a diagnosis of depression or dysthymia) were both related to lower adiponectin. Adiponectin may be more tied to the neurobiology of depression, as the underlying physiological correlates of stress and depression are different (in complex and poorly defined ways).

Alternatively, negative mood may represent a more stable or traitlike emotional state, compared to perceived stress, which more closely reflects changing objective environmental demands. Although caregiving status represents a chronic stressor, there are nevertheless varying levels of stress and negative mood within the caregiving group, which may be why individual differences in mood rather than group status are a more important factor here. It would have been helpful to assess negative mood with repeated measures over time to get a more traitlike measure.

Catecholamines are known to play a major role in fuel homeostasis and in counteracting insulin action (Rupp and Maisch, 2003), but their influence on adiponectin has scarcely been investigated. To our knowledge only one study investigated the effect of catecholamines on plasma adiponectin levels in vivo in mice (Delporte et al., 2002). In human and mouse adipose tissue a significant decrease of adiponectin mRNA was found after culture with ß-adrenergic agonists or cAMP (Delporte et al., 2002). Adrenergic dysregulation is common with stress and many psychiatric disease states and may further predispose to low adiponectin. Catecholamines may be the physiological substrate explaining the relationship of adiponectin and negative mood.

DHEA-S was negatively correlated with plasma adiponectin concentrations. Postulated consequences of low DHEA include insulin resistance (Schriock et al., 1988) and obesity (Nestler et al., 1988). While elevated circulating DHEA-S concentrations have been associated with a reduced incidence of cardiovascular disease in men (Barrett-Connor and Ferrara, 1996), relationships may be the opposite in women: While DHEA-S may have neuroprotective (Juhasz-Vedres et al., 2006) and anxiolytic (van Niekerk et al., 2001) features on the one hand, increased DHEA-S concentrations also have been found to be correlated with increased abdominal fat in premenopausal women, and in postmenopausal women, with glucose intolerance (Barrett-Connor and Ferrara, 1996) and cardiovascular disease (Williams et al., 1993). If high levels of DHEA-S promote metabolic disease in women (Barrett-Connor and Ferrara, 1996; Williams et al., 1993), the present study suggests that DHEA-S might act in part through affecting adiponectin levels.

In the present study the relationship between negative mood and adiponectin does not seem to be mediated by cortisol levels, as there was no correlation between adiponectin levels and cortisol. However, true mediation must be assessed over time and snap shot measures of cortisol do not closely reflect past history of HPA axis activity. Other findings on the association between cortisol and adiponectin are

mixed. On one hand, since the promoter region of Apm1 contains consensus sequences for glucocorticosteroid receptor binding, adiponectin could potentially be modified by environmental stress (Comuzzie et al., 2001). Further, it has been demonstrated that dexamethasone, a synthetic corticosterone decreases adiponectin gene expression (Fasshauer et al., 2002). These results were obtained from cell culture research and it needs to be clarified whether this holds for plasma concentrations in vivo as well. However, others found a positive correlation between fasting morning cortisol and circulating adiponectin concentrations (Fernandez-Real et al., 2003), supporting the role of adiponectin in anti-inflammatory feedback. Urine measures average over time and thus obscure any variance from dysregulation of the diurnal peak, nadir, or morning waking response. Further studies are needed to specifically examine specific aspects of HPA axis dysregulation in relation to adiponectin.

Since adiponectin levels are associated with certain risk factors of the metabolic syndrome such as obesity, diabetes mellitus and reduced insulin sensitivity, these findings raise the possibility that adiponectin may in part mediate the relationship between depression, negative mood, and metabolic health (Lihn et al., 2005). Other authors have shown a difference in adiponectin concentrations with age (Gavrila et al., 2003). This difference has been attributed to changes in body composition. In the present study adiponectin concentrations were related to BMI in both groups and groups were not different concerning BMI. This suggests, in accordance with others (Jurimae and Jurimae, 2007), that menopausal status, rather than body composition has a major influence on the difference in adiponectin concentrations between premenopausal and postmenopausal women.

There are many limitations to these initial studies. The samples included women only, and it is unknown if these relationships would have been found in men. Due to a small number of participants examined in the follow up study at 12 months, we are limited in our conclusions Many correlations were performed with relatively small samples. Further studies are needed to replicate the prospective relationship between negative mood and adiponectin levels found in the present study. Negative mood may work through behaviors. For example, it is linked to changes in diet, either increased intake or increase of certain sugars that are linked to decreased adiponectin, and dietary analyses as well as insulin sensitivity assessment would have been helpful. It would have been helpful to examine the roles of inflammatory markers as possible mediators in the relationships between negative mood with adiponectin. Nevertheless, this is to our knowledge the first study demonstrating links between depressed and negative affect with adiponectin. These factors might prove to be a helpful new target for the prevention of features of the metabolic syndrome.

Conflict of interest

None of the authors reports a conflict of interest.

References

Adam, T.C., Epel, E.S., 2007. Stress, eating and the reward system. Physiol. Behav. 91, 449–458.

Barrett-Connor, E., Ferrara, A., 1996. Dehydroepiandrosterone, dehydroepiandrosterone sulfate, obesity, waist-hip ratio, and noninsulin-dependent diabetes in postmenopausal women: the Rancho Bernardo Study. J. Clin. Endocrinol. Metab. 81, 59–64.

Brummett, B.H., Barefoot, J.C., Siegler, I.C., Clapp-Channing, N.E., Lytle, B.L., Bosworth, H.B., Williams Jr., R.B., Mark, D.B., 2001. Characteristics of socially isolated patients with coronary artery disease who are at elevated risk for mortality. Psychosom. Med. 63, 267–272.

Brunner, E.J., Hemingway, H., Walker, B.R., Page, M., Clarke, P., Juneja, M., Shipley, M.J., Kumari, M., Andrew, R., Seckl, J.R., Papadopoulos, A., Checkley, S., Rumley, A., Lowe, G.D., Stansfeld, S.A., Marmot, M.G., 2002. Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: nested case-control study. Circulation 106, 2659–2665.

Chrousos, G.P., 2000a. Stress, chronic inflammation, and emotional and physical well-being: concurrent effects and chronic sequelae. J. Allergy Clin. Immunol. 106, S275–S291.

Chrousos, G.P., 2000b. The role of stress and the hypothalamic–pituitary–adrenal axis in the pathogenesis of the metabolic syndrome: neuro-endocrine and target tissue-related causes. Int. J. Obes. Relat. Metab. Disord. 24 (Suppl 2), S50–S55.

Cohen, S., Kamarck, T., Mermelstein, R., 1983. A global measure of perceived stress. J. Health Soc. Behav. 24, 385–396.

Cohen, S., Tyrrell, D.A., Smith, A.P., 1991. Psychological stress and susceptibility to the common cold. N. Engl. J. Med. 325, 606–612.

Comuzzie, A.G., Funahashi, T., Sonnenberg, G., Martin, L.J., Jacob, H.J., Black, A.E., Maas, D., Takahashi, M., Kihara, S., Tanaka, S., Matsuzawa, Y., Blangero, J., Cohen, D., Kissebah, A., 2001. The genetic basis of plasma variation in adiponectin, a global endophenotype for obesity and the metabolic syndrome. J. Clin. Endocrinol. Metab. 86, 4321–4325.

Delporte, M.L., Funahashi, T., Takahashi, M., Matsuzawa, Y., Brichard, S.M., 2002. Pre- and post-translational negative effect of beta-adrenoceptor agonists on adiponectin secretion: in vitro and in vivo studies. Biochem. J. 367, 677–685.

Fallo, F., Scarda, A., Sonino, N., Paoletta, A., Boscaro, M., Pagano, C., Federspil, G., Vettor, R., 2004. Effect of glucocorticoids on adiponectin: a study in healthy subjects and in Cushing's syndrome. Eur. J. Endocrinol. 150, 339–344.

Fantuzzi, G., 2005. Adipose tissue, adipokines, and inflammation. J. Allergy Clin. Immunol. 115, 911–919 quiz 920.

Fasshauer, M., Klein, J., Neumann, S., Eszlinger, M., Paschke, R., 2002. Hormonal regulation of adiponectin gene expression in 3T3-L1 adipocytes. Biochem. Biophys. Res. Commun. 290, 1084–1089.

Fernandez-Real, J.M., Lopez-Bermejo, A., Casamitjana, R., Ricart, W., 2003. Novel interactions of adiponectin with the endocrine system and inflammatory parameters. J. Clin. Endocrinol. Metab. 88, 2714–2718.

Flier, J.S., 1995. The adipocyte: storage depot or node on the energy information superhighway? Cell 80, 15–18.

Flier, J.S., 2001. Diabetes. The missing link with obesity? Nature 409, 292–293.

Gavrila, A., Chan, J.L., Yiannakouris, N., Kontogianni, M., Miller, L.C., Orlova, C., Mantzoros, C.S., 2003. Serum adiponectin levels are inversely associated with overall and central fat distribution but are not directly regulated by acute fasting or leptin administration in humans: cross-sectional and interventional studies. J. Clin. Endocrinol. Metab. 88, 4823–4831.

Greendale, G.A., Unger, J.B., Rowe, J.W., Seeman, T.E., 1999. The relation between cortisol excretion and fractures in healthy older people: results from the MacArthur studies-Mac. J. Am. Geriatr. Soc. 47, 799–803.

Habib, K.E., Gold, P.W., Chrousos, G.P., 2001. Neuroendocrinology of stress. Endocr. Metab. Clin. N. Am. 30, 695–728 vii-viii.

Hansen, P.A., Han, D.H., Nolte, L.A., Chen, M., Holloszy, J.O., 1997. DHEA protects against visceral obesity and muscle insulin resistance in rats fed a high-fat diet. Am. J. Physiol. 273, R1704–R1708.

Herrington, D.M., Gordon, G.B., Achuff, S.C., Trejo, J.F., Weisman, H.F., Kwiterovich Jr., P.O., Pearson, T.A., 1990. Plasma dehydroepiandrosterone and dehydroepiandrosterone sulfate in patients undergoing diagnostic coronary angiography. J. Am. Coll. Cardiol. 16, 862–870.

Juhasz-Vedres, G., Rozsa, E., Dobszay, M.B., Kis, Z., Wolfling, J., Toldi, J., Parducz, A., Farkas, T., 2006. Dehydroepiandrosterone sulfate (DHEAS) is neuroprotective when administered either pre- or post-injury in a focal cortical cold lesion model. Endocrinology 147, 683–866.

Jurimae, J., Jurimae, T., 2007. Plasma adiponectin concentration in healthy pre- and postmenopausal women: relationship with body composition, bone mineral, and metabolic variables. Am. J. Physiol. Endocrinol. Metab. 293, E42–E47.

Kajita, K., Ishizuka, T., Mune, T., Miura, A., Ishizawa, M., Kanoh, Y., Kawai, Y., Natsume, Y., Yasuda, K., 2003. Dehydroepiandrosterone down-regulates the expression of peroxisome proliferator-activated receptor gamma in adipocytes. Endocrinology 144, 253–259.

Karbowska, J., Kochan, Z., 2005. Effect of DHEA on endocrine functions of adipose tissue, the involvement of PPAR gamma. Biochem. Pharmacol. 70, 249–257.

Kern, P.A., Di Gregorio, G.B., Lu, T., Rassouli, N., Ranganathan, G., 2003. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. Diabetes 52, 1779–1785.

Kwon, K., Jung, S.H., Choi, C., Park, S.H., 2005. Reciprocal association between visceral obesity and adiponectin: in healthy premenopausal women. Int. J. Cardiol. 101, 385–390.

Leo, R., Di Lorenzo, G., Tesauro, M., Cola, C., Fortuna, E., Zanasi, M., Troisi, A., Siracusano, A., Lauro, R., Romeo, F., 2006. Decreased plasma adiponectin concentration in major depression. Neurosci. Lett. 407, 211–213.

Lihn, A.S., Pedersen, S.B., Richelsen, B., 2005. Adiponectin: action, regulation and association to insulin sensitivity. Obes. Rev. 6, 13–21.

Miller, K.K., Rosner, W., Lee, H., Hier, J., Sesmilo, G., Schoenfeld, D., Neubauer, G., Klibanski, A., 2004. Measurement of free testosterone in normal women and women with androgen deficiency: comparison of methods. J. Clin. Endocrinol. Metab. 89, 525–533.

Nestler, J.E., Barlascini, C.O., Clore, J.N., Blackard, W.G., 1988. Dehydroepiandrosterone reduces serum low density lipoprotein levels and body fat but does not alter insulin sensitivity in normal men. J. Clin. Endocrinol. Metab. 66, 57–61.

Orentreich, N., Brind, J.L., Rizer, R.L., Vogelman, J.H., 1984. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. J. Clin. Endocrinol. Metab. 59, 551–555.

Parker, L.N., 1991. Control of adrenal androgen secretion. Endocrinol. Metab. Clin. North Am. 20, 401–421.

Poehls, J., Wassel, C.L., Harris, T.B., Havel, P.J., Swarbrick, M.M., Cummings, S.R., Newman, A.B., Satterfield, S., Kanaya, A.M., 2009. Association of adiponectin with mortality in older adults: the Health, Aging, and Body Composition Study. Diabetologia 52, 591–595.

Rosmond, R., 2005. Role of stress in the pathogenesis of the metabolic syndrome. Psychoneuroendocrinology 30, 1–10.

Rupp, H., Maisch, B., 2003. Abdominal fat and sympathetic overactivity. From calorie intake to postmenopausal hypertension. Herz 28, 668–673.
Schriock, E.D., Buffington, C.K., Hubert, G.D., Kurtz, B.R., Kitabchi, A.E., Buster, J.E., Givens, J.R., 1988. Divergent correlations of circulating dehydroepiandrosterone sulfate and testosterone with insulin levels and insulin receptor binding. J. Clin. Endocrinol. Metab. 66, 1329–1331.
Stefan, N., Vozarova, B., Funahashi, T., Matsuzawa, Y., Weyer, C., Lindsay, R.S., Youngren, J.F., Havel, P.J., Pratley, R.E., Bogardus, C., Tataranni, P.A., 2002. Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. Diabetes 51, 1884–1888.
Stewart-Brown, S., 1998. Emotional wellbeing and its relation to health. Physical disease may well result from emotional distress. BMJ 317, 1608–1609.
Swarbrick, M.M., Havel, P.J., 2008. Physiological, pharmacological, and nutritional regulation of circulating adiponectin concentrations in humans. Metab. Syndr. Relat. Disord. 6, 87–102.
Tsigos, C., Chrousos, G.P., 2002. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. J. Psychosom. Res. 53, 865–871.
van Niekerk, J.K., Huppert, F.A., Herbert, J., 2001. Salivary cortisol and DHEA: association with measures of cognition and well-being in normal older men, and effects of three months of DHEA supplementation. Psychoneuroendocrinology 26, 591–612.
Vitaliano, P.P., Scanlan, J.M., Zhang, J., Savage, M.V., Hirsch, I.B., Siegler, I.C., 2002. A path model of chronic stress, the metabolic syndrome, and coronary heart disease. Psychosom. Med. 64, 418–435.
Watson, D., Clark, L., Tellegen, A., 1988. Development and validation of breif measure of positive and negative affect: the PANAS scales. J. Pers. Soc. Psychol. 54, 1063–1070.
Weyer, C., Funahashi, T., Tanaka, S., Hotta, K., Matsuzawa, Y., Pratley, R.E., Tataranni, P.A., 2001. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J. Clin. Endocrinol. Metab. 86, 1930–1935.
Williams, D.P., Boyden, T.W., Pamenter, R.W., Lohman, T.G., Going, S.B., 1993. Relationship of body fat percentage and fat distribution with dehydroepiandrosterone sulfate in premenopausal females. J. Clin. Endocrinol. Metab. 77, 80–85.
Wolf, O.T., Kirschbaum, C., 1999. Actions of dehydroepiandrosterone and its sulfate in the central nervous system: effects on cognition and emotion in animals and humans. Brain Res. Brain Res. Rev. 30, 264–288.
Yamaguchi, Y., Tanaka, S., Yamakawa, T., Kimura, M., Ukawa, K., Yamada, Y., Ishihara, M., Sekihara, H., 1998. Reduced serum dehydroepiandrosterone levels in diabetic patients with hyperinsulinaemia. Clin. Endocrinol. (Oxf.) 49, 377–383.
Yilmaz, Y., 2008. Psychopathology in the context of obesity: the adiponectin hypothesis. Med. Hypotheses 70, 902–903.