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Impact of Acute Psychological Stress on Cardiovascular Risk Factors in Face of Insulin Resistance

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Abstract

Individuals with insulin resistance (IR) are at greater risk for cardiovascular disease (CVD). Psychological stress may contribute to develop CVD in IR although mechanisms are poorly understood. Our aim was to test the hypothesis that individuals with IR have enhanced emotional and physiological responses to acute psychological stress, leading to increased CVD risk. Sixty participants were enrolled into the study, and classified into IR group (n=31) and insulin sensitive group (n=29) according to the Quantitative insulin sensitivity check index, which was calculated based on an oral glucose tolerance test. The Trier social stress test, a standardized experimental stress paradigm, was performed on each participant, and emotional and physiological responses were examined. Blood was collected from each subject for insulin, cytokines and cortisol measurements. Compared with insulin sensitive group, individuals with IR had significantly lower ratings of energy and calm, but higher fatigue levels in response to acute stressors. Individuals with IR also showed blunted heart rate reactivity following stress. In addition, the IR status was worsened by acute psychological stress as demonstrated by further increased insulin secretion. Furthermore, individuals with IR showed significantly increased levels of leptin and interleukin-6, but decreased levels of adiponectin, at baseline, stress test and post-stress period. Our findings in individuals with IR under acute stress would allow a better understanding of the risks for developing CVD and to tailor the interventions for better outcomes.

Keywords

acute psychological stress; cardiovascular disease; risk factors; insulin resistance; cortisol; cytokines

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Declaration of Interest

The authors report no conflicts of interest.

Introduction

Insulin resistance (IR) is a pathological condition characterized by a reduced physiological response of the peripheral tissues to insulin secreted by pancreas β -cells (Desouza et al., 2001; Ingram et al., 2012; Kendall et al., 2002; Matsuda et al., 1999). It is well-established that IR is central to the development of type 2 diabetes (Kendall et al., 2002; Weyer et al., 1999; 1999). In addition, IR is also associated with cardiovascular disease (CVD) although the underlying mechanisms linking IR to CVD are not fully understood (Kendall et al., 2002; Reaven, 2003). Stress, whether actual or perceived, is a state of threatened homeostasis provoked by a psychological, environmental or physiologic stressor, leading to disruption of normal physiological functions (Black 2002). Emotional stressors are increasingly recognized as having detrimental effects on the pathogenesis of CVD and its adverse events such as myocardial infarction and sudden cardiac death in patients with pre-existing heart diseases (Brotman et al., 2007; Hamer et al., 2008). In addition, even in the absence of underlying CVD, severe acute emotional stress could also precipitate a specific type of myocardial dysfunction associated with a transient reduction in left-ventricular systolic function (Lampert et al., 2002; Wittstein et al., 2005). Therefore, emotional stress plays a critical role in health outcomes in individuals with or without pre-existing CVD.

A number of studies indicate that psychological stress activates the stress response system, including the hypothalamic-pituitary-adrenal axis, the autonomic nervous system, and the cardiovascular, metabolic and immune systems, to protect the body from stressors (Fredrikson et al., 1992; Gerra et al., 2001). These activated neuroendocrine and autonomic nervous system pathways during acute psychological stress induce the physiological stress response, which then contribute to increased CVD risk (Dimsdale 2008). Therefore, individuals with IR who respond greatly to psychological stress may have a much higher likelihood of suffering from CVD (Raikkonen et al., 2004). However, there is limited evidence for the mechanisms linking acute stress response and CVD in IR population. In addition, direct experimental evidence to support their relationship is also lacking.

Acute psychological stress test, involving measurement of emotional and physiological responses to laboratory-induced stress, is a validated approach to answer these questions (Birkett 2011; Kirschbaum et al., 1993). The objective of this study was to determine if there were differences in stress responses in individuals with IR compared to insulin sensitive group that may account for the greater vulnerability to stress-induced CVD. With these considerations in mind, we undertook to study the emotional and physiological responses to acute psychological stress using the Trier Social Stress Test (TSST). The TSST is a standardized procedure for the induction of acute psychological stress in the laboratory setting (Birkett 2011; Kirschbaum et al., 1993). In the current study, we tested the hypothesis that people with IR, as compared to insulin sensitive group, had exaggerated emotional and physiological responses to acute psychological stress, contributing to a greater risk for CVD.

Methods

Participants

For this particular study, 71 participants were screened and recruited from the clinics at the University of Alabama at Birmingham or the Birmingham, AL community, but 11 participants failed to complete the study. The study protocol was approved by the University of Alabama at Birmingham institutional review board, and written informed consent was obtained from all participants. Participants were between 19 and 55 years of age. Participants were excluded if they: (1) had been taking corticosteroids, antibiotics or anti-inflammatory medication; (2) had current infectious diseases or a history of autoimmune, endocrine, inflammatory, or neurological disorders; (3) were pregnant or lactating; or (4) had a history of diabetes.

After at least 10-h of overnight fasting, all participants underwent a 2-h oral glucose tolerance test as recommended by the American Diabetes Association (Weyer et al., 1999; 1999). Blood samples were drawn at 0, 0.5, 1 and 2-h for the determination of glucose and insulin levels. Glucose was measured by the glucose oxidase method using a glucose analyzer (Beckman Coulter Unicell DxC 800). Blood insulin levels were determined using a solid phase, enzyme labeled, chemiluminescence immunoassay (Siemens). The Quantitative insulin sensitivity check index (QUICKI) for each participant was calculated from the fasting glucose and insulin values (Ascaso et al., 2003; Hrebicek et al., 2002; Muniyappa et al., 2008). The QUICKI has proved to be a robust tool for the surrogate assessment of insulin sensitivity (Ascaso et al., 2003; Hrebicek et al., 2002; Muniyappa et al., 2008). Using the QUICKI and a cut-off point of <0.33 , thirty-one subjects were considered to have IR and 29 subjects were in group of normal insulin sensitivity (Table 1). Body weight and height were measured to calculate body mass index (BMI) using the Quetelet index (kg/m^2) (Rosenbaum 1999). Waist and hip circumferences were measured for the calculation of waist-to-hip ratio.

Mental stress tasks

Acute mental stress was induced using the TSST. Participants reported to the laboratory at 13:00h and a physician examined them for past and current health problems. After a resting period of 30 min, participants were exposed to the TSST, which consists of a 3 min preparation period, a 5 min free speech, and a 5 min mental arithmetic task in front of 2-3 audience (Birkett 2011; Kirschbaum et al., 1993). Monitoring of the post-stress recovery period continued for another 90 min. A total of 4 blood samples for the determination of cytokines, insulin and free cortisol were collected at baseline (1-2 min pre-TSST), immediately following the test (IM-TSST), and 15 min and 90 min post-TSST. Cardiovascular activity, including heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), was recorded using an autonomic blood pressure monitor (OMRON, R5-1) across the TSST: baseline, the 2 task periods, and 15- and 90 min post-stress recovery periods. Participants were asked to rate how stressful they perceived the TSST situation on a visual analogue scale ranging from 0=not at all to 10=very at baseline (5 min pre-TSST), immediately after the TSST and 90 min post-TSST. Six subscales of emotions for each participant were assessed, including happy, anxious, fatigue, energetic,

calm, and angry (Table 2). The visual analogue scale has been used in a large number of previous studies employing the TSST, and has proven useful in assessing acute stressfulness of the situation (Kirschbaum 1999).

Blood samples measurement

Ten milliliters of blood were drawn from each participant at the four time points, i.e. pre-TSST, immediately, 15 min and 90 min after the TSST, and centrifuged at 3000g for 10 min, immediately divided into aliquots, and frozen at -80°C until analysis. The analysis for inflammatory factors, including interferon- γ (IFN γ), interleukin (IL)-1 β , IL-6, IL-8, IL-10, IL-12 and tumor necrosis factor-alpha (TNF α), was performed from blood samples using a Meso Scale Discovery multiplex spot assay and analyzed with MSD Discovery Workbench software (Gaithersburg, MD). Concentrations for cytokines were expressed in pg/ml. Plasma concentrations of leptin and adiponectin at the same time points as above were assayed (expressed in ng/ml and $\mu\text{g/ml}$, respectively) using commercially available radioimmunoassay kits according to the procedures supplied by the manufacturer (Millipore Corp, MA). Free cortisol was measured by immunofluorescence on a TOSOH AIA-II analyzer (TOSOH Bioscience, South San Francisco, CA). All samples were assayed in duplicate and mean values were analyzed.

Statistical analysis

All data are presented as mean $\pm$ standard error unless otherwise stated. All statistical analyses were performed using the Statistical Package for the Social Sciences version 22 (SPSS Inc., IL). All testing was two-tailed with the significance level set at $p < 0.05$. All variables were tested for normality of distribution by means of Kolmogorov-Smirnoff tests. Nonparametric tests were applied for data that were not from a normal distribution, including IFN γ , IL- β , IL-10, IL-12 and insulin. All analyses of data were adjusted for BMI and waist to hip ratio. Independent samples t -tests were carried out to detect the differences at the four time points between two groups. Repeated measures analyses were conducted using all measures (baseline, immediately after the stress, 15- and 90 min post-stress) to capture a within-subjects contrast for the effect of time. The associations between variables were tested by the Pearson correlation analysis. Both insulin and cortisol were also analyzed by computing area under the curve (AUC) with respect to ground using procedures described previously to measure total insulin and cortisol output across the mental stress test (Pruessner et al., 2003).

Results

Participant characteristics

The IR and insulin sensitive groups did not differ in age, gender, race, paid employment and education level (Table 1). As expected, BMI and waist to hip ratio were greater in subjects with IR than the controls ($t(58) = -3.058$, $p < 0.01$; $t(58) = -2.52$, $p = 0.02$, respectively).

Emotional responses to acute mental stress

Acute psychological stress-induced changes in emotions were presented in Tables. 2 and 3. Compared with the insulin sensitive group, subjects with IR reported significantly lower on

ratings of energy and calm immediately following the stress test ($t(58)=2.23$, $p=0.03$; $t(58)=2.301$, $p=0.025$, respectively). Energy sensation remained low at 90 min after the test in the IR group. There were no significant differences between the two groups for other emotion ratings, however, the IR subjects felt more fatigued at baseline ($t(55)=-1.97$, $p=0.048$).

Cardiovascular responses to acute mental stress

Systolic and diastolic blood pressure rose during the stress test and returned towards baseline levels over the post-stress recovery period in the two groups (Fig. 1A and B), however, both systolic and diastolic blood pressure did not differ between these two groups. In the insulin sensitive group, heart rate slightly decreased immediately following the test and further decreased during the post-stress period. In contrast, heart rate did not change throughout the test in the IR, indicative of a reduced heart rate reactivity to acute stress in IR (Fig. 1C).

Endocrine stress response

As expected, baseline insulin levels were higher in the IR subjects than in controls ($t(40)=-1.882$, $p=0.046$, Fig. 2A). Insulin levels continued to rise to even higher levels in subjects with IR following the acute stress tasks, and the highest levels were seen at 15 min after the tasks. In contrast, a relative blunted response was observed in the insulin sensitive subjects (Fig. 2A). In line with this observation, insulin iAUC was significantly greater in the IR group ($t(40)=-2.37$, $p<0.01$, Fig. 2B), indicative of IR with the presence of adequate β -cells secretion. Repeated-measures ANOVA of insulin secretion revealed the contrasts for time were significant in the IR group ($F(2, 45)=7.315$, $p<0.01$), but not in the controls.

There was no difference in baseline cortisol levels in the two groups. Cortisol stress responses at IM, 15-, and 90-min post-test were also measured and were comparable between the two groups (Fig. 2C) as was the cortisol iAUC with respect to ground ($p=0.52$, Fig. 2D), indicating a lack of differential HPA axis stress responses between groups. Moreover, individuals in the insulin sensitive group showed good cortisol responses as demonstrated by repeated-measures ANOVA of cortisol levels over time ($F(2, 45)=10.915$, $p<0.01$).

Activation of immune system in response to acute mental stress

We next tested if the TSST could induce differential changes in cytokine levels in the subjects with IR. There were no significant differences in cytokine levels, including IFN γ , IL-8, IL-10, IL-12 and TNF α , between the two groups, at the four time points that were examined (data not shown). IL-1 β levels did not differ between groups except at 15 min after the TSST (Fig. 3A, Table. 3). This was primarily related to the fact that IL-1 β decreased in the insulin sensitive but not the IR group at the 15 min point compared with baseline. Compared with levels at baseline, IL-6 levels increased following the stress test in both groups although the IR group started higher at baseline ($t(55)=-2.111$, $p=0.039$, Fig. 3B, Table. 3). IL-6 levels did not return to baseline at the 90 min of post-test for either group (Fig. 3B). Repeated-measures ANOVA of IL-6 revealed the contrasts for time were significant in the IR group ($F(2, 33)=16.35$, $p=0.02$), but not in the controls. Similarly, leptin

level started higher in the IR group at baseline ($t(56)=-3.498$, $p<0.01$). An increase in the levels of leptin was observed in the IR subjects but not the insulin sensitive group, with the highest level seen in the IR group at the 15 min after the tasks (Fig. 3C, Table. 3). Compared with the insulin sensitive subjects, adiponectin levels at baseline were lower and remained lower following the stress in IR participants ($t(56)=2.393$, $p<0.01$, Fig. 3D). However, repeated-measures ANOVA of leptin and adiponectin did not reveal the contrasts for time were significant in the IR or control groups.

Correlations

QUICKI values were negatively associated with BMI ($r=-0.36$, $p<0.01$, Fig. 4A) and waist to hip ratio ($r=-0.40$, $p<0.01$, Fig. 4B). QUICKI values were inversely associated with IL-6 levels at the 15- and 90 min after the tasks in all participants ($r=-0.27$, -0.28 , respectively, $p<0.05$ for both).

Discussion

This study investigated whether individuals with IR have altered emotional and physiological reactivity to acute psychological stress compared with insulin sensitive people. Individuals with IR had significantly negative changes in perceived energy and calm in response to acute psychological test. Individuals with IR also showed a further increase in insulin levels in response to the stressors despite the elevated insulin at baseline. A blunted heart rate response to the stress was seen in the IR subjects. IR participants also showed significantly higher levels of leptin and IL-6, and lower levels of adiponectin from baseline to post-test recovery period. Taken together, IR is associated with enhanced emotional and physiological responsiveness to acute psychological stress, which may promote an increased vulnerability for the development of stress-related CVD in this particular population.

Both physical and emotional stressors are well-known triggers of CVD although the mechanisms remain unclear. One study found that emotional stress is a common precipitant of acute infarction (Wittstein et al., 2005), and the risk of acute myocardial infarction in patients with coronary heart disease was doubled in the short period after an anger outburst (Mittleman et al., 1997; Strike et al., 2005). Therefore, strongly negative emotional responses to the stressors appear to increase the short-term risk of myocardial infarction. Studies also demonstrated that individuals with IR and high levels of psychological stress have a much higher likelihood of suffering from cardiac events (Raikonen et al., 2004). The current study found increased fatigue and decreased feelings of calm and energy in the IR participants during and after the acute psychological test. Thus our findings may provide a mechanism linking IR with an increased risk of CVD, which is exaggerated negative emotional response to acute psychological stress.

IR is usually characterized by a compensatory increase in plasma concentrations of insulin (Weyer et al., 1999; 1999). In accordance, this study observed that at baseline insulin levels were significantly greater in subjects with IR. Moreover, insulin concentrations surged to an even higher level in response to acute stressors, indicating that IR subjects had normal β -cell functional reserve to compensate for reduced insulin sensitivity. In contrast, cortisol secretion responded equivalently to acute psychological stress in both groups. Since there

was no difference between groups in cortisol stress response, differences in emotion and insulin levels between groups might not be due to the HPA response to acute psychological stress. Further studies are required to explore other underlying mechanisms.

Emerging evidence indicates that inflammation is one of consequences of psychological stress, which provides the linkage of psychological stress with various diseases (Black 2006). Pro-inflammatory cytokines, including IL-6 and leptin, at baseline (prior to the TSST) were increased in subjects with IR, which is consistent with other reports (Fernandez-Real et al., 1999; 1999; 2000; 2000). Further, the levels of both IL-6 and leptin increased in response to acute psychological stress in the IR group. In contrast, adiponectin, an anti-inflammatory adipokine (Balsan et al., 2015; Smitka et al., 2015), was low at baseline and remained to be low during and after the stress test in IR. Thus reduced levels of adiponectin may explain at least, in part, the increased inflammation at baseline and in response to acute stressors since it is anti-inflammatory. Taken together, the inflammatory process, manifested by increased IL-6 and leptin levels and decreased adiponectin levels, was present in the IR at baseline, during and post-acute stress test. The altered inflammatory process could combine with other risk factors to increase the vulnerability for CVD in face of IR.

The TSST is a standardized psychological stress test, which provides a controlled way to examine the effects of social and mental stress on emotional and physiological variables. The exaggerated emotional and physiological effects and cross-talk between the affected variables in face of IR may explain in part the association between IR and CVD risk. Psychological stress is an important and potentially modifiable risk factor for acute and chronic cardiac events, and it may also provide an intervention target to reduce future CVD and cardiac events. Actually several studies have demonstrated that lifestyle changes and psychosocial intervention programs may ameliorate the risk for developing CVD (Blumenthal et al., 2005; Hamer 2006; Rees et al., 2004; Walton et al., 2004). Stress reduction and negative emotion management to alleviate unnecessary psychosocial strain may need to be integrated in patient care in the hope that a better health outcome could be achieved in individuals with IR.

The results presented in this study may need to be interpreted in the light of several limitations. First, the number of participants investigated in the current study is relatively small and participants with CVD failed to complete the study. However, data analyses were completed in 60 participants who were thoroughly investigated, which allowed us to obtain meaningful results in a relative small sample. Second, measures of heart rate variability were not reported in our study although it was significantly associated with the risk for a cardiac event (Tsuji et al, 1996). The measure of heart rate variability could also reflect the effects of the autonomic nervous system on heart rate. Therefore, future study should include the measure of heart rate variability. Last, due to the nature of a cross-sectional study, some questions could not be answered. For example, an association rather than a causal conclusion between IR and CVD risk can be drawn from our findings. Further longitudinal investigations of the development of IR and CVD in the circumstances of psychological stress, or their relationship over time, would be important.

In summary, we have shown that IR is associated with enhanced emotional and physiological responses to acute psychological stress. The enhanced responses to acute stressful events may provide a novel therapeutic strategy to modify CVD risk factors in the hope of improving physical and psychological vulnerability in this particular population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Systolic blood pressure (A), diastolic blood pressure (B) and heart rate (C) at baseline, stress test, 15- and 90 min post-stress test in the insulin resistant subjects (solid line) and insulin sensitive subjects (dash line). Data are presented as the mean $\pm$ standard error in each group. Compared with control group at the same time point, *, $p < 0.05$; #, $p < 0.01$. IM, immediately; TSST, trier social stress test; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Figure 2.

Blood insulin (A) and free cortisol (C) in the insulin resistant subjects (solid line) and insulin sensitive subjects (dash line). Insulin and cortisol were sampled at baseline, immediately, 15 min and 90 min after stress test. Bar graph of insulin area under the curve (B) and cortisol area under the curve (D) across the stress test. Data are presented as the mean $\pm$ standard error in each group. Compared with control group at the same time point, *, $p < 0.05$. IM, immediately; TSST, trier social stress test; IS, insulin sensitive; IR, insulin resistant.

Figure 3.

Comparison of levels for interleukin-1 β (A), interleukin-6 (B), leptin (C) and adiponectin (D) between subjects with insulin resistance (solid line) and insulin sensitive subjects (dashed line). Data are presented as mean $\pm$ standard error. Compared with the insulin sensitive group at the same time point, *, $p < 0.05$; #, $p < 0.01$. IM, immediately; TSST, trier social stress test; IS, insulin sensitive; IR, insulin resistant; IL, interleukin.

Figure 4. Scatter plot indicating the association between the Quantitative insulin sensitivity check index scores and body mass index (A, correlation coefficient was -0.36 , $p < 0.01$) or waist to hip ratio (B, correlation coefficient was -0.40 , $p < 0.01$). BMI, body mass index.

Table 1

Demographic and Clinical Characteristics of Participants

Variables	Insulin sensitive (N=29)	Insulin resistant (N=31)	<i>P</i> value
QUICKI	0.37 ± 0.004	0.31 ± 0.004	0.000
Age (years)	42.7 ± 2.1	40.8 ± 2.2	0.534
Sex (male, N (%))	11 (38%)	9 (28%)	0.465
Race (N, C/AA)	13/16	17/14	0.611
Paid employment, N(%)	17 (58.6%)	13 (41.9%)	0.309
Education level 12 years, N (%)	24 (82.8%)	22 (71.0%)	0.507
Depressive score	11.6 ± 2.3	18.0 ± 2.8	0.087
Body mass index (kg/m ²)	27.7 ± 1.2	32.8 ± 1.2	0.003
Waist-hip ratio	0.81 ± 0.03	0.89 ± 0.01	0.020
Medication, N (%)			
Aspirin	1 (3%)	1 (3%)	0.674
Statins	0	0	
Anti-hypertensive medication	0	0	

Note: QUICKI, Quantitative insulin sensitivity check index; C, Caucasian; AA, African-Americans

Table 2

Behavioral Response to the TSST

	Insulin Sensitive			Insulin Resistant		
	Baseline	IM	90 min after TSST	Baseline	IM	90 min after TSST
Happy	7.6±0.5	6.6±0.5	8.0±0.4	7.3±0.5	6.2±0.5	7.4±0.4
Anxious	2.1±0.4	2.9±0.5	2.1±0.5	3.0±0.6	3.8±0.6	2.1±0.5
Fatigue	3.2±0.5	3.6±0.5	4.7±0.5	4.5±0.5	4.6±0.6	4.7±0.5
Energetic	5.7±0.5	5.8±0.4	5.8±0.5	4.7±0.5	4.2±0.5 *	4.5±0.4 *
Calm	6.8±0.5	6.3±0.5	7.2±0.5	6.6±0.5	4.5±0.6 *	7.2±0.5
Angry	1.8±0.5	2.4±0.5	1.7±0.5	2.3±0.5	3.3±0.7	2.1±0.5

Note:

* compared with insulin sensitive group at the same time point, $p<0.05$. TSST, trier social stress test; IM, immediately.

Table 3Effect sizes and *p*-values in variables

	Baseline	IM	15-min	90-min	
	ES/ <i>P</i>	ES/ <i>P</i>	ES/ <i>P</i>	ES/ <i>P</i>	
Fatigue	0.53/0.048	ns	n/a	ns	Tab. 2
Energetic	ns	0.61/0.030	n/a	0.50/0.046	Tab. 2
Calm	ns	0.68/0.025	n/a	ns	Tab. 2
Heart rate	ns	ns	0.81/0.013	0.83/0.004	Fig.1c
Insulin	0.93/0.043	2.55/0.047	ns	ns	Fig.2a
IL-1 β	ns	ns	0.76/0.036	ns	Fig.3a
IL-6	0.61/0.039	0.32/0.024	0.93/0.024	0.85/0.018	Fig.3b
Leptin	1.19/0.001	1.77/<0.001	2.26/<0.001	2.10/<0.001	Fig.3c
Adiponectin	0.53/0.020	0.55/0.038	0.68/0.048	ns	Fig.3d

Note: ES, effect size; ns, not significant; na, not available (emotional response was not measured at 15-min post-TSST).