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Blunted glucocorticoid and mineralocorticoid sensitivity to stress in people with diabetes

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Summary Psychological stress may contribute to type 2 diabetes but mechanisms are still poorly understood. In this study, we examined whether stress responsiveness is associated with glucocorticoid and mineralocorticoid sensitivity in a controlled experimental comparison of people with type 2 diabetes and non-diabetic participants. Thirty-seven diabetes patients and 37 healthy controls underwent psychophysiological stress testing. Glucocorticoid (GR) and mineralocorticoid sensitivity (MR) sensitivity were measured by dexamethasone- and prednisolone-inhibition of lipopolysaccharide (LPS)-induced interleukin (IL) 6 levels, respectively. Blood pressure (BP) and heart rate were monitored continuously, and we periodically assessed salivary cortisol, plasma IL-6 and monocyte chemotactic protein (MCP-1). Following stress, both glucocorticoid and mineralocorticoid sensitivity decreased among healthy controls, but did not change in people with diabetes. There was a main effect of group on dexamethasone ($F_{(1,74)} = 6.852$, $p = 0.013$) and prednisolone ($F_{(1,74)} = 7.295$, $p = 0.010$) sensitivity following stress at 45 min after tasks. People with diabetes showed blunted stress responsivity in systolic BP, diastolic BP, heart rate, IL-6, MCP-1, and impaired post-stress recovery in heart rate. People with Diabetes had higher cortisol levels as measured by the total amount excreted over the day and increased glucocorticoid sensitivity at baseline. Our study suggests that impaired stress responsivity in type-2 diabetes is in part due to a lack of stress-induced changes in mineralocorticoid and glucocorticoid sensitivity.

1. Introduction

Patients with type 2 diabetes have a substantially increased risk of developing coronary heart disease (CHD) as well as poorer long-term prognosis following myocardial infarction

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(Haffner et al., 1998; Mukamal et al., 2001; Yusuf et al., 2004). Recently, some mechanisms on how inflammation could play a role in diabetes have been described, and could play a role in CHD risk. For example, low-grade local and systemic inflammation in β-cells of pancreatic islets and peripheral tissues to induce β-cells' dysfunction and apoptosis, insulin resistance, and ultimately, overt type 2 diabetes mellitus (T2DM) (Akash et al., 2013a). Despite this, the mechanisms underlying the association between diabetes and CHD are not completely clear. Psychological stress may contribute to risk of developing CHD in people with diabetes. Longitudinal studies have also confirmed an increased risk of developing diabetes in people with high levels of stress (Eriksson et al., 2008; Chida and Hamer, 2008; Nyberg et al., 2014). People who experience depression also present increased risk of future diabetes (Rotella and Mannucci, 2013).

Psychological stress has been linked to production of pro-inflammatory markers and these effects may mediate the influence of psychosocial factors on cardiovascular risk in people with diabetes (Steptoe et al., 2007). There is evidence that elevated inflammatory responses in people with diabetes play an important role in linking diabetes with increased incidence of atherosclerosis (Ray et al., 2009). Diabetes patients with raised levels of C-reactive protein are 30% more likely to have cardiovascular events than those without inflammation (Akash et al., 2013b). Treatment with anti-inflammatory drugs are currently being investigated to dampen the effects of T2DM inducers (Akash et al., 2012, 2013c).

Apart from traditional risk factors, stress-induced inflammation may be an additional mechanism in people with diabetes. Psychological stress activates the hypothalamus—pituitary—adrenal (HPA) axis that regulates inflammation. Hyperactivation of the HPA axis has been reported in patients with diabetes (Cameron et al., 1984; Roy et al., 1990, 1993), and is associated with coronary heart disease and its risk factors (Reynolds et al., 2010). Patients with diabetes present alterations of the HPA axis negative feedback (Bruehl et al., 2007) suggestive of an impairment of corticosteroid receptor sensitivity. HPA axis disturbance seems to be particularly important in people with diabetes since the degree of cortisol secretion is related to the presence and number of diabetes complications (Chiodini et al., 2007).

Psychosocial stress regulates the effect of corticosteroids on target tissues via dynamic modulation of corticosteroid sensitivity (Rohleder et al., 2003). Two distinct intracellular sensitivity subtypes mediate the effect of cortisol: the type I or mineralocorticoid sensitivity (MR) and the type II or glucocorticoid sensitivity (GR) (de Kloet et al., 1998). Dexamethasone activates human-GR-mediated gene transcription, but even at the highest concentrations is unable to fully activate human-MR-mediated gene transcription (Rupprecht et al., 1993). On the other hand, prednisolone is a synthetic glucocorticoid that is more similar to cortisol in its capacity to bind and activate the GR and the MR, especially when compared with dexamethasone. Thus, the effect of corticosteroids on the regulation of inflammation during stress will depend not only on the actual basal levels of cortisol, but also on stress-induced changes in the sensitivity of both glucocorticoid and mineralocorticoid receptors.

As part of a larger study of stress processes in type 2 diabetes participants, we assessed stress-related modulation of GR and MR sensitivity in a subset of patients randomly selected. Such alterations may provide a new biological mechanism linking diabetes with elevated levels of inflammation and the elevated risk of acute cardiovascular syndrome following stress. We analysed the glucocorticoid and mineralocorticoid sensitivity of lipopolysaccharide (LPS)-induced IL-6 production in whole blood of people with diabetes and healthy controls. All participants underwent a standardized acute psychological stress test (Zalli et al., 2014), and we measured MR and GR sensitivity of IL-6 production at different time points before and after stress. We measured IL-6 because it seems to play an important role in how psychological stress contributes to physical and mental illness. IL-6 is also involved in the activation of the inflammatory cascade that leads to the production of C-reactive protein by the liver. To obtain each measure of glucocorticoid and mineralocorticoid sensitivity we calculated the amount of dexamethasone and prednisolone, respectively that was necessary to suppress LPS-induced IL-6 levels by 50%. Moreover, we measured blood pressure, heart rate, salivary cortisol, and inflammatory cytokines such as IL-6 and MCP-1 before and after stress to assess the amount of stress induced by the behavioural tasks.

2. Methods

2.1. Participants

This is a sub-study of a larger cohort of type 2 diabetic patients (T2DM) recruited from primary care clinics in the London area who participated in a mental stress protocol (Steptoe et al., 2001, 2002a). For this particular study, cells were collected from thirty-seven diabetes participants and 37 healthy controls by simple random sampling. Glucocorticoid sensitivity function was analysed in a subgroup of 20 people from each group. Participants gave fully informed written consent to participate in the study and ethical approval was obtained from the National Research Ethics Service. We limited enrolment to diabetes participants without a history or previous diagnosis of coronary heart disease (CHD), inflammatory diseases, allergies or mood disorders, but had no other exclusion criteria. Healthy controls were recruited from the subsample of the Whitehall II epidemiological cohort recruited between 2006 and 2008 to investigate socioeconomic and psychosocial factors, physiological stress responsivity, and subclinical coronary artery disease (Hamer et al., 2010). Healthy participants were white European origin with no history or objective signs of CHD, no previous diagnosis or treatment for hypertension, diabetes, inflammatory diseases, or allergies. The absence of diabetes was confirmed by low glycated haemoglobin (HbA1c) levels ($\leq$6.5%) and negative oral glucose tolerance tests over the previous 20 years. Participants underwent identical mental stress testing to that carried out with the diabetes group.

2.2. Mental stress tasks

Mental stress was induced in the laboratory using two 5-min behavioural tasks: the Stroop colour-word interference