Stress and Diabetes: A Review of the Links

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Abstract

Evidence suggests that stressful experiences might affect diabetes, in terms of both its onset and its exacerbation. In this article, the authors review some of this evidence and consider ways in which stress might affect diabetes, both through physiological mechanisms and via behavior. They also discuss the implications of this for clinical practice and care.

In recent years, the complexities of the relationship between stress and diabetes have become well known but have been less well researched. Some studies have suggested that stressful experiences might affect the onset and/or the metabolic control of diabetes, but findings have often been inconclusive. In this article, we review some of this research before going on to consider how stress might affect diabetes control and the physiological mechanisms through which this may occur. Finally, we discuss the implications for clinical practice and care. Before going any further, however, the meaning of the term *stress* must be clarified because it can be used in different ways. Stress may be thought of as *a*) a physiological response to an external stimulus, or *b*) a psychological response to external stimuli, or *c*) stressful events themselves, which can be negative or positive or both. In this article, we address all three aspects of stress: stressful events or experiences (sometimes referred to as stressors) and the physiological and psychological/behavioral responses to these.

Role of Stress in the Onset of Diabetes

Stressful experiences have been implicated in the onset of diabetes in individuals already predisposed to developing the disease. As early as the beginning of the 17th century, the onset of diabetes was linked to "prolonged sorrow" by an English physician.[1]

Since then, a number of research studies have identified stressors such as family losses and workplace stress as factors triggering the onset of diabetes, both type 1 and type 2. For example, Thernlund et al.[2] suggested that negative stressful experiences in the first 2 years of life may increase the risk of developing type 1 diabetes in children. Other factors, such as high family chaos and behavioral problems, were also implicated. Other research has also supported the hypothesis that stressful experiences can lead to increased risk for developing type 1 or type 2 diabetes.[3–5]

In a large population-based survey of glucose intolerance, Mooy et al.[6] demonstrated an association between stressful experiences and the diagnosis of type 2 diabetes. Although this was a cross-sectional study, the authors investigated stress levels in people with previously undetected diabetes in order to rule out the possibility that the disease itself influenced reports of stressful experiences. They also took other factors into account, such as alcohol consumption, physical activity level, and education.

Bjorntop[7] has attempted to explain the physiological links between stressful experiences and the onset of diabetes. He argues that the psychological reaction to stressors of defeatism or helplessness leads to the activation of the hypothalamo-pituitary-adrenal (HPA) axis, leading in turn to various endocrine abnormalities, such as high cortisol and low sex steroid levels, that antagonize the actions of insulin. At the same time, an increase in visceral adiposity (increased girth) is seen, which plays an important role in diabetes by contributing to insulin resistance.[8] Increased visceral adiposity can be measured by waist-to-hip ratio. In the Mooy et al. study of type 2 diabetes,[6] there was only a weak

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Hypoxia-Induced Gene Expression in Human Macrophages

Implications for Ischemic Tissues and Hypoxia-Regulated Gene Therapy

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Macrophages accumulate in ischemic areas of such pathological tissues as solid tumors, atherosclerotic plaques and arthritic joints. Studies have suggested that hypoxia alters the phenotype of macrophages in a way that promotes these lesions. However, the genes up-regulated by macrophages in such hypoxic tissues are poorly characterized. Here, we have used cDNA array hybridization to investigate the effects of hypoxia on the mRNAs of 1185 genes in primary human monocyte-derived macrophages. As shown previously in other cell types, mRNA levels for vascular endothelial growth factor (VEGF) and glucose transporter 1 (GLUT-1) were up-regulated by hypoxia. However, the mRNAs of other genes were also up-regulated including matrix metalloproteinase-7 (MMP-7), neuromedin B receptor, and the DNA-binding protein inhibitor, Id2. The promoters of GLUT-1 and MMP-7 confer hypoxic inducibility on a reporter gene in RAW 264.7 macrophages, indicating that the hypoxic up-regulation of these mRNAs may occur, at least in part, at the transcriptional level. GLUT-1 and MMP-7 mRNA were also shown to be up-regulated in hypoxic macrophages *in vitro* by real-time RT-PCR, and these proteins were elevated in hypoxic macrophages *in vitro* and in hypoxic areas of human breast tumors. The hypoxia up-regulated genes identified could be important for the survival and functioning of macrophages in hypoxic diseased tissues, and their promoters could prove useful in macrophage-delivered gene therapy. *(Am J Patbol 2003, 163:1233–1243)*

The presence of areas of low oxygen tension (hypoxia) is a feature common to malignant tumors,[1] wounds,[2] arthritic joints[3] and atherosclerotic plaques.[4] These areas form when the local blood supply is poorly organized, occluded, or simply unable to keep pace with the growth and/or infiltration of cells in a given area. Macrophages accumulate in large numbers in such hypoxic/ischemic tissues[5] and respond to hypoxia by up-regulating a number of transcription factors. Among the most prominent of these are the hypoxia-inducible factors (HIFs) 1 and 2, increased levels of which are seen in macrophages in ischemic areas of malignant tumors,[6,7] the inflamed synovial lining of joints with rheumatoid arthritis[8] and human dermal wounds.[9] Interestingly, conditional ablation of HIF-1α in macrophages renders them incapable of migrating into damaged/diseased tissue and performing their normal inflammatory and microbicidal functions in such sites.[10]

HIFs 1 and 2 are heterodimers consisting of different hypoxia-inducible α subunits and a common, constitutively expressed β subunit. Under normal oxygen tensions ("normoxia"), the α subunits are rapidly ubiquitinated and degraded by the proteasome. Hypoxia inhibits ubiquitination of HIFs, causing them to accumulate in the nucleus, where they bind to short DNA sequences called hypoxia response elements (HREs) near oxygen-sensitive genes,[11] stimulating their transcription. Such genes include vascular endothelial growth factor (VEGF).[12] Expression of VEGF by macrophages is markedly increased by exposure to hypoxia *in vitro*[13] and in poorly vascularized areas of malignant tumors[14] where it promotes the formation of new blood vessels, increasing the supply of oxygen and nutrients to the area. Macrophages are also known to release PR-39, a 39 amino acid peptide that inhibits the degradation of HIF-1α protein by neighboring cells, thereby stimulating their expression of VEGF.[15] Together, these observations may explain pre-

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A QUANTITATIVE COMPARISON OF MOTOR AND SENSORY CONDUCTION VELOCITIES IN SHORT- AND LONG-TERM STREPTOZOTOCIN- AND ALLOXAN-DIABETIC RATS

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SUMMARY

Motor and sensory conduction velocities were measured in the sural and tibial nerves of streptozotocin (stz)-diabetic, alloxan-diabetic, and age-matched control rats. Conduction velocity (CV) determinations were made 2 weeks and 2, 4, 8, and 12 months following the induction of diabetes. CVs of control, stz-diabetic, and alloxan-diabetic rats were compared at each time period by one way analysis of variance and when appropriate by the Newman–Keuls multiple range test for multiple comparisons. Reductions of 10–20% in CV of diabetic rats were observed in several classes of sensory and motor nerve fibers. Larger reductions (31 and 38%) were seen in 2 classes of sensory nerve fibers in 12 month stz-diabetic rats. Sensory CV was slowed earlier and more frequently than motor CV.

Differential involvement was also seen among the several classes of sensory nerve fibers examined. Slower conducting sensory fibers appeared to be affected earlier and more frequently than faster conducting sensory fibers. Comparing alloxan-diabetic with stz-diabetic rats revealed significant differences in CV 8 months after the induction of diabetes. Motor and sensory CVs of the tibial nerve were slower in stz-diabetic rats than in alloxan-diabetic rats. In general, the neuropathy appeared to be less severe and to develop later in the alloxan-diabetic rats. These data suggest that the neuropathy of stz- and alloxan-diabetes is primarily sensory

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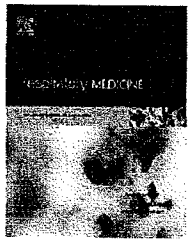

Persistent systemic inflammation and symptoms of depression among patients with COPD in the ECLIPSE cohort

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KEYWORDS
Chronic Obstructive Pulmonary Disease;
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Summary
Background: Depression is highly prevalent among patients with Chronic Obstructive Pulmonary Disease (COPD). The relationship of depression with systemic inflammation in COPD remains unknown. The objective of this observational study was to compare depression scores at baseline and after 36 months follow-up between COPD patients with persistent systemic inflammation (PSI) and never inflamed patients (NI) in the ECLIPSE cohort.
Methods: The ECLIPSE study included 2164 COPD patients. Parameters assessed at baseline and at 36 months follow-up included: demographics, clinical characteristics and symptoms

Abbreviations: PSI, persistent systemic inflammation; NI, never inflamed patients.

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A role for inflammatory metabolites as modulators of the glutamate N-methyl-D-aspartate receptor in depression and suicidality

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ABSTRACT

Background: Patients with depression and suicidality suffer from low-grade neuroinflammation. Pro-inflammatory cytokines activate indoleamine 2,3-dioxygenase, an initial enzyme of the kynurenine pathway. This pathway produces neuroactive metabolites, including quinolinic- and kynurenic acid, binding to the glutamate N-methyl-D-aspartate-receptor, which is hypothesized to be part of the neural mechanisms underlying symptoms of depression. We therefore hypothesized that symptoms of depression and suicidality would fluctuate over time in patients prone to suicidal behavior, depending on the degree of inflammation and kynurenine metabolite levels in the cerebrospinal fluid (CSF).
Methods: We measured cytokines and kynurenine metabolites in CSF, collected from suicide attempters at repeated occasions over 2 years (total patient samples $n = 143$, individuals $n = 30$) and healthy controls ($n = 36$). The association between the markers and psychiatric symptoms was assessed using the Montgomery Åsberg Depression Rating Scale and the Suicide Assessment Scale.
Results: Quinolinic acid was increased and kynurenic acid decreased over time in suicidal patients versus healthy controls. Furthermore, we found a significant association between low kynurenic acid and severe depressive symptoms, as well as between high interleukin-6 levels and more severe suicidal symptoms.
Conclusions: We demonstrate a long-term dysregulation of the kynurenine pathway in the central nervous system of suicide attempters. An increased load of inflammatory cytokines was coupled to more severe symptoms. We therefore suggest that patients with a dysregulated kynurenine pathway are vulnerable to develop depressive symptoms upon inflammatory conditions, as a result the excess production of the NMDA-receptor agonist quinolinic acid. This study provides a neurobiological framework supporting the use of NMDA-receptor antagonists in the treatment of suicidality and depression.

1. Introduction

Suicide accounts for 1.5% of all deaths and is the tenth leading cause of death worldwide (Heron, 2012). Unfortunately, progress in the prevention of suicide is limited by the large number, high prevalence, and wide distribution of suicide risk factors (Olfson et al., 2014). Moreover, the biological changes associated with symptoms of suicidality are incompletely known and a previous suicide attempt is currently the best predictor of a future completed suicide (Harris and Barraclough, 1997).

Patients with depression and suicidality show signs of inflammation in peripheral blood as well as within the brain (Dowlati et al., 2010; Valkanova et al., 2013). For example, depressed patients have elevated blood levels of interleukin (IL)-1β (Thomas et al., 2005; Dahl et al., 2014), tumor necrosis factor (TNF)-α (Hestad et al., 2003), IL-8 (Mikova et al., 2001) and IL-6 (Dahl et al., 2014; Berk et al., 1997). Interestingly, several reports have described emerging depression and suicidality in previously

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Clinical research

Markers of inflammation in patients with coronary artery disease are also associated with glycosylated haemoglobin A_{1c} within the normal range

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KEYWORDS
Inflammation;
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Aims Diabetes is a risk factor for atherosclerosis and low-degree inflammation may play a central role in both diseases. Glycosylated haemoglobin A_{1c} (HbA_{1c}) is an established measure of long-term glycaemic control but data on its correlation with markers of inflammation are limited, especially in patients with atherosclerotic manifestations. The aim of the present study was thus to investigate the associations between HbA_{1c} and a panel of inflammation-sensitive parameters in patients with and without diabetes.

Methods and results This single centre cross-sectional study comprised 314 consecutive subjects who underwent coronary angioplasty for stable coronary artery disease. Sixty-six patients had diabetes mellitus. Haemoglobin A_{1c} and markers of inflammation, i.e., plasma levels of CRP, fibrinogen, and albumin, erythrocyte sedimentation rate and white blood cell count were measured. All inflammation markers were altered in a more inflammatory direction in diabetic patients. Furthermore, when non-diabetic patients with HbA_{1c} levels within the normal range were studied separately, all inflammation-sensitive parameters except albumin correlated significantly with HbA_{1c}.

Conclusion In subjects with known coronary atherosclerosis, low-degree inflammatory activity is not only increased in diabetic patients, but also increased with increasing HbA_{1c} in non-diabetic individuals with HbA_{1c} within the normal range, i.e., at a pre-diabetic level of glucose metabolism derangement.

Introduction

Inflammation has been suggested to play a central role in the development of atherosclerosis.[1,2] Diabetes is not only a well known risk factor for atherosclerosis but is also associated with increased levels of sensitive markers of subclinical systemic inflammation.[1–4] However, less data are available about the relationship between glycosylated haemoglobin A_{1c} (HbA_{1c}), a measure of long term glycaemic control, and markers of inflammation. Wu et al.[5] studied 5342 adult individuals who reported not having diabetes. In that study, elevated levels of C-reactive protein (CRP) were associated with higher HbA_{1c} and insulin levels, and also with increased fasting glucose levels in women. Another study by Festa et al.[6] found a

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