Psychoneuroendocrinology (2014) 43, 62—70

Available online at www.sciencedirect.com

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

Elevated systemic expression of ER stress related genes is associated with stress-related mental disorders in the Detroit Neighborhood Health Study

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Received 24 September 2013; received in revised form 22 January 2014; accepted 22 January 2014

KEYWORDS
Endoplasmic reticulum stress;
Unfolded protein response;
Epidemiology;
Matched-pair analysis;
Case—control studies;
Gene expression pattern analysis;
Cardiovascular diseases;
Metabolic diseases

Summary
Background: The role of endoplasmic reticulum (ER) stress response in mental illness is not well understood. Human studies and animal models of depression show elevated brain ER stress response. In addition, some ER stress associated disorders (e.g. cardiovascular disease) show higher rates of depression compared to the general population, raising the possibility that ER stress response contributes to depression risk. It remains unknown, however, if ER stress response is present among individuals suffering from other stress-related mental illness, and whether such a response would be evident in a non-clinical sample. This study tests for systemic changes in ER stress response associated with Major Depressive Disorder (MDD) or post-traumatic stress disorder (PTSD) among community-dwelling individuals.
Methods: We analyzed expression of *BiP*, *EDEM1*, *CHOP*, and *XBP1*, the major indicators of ER stress response, with real-time PCR in leukocyte-derived RNA samples from 86 participants of the Detroit Neighborhood Health Study. Participants were selected based on the presence of either past year MDD or past year PTSD; controls were age and sex matched.

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0306-4530/$ — see front matter
http://dx.doi.org/10.1016/j.psyneuen.2014.01.013

Results: Relative to controls, MDD is associated with a 1.34-fold increase in *BiP* ($P = 0.004$), 1.35-fold increase in *EDEM1* ($P = 0.001$), 1.68-fold increase in *CHOP* ($P = 0.002$), and 1.60-fold increase in *XBP1* ($P = 0.004$). These results remained significant after correction for multiple testing. In contrast, PTSD is associated with a 1.27-fold increase in *EDEM1* expression only ($P = 0.027$), a result that is attenuated to non-significance following adjustment for multiple testing; however, a subsample of participants with past month PTSD showed elevated expression of *BiP* and *EDEM1* (uncorrected *P* value 0.049 and 0.017, respectively).
Conclusions: These data indicate systemic and persistent activation of the ER stress response pathway in MDD among community-dwelling individuals. Systemic activation of the ER stress response may also occur in PTSD among persons with more recent symptoms.

1. Introduction

Several human studies and animal models suggest that the endoplasmic reticulum (ER) stress response may play a role in psychiatric disease (Bown et al., 2000; Gold et al., 2013). The ER is an intracellular organelle that is responsible for protein folding and assembly, calcium storage, and lipid and sterol biosynthesis (Back et al., 2005). A variety of pharmacological, pathophysiological, and environmental stimuli can impose stress on the ER and subsequently interrupt the protein folding process in the ER, leading to accumulation of unfolded or misfolded proteins in the ER lumen (Zhang and Kaufman, 2004). This condition is referred to as ''ER stress'' (Zhang and Kaufman, 2004). To cope with ER stress, highly specific signaling pathways localized to the ER have evolved, which are collectively called the ER stress response or the ''Unfolded Protein Response (UPR)''. The primary function of the UPR is to restore ER homeostasis and help the cells adapt to ER stress conditions. However, when ER stress is prolonged or the degree of ER stress is too severe, UPR signaling can initiate programmed cell death by activating stress-induced pro-apoptotic factors (Zhang and Kaufman, 2004). Dysregulation or hyper-activation of the UPR pathway is critically involved in the initiation and progression of a variety of life-threatening diseases, such as cardiovascular disease, metabolic disease, neurodegenerative disease, and cancer (Zhang and Kaufman, 2008).

ER stress related protein expression has been shown to be elevated within the temporal cortex among individuals who had Major Depressive Disorder (MDD) and died of suicide compared with individuals who had MDD and died of other causes (Bown et al., 2000). A recent paper suggests that ER stress and parainflammation — i.e. a tissues' stress response with features intermediate between a normal state and an acute inflammatory state — are interrelated processes each influencing many phases of the stress response pathway and as such these pathways may be valid targets for intervention in MDD and bipolar disorder (Gold et al., 2013). Some pharmacological interventions used to treat affective disorders target genes which interact with the UPR pathways (e.g. Wang et al., 1999). For example, valproate and carbamazepine are mood stabilizing drugs which increase expression of 78-kDa glucose-regulated protein (*GRP78*), also known as Binding immunoglobulin protein (*BiP*) (Wang et al., 1999). *BiP*/*GRP78* is a member of the ER stress gene family believed to inhibit ER stress response activation and to inhibit UPR induced apoptosis (Reddy et al., 2003). Furthermore, lithium is a treatment employed for some mood disorders and is known to directly target and inhibit the protein encoded by Glycogen synthase kinase-3 (*GSK3*); GSK3 has been shown to regulate ER stress induced apoptosis in neuronal cells (Meares et al., 2011). Several mouse models of depression-like behavior implicate genes which interact with the UPR pathways, e.g. Calreticulin (*CALR*) (Liu et al., 2011), Bax inhibitor 1 (*BAX*) (Hunsberger et al., 2011), Glycogen synthase kinase-3 (*GSK3B*) (Mines et al., 2010; Meares et al., 2011), Interferon-gamma (*IFNG*) (O'Connor et al., 2009), and tumor necrosis factor-α (*TNF*) (Kaster et al., 2012). These human studies and animal models suggest that the UPR pathways may be activated or up regulated within brain tissue in the presence of some affective disorders.

Despite the suggestive evidence of ER stress in mental disorders in both animal (Hunsberger et al., 2011; Liu et al., 2011) and human (Bown et al., 2000; So et al., 2007) studies, to date there has to our knowledge been no report of ER stress and the UPR among living individuals suffering from such disorders. More specifically, it is not known whether the ER stress response pathway is activated at a systemic level among community-dwelling individuals suffering from MDD. Here we test whether ER stress-related gene expression is elevated in leukocytes derived from individuals diagnosed with MDD in the Detroit Neighborhood Health Study (DNHS). The DNHS is a longitudinal community-based study of mental and physical health and their interaction with social-environmental factors (Uddin et al., 2010; Goldmann et al., 2011). Elevated ER stress response may be specific to MDD or it may be associated with additional mental disorders in which stress plays a contributing role. To test this, we also investigate whether ER stress response-related gene expression is elevated in leukocytes derived from individuals diagnosed with post-traumatic stress disorder (PTSD) in the Detroit Neighborhood Health Study (DNHS). To our knowledge this is the first consideration of whether PTSD is associated with elevated ER stress response and is facilitated by the relatively high burden PTSD in the DNHS population (Uddin et al., 2010). Results from this work may provide insight into biological processes relevant to psychological stress that occur in non-clinical settings.

2. Methods

2.1. Sample

Details of the Detroit Neighborhood Health Study (DNHS) have been previously reported (Uddin et al., 2010; Goldmann et al., 2011; Uddin et al., 2011). The University of Michigan