The effect of mindfulness meditation training on biological acute stress responses in generalized anxiety disorder

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ABSTRACT

Mindfulness-Based interventions have increased in popularity in psychiatry, but the impact of these treatments on disorder-relevant biomarkers would greatly enhance efficacy and mechanistic evidence. If Generalized Anxiety Disorder (GAD) is successfully treated, relevant biomarkers should change, supporting the impact of treatment and suggesting improved resilience to stress. Seventy adults with GAD were randomized to receive either Mindfulness-Based Stress Reduction (MBSR) or an attention control class; before and after, they underwent the Trier Social Stress Test (TSST). Area-Under-the-Curve (AUC) concentrations were calculated for adrenocorticotropic hormone (ACTH) and pro-inflammatory cytokines. MBSR participants had a significantly greater reduction in ACTH AUC compared to control participants. Similarly, the MBSR group had a greater reduction in inflammatory cytokines' AUC concentrations. We found larger reductions in stress markers for patients with GAD in the MBSR class compared to control; this provides the first combined hormonal and immunological evidence that MBSR may enhance resilience to stress.

1. Introduction

Chronic or repeated psychological stress has been associated with abnormalities in stress hormones and inflammatory markers. These hormonal and immune abnormalities are in turn associated with negative health consequences such as cardiovascular disease risk and metabolic syndrome (Chrousos, 2000; Ridker et al., 2000). For example, chronic over-secretion of cortisol is associated with metabolic and hemodynamic disturbances such as high systolic blood pressure, fasting glucose, and insulin (Kaur, 2014). In addition, higher levels of circulating pro-inflammatory cytokines such as interleukin-6 (IL-6) are associated with other metabolic syndrome elements including higher body-mass index and the development of type 2 diabetes, and with an increased risk for coronary artery disease (Pradhan et al., 2002).

The causal link between hormonal and inflammatory markers and stress suggested by this body of cross-sectional data is supported by studies showing changes in these biomarkers in response to an experimental stress. Paralleling the epidemiological observations of chronically stressed populations, laboratory stress challenge tests have thus been found to provoke similar elevations in stress hormones (cortisol and adrenocorticotropic hormone (ACTH)) and markers of inflammation (tumor necrosis factor-alpha (TNF-alpha), and IL-6) in the bloodstream (Kirschbaum et al., 1993; Pace et al., 2006; von Kanel et al., 2005).

Mindfulness-Based interventions have greatly increased in popularity and have been used to treat anxiety in recent years. However, randomized and adequately controlled trials are needed to validate waitlist-controlled findings and provide additional confirmation of biological effects (Chiesa and Serretti, 2010; Goyal et al., 2014). Given that mindfulness meditation focuses on one's present experience is often ignored or avoided in Generalized Anxiety Disorder (GAD), we conducted a randomized, controlled study comparing Mindfulness-Based Stress Reduction (MBSR), a standardized and manualized mindfulness meditation training course, with an attention control, Stress Management Education (SME) in individuals with GAD. We measured the effect of MBSR vs. SME on clinical anxiety measures, and found a greater drop in anxiety ratings in most of our measures (see (Hoge et al., 2013) for detailed results). In a group of these patients, we

examined resilience to subsequent stress by measuring hormones and inflammatory markers during the laboratory-based Trier Social Stress Test (TSST). Resilience is "the ability of individuals to adapt successfully in the face of acute stress, trauma, or chronic adversity, maintaining or rapidly regaining psychological well-being and physiological homeostasis" (Charney, 2004), and the TSST, which provides a way to measure coping and recovery from a standardized stressor, has been used to assess resilience in the laboratory (Rose et al., 2013). Prior research has demonstrated that patients with GAD, like other chronically stressed populations, have an exaggerated stress hormone response to the TSST or other laboratory stress provocation, compared to healthy controls (Gerra et al., 2000).

Although participants' ratings of *subjective* stress were reduced more after MBSR compared to SME in our clinical study, we wanted to examine biomarkers in a separate planned analysis using blood markers previously linked to acute and chronic stress, such as the stress hormones cortisol and ACTH, and markers of inflammation, TNF-alpha and IL-6. We were interested in whether MBSR could improve coping and mitigate the physiological effects of acute stress. In addition, decreases in stress hormones and chronic inflammatory markers after mindfulness meditation, compared to a control intervention, would provide some support to the hypothesis that mindfulness meditation training may contribute to improvements in overall medical (cardiovascular and metabolic) health through reductions in stress related biological responses. We hypothesized that mindfulness meditation would mitigate the previously reported elevated response to acute stress observed in GAD, evidenced by a greater reduction in stress hormones and inflammatory markers with treatment.

2. Methods

2.1. Participants and procedures

The procedures of the clinical randomized controlled trial have been described in detail previously (Hoge et al., 2013). Briefly, individuals age 18 and older with GAD, as determined by the Structured Clinical Interview for the DSM-IV (SCID) (First et al., 2002), were randomized to either a modified group MBSR or group SME (see below for course descriptions). Exclusion criteria included lifetime history of psychotic disorder, intellectual disability, organic medical disorders (such as endocrine diseases such as Addison's and Cushing's or chronic inflammatory diseases), bipolar disorder, posttraumatic stress disorder or obsessive compulsive disorder; current alcohol or substance abuse or dependence; significant suicidal ideation or behaviors; and concurrent psychotherapy for GAD. Additional inclusion criteria for this biomarker ancillary study were completion of the pre- and post-treatment TSST experiments, and the availability of blood specimens with adequate volume from all three TSST time periods: pre-stress, immediate post-stress, and later post-stress. In addition, we excluded patients taking antidepressants and benzodiazepines, as prior data suggest they may artificially alter the hormone response during the TSST (Bremner et al., 2003; Carpenter et al., 2007).

Prior to the start of the intervention class, and after baseline questionnaire measurements, participants came to the lab for a testing day, in which they completed the TSST and all blood testing (see details in Section 2.2 below). After the end of the 8-week intervention, they returned to the lab for the second TSST. All study procedures were given ethical approved by the Massachusetts General Hospital /Partners Health Care institutional review board and all participants gave informed written consent before beginning the study.

Seventy-nine participants completed treatment in the parent RCT study (Hoge et al., 2013). Eligible for the biomarker analysis were the 72 participants (MBSR, n=43; SME, n=29) who agreed to blood collection. Some data were missing due to occasional processing or assay problems: intravenous catheter failure (n=1, MBSR), insufficient

plasma quantity for multiple assays (n=5 in MBSR, n=4 in SME). Thus, because a minimum of three time points were required to calculate an Area Under the Curve (AUC), some participants' biomarkers AUC's could not be calculated. One participant was excluded from the biomarker analysis due to a post-randomization acute medical issue, and another due to lab error. Thus, the final sample size that contained both time points varied slightly for each stress marker: n=67 for ACTH, n=68 for cortisol, n=65 for TNF-alpha, and n=62 for IL-6.

2.2. The TSST

The TSST and blood collection procedures were conducted between 1:00 p.m. and 4:30 p.m. to control for hormonal diurnal variation. The TSST consists of an 8-min public speaking task and a subsequent 5-min mental arithmetic task (serial subtraction) performed in front of a panel of "evaluators" dressed in white lab coats and holding clipboards and a large, conspicuous video camera. The TSST procedure followed a detailed script to ensure its systematic and controlled delivery.

Because the TSST was administered before and at the end of the trial, several measures were taken to lower the potential for stress habituation and to improve methodological rigor for the second TSST: 1) the evaluators were switched so that they would be strangers the second time, 2) the TSST was moved to a different room, 3) a different arithmetic task was employed to avoid practice effects and 4) participants were told that their performance on the first speech was in the low range, and that this was their chance to improve their score [26].

2.3. Treatments

MBSR is an 8-week group-based intervention with a single weekend "retreat" day and daily home practice guided by audio recordings. In-class practices (breath-awareness, a body-scan, and gentle Hatha yoga) are used to cultivate awareness of internal present-moment experiences with an accepting, non-judgmental stance. The SME class was designed as an attention control intervention for MBSR to control for the non-specific effects of treatment, such as group support, attention from the instructor, and participants' expectations. The course is taught in a didactic format, and provides lectures on overall health and wellness such as diet, exercise, sleep, and time management. Importantly, SME does not contain any meditation or other mind-body intervention (Hoge et al., 2013).

2.4. Blood collection

An intravenous catheter was placed at time 0, and then the participant rested while pre-stress blood samples were collected (time +5, +10, +15, and +20 min). At +22 min, the speech task instructions were read to the participant. At the end of the 8-min speech preparation time, blood was collected (time +28), and the participant was led to the testing room with the audience of evaluators. After the speech and arithmetic tasks, the subject was led back to the phlebotomy room where post-stress blood samples were collected (+40, +45, +50, +55, and +80 min).

To assess effects of acute stress on the Hypothalamic-Pituitary-Adrenal (HPA) axis, we measured blood levels of cortisol and ACTH. To measure effects of acute stress inflammation, we assessed IL-6 and TNF- alpha.

2.5. Statistical analyses

To be consistent with earlier published trials measuring hormone and cytokine response to the TSST, we compared the pattern of blood markers during stress pre- and post-treatment using an area under the curve (AUC) calculation (Pruessner et al., 1997; Wirtz et al., 2007). We calculated AUC with respect to increase for blood markers of stress for patients with cortisol, ACTH, TNF-alpha, and IL-6, with time point +5