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Cognitive Behavioral Therapy and Tai Chi Reverse Cellular and Genomic Markers of Inflammation in Late-Life Insomnia: A Randomized Controlled Trial

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ABSTRACT

BACKGROUND: Sleep disturbance is associated with activation of systemic and cellular inflammation, as well as proinflammatory transcriptional profiles in circulating leukocytes. Whether treatments that target insomnia-related complaints might reverse these markers of inflammation in older adults with insomnia is not known.

METHODS: In this randomized trial, 123 older adults with insomnia were randomly assigned to cognitive-behavioral therapy for insomnia (CBT-I), tai chi chih (TCC), or sleep seminar education active control condition for 2-hour sessions weekly over 4 months with follow-up at 7 and 16 months. We measured C-reactive protein (CRP) at baseline and months 4 and 16; toll-like receptor-4 activated monocyte production of proinflammatory cytokines at baseline and months 2, 4, 7, and 16; and genome-wide transcriptional profiling at baseline and month 4.

RESULTS: As compared with sleep seminar education active control condition, CBT-I reduced levels of CRP (months 4 and 16, $ps < .05$), monocyte production of proinflammatory cytokines (month 2 only, $p < .05$), and proinflammatory gene expression (month 4, $p < .01$). TCC marginally reduced CRP (month 4, $p = .06$) and significantly reduced monocyte production of proinflammatory cytokines (months 2, 4, 7, and 16; all $ps < .05$) and proinflammatory gene expression (month 4, $p < .001$). In CBT-I and TCC, TELiS promoter-based bioinformatics analyses indicated reduced activity of nuclear factor-κB and AP-1.

CONCLUSIONS: Among older adults with insomnia, CBT-I reduced systemic inflammation, TCC reduced cellular inflammatory responses, and both treatments reduced expression of genes encoding proinflammatory mediators. The findings provide an evidence-based molecular framework to understand the potential salutary effects of insomnia treatment on inflammation, with implications for inflammatory disease risk.

Keywords: Aging, Cognitive-behavioral therapy, Gene expression, Inflammation, Insomnia, Tai chi

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Insomnia, diagnosed by difficulties in initiating sleep, frequent awakenings, or inability to return to sleep, which are associated with daytime impairments (1), occurs in over 15% of older adults (2). Given that poor sleep prospectively predicts depression (3–5), chronic disease risk (6), and mortality (7), increasing attention has focused on the association between sleep disturbance and inflammation (8). Activation of cellular signals that initiate the production of inflammatory cytokines and markers of systemic inflammation (i.e., C-reactive protein [CRP]) are associated with risk of depression (9) and a wide spectrum of medical conditions (10–14).

The causal relationship between insomnia and inflammation remains unclear. Exogenously triggered activation of inflammation induces depressive symptoms (15,16) and also alters sleep in humans (17,18). Conversely, insomnia is associated with elevated levels of proinflammatory cytokines (8,19). Indeed, decreases in sleep duration are prospectively associated with increases in CRP (20), and experimental sleep disruption induces increases in CRP (21), increases in cellular inflammation (22,23), and increases in the expression of inflammatory response genes (23) via activation of the transcription factor, nuclear factor (NF)-κB (24). In the present study, we sought to determine whether two experimental interventions that improve insomnia symptoms (25) might reduce systemic and cellular markers of inflammation and reverse inflammatory gene expression and activation of transcriptional signaling.

In persons experiencing significant life adversity, cognitive behavioral stress management, as well as meditation, can at least partially reverse the pattern of leukocyte proinflammatory transcriptional alterations associated with stress (26–28). However, these small randomized controlled trials have not targeted patients with insomnia nor comprehensively captured a

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vertically integrated assessment of inflammation including systemic levels (e.g., CRP), upstream cellular production of proinflammatory cytokines (e.g., toll-like receptor [TLR]-4 activation of monocytic production of proinflammatory cytokines), and gene expression with promoter based bioinformatics analyses of several specific transcription factors (TF). TLR-4 activation mediates innate immune responses to common pathogens (29), and aberrant increases of TLR-4 activity are linked to inflammatory (30) and cardiovascular disease (31).

Cognitive-behavioral therapy for insomnia (CBT-I), a multicomponent behavioral intervention that provides sleep education, stimulus control (strengthening associations between bed and sleep), and therapy for anxiety-provoking beliefs about sleep, primarily targets sleep behaviors with effects on arousal mechanisms. CBT-I is an effective treatment for insomnia in older adults (25,32) and adults (33), with an efficacy that is better sustained than pharmacotherapy (34). As a comparison with CBT-I, tai chi chih (TCC), a westernized version of tai chi (35–37), is thought primarily to target arousal mechanisms with secondary effects on insomnia (38–40), which in turn decreases sympathetic activation and related inflammation (41,42). TCC improves sleep quality (43–45) and reduces inflammation in older adults (25,46–49).

In a randomized, controlled, comparative efficacy trial over 4 months with follow-up at 7 and 16 months in 123 older adults with insomnia, we previously reported that CBT and TCC were associated with improvements in sleep quality, fatigue, and depressive symptoms as compared with an active control, sleep seminar (SS) (25). In addition, remission of insomnia was associated with reduced proportion of having high CRP (>3.0 pg/mL) at month 16. SS controlled for nonspecific factors (e.g., expectation, group, and attention). Given evidence linking sleep disturbance, as well as related arousal mechanisms to inflammatory dynamics (8), we hypothesized that both CBT-I and TCC in this same sample (n = 123) would reverse increases in levels of CRP, increases in TLR-4 induced activation of monocyte production of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF), and increases in proinflammatory gene expression programs and the specific pattern of bioinformatically inferred TF activation (i.e., increased activity of NF-κB/Rel and AP-1 TFs) relative to SS. Because levels of CRP are relatively stable and changes in CRP in response to behavioral interventions (i.e., exercise) are found after year-long, not months, administration (50–52), CRP was measured at baseline, month 4 (postintervention), and month 16. In contrast, because changes in TLR-4 induced monocytic production in IL-6 and TNF have been found immediately after sleep disturbance (23), this marker was measured at baseline, month 2 (mid-intervention), and months 4, 7, and 16. Postintervention differences in the expression of a priori defined proinflammatory gene programs and bioinformatically inferred TF activation were tested in a subsample.

METHODS AND MATERIALS

Participants

This randomized controlled trial was conducted from April 2006 to August 2011 with University of California, Los Angeles Institutional Review Board approval. As described (25), 123 community-dwelling adults older than 55 years of age who fulfilled criteria for primary insomnia in DSM-IV (53) and for general insomnia in the International Classification of Sleep Disorders (54) were randomly assigned to CBT-I, TCC, or SS (2:2:1). Complete inclusion criteria are provided in Supplement 1.

Interventions

Each group participated in 120 minutes of class time weekly for 4 months with 7- and 16-month follow-up. CBT-I was modified to teach behavioral strategies for management of daytime activity levels and enhancement of mood (33). TCC, a movement meditation, emphasized control over arousal mechanisms, which are thought to contribute to insomnia (55,56). Sleep seminar provided sleep hygiene information and education about physical, medical, and psychosocial factors in relation to aging and insomnia. Supplement 1 provides information about the treatments, acceptance, credibility, and expectations for change (25).

Outcomes

Insomnia outcomes included remission of insomnia diagnosis by DSM-IV criteria using a structured interview and checklist and improvements in patient-reported outcomes of insomnia symptom severity and daily sleep diaries (25). In this study, assessment of inflammation included three levels of analysis: systemic (i.e., CRP levels), cellular (i.e., TLR-4 activation of monocytic production of inflammatory cytokines TNF and IL-6), and genomic (i.e., gene expression and bioinformatics analyses of transcription pathways). Before each blood sampling, subjects were queried about recent (i.e., past month) infection, illness, or vaccination, and sampling was rescheduled if subjects reported any one of these issues. All blood samples were nonfasting and collected between 8:00 AM and 10:00 AM.

CRP levels were measured (25). To clarify the functional basis for altered CRP, production of proinflammatory cytokines by monocytes following ligation of the TLR-4 with lipopolysaccharide was assessed (23). To evaluate the upstream sources of cellular inflammatory cytokine expression, RNA from peripheral blood mononuclear cells was collected for evaluation of gene expression profiling and bioinformatic analysis in a random subsample at 4 months for comparison with CBT-I or TCC relative to SS (n = 78). Additionally, we determined whether gene expression profiles were comparable in three groups at baseline before intervention (n = 24), given the effects of sleep on inflammatory gene expression (23). RNA was extracted (Qiagen PAXgene Blood RNA Kit; Qiagen, Valencia, California) and subject to genome-wide transcriptional profiling using Illumina HT-12 v4 BeadArrays following the manufacturer's standard protocol (Illumina Inc., San Diego, California). Quantile-normalized gene expression values were log2 transformed and subject to general linear model analysis to provide maximum likelihood point estimates of differential transcript abundance across conditions, which provide maximally replicable inputs into the two higher-order set-based bioinformatics analyses (57–59).

TELiS promoter-based bioinformatics analyses (http://www.telis.ucla.edu/) tested the hypothesis that peripheral blood mononuclear cells from older adults with insomnia who were