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Partial sleep deprivation activates the DNA damage response (DDR) and the senescence-associated secretory phenotype (SASP) in aged adult humans

Judith E. Carroll [a,*], Steven W. Cole [a,c], Teresa E. Seeman [b], Elizabeth C. Breen [a], Tuff Witarama [a], Jesusa M.G. Arevalo [c], Jeffrey Ma [c], Michael R. Irwin [a]

[a] University of California, Los Angeles, Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience and Human Behavior, United States
[b] University of California, Los Angeles, Department of Geriatrics, David Geffen School of Medicine, United States
[c] Department of Medicine, Division of Hematology-Oncology, UCLA School of Medicine, United States

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ABSTRACT

Age-related disease risk has been linked to short sleep duration and sleep disturbances; however, the specific molecular pathways linking sleep loss with diseases of aging are poorly defined. Key cellular events seen with aging, which are thought to contribute to disease, may be particularly sensitive to sleep loss. We tested whether one night of partial sleep deprivation (PSD) would increase leukocyte gene expression indicative of DNA damage responses (DDR), the senescence-associated secretory phenotype (SASP), and senescence indicator $p16^{INK4a}$ in older adult humans, who are at increased risk for cellular senescence. Community-dwelling older adults aged 61–86 years ($n = 29$; 48% male) underwent an experimental partial sleep deprivation (PSD) protocol over 4 nights, including adaptation, an uninterrupted night of sleep, partial sleep deprivation (sleep restricted 3–7 AM), and a subsequent full night of sleep. Blood samples were obtained each morning to assess peripheral blood mononuclear cell (PBMC) gene expression using Illumina HT-12 arrays. Analyses of microarray results revealed that SASP ($p < .05$) and DDR ($p = .08$) gene expression were elevated from baseline to PSD nights. Gene expression changes were also observed from baseline to PSD in *NFKB2*, *NBS1* and *CHK2* (all p's $< .05$). The senescence marker $p16^{INK4a}$ (*CDKN2A*) was increased 1 day after PSD compared to baseline ($p < .01$), however confirmatory RT-PCR did not replicate this finding. One night of partial sleep deprivation activates PBMC gene expression patterns consistent with biological aging in this older adult sample. PSD enhanced the SASP and increased the accumulation of damage that initiates cell cycle arrest and promotes cellular senescence. These findings causally link sleep deprivation to the molecular processes associated with biological aging.

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1. Introduction

Aged adults experience more sleep complaints than younger individuals, with estimates that as much as 50% of adults aged 65 years or more experience insomnia symptoms (Ohayon, 2002) and other sleep difficulties (Petit et al., 2003; Foley et al., 1995). Moreover, sleep loss is thought to interact with numerous regulatory systems to influence health and chronic disease risk (McEwen, 2006; Robles and Carroll, 2011; Chen et al., 2014; Mullington et al., 2009; Van Cauter et al., 2007; Ju and Choi, 2013; Palesh et al., 2014), findings that are particularly salient for older adults with sleep difficulties. Disease morbidity and mortality risk are elevated among those with short sleep duration and poor sleep quality (Ohayon, 2002; Center for Disease Control, 2011; Colten and Altevogt, 2006; Motivala, 2011). However, the specific molecular pathways altered by sleep loss, which impact human disease, are poorly defined. Potential pathways include an increase in unrepaired cellular stress and accumulation of damage (Everson et al., 2014; Naidoo, 2009, 2012; Naidoo et al., 2008; Brown and Naidoo, 2010), which is thought to contribute to biological aging (Cribbet et al., 2014; Jackowska et al., 2012; Prather et al., 2011, 2015; Liang et al., 2011; Chen et al., 2014). Initial evidence has linked poor sleep quality and short sleep duration with greater cellular aging, as indicated by shorter leukocyte telomere length

* Corresponding author at: Psychiatry and Biobehavioral Science, Cousins Center for Psychoneuroimmunology, UCLA Semel Institute for Neuroscience and Human Behavior, 300 UCLA Medical Plaza, Suite 3153, Los Angeles, CA 90095-7076, United States.

E-mail address: jcarroll@mednet.ucla.edu (J.E. Carroll).

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(Cribbet et al., 2014; Jackowska et al., 2012; Prather et al., 2011, 2015; Liang et al., 2011; Chen et al., 2014).

The accumulation of damage is part of the pathology of common chronic diseases of aging (López-Otín et al., 2013), and is suspected to be a mechanism by which aging itself promotes disease (Kennedy et al., 2014). Accumulated damage from chronic low grade inflammation (Franceschi and Campisi, 2014; Jurk et al., 2014), for example, leads to imbalance in the redox system, mitochondrial dysfunction, and reduced ability to repair (López-Otín et al., 2013). Driven in part by these processes, aging is also associated with an accrual of senescent cells (Campisi, 2005; Liu et al., 2009; Effros, 2005). Cellular senescence is a state of cell cycle arrest, commonly reached by replicative (e.g., critically short telomeres) or cell stress (e.g., DNA damage) pathways, and preceded by signaling of DNA damage response (DDR) elements derived from telomeric or non-telomeric damage (Campisi, 2005; Effros, 2005; Blackburn, 2005, 2000; Campisi and d'Adda di Fagagna, 2007).

Accrual of senescent cells is thought to effect the aging process, as removal of senescent cells in mice slows aging (Baker et al., 2011). These senescent cells have a unique secretory pattern, termed the senescence associated secretory phenotype (SASP), which is characterized by increased release of inflammatory cytokines and chemokines (e.g., IL-6, IL-8, monocyte chemotactic protein (MCP)-2, MCP-4, chemokine C-X-C motif ligand (CXCL)-1, CXCL-2, CXCL-3, granulocyte macrophage colony-stimulating factor (GM-CSF), intracellular adhesion molecule (ICAM)-1) that promote disease (Effros, 2005; Campisi and d'Adda di Fagagna, 2007; Erusalimsky, 2009; Coppé et al., 2010; Freund et al., 2010). Removing the senescent cells may reduce the development of the aging phenotype in mice by eliminating the inflammatory secretory patterns that contribute to the pathology. Indeed, genetically modified mice (*NFKB1−/−*) that have an enhanced inflammatory signal show accelerated aging through accumulation of senescent cells and enhancement of the SASP (Jurk et al., 2014). Furthermore, accumulation of senescence predicts shortened lifespan (Jurk et al., 2014).

Given these findings that aging is associated with an increase in DNA damage, accumulation of senescent cells, and enhancement of the inflammatory secretome, it is possible that these pathways serve as molecular links between short sleep duration and increases in age-related chronic disease burden in late life. In this experimental study, we test the hypothesis that sleep loss alters these molecular pathways by examining whether partial night sleep deprivation (PSD) in aged humans increases peripheral blood mononuclear cell (PBMC) expression of genes indicative of rises in DNA damage responses (DDR), increases in proinflammatory senescent associated secretory phenotype (SASP), and increases in cellular senescent signal expression ($p16^{INK4a}$). PSD replicates the kind of sleep loss that is ubiquitous in the general population and also resembles the reduction of sleep duration that is often found in persons with age-related medical disorders, however, its effects on physiological process has been examined almost exclusively in adult (Irwin et al., 2008; Irwin and Ziegler, 2005; Irwin et al., 2006, 1996, 2002, 2015), as opposed to older adult populations (Carroll et al., 2015).

2. Materials and methods

2.1. Participants

All subjects gave informed consent and the University of California, Los Angeles (UCLA) institutional review board approved the protocols. Initial medical interview, physical examination, and screening laboratory tests determined eligibility for the PSD. Subjects were invited to participate in the experimental session if they were deemed physically healthy including no past history of cancer or inflammatory disorders, were non-smokers, and had a body mass index (BMI) < 40 (calculated as weight (kg) divided by the square of height (m)). Participants completed a 2 week sleep diary, and were excluded if their normal sleep pattern was less than 7 h nightly and or they showed signs of circadian phase shifting (early or delayed sleep onset by more than 2 h); had atypical sleeping hours not occurring between 11 PM and 7 AM. Additional exclusion criteria included: current diagnosis of mental illness based on the Diagnostic and Statistical Manual of Mental Disorders (Editions IV (revised) or V); sleep apnea, restless leg syndrome, or other sleep disorders as identified during the night of adaptation to the sleep laboratory; chronic or acute (<2 weeks) infection; and comorbid uncontrolled chronic disease. The present analysis includes 29 participants who underwent the PSD protocol and had samples collected for RNA analyses.

2.2. Procedures

After eligibility and medical evaluation, subjects were invited for a four night stay at the UCLA Clinical Translational Research Center (CTRC) where they underwent experimental procedures. Following the first night, which served as an adaptation night, subjects had an uninterrupted night of sleep from 11 PM to 7 AM (baseline). On the third night, the partial sleep deprivation night was assigned. On this night, subjects were not allowed to sleep from 11 PM to 3 AM, sleep occurred between 3 AM and 7 AM (PSD), and awakening occurred regardless of sleep stage. The fourth night (1 day after the PSD) subjects were allowed to sleep uninterrupted from 11 PM to 7 AM. Blood samples were obtained each morning prior to eating and following baseline, PSD, and recovery nights for the assessment of cellular gene expression. Sleep patterns were monitored using polysomnography (PSG) recordings of sleep each night, and are reported separately (Carroll et al., 2015).

2.3. Measures

2.3.1. PBMC gene expression patterns

Samples of quality-verified RNA extracted (RNeasy; Qiagen) from approximately 2 million PBMC were assayed by Illumina HT-12 arrays (Illumina Inc., San Diego, CA) in the UCLA Neuroscience Genomics Core Laboratory as previously described (Fredrickson et al., 2013). Briefly, RNA was tested for integrity and converted to fluorescent cRNA for hybridization to Illumina Human HT-12 v4 BeadArrays, following the manufacturer's standard protocol. Quintile-normalized gene expression values were generated for more than 35,000 probes derived from the National Center for Biotechnology Information Reference Sequence (NCBI) and other sources, and provides genome-wide transcriptional coverage of well-characterized genes, gene candidates, and splice variants.

2.3.2. Senescence associated secretory phenotype (SASP)

Genes representative of key components of the SASP were selected a priori based on prior work showing differential gene expression patterns, with confirmatory protein quantification, in replicative and damage induced senescent cells (Coppé et al., 2008; Laberge et al., 2012). These included the following genes: *IL6*, *CSF2*, *CCL8*, *IL8*, *CCL13*, *ICAM1*, *CXCL1*, *CXCL2*, *CXCL3*, which were z-transformed and then summed to create a composite measure of SASP. Signals known to be upregulated during the **DNA damage response (DDR)** Jackson and Bartek, 2009 were selected to create a composite index by z-transforming and summing the following genes: *GADD45GIP1*, *TP53BP1*, *CHEK1*, *TP53*, *TERF2*, *SIRT1*, *TERT*,

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