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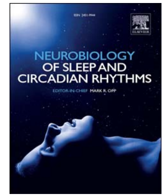

Research Paper

Interleukin 37 expression in mice alters sleep responses to inflammatory agents and influenza virus infection

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ABSTRACT

Multiple interactions between the immune system and sleep are known, including the effects of microbial challenge on sleep or the effects of sleep loss on facets of the immune response. Cytokines regulate, in part, sleep and immune responses. Here we examine the role of an anti-inflammatory cytokine, interleukin-37 (IL-37) on sleep in a mouse strain that expresses human IL-37b (*IL37*tg mice). Constitutive expression of the *IL-37* gene in the brains of these mice under resting conditions is low; however, upon an inflammatory stimulus, expression increases dramatically. We measured sleep in three conditions; (a) under baseline conditions and after 6 h of sleep loss, (b) after bolus intraperitoneal administration of lipopolysaccharide (LPS) or IL-1β and (c) after intranasal influenza virus challenge. Under baseline conditions, the *IL37*tg mice had 7% more spontaneous non-rapid eye movement sleep (NREMS) during the light period than wild-type (WT) mice. After sleep deprivation both WT mice and *IL37*tg mice slept an extra 21% and 12%, respectively, during the first 6 h of recovery. NREMS responses after sleep deprivation did not significantly differ between WT mice and *IL37*tg mice. However, in response to either IL-1β or LPS, the increases in time spent in NREMS were about four-fold greater in the WT mice than in the *IL37*tg mice. In contrast, in response to a low dose of mouse-adapted H1N1 influenza virus, sleep responses developed slowly over the 6 day recording period. By day 6, NREMS increased by 10% and REMS increased by 18% in the *IL37*tg mice compared to the WT mice. Further, by day 4 *IL37*tg mice lost less weight, remained more active, and retained their body temperatures closer to baseline values than WT mice. We conclude that conditions that promote IL-37 expression attenuate morbidity to severe inflammatory challenge.

1. Introduction

Cytokine involvement in sleep regulation is extensively characterized (reviewed Imeri and Opp, 2009; Krueger, 2008; Krueger et al., 2008; Mullington et al., 2010; Simpson and Dinges, 2007; Zielinski and Krueger, 2011). Interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα) are pro-inflammatory sleep regulatory cytokines, although several other cytokines, including anti-inflammatory cytokines, are implicated in sleep-wake regulation. Injections of low doses of IL-1β promote sleep; in contrast high doses inhibit sleep (Opp et al., 1991). Similarly, even low doses of TNFα promote a sleep-like state *in vitro* whereas high doses disrupt neuronal action potential patterns in co-cultures of neurons and glia (Jewett et al., 2015). Sleep deprivation (Taishi et al., 1998; 1999), stimulation of afferent neurons (Churchill et al., 2008; Hallett et al., 2010) or optogenetic stimulation of neurons in culture (Jewett et al., 2015) up-regulate several brain cytokines including IL-1β and TNFα (reviewed Krueger, 2008). Localized sleep intensity, as determined from the amplitude of electroencephalogram (EEG) slow waves (0.5–4 Hz), is enhanced by local application of IL-1β or TNFα or locally enhanced neuronal activity (Yasuda et al., 2005; Yoshida et al., 2004; Kattler et al., 1994). Conversely, inhibition of cortical TNFα expression inhibits local sleep intensity (Yoshida et al., 2004).

Microbial infections or systemic or central administration of various microbial products enhances sleep and these responses are associated with pro-inflammatory/pro-somnogenic cytokine expres-

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sions (reviewed Majde and Krueger, 2005). Influenza virus infections in mice are accompanied by changes in sleep and multiple cytokines (Alt et al., 2007; Chen et al., 2004; Fang et al., 1995; Jhaveri et al., 2006; Kapás et al., 2008; Lupfer et al., 2013). In mice, deficiency of a specific cytokine involved in the responses to influenza virus alters the sleep and morbidity responses to the virus (Alt et al., 2007; Chen et al., 2004; Davis et al., 2015; Traynor et al., 2007). Systemic or central administration of lipopolysaccharide (LPS) also can enhance sleep (Toth and Opp, 2001). Similar to the dose-dependent effects of bolus injections of IL-1β or TNFα, or severe infections, high doses of LPS induce sleep fragmentation suggesting that these effects are the result of stimulating high levels of pro-inflammatory cytokines (Bettis et al., 2006; Lundkvist et al., 2004; Olivadoti and Opp, 2008; Morrow and Opp, 2005).

The dose-dependencies of the direction of effects induced by IL-1β or TNFα suggest negative feedback steps are engaged. Anti-somnogenic cytokines such as IL-4 (Kushikata et al., 1998) and IL-10 (Opp et al., 1995) are less well studied, although their actions on sleep are generally inhibitory. Further, the IL-1 receptor antagonist (Takahashi et al., 1997), as well as cytokine soluble receptors, e.g. the TNF soluble receptor (Takahashi et al., 1995) inhibit sleep. Collectively, the sleep responses to pro- and anti-inflammatory cytokines and those in response to infectious challenge or specific microbial products indicate the involvement of the cytokine network in sleep regulation whether in health or disease.

IL-37b (hereafter called IL-37) is one of 5 isoforms of the IL-1 family of cytokines, formerly called IL-1F7 (Dinarello, 2010; Dinarello et al., 2016; Smith et al., 2000). IL-37 is up-regulated by microbial products, TNFα, IL-1β, IL-18 (Nold et al., 2010). Recombinant IL-37 reduces the production of several pro-inflammatory, pro-somnogenic cytokines including TNFα, IL-1β, and IL-6, while sparing anti-inflammatory/anti-somnogenic cytokines, e.g. IL-10 and the IL-1 receptor antagonist (Nold et al., 2010, Sharma et al., 2008). Such feedback actions result in a dampening of pro-inflammatory responses (the cytokine storm), although the dynamics of such actions are complex and understudied. Humans express IL-37 in various tissues including the brain (Pan et al., 2001). A role for IL-37-driven cytokine regulation is demonstrated in multiple pathologies including microbial infections (Fujita et al., 2013; Imaeda et al., 2013; Li et al., 2013a, 2013b; McNamee et al., 2011; Pei et al., 2013, Teng et al., 2014). The mouse IL-37 homologue has not been found (Taylor et al., 2002) and the IL-37 gene is also not present in chimpanzees (Newman et al., 2005). Human cell lines and mouse macrophages transfected with IL-37 have attenuated pro-inflammatory cytokine responses to LPS. A transgenic mouse strain expressing human IL-37 (*IL37*tg) exhibits attenuated pro-inflammatory cytokine levels in response to LPS (Nold et al., 2010) and dextran sulfate sodium-induced colitis (McNamee et al., 2011). However, in the absence of cytokine or microbial stimulation, IL-37 expression is low in the *IL37*tg mice (Nold et al., 2010). Similarly, in pilot studies we found that *IL-37* mRNA was not detected in WT mice. Further, *IL-37* mRNA was detectable in *IL37tg* mice in the somatosensory cortex and liver following sleep deprivation or LPS treatment.

Although the *IL-37* gene is absent in WT mice, the *IL37*tg line has contributed to the mechanistic understanding of immune responses (Bulau et al., 2014; Coll-Miro et al., 2016; Dinarello et al., 2016; McNamee et al., 2011; Luo et al., 2014; Nold et al., 2010; Nold-Petry et al., 2015) and provides a unique model to examine pro- and anti-inflammatory signaling in sleep responses to inflammatory challenges. Here we describe the effects of the presence of the IL-37 gene in mice on sleep. Three distinct conditions were examined. First, we determined spontaneous sleep and sleep responses to mild sleep loss in otherwise unchallenged mice; the presence of IL-37 had little effect on mouse sleep in these conditions. Second, we challenged the *IL37*tg mice with bolus injections of somnogenic doses of IL-1β or LPS; the anticipated sleep responses to these substances were greatly attenuated. Third, we determined sleep responses to a more pernicious stimulus, influenza virus challenge; in this case the presence of IL-37 enhanced sleep responses and simultaneously reduced morbidity. We conclude that IL-37 plays a central, albeit complex, role in attenuating severe inflammatory challenge.

2. Methods

2.1. Animals and surgery

Male mice (8–10 weeks old) expressing human IL-37 isoform b precursor transgene on a C57BL6 mouse background were locally bred as homozygotes for 8 generations. As previously described (Nold et al., 2010), fertilized eggs of C57BL/6 mice were injected with an IL-37b pIRES plasmid driven by a CMV promoter and contained a GFP expression sequence and a FLAGged C terminus. The eggs were subsequently implanted into C57BL6 females after which male founders mated C57BL6 WT females. A separate colony of C57BL6, WT mice (Jackson Laboratories, Sacramento, CA) were bred in our vivarium and served as controls. Mice were individually housed in sound-attenuated environmental chambers, maintained on a 12:12 h light:dark cycle (light onset=ZT0), at 23 ± 2 °C and provided food and water *ad libitum*. Mice used for polysomnographic analyses were implanted with electroencephalogram (EEG) electrodes over the right and left parietal cortices (1 mm caudal of bregma and either ± 2 mm lateral of bregma) and a ground electrode over the cerebellum (−0.5 mm caudal of lambda; Franklin and Paxinos, 2007). An electromyogram (EMG) electrode was placed in the nuchal muscles. Ketamine-xylazine (87 and 13 mg/kg, respectively) anesthesia was used for surgical procedures as previously described (Davis et al., 2015). Electrodes were mounted onto the skulls with dental cement and the mice were tethered to amplifiers using wire cables. Mice were allowed at least 7 days of recovery from surgery before use. Separate mice were surgically implanted with temperature and activity tracking transponders (TAE-mitters, Mini Mitter, Bend, OR) intraperitoneally under ketamine/xylazine anesthesia and allowed at least 1 week of recovery prior to the experiment. At the conclusion of each experiment mice were euthanized, tails collected and genotypes confirmed by Transnetyx Inc. (Cordova, TN). All experimental protocols were approved by the Washington State University Animal Care and Use Committee and were in compliance with National Institutes of Health Office of Laboratory Animal Welfare guidelines.

2.2. Sleep, temperature and activity recording analyses

Analog EEG (filtered below 0.1 Hz and above 100 Hz with a 60 Hz notch filter) and EMG amplified signals were digitized at 128 Hz and recorded to the local hard drive. Sleep analyses were conducted using Sleep Sign Software (Kissei Comtec Co., Ltd, Japan). EEG wave forms and EMG amplitudes, which reflect brain and muscle activity respectively, are characteristic properties of sleep states in mammals and birds. NREMS, REMS, and waking vigilance states were determined manually off-line in 10 s epochs as previously described (Davis et al., 2015). NREMS was identified by high-amplitude EEG signals and low EMG activity. Regular low-amplitude EEG and minimal EMG activity characterized REMS. Wake periods were recognized by low amplitude fast EEG and high EMG activity. Because mice are mostly active during the dark phase and sleep most of the time during daylight hours, vigilance state durations were calculated in 12 h blocks corresponding to the light (ZT0-12) and dark (ZT12-0) periods. Another measure often used to determine the depth (intensity) of NREMS is the amplitude of EEG slow waves. Although EEG delta wave (0.5–4.0 Hz) amplitudes are regulated independently from duration of sleep, during normal sleep the two measures correlate with each other (Davis et al. 2011). Fast Fourier transformations of Hanning filtered EEG signals (μV^2) of each artifact free epoch were used to calculate NREMS EEG delta power [0.5–4 Hz range; also known as slow-wave activity

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