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Sleep–immune system interaction: advantages and challenges of human sleep loss model

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INTRODUCTION

Sleep and its functional interaction with immune system is well recognized (Majde and Krueger, 2005; Krueger and Majde, 2011). Sleep synchronized changes in brain activity are implicated in direct rather than indirect immune function (Bryant et al., 2004). Sleep or at least its homeostatic component has been suggested to have an active auto-regulatory and/or auto-modulatory mechanism (Krueger et al., 2008; Kumar, 2010). This mechanism operates through adenosine and other sleep regulating substances (SRSs) like interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), growth-hormone-releasing hormone (GHRH), corticotropin-releasing hormone (CRH), nitric oxide (NO), prostaglandin D_2 (PGD2), etc. These SRSs are most likely the connecting link between sleep and immune system (Krueger et al., 2008). The issue of peripheral cytokines affecting brain signaling in sleep has been reviewed comprehensively with three suggested routes for transfer of peripheral cytokines to the brain (Krueger and Majde, 2003). These routes may also be involved in transfer and hence in transmitting the signals from peripheral SRSs. Sleep–immune system co-relations has been investigated across a wide range of immune parameters out of which cytokines, immune cells, antibodies, and neuro-endocrine system constitute the focal group. Human sleep loss (SL) models have been of great help in mechanistic characterization of cytokines (IL-1β and TNF-α role) in sleep and neuroendocrine components (GHRH and CRH) in non-REM sleep, respectively (Majde and Krueger, 2005; Krueger and Majde, 2011). The paradigm has helped establish sleep's functional characterization because of practical simplicity (Reynolds and Banks, 2010) and often non-ambiguous results. However, there may be certain limitations with SL model in context of result translation pertaining to different parameter patterns. The comment has been surmised to highlight these challenges which may give direction to future research in minimizing the variable factors. It may also help to compare the results from available literature objectively.

SLEEP LOSS MODEL: ADVANTAGES AND CHALLENGES

Sleep loss is one of the models which have been employed to study sleep–immune system inter-relationship. It is subdivided into three categories namely total sleep deprivation (TSD), chronic sleep restriction/partial sleep deprivation (PSD), and sleep fragmentation/disruption. TSD (both acute and chronic variations) and PSD have been used widely, however, sleep disruption has been very rarely employed (Reynolds and Banks, 2010). Human SL model has helped in establishing sleep–immune interaction and is practically hassle free in planning. The outcomes of these studies have usually been non-ambiguous. Various groups have reported similar trends with disparities, mainly because of differences in SL design (Majde and Krueger, 2005; Krueger and Majde, 2011). For instance, sTNF-R p55 level did not alter on PSD (Haack et al., 2007; Boudjeltia et al., 2008) but it increased on three nights of TSD (Haack et al., 2007). Sometimes, PSD and acute TST (one/two night) studies have yielded similar trends like in case of white blood cell (WBC; Dinges et al., 1994; Boudjeltia et al., 2008; Liu et al., 2009), neutrophil (Boudjeltia et al., 2008; Liu et al., 2009), and serum IL-1β (Frey et al., 2007; van Leeuwen et al., 2009).

Human sleep deprivation studies have been asserted not to have the problem of stress-induced forced wakefulness as is done in animal experiments (Dinges et al., 1994; Redwine et al., 2004; Krueger and Majde, 2011). There was no behavioral/physiological symptom of stress after one night of TSD, though there was some evidence of neurobehavioral stress after 63 h without sleep (Dinges et al., 1994). The study has quoted seven articles on glucocorticoid–SL interaction pattern and concluded that SL without physical/mental demand is not affected by stress in laboratory conditions. The study further illustrated an increase in peripheral total WBC, granulocytes, monocytes, and natural killer cells activity with striking consistency, irrespective of gender, race, or time of the year (Dinges et al., 1994). However, a more recent article cited non-uniformity (TSD effect) on cortisol pattern, with three studies reporting an increase, three reporting a decrease, and seven reporting no change. It also reported a significant increase in subjective stress with 40 h TSD (Frey et al., 2007). Moreover, the co-relationship between stress and blood pressure (Gasperin et al., 2009) and increase in blood pressure on TSD with different SL designs has been reported by three studies (Meier-Ewert et al., 2004). Similarly, increase in heart rate, suggesting stress during PSD, has also been reported (van Leeuwen et al., 2009). The inconclusiveness of the evidences vis-a-vis cortisol pattern and SL; subjective stress and SL; and stress–blood pressure–SL leave little to doubt about elusiveness of consensus on the issue of stress–SL interaction. Most importantly, there is very significant gap in the literature in terms of SL study data of children, adolescent, and elderly. It is may be more than interesting for future studies to delve into the dimension, which may open new dimension in context of SL effect on stress marker(s).

Many other elements have also been implicated by other groups to affect the immune variables during SL studies. The duration of SL, circadian phase, posture control, light exposure, blood sampling frequency, nutrition (type and timing), assay sensitivity, body mass index (BMI), and obesity may limit comparability of SL results. These factors were enumerated to explain the disparities in reports of interleukin-6 (IL-6), C-reactive protein (CRP), and cortisol outcome by different groups (Frey

et al., 2007). The blood samplings through intravenous catheter limit the investigation of diurnal variations in immune functions. The intravenous catheter induces local alterations in cytokines and soluble cytokine receptors production (Haack et al., 2000). IL-6 level increased with the use of an intravenous catheter across 24 h regardless of sleep deprivation (Haack et al., 2002). The volunteer age and gender had also been shown and/or indicated to affect sleep deprivation effect on some immune variables. The activation of cellular inflammation markers (IL-6 and TNF-α) on PSD is gender dependent (Irwin et al., 2010). The contrasting pattern of monocyte in young men and postmenopausal women may be attributed to age and gender (Boudjeltia et al., 2008). The likely influence of sleep deprivation on melatonin amplitude has been described with the possible involvement of age (Zeitzer et al., 2007). The finding is very important because melatonin and its' rhythm dynamics has intricate co-relationship with cortisol, catecholamine, and other rhythm markers (Manzar and Hussain, 2011). This may have entailments for circadian pattern of immune parameter and their variations with SL designs. PSD decreased Mac-1 positive lymphocytes; and increased L-selectin positive lymphocytes and monocytes. However, the differences were discernible at 06:30 h and not at 03:00 hours. This may reflect more of sleep rebound (homeostatic-sleep expression) than PSD effect (Redwine et al., 2004).

The auto-regulatory/auto-modulatory characteristic of sleep and/or its homeostatic part (Krueger et al., 2008; Kumar, 2010) operate through adenosine and other SRSs like IL-1β, TNF-α, GHRH, CRH, NO, PGD2, etc. The majority of these mediators are either cytokine or endocrine components. The colligating attribute of SRSs in the sleep–immune interplay has been described (Krueger et al., 2008). The indication of three routes for transfer and hence transmittance of peripheral (production site) SRSs borne signal to brain foregrounds the sleep–immune system relation (Krueger and Majde, 2003). Sleep regulation depends on the interplay of three elements namely circadian, homeostatic, and allostatic components (Saper et al., 2005). Their involvement in SL study results have been connoted and/or evidenced (Redwine et al., 2004; McEwen, 2006; Zeitzer et al., 2007). Hence, it is advisable to keep these generalizations in consideration during comparison of SL study results and/or designing future studies:

(i) Interaction between specific SL design with circadian, homeostatic, and allostatic characteristic of sleep.
(ii) Implications for the rhythm dynamics of immune parameter being investigated with the design of SL study.
(iii) The differences in design of TSD, PSD, and sleep disruption studies from different laboratories.

Furthermore, there are some studies which suggest inhibition of hippocampal neurogenesis, independent of adrenal stress hormones on prolonged SL, with the possibility of cognitive dysfunction and mood disorders. Even, modest sleep restriction may interfere with neurogenesis enhancement associated with learning processes (Meerlo et al., 2009). Future studies should address the ethical issues of exposing the volunteers to chronic SL and appropriate remedial management like cognitive function assessment and mood analysis tests.

The opinion highlighted the advantages like practical simplicity; often non-ambiguous results, lack of consensus on the issue of stress non-interference, important gap in literature on stress–SL interaction, challenges complicating generality, and future directions. All factors implicated to affect the result should be taken into consideration while comparing results from other and/or older studies. The opinion may give directions to future studies to minimize and/or clearly report about outcomes affecting factors in literature; filling in of literature gap; and some ethical management.

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