COMMENTARY ARTICLE ON „THE INFLUENCE OF CYTOKINES ON WAKEFULNESS REGULATION: CLINICAL RELEVANCE, MECHANISMS AND METHODOLOGICAL PROBLEMS“

Sleep is an absolute prerequisite for the survival of humans and higher animals. Prolonged total sleep deprivation leads to death in rats (Rechtschaffen et al. 2002). A failure of host defense as a reason for the lethal effect of sleep deprivation was discussed. Growth hormone-releasing hormone (GHRH) is an important sleep-promoting factor, at least in males (Obál & Krueger 2004, Steiger 2007). GHRH is involved in sleep promotion after proinflammatory cytokine interleukin-1β (IL-1) (Obál et al. 1995). The interactions between infection, GHRH and sleep-wake-behavior are illustrated by a study comparing GHRH receptor-deficient and -intact mice (Alt et al. 2003). Following influenza A virus infection sleep-wake behavior was compared between dwarf lit/lit mice with a nonfunctional GHRH receptor and normal control mice. In the infected dwarf mice non-rapid eye movement (nonREM) sleep and delta power in the electroencephalogram (EEG) decreased, whereas these variables increased in the control mice. The dwarf mice showed a higher death rate after influenza infection than the control animals. The authors concluded that GHRH signaling is involved in the nonREM sleep response to influenza infection. These findings suggest that sufficient sleep is essential for survival and for recovery from infection. Due to the importance of sleep in humans and higher animals it is regulated in a redundant fashion. Beside of biogenic amines, neuropeptides, steroids and adenosine also cytokines participate in sleep-wake regulation. The review by Weschenfelder et al. in this issue is focused on the role of cytokines in wakefulness regulation. This review highlights the clinical relevance of this underresearched topic. As the authors point out convincingly this issue is relevant due to the social consequences of sleepiness, fatigue syndrome associated with inflammatory diseases, cancer and obesity, the role of wakefulness regulation and the pathophysiology of affective and sleep disorders and sedation due to psychopharmacologic drugs. Furthermore the authors raise important methodological and theoretical points for further research.

I would like to add some more comments and questions to the issues submitted by the authors. They mention that fatigue is a frequent symptom in patients with inflammatory diseases including multiple sclerosis. In line with these finding is the observation that the time spent in slow wave sleep was enhanced significantly in young female patients with multiple sclerosis compared to normal controls (Antonijevic & Steiger 2003). Furthermore the authors mentioned a relationship between metabolic disorders, impaired sleep and proinflammatory cytokines (Vgontzas et al. 2006, Himmerich et al. 2006). It should be kept in mind that the neuropeptide ghrelin promotes sleep and appetite as well (see review in Steiger et al. 2011, Kluge et al. 2010, Tschöp et al. 2000). Sleep curtailment prompts increases of ghrelin and appetite (Spiegel et al. 2004). A complex role of ghrelin in energy imbalance-induced inflammation was described (Stevanovic et al. 2012). Finally the role of sex and age in the effects of cytokines on wakefulness regulation should be investigated in detail. In endocrine sleep regulation marked gender differences were observed as exogenous GHRH promotes sleep in men, whereas it impairs sleep in women (Antonijevic et al. 2000). Ghrelin has similar sleep-promoting effects in male subjects (Weikel et al., 2003) whereas it does not affect sleep in women (Kluge et al. 2007). It is unclear whether similar sexually dimorphic effects of cytokines on the regulation of sleep-wake behavior exist. Sleep quality declines during ageing (Bliwise 1993). Possibly a relationship exists between maintained sleep quality, immune function and longevity in older age. This hypothesis needs to be tested.

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REFERENCES

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