THE INFLUENCE OF CYTOKINES ON WAKEFULNESS REGULATION: CLINICAL RELEVANCE, MECHANISMS AND METHODOLOGICAL PROBLEMS

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SUMMARY

Sleep-wake-regulation has been shown to be substantially influenced by cytokines. The clinical relevance of this issue arises from (1) the frequency of accidents, injuries and impairment in social functioning due to sleepiness, (2) the occurrence of fatigue syndromes associated with inflammatory diseases, cancer or obesity, (3) the role of wakefulness regulation for the pathophysiology of affective and sleep disorders and (4) sedation as a side effect of psychopharmacological therapy. Experimental studies confirm the somnogenic influence of pro-inflammatory cytokines such as interleukin (IL)-1ß, IL-6 and tumor necrosis factor-α (TNF-α). These cytokines modulate centers of wakefulness regulation located in the hypothalamus, the basal forebrain and the brain stem by influencing substances involved in sleep-wake-behavior such as adenosine, nitric oxide (NO), nuclear factor-κB (NF-κB), prostaglandin D2 (PGD2), the neurotransmitters γ-aminobutyric acid (GABA), glutamate and norepinephrine, as well as hormones such as growth hormone-releasing hormone (GHRH) and corticotropin-releasing hormone (CRH). Clinical studies of the influence of cytokines on wakefulness regulation are underrepresented in the research literature and objective measures of wakefulness such as the Multiple Sleep Latency Test (MSLT) are seldom reported.

Key words: *wakefulness – vigilance – cytokines - sleepiness*

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INTRODUCTION

The immune system and the central nervous system (CNS) share the ability to respond to external stimuli and to form memory (Steinman 2004). They also influence each other via a variety of signaling molecules. Sleep-wake-regulation is one example of a CNS function that is influenced by cytokines (Arias-Carrión et al. 2011). In turn, length and quality of sleep as well as sleep deprivation influence the activity of the immune system and cytokine release (Lange et al. 2011, Bryant et al. 2004, Lorton et al. 2006, Dimitrov et al. 2007). Despite the fact that the effects of sleep on cytokine production and the role of cytokines in the sleep-wake-cycle have been extensively investigated, the influence of cytokines on wakefulness regulation is still an underrepresented area of research.

Due to the heterogeneity of methods for the measurement of wakefulness as well as the function of the cytokine system, studies are difficult to compare. Nevertheless, it is important to attempt to identify the principle mechanisms whereby cytokines influence the sleep-wake-cycle and wakefulness regulation because of the substantial clinical and scientific importance. Impaired wakefulness and fatigue not only negatively affect quality of life, for example in several inflammatory and malignant diseases; they are also a direct serious risk factor for impaired social functioning, accidents and injuries.

CLINICAL RELEVANCE

Excessive daytime sleepiness (EDS)

EDS is a common symptom affecting approximately 5–15% of the general population of developed countries. EDS is the major complaint of patients referred to sleep disorders centers (Ohayon et al. 1997). EDS deleteriously affects work activities, social and marital life, and has a negative socioeconomic impact. It has been identified as a major debilitating and even life-threatening factor in working populations. The National Highway Traffic Safety Administration estimates that 100,000 car crashes in the US per year and at least 1500 deaths per year can be attributed to driver's EDS (Annual estimates 2009, Young et al. 2004, Slater 2008). Despite the high prevalence and associated morbidity, EDS and associated sleep/wake disorders are often unrecognized and therefore not treated in the primary care setting (Roth et al. 2010). Medical disorders with a high prevalence of EDS include ulcers, migraines, depression (Stroe et al. 2010) and sleep disorders.

Sleep disorders

Obstructive sleep apnea (OSA), narcolepsy and idiopathic hypersomnia are the most common disorders associated with EDS (American Sleep Disorders Association Diagnostic Classification Steering Committee

1990). There is growing evidence that cytokines may be involved in their pathophysiology (Vgontzas et al. 1997, Minoguchi et al. 2004), as detailed below, using the example of narcolepsy.

Narcolepsy is a disabling sleep disorder characterrized by EDS, cataplexy and other abnormal manifesttations of REM sleep, such as sleep paralysis and hypnagogic hallucinations (Nishino & Kanbayashi 2005). Since the discovery of the close association of narcolepsy and a specific human leukocyte antigen (HLA-DR2), and given that HLA haplotypes are linked to a number of autoimmune diseases, it has been suggested that the immune system might play a pathogenic role in narcolepsy. In humans with narcolepsy, a dramatic reduction in the number of hypocretin (Hcrt) neurons is observed. Because of the association of narcolepsy with HLA-DR2, it was hypothesized that the loss of Hcrt neurons might be caused by an autoimmune process that also involves a dysregulation of cytokine signaling (Himmerich et al. 2009, Berthold-Losleben et al. 2008). Furthermore, some authors suggest that certain cytokine-producing genes may predispose to narcolepsy. Hohjoh et al. (1999) found a significant association of a single nucleotide polymorphism (SNP) in the tumor necrosis factor-α (TNF-α) gene promoter with human narcolepsy and a significant association of the tumor necrosis factor receptor p75 (TNF-R p75) gene with human narcolepsy (Hohjoh et al. 2000). Additionally, it was demonstrated that narcoleptic patients have a functional alteration of the TNF-α cytokine system (Himmerich et al. 2006). In 2011, the pathophysiological gap between the TNF-α system and the Hcrt system was bridged when Zhan et al. (2011) found that TNF-α regulates the Hcrt system via mRNA degradation.

Hor et al. (2010) performed a genome-wide association study (GWAS) to further define the genetic basis of narcolepsy risk in 562 European individuals with narcolepsy and 702 ethnically matched controls, with independent replication in 370 cases and 495 controls. They found an association with a protective variant near HLA-DQA2, which suggests a causal involvement of the HLA region in narcolepsy susceptibility and highlights the role of the immune system in sleep disorders.

Fatigue

Fatigue is a clinical syndrome in which sleepiness is a guiding symptom. Fatigue syndromes develop on the basis of autoimmune diseases, inflammatory diseases and cancer all of which lead to the production of cytokines. The relationship between inflammation and fatigue is evident in the common lethargy of acute infections as well as the frequently reported fatigue among patients with inflammatory diseases such as multiple sclerosis (MS), systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) (Norheim et al. 2011, Krupp et al. 1988, Hewlett et al. 2005). Impor-

tantly, several recent studies of biological agents in RA indicate that anti-cytokine drugs have a beneficial effect on fatigue (Norheim et al. 2011, Hoving et al. 2009, Minnock et al. 2009, Keystone et al. 2008). Fatigue also appears independently of inflammatory or infectious diseases in the setting of chronic fatigue syndrome (CFS), characterized by severe and disabling fatigue without a pathophysiological explanation (Afari & Buchwald 2003). Despite many years of intense investigation there is little consensus on the presence, nature and degree of immune dysfunction in this condition. However, slightly increased parameters of inflammation and pro-inflammatory cytokines such as IL-1ß, IL-6 and TNF-α are likely present (Bansal et al. 2011).

Metabolic disorders

In a modern world with an oversupply of food, metabolic disorders are an increasing world-wide problem. The most common clinical metabolic syndrome associated with EDS and fatigue is obesity. Sleep apnea, sleep disruption, psychological distress, over-activation of the hypothalamic-pituitary-adrenal (HPA) axis with hypercortisolemia and increased production of pro-inflammatory cytokines have been shown to be associated with obesity-related low sleep efficiency, fatigue and daytime sleepiness (Vgontzas et al. 2006). Pro-inflammatory cytokines that correlate with body mass index (BMI) include TNF-α, its receptors TNF-R p55 and TNF-R p75 and IL-6 (Himmerich et al. 2006).

Psychiatric Disorders

Affective disorders such as major depressive disorder (MDD) and bipolar disorder (BD) with manic and depressive episodes can show a rapid response to sleep deprivation (Giedke & Schwarzler 2002, Hemmeter et al. 2010, Wu & Bunney 1990). It is sometimes used as a therapy against depression. Sleep deprivation can also lead to the onset of a manic episode.

Hegerl et al. have recently proposed a theory of the pathogenesis of affective disorders which attributes an important pathogenetic role to the regulation of vigilance, meaning different arousal states which can be assessed using the EEG (Hegerl et al. 2009, Hegerl et al. 2011, Cantero et al. 1999, Cantero et al. 2002). Mania and Attention Deficit Hyperactivity Disorder (ADHD) are both assumed to show an unstable vigilance regulation (Bschor et al. 2001, Schönknecht et al. 2010, Sander et al. 2010, Hegerl et al. 2010), whereas symptoms of MDD are explained as sensation avoidance as a consequence of a hyperstable vigilance regulation. In a study of 30 patients with MDD without psychotropic medication and 30 age- and sex-matched controls, it was found that patients with depression show less declines into lower EEG vigilance stages under resting conditions than healthy controls (Hegerl et al. 2011).

Interstingly, in affective disorders such as depression (Himmerich et al. 2008) and mania (Drexhage et al. 2011) as well as in ADHD (Oades et al. 2010), a pathophysiological role of the cytokine system has also been hypothesized. Therefore, cytokines could lead to the changes in vigilance seen in affective disorders. Alternatively, vigilance dysregulations could induce changes in the cytokine system, which could contribute to the pathophysiology of affective disorders. However, this hypothesis requires empirical validation.

Psychopharmacological therapy

Besides psychiatric disorders themselves, psychopharmacological therapy can lead to sleepiness or tiredness. This clinically important problem is encountered during treatment with antidepressant as well as with antipsychotic drugs. There may also be a link between sleep propensity and activation of cytokine production. For example, every analyzed drug that leads to sedation or daytime sleepiness, like clozapine (Asenio Lobos 2010), olanzapine (McCormack et al. 2010), amitryptiline (Doerr et al. 2010) or mirtazapine (Biswas et al. 2003), activates the TNF-α system. This activation leads to increased concentrations of soluble TNF-α receptors (sTNF-Rs) and TNF-α plasma levels. An activation of the TNF-α system seems to be specific to those drugs that induce drowsiness, because drugs that hardly induce sedation like paroxetine or venlafaxine, do not activate the TNF-α system (Hinze-Selch et al. 2000, Kraus et al. 2002). Furthermore, bupropion has shown to have an anti-inflammatory action against pro-inflammatory cytokines TNF-α and to shorten sleep time and act against EDS (Wilkes 2006). In a study by Kluge et al. clozapine and olanzapine led to an increase of pro-inflammatory cytokine levels in the plasma (Kluge et al. 2009) and induced increased daytime sleep propensity (Kluge et al. 2012).

Taken together, the fact that idiopathic, inflammatory, sleep, psychiatric and metabolic disorders are associated with elevated cytokine production and lead to decreased wakefulness, and that anti-cytokine therapy leads to decreased fatigue, suggest a major role of cytokines in wakefulness regulation.

DEFINITIONS AND MEASUREMENT OF WAKEFULNESS

Studying the literature regarding wakefulness regulation, several heterogeneous terms are used to describe wakefulness such as arousal (Imerai et al. 2011), alertness (Zamarron et al. 2004), and vigilance (Vanitallie 2006, Hegerl et al. 2010) or states of reduced wakefulness like drowsiness (Slater et al. 2008), sleepiness (Vgontzas et al. 1997), tiredness (Pirinen et al. 2010), somnolence (Sherkat et al. 2011), and fatigue (Heesen et al. 2006). The first three and the latter five are often used synonymously, although they reflect

different theoretical constructs and are measured with different instruments. Due to the methodological heterogeneity of the applied methods in measuring wakefulness, it is difficult to draw conclusions from the available studies. Therefore, we would like to briefly clarify some terms and describe how these constructs can be measured; for a review see also (Mathis & Hess 2009).

Arousal

The term arousal is used to describe the state of physiological activation. Arousal is controlled by the ascending reticular activation system (ARAS, Morouzzi & Magoun 1949) and a certain amount of cortical arousal (i.e. a general, non-specific activation of the brain) is a prerequisite for all forms of higher cognitive processes (Pfaff, 2008). Since arousal is a physiologic state, it can best be assessed using objective measurement such as electroencephalography (EEG), where higher arousal is reflected in a more desynchronized EEG activity (Munk et al. 1996), assessment of skin conductance (Bach et al. 2010), heart rate variability (HRV, Berntson et al. 1997, Udo et al. 2009) or peripheral arterial tonometry (PAT, Tauman et al. 2004), although there have been attempts to use subjecttive assessments as well (Thayer 1967, Mackay et al. 1978)

Alertness

Alertness is the state of paying close and continuous attention, being watchful and prompt to meet danger or emergency, or being quick to perceive and act. Therefore, higher cognitive processes are involved. Alertness is assessed in specific tasks, where changes in performance (i.e. reaction times) can be used to describe differences in alertness. There are elaborate approaches to estimating alertness levels during cognitive tasks - e.g. estimating alertness from the EEG power spectrum (Makeig & Jung 1997). Another measure of alertness is the alpha attenuation test (AAT, Hagiwara et al. 1997), an EEG-based assessment where subjects are recorded under resting conditions with open and closed eyes (EO/EC) and an alpha attenuation coefficient (AAC) is calculated as the ratio between EO and EC alpha power.

Vigilance

The term vigilance is used in at least three different contexts (Oken et al. 2006). When the term vigilance was first introduced by Henry Head (Head 1923), it described a state of maximal physiologic efficiency, during which an organism is most receptive for information. Later, the term was adopted by psychologists studying attention and since then vigilance is often synonymously used for sustained attention and is defined as the ability to maintain attention and alertness over prolonged periods of time (Warm et al. 2008). Accordingly, vigilance is often

measured using a continuous performance test (CPT) or the psychomotor vigilance test (PVT).

Furthermore, in the clinical context vigilance is used to describe different states of consciousness (awareness, somnolence, coma) or to describe different states of wakefulness (awake vs. different sleep stages). Besides the distinction of sleep stages, several so called vigilance stages can be separated during the transition from active wakefulness to sleep onset. These vigilance stages can best be assessed using EEG, since they exhibit specific EEG-characteristics (Loomis et al. 1937, Roth 1961, Bente 1964, Klimesch 1999, Olbrich et al. 2009). Conceptually, vigilance stages are seen as global, functional brain states (Hegerl et al. 2009). Therefore, there is a close association with the arousal concept.

Sleepiness

One generally accepted definition of sleepiness is that of one's tendency to fall asleep, also referred to as sleep propensity. Since a high sleepiness entails a readily observable behavioral and physiological phenomenon - the act of falling asleep - sleepiness is best measured using standardized assessment protocols such as the Multiple Sleep Latency Test (MSLT, Richardson et al. 1978). The MSLT can only be performed in a sleep laboratory, where subjects are placed in bed at several times during the day and it is polysomnographically recorded whether or not they fall asleep during 20 minutes and if so, whether REM sleep is reached during 15 minutes of sleep. The MSLT has been shown to be a reliable instrument for measuring sleepiness under various conditions, for example it is not influenced by the fact whether or not the examined subject had a polysomnography the night prior to MSLT (Wichniak et al. 2002).

However, sleepiness can also be assessed subjectively: The current level of sleepiness can be measured using the Stanford Sleepiness Scale (SSS, Hoddes et al. 1972) or the Karolinska Sleepiness Scale (KSS, Åkerstedt & Gillberg 1990). However, it is not unusual to find marked differences in objectively vs. subjectively measured sleepiness (Vgonzas et al. 2008), which is mainly due to the fact that subjects misinterpret tiredness or fatigue for actual sleepiness and therefore overestimate their real sleep propensity. The general amount of sleepiness over a certain period of time can be quantified by the Epworth Sleepiness Scale (ESS, Johns 1991), which can be used to assess EDS defined as difficulty maintaining wakefulness and increased sleep propensity, especially in inappropriate circumstances and situations that adversely interfere with activities of daily living.

Drowsiness

Drowsiness has been defined as a state of impaired awareness associated with a desire or inclination to sleep (Stedman's Medical Dictionary 2008). However, whereas sleepiness reflects the basic physiological need for sleep occurring i.e. after prolonged periods of wakefulness, drowsiness is often seen as a concomitant of an abnormal brain state, i.e. following drug administration. Due to the close association drowsiness is assessed using the same methods as when assessing sleepiness.

Tiredness

Tiredness is a temporarily loss of energy or strength due to exhausting physical or mental work. Although associated with a need for sleep, a tired state can be negotiated by rest or relaxation, therefore differing from sleepiness.

Fatigue

Originally the term fatigue was used to describe the growing performance decrement with increasing time-on-task (Mathis & Hess 2009). In this meaning, fatigue could be overcome by simply changing the task. However, in the clinical context, fatigue is defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion. It is different from normal experiences such as tiredness or sleepiness. As a symptom, it is non-specific and highly subjective, and therefore not easily evaluated and quantified (Krupp et al. 1996, Krupp et al. 1989, Norheim et al. 2011). There are a variety of fatigue-measuring instruments, all principally based on self-reported symptoms, feelings and problems encountered by the patients: for example the Fatigue Severity Scale (FSS, Krupp et al. 1989), the Chalder Fatigue Scale (CFS; Chalder et al. 1993), the Fatigue Impact Scale (FIS, Shen et al. 2011), or the Multidimensional Fatigue Inventory (MFI-20, Smets et al. 1995). Some of these scales are designed to be disease specific, while others are validated and usable across a number of diseases (Norheim et al. 2011).

To conclude, we have to distinguish between different terms and theoretical constructs describing different aspects of vigilance. Accordingly, we have also to distinguish between objective measures such as the MSLT or EEG-based classification of vigilance stages and various subjective questionnaires.

NEUROANATOMY AND BIOCHEMISTRY OF WAKEFULNESS REGULATION

Neuroanatomy

Sleep and wakefulness are controlled by a complex, distributed and interconnected system of sleep-promoting and arousal-promoting neural systems. Considerable difficulties persist in conceptually and neurobiologically distinguishing arousal-promoting from wake-promoting systems. The generation of

cortical arousal and the promotion of wakefulness are mainly mediated by monoaminergic cell groups situated in the brain stem: noradrenergic cells in the Locus coeruleus (LC), serotonergic cells in the dorsal and medial raphe nuclei (DRN/MNR), histaminergic neurons in the tuberomamillar nucleus (TMN) and dopaminergic neurons of the ventral-tegmental area (VTA). Furthermore, wakefulness-promoting neurons have been identified in the basal forebrain (BF), most of which contain acetylcholine or gamma-aminobutyric acid (GABA). It is important to note that the wakefulness-promoting cell groups are reciprocally connected to sleep-promoting cell groups located in the ventral-lateral preoptic area (VLPO) and the median preoptic nucleus (MnPN) of the preoptic area. Therefore, during wakefulness the arousal-systems promote each other while inhibiting the sleep-systems, whereas during sleep the arousal-systems are inhibited by the sleep-systems. This has been described as the flip-flop model of sleep-wake-regulation (Saper et al. 2005). In this model, switches between states are reduced by the reciprocal connections; however, if one side is strengthened a rather abrupt switch might result. To ensure an undisturbed wake phase (or sleep respectively) there needs to be a stabilizing influence, guaranteeing the dominance of the wake-promoting systems. A small group of previously mentioned Hcrt neurons in the lateral hypothalamus has been identified as such a wake-stabilizing system. Based on their extensive projections to all other arousal-promoting systems, the Hcrt neurons are considered the most important wake-executive system (Rosenwasser 2009). Lack of Hcrt neurotransmission results in frequent transitions between wake and sleep as can be seen in narcolepsy (Arrigoni et al. 2010). Although connected to all arousal systems, Hcrt neurons seem to have a considerable influence on the LC and neural activity in the noradrenergic LC correlates with periods of wakefulness and arousal. A growing body of evidence from anatomical, pharmacological and electrophysiological studies research additionally suggests that the BF may be a key site through which the Hcrt-producing neurons promote arousal (Arrigoni et al. 2010).

Biochemistry

The basic molecular mechanisms that underlie circadian rhythm generation at a cellular level are not restricted to those mentioned above as key structures of wakefulness regulation but are broadly distributed in the brain and body (Rosenwasser 2009). Nevertheless, they play an important role in the above mentioned centers of vigilance steering and control.

Many substances have now been implicated in sleep/wake regulation. According to the present literature, the most important ones – besides the cytokines IL-1ß and TNF-α – are the purine nucleoside adenosine, the diatomic gaseous neurotransmitter nitric oxide (NO), the transcription factor nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), which also plays an important role as a second messenger in TNF-α signaling, the neurotransmitters γ-aminobutyric acid (GABA) and glutamate, and the prostaglandin D2 (PGD2), which is produced by mast cells, Th2 lymphocytes and dendritic cells, influences recruitment of immunological cells and modulates cytokine production (Pettipher 2007).

PGD2 and adenosine are potent humoral sleep-inducing factors that accumulate in the brain during prolonged wakefulness. PGD2 is produced in the brain in the leptomeninges, choroid plexus and oligodendrocytes, and circulates in the cerebrospinal fluid as a sleep hormone. It stimulates the prostaglandin D type 1 receptors (DP1) on leptomeningeal cells of the basal forebrain to release adenosine to promote sleep. Adenosine activates adenosine A2A receptor-expressing sleep-active neurons in the basal forebrain and the ventrolateral preoptic area (Huang et al. 2007).

NO has been implicated in the regulation of multiple pathological and physiological processes including the regulation of sleep. NO levels are higher in the cortex and in the BF during arousal. Both adenosine and nitric oxide (NO) are known for their role in sleep homeostasis. For example, sleep deprivation (SD) induces the production of NO in BF, leading to enhanced release of adenosine (Kalinchuk et al. 2011). SD additionally activates NFκB within the hypothalamus and cortex (Brand et al. 2004, Chen et al. 1999). Adenosine also elicits NFκB nuclear translocation in the BF via the adenosine receptor A1 (A1AR) which may be one of its sleep-inducing mechanisms (Basheer et al. 2001).

Glutamate is the most common excitatory transmitter in the brain, and is likely to have the greatest direct impact on neuronal activity (Jones et al. 2005), whereas GABA is the most prominent inhibitory neurotransmitter in the brain. The ubiquitous distribution of GABAergic neurons in the brain implies multiple targets of action (Jones et al. 2005). The sleep-active GABAergic neurons in the VLPO and BF may have a crucial role in the induction and maintenance of sleep by inhibiting wake-promoting cell groups (Manns et al. 2003, Sherin et al. 1996).

Additionally, certain hormones play a specific role in sleep regulation. A reciprocal interaction of the neuropeptides growth hormone (GH)-releasing hormone (GHRH) and corticotropin-releasing hormone (CRH) plays a key role in sleep regulation. In males, GHRH is a common stimulus of non-rapid eye movement sleep (NREMS) and GH and inhibits the HPA hormones, whereas CRH exerts opposite effects. Furthermore CRH may enhance rapid eye movement sleep (REMS) and ultimately boosts the production of the wake-hormone cortisol. Besides CRH, somatostatin impairs sleep, whereas the hormones ghrelin, galanin and neuropeptide Y seem to promote sleep (Steiger et al. 2007).

CYTOKINES AND WAKEFULNESS REGULATION

Immune system and cytokines

The human immune system is divided into two major components: the innate immune system and the adaptive immune system. The innate immune system provides an immediate, but non-specific response. Natural killer cells, mast cells, eosinophils, basophils, and the phagocytic cells including macrophages, neutrophils and dendritic cells belong to the innate immune system. They are able to immediately identify and eliminate pathogens and influence the response of the adaptive immune system through the production of cytokines and the modulation of the cytokine system (Janeway et al. 2001, Berthold-Losleben et al. 2009). Interferon (IFN)-α, for example is a cytokine of the innate immune system which directly inhibits viral replication in infected cells and subsequently triggers adaptive T cell-mediated immunity (Müller et al. 1994).

Cytokines are not only produced in the peripheral blood and the lymphatic organs but also in the CNS, for example by astrocytes and cells of the microglia (Merill et al. 1992, Müller & Ackenheil 1998). Cytokines produced within the CNS include interleukin (IL)-1ß, IL-6, IFN-γ and TNF-α. Increased concentrations of IL-1ß, IL-6 and TNF-α are found in injured brain areas, infections, stroke and cerebral inflammatory and neurodegenerative diseases and can lead to apoptosis as well as reduction of synaptic function and reduced hippocampal neurogenesis (Himmerich et al. 2007). Microglia are activated in most pathological conditions of the CNS and play an important role in sensing and propagating inflammatory signals in response to activation of the peripheral innate immune system (Hanisch et al. 2007).

Cytokines and abnormal sleep-wake-regulation

Several cytokines are involved in the modulation of sleep and wakefulness. These cytokines include interleukin IL-1ß, IL-1 receptor antagonist (ra), IL-2, IL-2r, IL4, IL-9, IL-10, IL-13, the IL-1 receptor antagonist, the transforming growth factor (TGF)-ß, IL-6, IL-18, IFN-α, IFN-γ, TNF-α and its receptors p55 and p75 (Krueger et al. 2007, Chen et al. 2011, Nas et al. 2011, Ormstad et al. 2011, Himmerich et al. 2006). So-called pro-inflammatory cytokines are more likely to induce sleep, whereas anti-inflammatory cytokines show anti-somnogenic effects or do not effect sleep-wake-regulation. Pro-inflammatory cytokines such as IL-1ß, IL-6, and TNF-α augment the immune response to help speed the elimination of pathogens and the resolution of the inflammatory challenge. Anti-inflammatory cytokines, in contrast, serve to dampen the immune response to prevent an overreaction of the organism against allergens or pathogens. Examples of anti-inflammatory cytokines are IL-4, IL-10, and IL-13

(Kronfol & Remick 2000). Table 1 provides an overview of pro- and anti-somogenic effects of cytokines involved in sleep-wake-regulation.

Table 1. Cytokines involved in sleep-wake-regulation (according to Capuron & Miller 2011, Sugama et al. 2008, Radomski et al. 1994; Krueger & Majde JA 1994). Abbreviations: Interleukin (IL), tumor necrosis factor factor (TNF), interferon (IFN), transforming growth factor (TGF), soluble TNF receptor (sTNF-R), IL-1a receptor antagonist (IL-1ra)

Pro-somnogenic cytokines	Anti-somnogenic cytokines
IL-1ß	IL-4
IL-1a	IL-10
IL-2	IL-13
IL-6	TGF-ß
IL15	sTNF-R
IL-18	IL-1ra
TNF-α	
TNF-ß	
IFN-α	
IFN-γ	

Cytokines such as IL-1β and TNF-α are involved in sleepiness during acute infections (Krueger et al. 2003; Dinarello et al. 1988; Kelley et al. 2003) and in several other abnormal sleep situations. For example, the TNF-α system is involved in sleepiness during chronic diseases such as human immunodeficiency virus infection, rheumatoid arthritis and fibromyalgia (Darko et al. 1995, Feldmann & Maini 1999, Zamarron et al. 2004, Moldofsky et al. 1993). TNF-α and IL-6 seem to play a pivotal role in obstructive sleep apnea syndrome which is also typically associated with daytime sleepiness and IL-1β. And additionally, TNF-α and IL-6 respond to sleep deprivation (Redwine et al. 2000, Vgontzas et al. 2004). For a comprehensive review see (Kapsimalis et al. 2008).

Methodological Problems

It is difficult to describe general mechanisms as to how cytokines influence wakefulness regulation, because different measures and methods have been applied in studies investigating wakefulness, sleepiness, vigilance or fatigue. Additionally, different measures are frequently used in one single experiment, leading to seemingly conflicting results: For example, IFN-α was reported to induce fatigue as measured using the MFI, not to influence daytime sleepiness as measured using the ESS and even to decrease the propensity to fall asleep during daytime nap opportunities as measured using the MSLT in patients suffering from hepatitis C (Raison et al. 2010). In patients with multiple sclerosis, the stimulated cytokine production of IFN-γ and TNF-α but not of the anti-inflammatory cytokine IL-10 correlated significantly with the modified Fatigue Impact

Scale (MFIS) scores, but only TNF-α values correlated significantly with daytime sleepiness as measured by the ESS (Heesen et al. 2006).

Furthermore, since there is no established gold standard, several different approaches are also used in cytokine research: Cytokines are studied within the plasma (Himmerich et al. 2006) or the cerebrospinal fluid (Lue et al. 1988); sometimes stimulated cytokine expression from whole blood essays is investigated (Heesen et al. 2006) or cytokines and other immuno-stimulants are injected into the blood (Schuld et al. 2005) or the brain (Dickstein et al. 1999) of humans or animals. Genetic studies either determine cytokine genes (Khalyfa et al. 2011) or gene expression (Shimada et al. 2010). Nevertheless, we endeavor to summarize and condense the most important findings on cytokine research regarding sleep-wake-regulation.

Fatigue as one symptom of "sickness behavior"

Elevated cytokine production during an inflammatory response leads to a specific cluster of symptoms including fever, sleepiness and a general feeling of achiness (Watkins & Maier 2000). Collectively, this constellation of physiological changes caused by acute activation of the immune system was coined as sickness behavior (Dantzer & Kelley 1989). In particular, pro-inflammatory cytokines such as TNF-α and IL-1ß have been regarded as key mediators of these symptoms in the early stages of acute phase response to viral and bacterial infections (Kelley et al. 2003, Kapsimalis et al. 2008). It has been observed that systemic administration of IL-1ß or TNF-α for immunotherapy in people with cancer produces symptoms of sleepiness similar to the acute phase response to infection (Dinarello et al. 1997) supporting further the notion that pro-inflammatory cytokines are the key mediators of sickness behavior. Administration of cytokine antagonists, such as IL-1 receptor antagonist IL-1ra, or anti-inflammatory cytokines such as IL-10, can block the behavioral effects of treatment with IL-1ß ß or lipopolysaccharide which acts as an endotoxin and elicits a strong immune response (Dantzer et al. 2008, Capuron & Miller 2011).

Experimental studies using objective measures of wakefulness

Vgontzas et al. investigated the effect of sleep restriction and daytime napping on pro-inflammatory cytokine levels measuring circadian cytokine profiles as well as the influence of cytokine blocking of sleep latency using the MSLT.

It could be shown that mild chronic sleep restriction in healthy sleepers leads to a significant increase in IL-6 plasma concentrations in males and females and to a significant increase in TNF-α levels in males (Vgontzas et al. 2004). Regarding the influence of daytime napping following a night of total sleep deprivation on IL-6 plasma levels it was found that a nap affected IL-6

plasma levels during and after the nap. IL-6 significantly decreased during the nap and tended to remain lower in the postnap period compared with the no-nap group (Vgontzas et al. 2007).

As the pro-inflammatory cytokines, TNF-α and IL-6 have been found to be elevated in OSA as mentioned above (Kapsimalis et al. 2008, Minoguchi et al. 2004). Vgontzas et al. (2004) tested the effects of etanercept, a medication that neutralizes TNF-α and is approved for the treatment of rheumatoid arthritis, in eight obese male apneics in a pilot, placebo-controlled, double-blind study during which nighttime polysomnography, MSLT, and plasma levels of IL-6 were obtained. There was a significant and marked decrease in sleepiness in the etanercept group, with significantly increased sleep latency during the multiple sleep latency test compared with placebo. Furthermore, IL-6 levels were significantly decreased after etanercept administration compared with placebo. The effect of this TNF-α blocker on objective sleepiness in patients with OSA was about 3-fold higher than the reported effects of continuous positive airway pressure. Also central administration of an IL-1ß receptor antagonist (Opp & Krueger 1991), or of antibodies directed against IL-1ß, or inhibition of cleavage of biologically active IL-1ß from its inactive precursor reduce spontaneous NREM sleep in normal animals and inhibits the physiological NREM sleep rebound that follows sleep deprivation (Opp & Krueger 1994a, Opp & Krueger 1994b, Imeri et al. 2006).

To our knowledge, studies comparing vigilance-EEG data and cytokine plasma levels do not exist, although this methodological approach would be most appropriate. To date, MSLT data and data derived from circadian cytokine profiles in experimental and clinical-experimental studies are the most objective and appropriate date available regarding the interrelation of objectively measurable wakefulness and cytokine production.

Complexity of cytokine signaling

In principal, cytokines have a mutual activating or suppressing influence on each other. Therefore the action of one cytokine has to be evaluated for this specific cytokine but also in the context of interaction with other cytokines. Additionally, the effect on wakefulness or sleep of the same cytokine, for example IL-1ß, IL-6 or IFN-α, can be the opposite, depending on time after injection, applied dose or amount of production, time of day or route of administration (Krueger et al. 2003).

These complex mechanisms must be taken into account while evaluating experimental studies as well as clinical observations on wakefulness regulation during infectious diseases. A strong activation of the HPA axis including an increased production of the wakefulness-inducing hormone cortisol by an overload of cytokines and the presence of fever, for example, disturb sleep. But a lesser amount of pro-inflammatory cytokines

increases the amount of non-rapid eye movement sleep (NREM) sleep (Kapsimalis et al. 2008, Schuld et al. 2005). Accordingly, diseases with high levels of pro-inflammatory cytokine production are known to be accompanied by sleep disturbance, even though pro-inflammatory cytokines are found to be above all somnogenic in the literature. Examples of such diseases include infectious diseases such as HIV infection (Lerdal et al. 2011), autoimmune diseases such as psoriasis (Carneiro et al. 2011), metabolic diseases such as obesity (Brietzke 2010) and psychiatric diseases such as depression (Himmerich et al. 2008). All of these diseases show sleep disturbances during the night and fatigue during daytime.

HOW CYTOKINES INFLUENCE WAKEFULNESS REGULATION

The influence on important brain regions

The mechanisms of cytokine-induced signaling of the brain are not well understood. Cytokines act through specific receptors in several regions of the CNS, such as the hypothalamus, the basal forebrain (Breder et al. 1988, Saper et al. 2001) and the brain stem (Opp et al. 2005).

Cytokines are relatively large molecules that do not freely pass through the blood brain barrier. Nevertheless, data indicate that cytokine signals are able to reach the brain through humoral, neural and cellular pathways. These pathways are comprised of several non-exclusive mechanisms, including passage of cytokines through leaky regions of the blood-brain barrier, including the choroid plexus and circumventricular organs, active transport via saturable cytokine-specific transport molecules on brain endothelium, activation of endothelial cells, responsible for the subsequent release of second messengers such as NO within the brain parenchyma, transmission of cytokine signals via afferent nerve fibers, such as the vagus nerve, and entry into the brain parenchyma of peripherally activated monocytes (Watkins et al. 1995, Capuron & Miller 2011).

Pro-inflammatory cytokines with sleep-wake-modulating effects have been shown to act on brain regions that are essential for vigilance regulation such as the hypothalamus, the basal forebrain and the brain stem. For example, evidence indicates that IL-1ß alters arousal state-dependent discharge rates of neurons in the preoptic area and basal forebrain (Alam et al. 2004). IL-1ß and TNF-α are expressed in the hypothalamus and IL-1ß and TNF-α mRNAs have been shown to have diurnal cycles in rats (Bredow et al. 1997, Taishi et al. 1998). Regarding the neural communication from the peripheral immune system to the central nervous system via the vagus nerve, there are IL-1ß binding sites on vagal paraganglia (Goehler et al. 1997), and vagal afferents terminate in the nucleus of the solitary tract in the brain stem. As such, immune activation of the peripheral vagus nerve results in rapid communication directly to the central nervous system structures that are important for wakefulness regulation (Opp et al. 2005).

Norepinephrine (NE) diffusing from LC neurons executes additional functions apart from its role as a classical neurotransmitter that are important for arousal. NE negatively regulates transcription of inflammatory genes in astrocytes and microglia (Feinstein et al. 2002). More specifically, NE, can bind to β-adrenergic receptors and activate cAMP-signaling, resulting in an inhibition of the expression of numerous genes involved in inflammation, including NO synthetases, IL-1ß, and TNF-α (Feinstein et al. 2002). Cells affected are astrocytes, microglia, and endothelial cells, which express functional adrenergic receptors (Mori et al. 2002). Therefore, it has been proposed that NE serves also as an endogenous anti-inflammatory agent (Heneka 2010). In turn, TNF-α seems to play a role in apoptotic processes within the LC, which may play a patho-physiological role in cocaine or opiate addiction (Dey & Snow 2007, Dyuizen & Lamash 2009).

The influence on molecular pathways

As mentioned above, adenosine, NO, NF-κB, PGD2, the neurotransmitters γ-aminobutyric acid (GABA), glutamate and norepinephrine, as well as hormones such as GHRH and CRH are important signalling molecules involved in sleep-wake-regulation. They form part of a complex biochemical cascade, initiated for example by pro-inflammatory cytokines such as TNF-α and IL-1ß (Krueger et al. 2001).

For example, TNF-α and IL-1ß could be shown to induce sleep by enhanced production of NO due to activation of NO synthetases (Chen et al. 2004). There is also evidence that one of the functions of IL-1ß is to increase the endogenous production of adenosine. In rat brain slices, application of IL-1ß caused a profound decrease of glutamate transmission, but not GABAergic inhibition which could be prevented by pharmacological blockade of A1 adenosine receptors (A1AR). Further, it was concluded that IL-1ß can effectively modulate glutamate excitation via an adenosine-dependent mechanism (Luk et al. 1999). In other studies, however, IL-1ß was reported to enhance GABA inhibitory effects acting at both pre- and post-synaptic levels (Brambilla et al. 2007). IL-1ß enhances GABA release in preoptic and anterior hypothalamic neurons (Tabarean et al. 2006) and it also enhances GABA-induced post-synaptic responses in different in vivo and in vitro experimental models (Miller et al. 1991, Luk et al. 1999, Serantes et al. 2006, Brambilla et al. 2007). The role of cytokines on other wakefulness-regulating neuro-transmitters such as NE (Dey & Snow 2007, Dyuizen & Lamash, 2009) and serotonin (5-HT) (Li & Ku 2000) may also be of clinical and scientific interest, but the physiological and clinical significance is not clear.
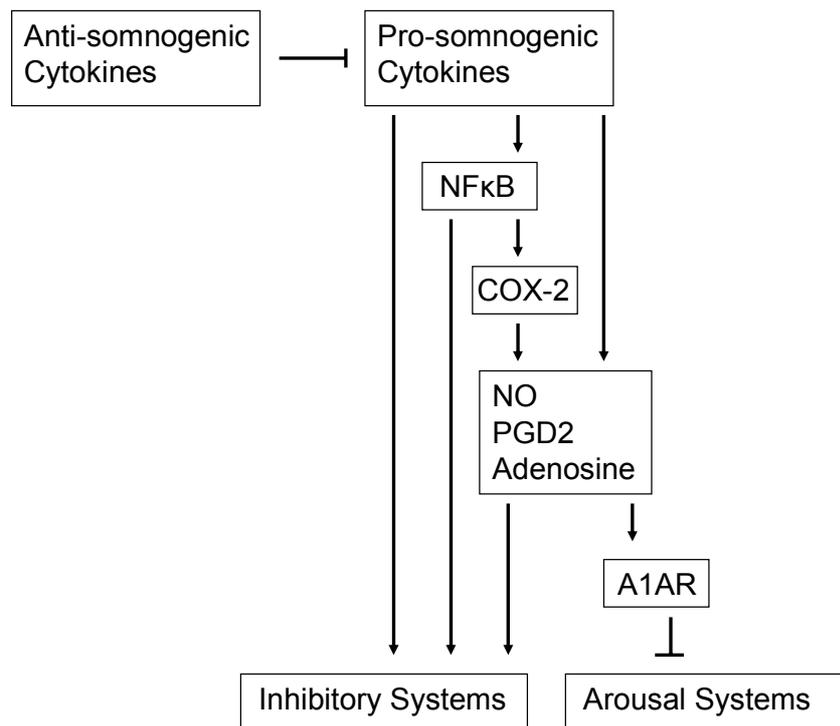
Figure 1. Simplified scheme how cytokines influence inhibitory and arousal systems: Pro-somnogenic cytokines can promote inhibitory systems via direct influence or via stimulating nitric oxide (NO) production, inducing transcription factor nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), cyclooxygenase-2 (COX-2) activity and prostaglandin D2 (PGD2) production. Additionally, stimulation of adenosine receptors A1 (A1AR) leads to a dampening of arousal systems

NFκB is a transcription factor that is activated by IL-1ß and TNF-α. NFκB, in turn, promotes the production of many other substances implicated in sleep regulation including A1AR and cyclooxygenase-2 (COX-2) (Krueger et al. 2007, Ahn et al. 2005). As mentioned before, NFκB is activated within the hypothalamus and cortex by sleep deprivation (Brand et al. 2004, Chen et al. 1999). Therefore it is not surprising that an inhibitor of NFκB inhibits NREMS (Kubota et al. 2000). COX-2 catalyzes the conversion of arachidonic acid to prostaglandin H2, the initial step in the formation of PGs of which PGD2 has been shown to be a sleep inducing factor (Huang et al. 2007).

Finally, the actions of the somnogenic pro-inflammatory cytokines and the sleep-inducing hormone GHRH seem to be linked to each other; e.g., IL-1ß induces GH release mediated via GHRH. Therefore, pro-inflammatory cytokines may also exert some of their sleep-modulating effects via GHRH (Krueger et al. 1999). Figure 1 shows a simplified scheme of how cytokines can influence wakefulness regulation.

DISCUSSION AND PERSPECTIVES

Although a large number of studies exist examining the influence of cytokines on sleep-wake-regulation or sleep architecture, definitive literature on cytokines and how they modulate wakefulness is limited, especially when searching for methodologically excellent studies using objective wakefulness assessment tools such as the MSLT or vigilance-EEG measurement.

Although it seems very clear that pro-inflammatory cytokines have somnogenic properties, these molecules might have opposite effects depending on certain circumstances such as day time and dose.

Within the CNS, several wakefulness-regulating systems coexist. Additionally, we have to face redundancies and overlaps with regard to the cytokines.

Taken together, cytokines seem to play a crucial role at least in modulating major systems responsible for wakefulness regulation. But limitations are that most studies investigated sleep and did not investigate wakefulness, that most studies did not use objective tools to measure wakefulness but psychological questionnaires instead, and that there is no standardized protocol how to measure cytokine production, stimulated cytokine production in-vitro or circadian profiles of cytokine production. Additionally, many knowledge gaps remain in the causal chain from cytokine signalling to changes in wakefulness.

Nevertheless, the theories and data on the mechanisms of action of somnogenic pro-inflammatory cytokines help to understand why psychopharmacological drugs that induce for example TNF-α production such as clozapine, olanzapine, amitriptyline or mirtazapine (Himmerich et al. 2009) also lead to sedation. As

patients with depression show less and later declines into lower EEG vigilance stages under resting conditions than healthy controls and as this finding suggests that depression is associated with a hyperstable vigilance regulation (Hegerl et al. 2011), sedating antidepressants such as amitriptyline or mirtazapine might exert one part of their antidepressant mechanism via induction of somnogenic cytokines leading to sedation and therefore break through the hyperstable wakefulness in depression.

Vice versa, one has to take into account that sleep deprivation or sleep disturbances may enhance pro-inflammatory cytokine production, e. g. TNF-α and IL-6 (Vgontzas et al. 2007, Chennaoui et al. 2011). The majority of patients with major depressive disorder report symptoms of insomnia (Ford & Kamerow 1989, Hamilton 1989), including difficulty initiating and/or maintaining sleep and early-morning awakening (Benca et al. 1992, Harvey 2011). There is robust evidence that insomnia is an independent risk factor for first and recurrent episodes of depression (Perlis et al. 2006, Harvey 2011); and it has repeatedly been shown that various sleep disturbances predict subsequent depresssion (Harvey 2011, Breslau 1997, Weissman 1997). Therefore, one can assume that these sleep disturbances lead to an elevation of pro-inflammatory cytokines. And the elevated cytokine production, in turn, might contribute to the pathophysiology of depression, as pro-inflammatory cytokines such as TNF-α might contribute to the pathogenesis of depression by an activation of the HPA axis, an activation of neuronal serotonin transporters, the stimulation of the indoleamine 2,3-dioxygenase which leads to tryptophan depletion, or by immunologically mediated destruction of neurons (Himmerich et al. 2009) and as these cytokines might lead to sleepiness and subsequent weakness which might share common symptoms with a depressive disorder.

Therefore, the interaction of vigilance and cytokine production may play a significant role for the pathophysiology and therapy of depression. However, as data on objective wakefulness measurements and cytokine production in depression are rare, and long-term studies on cytokine changes from the first appearance of sleep disturbances to the entire manifestation of a depressive disorder are not available, we only want to highlight the possibility that this interaction may be of significance for the development of depression.

CONCLUSION

The interaction of cytokines and wakefulness regulation has not yet been sufficiently examined, but given the results of studies regarding sleep and cytokine production and of preclinical in-vitro studies of the molecular mechanisms triggered by pro-inflammatory cytokines, one has to assume that this topic will be a potential high-yield area of scientific investigation.

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