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Humoral Sleep Regulation; Interleukin-1 and Tumor Necrosis Factor

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Abstract

Two substances, the cytokines interleukin-1 beta (IL1 β) and tumor necrosis factor alpha (TNF α), known for their many physiological roles, for example, cognition, synaptic plasticity, and immune function, are also well characterized in their actions of sleep regulation. These substances promote non-rapid eye movement sleep and can induce symptoms associated with sleep loss such as sleepiness, fatigue, and poor cognition. IL1 β and TNF α are released from glia in response to extracellular ATP. They bind to their receptors on neurons resulting in neuromodulator and neurotransmitter receptor up/downregulation (e.g., adenosine and glutamate receptors) leading to altered neuronal excitability and function, that is, a state change in the local network. Synchronization of state between local networks leads to emergent whole brain oscillations, such as sleep/wake cycles.

I. Introduction

Despite the importance of sleep to our everyday lives, its biochemical regulation continues to confound us. Many studies have provided strong evidence that sleep is regulated, in part, by humoral agents dubbed “sleepregulatory substances” or SRSs (Borbély and Tobler, 1989; Imeri and Opp, 2009; Inoue, 1989; Jouvet, 1984; Kilduff and Peyron, 2000; Krueger, 2008; Krueger *et al.*, 1990, 2008; Obál *et al.*, 2003; Roky *et al.*, 1995). The first discovery of SRSs that accumulated in cerebrospinal fluid during prolonged waking occurred over a century ago (Ishimori, 1909; Legendre and Piéron, 1913).

To be classified as an SRS, a substance must meet several criteria (Borbély and Tobler, 1980; Imeri and Opp, 2009; Jouvet, 1984; Krueger and Obál, 1994). These include (1) the substance and/or its receptor changes with sleep propensity, (2) administration of the substance increases or decreases sleep, (3) blocking the action or inhibiting the production of the substance changes sleep, (4) levels of the substance change during disease states associated with altered sleep, for example, infection, and finally (5) the substance acts on known sleep-regulatory circuits. While there are many substances meeting some of these criteria, including microRNAs, metabolites, hormones, growth factors, transcription factors, and various proteins and their receptors, only a few meet all the required characteristics.

II. Interleukin-1 β and Tumor Necrosis Factor α

Two well-characterized SRSs are the cytokines interleukin-1 beta (IL1 β) and tumor necrosis factor alpha (TNF α). While well known for their contribution to signaling in the peripheral immune system, cytokines and their receptors are constitutively expressed in the central nervous system of healthy organisms, supporting the notion that they have functions beyond immune responses (Opp, 2005; Szelényi, 2001).

Electrophysiological, biochemical, and molecular genetic studies of IL1 β and TNF α demonstrate specific effects on sleep–wake behavior. They seem to promote sleep via similar mechanisms, for example, both activate nuclear factor kappa-B (NF- κ B). Many of their downstream biochemical effectors, for example, adenosine, nitric oxide, nerve growth factor, growth hormone-releasing hormone, and prostaglandins, are also implicated in sleep-regulatory roles in health and disease (reviewed in Churchill *et al.*, 2008; Kapsimalis *et al.*, 2005; Krueger *et al.*, 2008). For instance, injection of IL1 β or TNF α into humans (mimicking their endogenous accumulation during wakefulness or sleep loss) induces symptoms associated with sleep loss, such as sensitivity to kindling (Yi *et al.*, 2004) and pain stimuli (Honore *et al.*, 2006; Kawasaki *et al.*, 2008; Kundermann *et al.*, 2008), depression (Anisman and Marali, 2003; Vollmer-Conna *et al.*, 2004), sleepiness (Moldofsky, 1995; Obál *et al.*, 2003; Tringali *et al.*, 2000), fatigue (Anisman and Marali, 2003; Carmichael *et al.*, 2006; Omdal and Gunnarsson, 2005), and impairments in cognition (Baune *et al.*, 2008; Gambino *et al.*, 2007; Trompet *et al.*, 2008), memory (Banks and Dinges, 2007; Dantzer, 2004; Pickering and O'Connor, 2007), and performance (Banks and Dinges, 2007). Some of these symptoms can be blocked with the administration of cytokine inhibitors (Depino *et al.*, 2004; Larsen *et al.*, 2007; Opp and Krueger, 1991). Chronic sleep disruption is also associated with multiple pathologies such as metabolic syndrome (Hristova and Aloe, 2006; Jager *et al.*, 2007; Larsen *et al.*, 2007), chronic inflammation (Frey *et al.*, 2007; Hu *et al.*, 2003), and cardiovascular disease (reviewed in Yndestad *et al.*, 2007), and IL1 β and TNF α play a role in the etiology of these diseases.

A. Interleukin-1 β

IL1 β is a somnogenic cytokine originally described as an endogenous pyrogen that induced fever in rabbits (Atkins and Wood, 1955). Immunologists working independently described lymphocyte-activating factor that subsequently was recognized as endogenous pyrogen, and both were given the new name interleukin-1. IL1 β is normally produced in response to infection, injury, or immunologic challenge; at minimal concentrations, it causes fever, hypotension, and production of additional proinflammatory cytokines, such as IL6 (Churchill *et al.*, 2008; Dinarello, 2000). IL1 β is a member of the interleukin 1 family that also includes IL1 α and IL1 receptor antagonist (IL1ra) (Gibson *et al.*, 2004). The IL1 family now comprises at least 11 different proteins (IL1F1–11) on the basis of their sequence homology, structure, and receptors (Allan *et al.*, 2005; Barksby *et al.*, 2007). IL1 β transcription may be induced by proinflammatory stimuli such as microorganisms or their products (Konsman *et al.*, 2002) and by proinflammatory cytokines, including type I interferons (Brandwein, 1986), TNF α (Williams *et al.*, 2000), and IL1 β itself (Churchill *et al.*, 2006; Granowitz *et al.*, 1992). Almost all nucleated cells produce IL1 β (Brough and

Rothwell, 2007). IL1 β is produced as a large ~36 kDa (Deak *et al.*, 2005) inactive precursor protein (pro-IL1 β) that requires cleavage by caspase-1 (also known as IL1 β -converting enzyme) to its active form (a 17 kDa protein) (Barksby *et al.*, 2007; Church *et al.*, 2008; Fogal and Hewett, 2008).

IL1 β binds to two receptor subtypes, one of which produces downstream signaling and activation and the other of which lacks an intracellular signaling moiety. Both receptors can also bind IL1 α and IL1 α . The receptor that produces activation is an 80 kDa membrane-bound receptor named IL1-receptor (IL1-R) type 1 or IL1-R1 which interacts with the cytoplasmic protein IL1-R accessory protein to form a complex that leads to the recruitment of adaptor molecules (Fitzgerald and O'Neill, 2000). This signaling can lead to the activation of NF- κ B and mitogen-activated protein (MAP) Kinase. Humoral Sleep Regulation; IL1 & TNF 243 kinase (Trinchieri and Sher, 2007). IL1 β also can bind to the IL1-R2, a receptor that lacks an intracellular signaling domain, and consequently, no signaling is activated, therefore, the IL1-R2 functions as a decoy receptor (Colotta *et al.*, 1993, 1994). In other words, IL1-R2 binds to IL1 β and thereby prevents it from associating with IL1-R1 (Allan *et al.*, 2005). Interestingly, IL1-R1 has a higher binding affinity for IL1 α than for IL1 β or IL1 α allowing IL1 α to act as a strong antagonist, whereas IL1-R2 has a higher affinity for IL1 β than for IL1 α supporting an important role for the receptor in regulating IL1 activity (Colotta *et al.*, 1993, 1994; Re *et al.*, 1996).

B. Tumor Necrosis Factor α

TNF α was first discovered as a product of lymphocytes and macrophages, capable of lysing certain cell types, especially tumor cells (Carswell *et al.*, 1975). TNF α is now associated with many physiological functions in both the normal and diseased body (Bertazza and Mocellin, 2008; Bradley, 2008; Perry *et al.*, 2002). TNF α is involved in synaptic scaling, neurogenesis, cognition, immune system coordination, systemic inflammation, and induction of apoptosis. However, like many other cytokines, TNF α has emerged as an important cell-signaling molecule with diverse roles in many tissues, including the brain. In the brain, TNF α is expressed in neurons, microglia, and astrocytes (Breder *et al.*, 1993; Inoue *et al.*, 2000).

TNF α is synthesized as a membrane-bound homotrimer (made up of 26 kDa monomers), pro-TNF α , that is cleaved by the TNF α -converting enzyme (Solomon *et al.*, 1999; Tracey *et al.*, 2008). After cleavage, the soluble cytokine is released as the 17 kDa form which can interact with TNF α cell-surface receptors. Additionally, membrane-bound pro-TNF α can function as a receptor for TNF α antagonists and as a ligand, binding to TNF α cell-surface receptors. Both actions can lead to the suppression of cytokine expression and apoptosis (Tracey *et al.*, 2008).

There are two TNF α cell-surface receptors, TNF-R1 and TNF-R2. The receptors are structurally related, forming trimeric complexes. However, they differ in their affinity for ligands, signaling mechanisms, and cellular expression (TNF-R1 is expressed on virtually all cell types, while TNF-R2 is usually inducible and expressed only in endothelial and immune cells) (Palin *et al.*, 2007; Tracey *et al.*, 2008). Both receptors lack intrinsic enzymatic activity in their intracellular domains and therefore signal by recruitment of cytosolic

adaptor proteins via protein–protein interaction domains to activate transcription factors such as NF- κ B and members of the MAP kinase pathway (Goeddel, 1999; Ledgerwood *et al.*, 1999). The activation of these transcription factors plays an important role in the induction of many other cytokines and immune-regulatory proteins, in many cases mediating an inflammatory response. In some cases, activation of these transcription factors can induce apoptosis or necrosis (Ledgerwood *et al.*, 1999; Liu, 2005).

III. Cytokine Production and Release

IL1 β and TNF α mRNAs are detectable in various areas of the brain in several species (reviewed by Vitkovic *et al.*, 2000). Because constitutive expression of IL1 β (Medana *et al.*, 1997; Taishi *et al.*, 1997) and TNF α (Bredow *et al.*, 1997) mRNAs is region specific and diurnal, some studies did not find them in normal rodent brains (reviewed by Vitkovic *et al.*, 2000). IL1 β protein is present in many areas in both neurons and glia in normal rat and mouse brains (Bandtlow *et al.*, 1990; Hagan *et al.*, 1993; Lechan *et al.*, 1990; Molenaar *et al.*, 1993; Quan *et al.*, 1998). IL1 β is detectable in the normal human cortex in glia but not neurons (da Cunha *et al.*, 1993a,b), although, in mice, neurons express IL1 β as determined by immunohistochemistry. Neuronal activity stimulated through activation of transfected channelrhodopsin-2 increases IL1 β expression in mouse neurons (Jewett *et al.*, 2011). TNF α protein is found in many areas of the rodent brain (Breder *et al.*, 1993; Ignatowski *et al.*, 1997; Saito *et al.*, 1996). TNF α protein has marked diurnal changes, for example, 10-fold changes in the cortex and hypothalamus, and correlates with mRNA rhythms (Bredow *et al.*, 1997; Floyd and Krueger, 1997). TNF α is found in rat neurons as determined by immunohistochemistry, and like IL1 β , expression is activity dependent. Whisker stimulation increases TNF α expression in the correspondingly activated somatosensory cortical columns (Churchill *et al.*, 2008).

Glia synthesize and exocytose a variety of molecules, including IL1 β and TNF α , that when injected either systemically or into the brain can increase sleep time or intensity (Halassa *et al.*, 2009; Pascual *et al.*, 2005). For example, IL1 β derived from cultured mouse astrocytes increases non-rapid eye movement sleep (NREMS) in rats when administered into the ventricles (Tobler *et al.*, 1984). Astrocytes release IL1 β and TNF α in response to neuronal signals, including extracellular ATP acting at purine type 2 (P2) receptors (Bianco *et al.*, 2005; Krueger *et al.*, 2010; Solle *et al.*, 2001; Suzuki *et al.*, 2004; Verderio and Matteoli, 2011). Microglia also synthesize and release cytokines such as IL1 β and TNF α in response to extracellular ATP, for example, during ischemia or inflammation (Ferrari *et al.*, 1997; Hide *et al.*, 2000; Inoue, 2002).

IV. Cytokines and Sleep

Cytokines have important roles in multiple physiological functions, including sleep regulation (Krueger *et al.*, 2001), memory (Yirmiya and Goshen, 2011), appetite (Andréasson *et al.*, 2007), cerebral circulation (Faraci and Heistad, 1998), temperature regulation (Leon, 2002), and insulin production (Fu *et al.*, 2006). Several cytokines, including the proinflammatory cytokines IL1 α , IL1 β , IL6, IFN α , IFN γ , TNF α , and TNF β , have the capacity to enhance NREMS (reviewed by Krueger and Majde, 2003; Krueger *et*

al., 2001). Two cytokines studied extensively for their relationship with sleep are IL1 β and TNF α (Opp, 2005). Endogenous production of IL1 β and TNF α and conditions that enhance their production, for example, excessive food intake (Hansen *et al.*, 1998) or infectious disease (Toth and Krueger, 1988), promote NREMS (Krueger *et al.*, 2007; Obál and Krueger, 2003). IL1 β and TNF α are constitutively expressed in the brain. In rats, IL1 β and TNF α mRNA and protein levels exhibit a diurnal variation in certain areas of the brain, with higher concentrations correlating with higher sleep propensity (Bredow *et al.*, 1997; Taishi *et al.*, 1997). Furthermore, after sleep deprivation, increases in NREMS as well as increases in IL1 β and TNF α expression in the brain occur (Krueger *et al.*, 2001; Taishi *et al.*, 1998; Takahashi *et al.*, 1997).

The sleep-promoting actions of IL1 β were initially demonstrated in rabbits. Central administration of IL1 β enhances NREMS in this species (Krueger *et al.*, 1983, 1984). Further, intracerebroventricular (ICV) injection with an IL1-R1 fragment, an IL1 β inhibitor, reduces sleep (Takahashi *et al.*, 1999). In rats, enhanced NREMS occurs after ICV injection of low doses of IL1 β (Opp *et al.*, 1991). In contrast, anti-IL1 antibodies or IL1ra reduce spontaneous sleep and inhibit sleep rebound after sleep deprivation (Obál, *et al.*, 1990). Mice display a robust increase in NREMS and suppressed rapid eye movement sleep (REMS) after intraperitoneal injection with IL1 β . These effects are abolished IL1-R1 knockout mice; the knockout mice also have less spontaneous sleep than corresponding controls (Fang *et al.*, 1998). Exogenous administration of IL1 β also increases NREMS in other species such as cats (Susi and Toti, 1989), monkeys (Friedman *et al.*, 1995), and humans (Dinarello, 1991). In humans, plasma IL1 β peaks at slow-wave sleep onset (Moldofsky *et al.*, 1986). The firing rate of hypothalamic sleep-active neurons is enhanced by IL1 β ; it inhibits wake-active neurons (Alam *et al.*, 2004). IL1 β injected into the locus coeruleus (De Sarro *et al.*, 1997) or the dorsal raphe nuclei (Manfridi *et al.*, 2003) promotes NREMS. These results suggest a role for IL1 β in the regulation of physiological sleep (Krueger, 2008).

The somnogenic effects of TNF α were first described after ICV injection of recombinant TNF α into rabbits (Shoham *et al.*, 1987). Intravenous or ICV administration of exogenous TNF α enhances the duration and intensity of NREMS and decreases REMS in this species (Kapás and Krueger, 1992; Shoham *et al.*, 1987). The use of anti-TNF α antibodies or the TNF-soluble receptor attenuates spontaneous sleep and reduces sleep rebound after sleep deprivation (Krueger *et al.*, 2001; Takahashi *et al.*, 1995, 1996). In rats, peripheral administration of TNF α increases NREMS (Kubota *et al.*, 2001). Unilateral microinjection of TNF α into the preoptic area of the anterior hypothalamus or the locus coeruleus increases NREMS in a dose-dependent manner (De Sarro *et al.*, 1997; Kubota *et al.*, 2002; Terao *et al.*, 1998). After intraperitoneal injection of TNF α , mice show a dose-dependent increase in NREMS. This effect is not observed in TNF-R1 knockout mice; they also have significantly less baseline NREMS and REMS than controls (Fang *et al.*, 1997). Finally, in sheep, ICV injection of TNF α results in an increase in NREMS (Dickstein *et al.*, 1999). These results suggest that TNF α also has a role in the regulation of physiological sleep (Krueger and Majde, 2003).

The sleep-regulatory roles of IL1 β and TNF α are closely related to each other (Baracchi and Opp, 2008). For example, IL1-R1/TNF-R1 double knockout mice have a reduced NREMS rebound (compared with wild type) and do not exhibit an REMS rebound in response to sleep deprivation (Baracchi and Opp, 2008). Furthermore, in TNF-R1 knockout mice that are nonresponsive to TNF α , whereas an injection of IL1 β increases NREMS in these mice (Fang *et al.*, 1997). Similarly, the IL1-R1 knockout mice show increased NREMS and decreased REMS after administration of TNF α (Fang *et al.*, 1998).

In addition to increasing time spent sleeping, central injection of IL1 β and TNF α can enhance electroencephalographic (EEG) delta (0.5–4 Hz) power (a measure of sleep intensity), also known as slow-wave activity (SWA), during NREMS but not during REMS or waking. Enhanced SWA is also seen after sleep deprivation (Borbély and Tobler, 1989; Pappenheimer *et al.*, 1975), suggesting that IL1 β and TNF α injections mimic the effects of sleep loss.

V. Cytokines in Sleep Regulation

The dominant paradigm in sleep research posits that sleep is initiated and regulated by subcortical neuronal networks (reviewed in Szymusiak and McGinty, 2008).

The arousal systems, for example, the noradrenergic locus coeruleus, serotonergic dorsal raphe nucleus, cholinergic neurons in the basal forebrain, and histaminergic neurons in the tuberomammillary nucleus, provide activating inputs to the diencephalon, limbic system, and neocortex (Saper, 1987). The hypocretin (orexin) neurons in the perifornical region of the lateral hypothalamus constitute another functionally important arousal regulatory cell group (Peyron *et al.*, 1998). GABAergic neurons with enhanced activity during and just prior to sleep are found in the ventrolateral preoptic area of anterior hypothalamus (Sherin *et al.*, 1996, 1998; Szymusiak *et al.*, 1998). These neurons are posited to impose sleep on the rest of the brain by their inhibition of the various arousal/activating systems (reviewed by Saper *et al.*, 2005).

There are many well-known phenomena that cannot be explained by the top-down sleep-regulatory center-imposed sleep paradigm. The most substantial evidence against a necessary top-down sleep-regulatory mechanism comes from lesion studies; if an animal or human survives a brain lesion (e.g., stroke) in any location, it will sleep. There are no reported cases of a complete loss of sleep, including in patients with fatal familial insomnia (Montagna, 2005). The top-down paradigm has little explanatory value for sleep homeostatic mechanisms or how performance is restored during sleep. The existence of parasomnias, such as sleepwalking, indicates that areas of the brain can be awake while other areas are asleep (Mahowald and Schenck, 2005). Many species of birds and marine mammals exhibit unihemispheric sleep (Lyamin *et al.*, 2002, 2008; Rattenborg *et al.*, 2001). Finally, isolated cortical islands retaining their blood flow but no afferent projections show periods of high-amplitude delta waves measured from the cortical surface (Kristiansen and Courtois, 1949).

Such considerations led to the theory that sleep is a local use-dependent phenomenon. The functional states (i.e., asleep or awake) of different parts of the brain can vary. For example,

dolphins do not exhibit high-amplitude EEG slow waves simultaneously in both cerebral hemispheres (Mukhametov *et al.*, 1977). During a visual discrimination task, when a monkey becomes drowsy, but is still behaving, some neurons in the cortical visual receptive fields exhibit the burst-pause sleep-like pattern before others as the animal enters sleep (Pigarev *et al.*, 1997). Which neurons switch to the burst-pause pattern depends on their topographic location within their receptive field, indicating that the transition from wake to sleep is a local network phenomenon. Similarly, using surface-evoked response potentials to characterize cortical column state, Rector *et al.* (2005) demonstrated that individual columns semiautonomously oscillate between sleep- and wake-like states. The duration of the localized sleep-like state of a cortical column is dependent on its prior wake-like state duration, suggesting that the local functional state of the column is use-dependent and homeostatic (Rector *et al.*, 2009).

Other studies also suggest the use-dependent regulation of local sleep. For example, during the first NREMS episode after a hand is stimulated prior to sleep by vibration, the EEG SWA is enhanced in the somatosensory cortex contralateral to the stimulated hand as compared to the ipsilateral side (Kattler *et al.*, 1994). Cerebral blood flow during sleep is increased in areas which are disproportionately stimulated during prior waking (Maquet, 2001). The neuronal electrical firing in the cortex and hippocampus during sleep replays the activation pattern learned during a waking task (Ji and Wilson, 2007). After a special motor-learning task just prior to sleep, the cortical area activated by this learning task has enhanced subsequent EEG SWA as compared to the unstimulated regions (Huber *et al.*, 2004).

The use-dependent regulation of sleep is, at least in part, mediated by the SRSs that are produced and released locally in response to the neuronal and glial activity during wakefulness. For instance, in rats, stimulation of whiskers leads to increased expression of TNF α in the corresponding cortical columns (Churchill *et al.*, 2008). When TNF α is applied directly to the cortex unilaterally, EEG SWA is enhanced on the side of injection (Yoshida *et al.*, 2004), and the sleep-like state of the underlying cortical column is increased (Churchill *et al.*, 2008). In addition, unilateral application of a TNF α small-interfering RNA to the cortex inhibits local EEG SWA and neuronal TNF α expression (Taishi *et al.*, 2007). Collectively, these experiments suggest that the production of SRSs depends on the prior activity of the cortical columns, and the functional states of cortical columns are affected by the SRSs. These studies support the theory that sleep is initiated at a local network level in the circuits most active during prior waking. Whole organism sleep is posited to emerge with the synchronization of local network state changes orchestrated in part by the known sleep-regulatory circuits (Krueger *et al.*, 2008; Roy *et al.*, 2008).

A mechanism linking cellular activity to sleep is based on extracellular adenosine triphosphate (ATP) and cytokines. ATP is released into the extracellular space during neuro and gliotransmission (reviewed in Burnstock, 2006, 2007; Halassa *et al.*, 2009). Extracellular ATP induces the release of SRSs like IL1 β and TNF α from glia via P2 receptors (reviewed by Bianco *et al.*, 2005; Hide *et al.*, 2000; Krueger *et al.*, 2010; Solle *et al.*, 2001; Suzuki *et al.*, 2004; Verderio and Matteoli, 2011). Thus local levels of SRSs reflect prior local network activity. These substances can then bind to receptors of nearby neurons, directly altering electrical activity (fast process) and altering gene transcription and

translation (slow process), leading to changes in receptor populations such as AMPA and adenosine receptors (reviewed by Obál and Krueger, 2003). Extracellular ATP can also be hydrolyzed by ectonucleotidases releasing extracellular adenosine that in turn acts on adenosine receptors (Fields and Stevens, 2000). All these processes can alter the responsiveness of neurons and their input–output relationships, leading to state changes and ultimately sleep.

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