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# Chronic Rhinosinusitis and Sleep: A Contemporary Review

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## Abstract

**Background—**Patients with chronic rhinosinusitis (CRS) exhibit centrally mediated behavioral changes commonly referred to as sickness behavior. Sleep alteration is a component of sickness behavior which is estimated to affect up to 70 million patients annually. Patients with CRS have poor sleep quality, and little is known about the underlying etiology and pathophysiology. This narrative review aims to further organize and present the current knowledge associating sleep and CRS.

**Methods—**A literature search was conducted of the OVID MEDLINE database using key search words including: “chronic rhinosinusitis”, “sleep”, “sleep disorders”, and “sleep dysfunction”. Additional keywords “nasal obstruction”, “nasal polyp”, and “fatigue” were identified and utilized to further delineate relevant articles.

**Results—**The articles that specifically addressed sleep and CRS were dissected and presented as follows; 1) chronic rhinosinusitis and sleep, 2) chronic rhinosinusitis and fatigue 3) chronic rhinosinusitis, nasal obstruction and sleep, 4) pathophysiology of sleep in chronic rhinosinusitis (cytokines in both sleep and chronic rhinosinusitis and their association to the neuroimmune biology of chronic rhinosinusitis).

**Conclusions—**Patients with CRS have sleep dysfunction that is associated with their disease severity and overall quality of life. The etiology of sleep dysfunction in CRS is most likely multifactorial. Increasing evidence suggests sleep dysfunction in patients with CRS is partly due to the inflammatory disease process, and sleep physiology in patients with CRS may be actively regulated by the inflammatory component of the disease.

### Keywords

Sinusitis; sleep; fatigue; rhinology; review

## INTRODUCTION

As the sun descends, we enter another state of consciousness. This phenomenon, sleep, occupies a third of our lives, yet most of us do not ponder sleeps’ origin or function until it is disturbed in disease states such as chronic rhinosinusitis (CRS). Throughout history, philosophers and physicians have struggled to understand sleep in both health and disease.

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Hippocrates hypothesized that sleep occurred due to heat loss from extremities into the core of the body while Aristotle suggested that stomach vapors produced during digestion are transported throughout the body to bring about sleep. It is now established that sleep is a component of sickness behavior which is an actively regulated process that may become maladaptive leading to sleep dysfunction.

As a component of health and disease, poor sleep is now widely investigated and estimated to affect up to 70 million patients annually.[1] In addition, many chronic diseases, such as CRS, have a high prevalence of pathological sleep dysfunction greater than that typically identified in the general population.[2] Sleep dysfunction has staggering effects on daily performance, quality-of-life (QOL), disease severity, healthcare costs, and mortality.[3] Given that up to 16% of the population of the United States has CRS, sleep dysfunction in CRS is an important concept for patients, physicians, and policymakers alike.

Patients with CRS have reduced sleep quality, although the underlying etiology or pathophysiology has received little attention.[2] The mechanism of sleep impairment in CRS is most likely multi-factorial including, but not limited to, nasal obstruction,[4] efferent and/or afferent neural signaling, or brain-immune signaling via immune mediators such as interleukin-1 (IL-1) and tumor necrosis factor (TNF).[5–7] Accumulating evidence is elucidating the sophisticated and intertwined communication between the central nervous system (CNS) and the immune system. This bidirectional communication elicits “sickness behavior” commonly seen in animals and is thought to explain, in part, the adaptive responses to infection such as increased sleepiness.[7–9] Furthermore, sleep disruption and altered inflammatory cytokine levels are associated with CRS and other chronic inflammatory diseases [10–20], providing further insight into the biochemical regulation of sleep. This review aims to organize and present our current understanding of the association between CRS and sleep dysfunction. We further explore the physiology of sleep in disease as it relates to CRS.

## METHODS

There are very few published studies that have specifically addressed sleep disturbance in patients with CRS. An OVID MEDLINE database search (1946–2013) was performed limiting the articles to the English language and using the keywords “chronic sinusitis” OR “rhinosinusitis” OR “chronic rhinosinusitis” AND “sleep” OR “sleep disorders” OR “sleep dysfunction”. This search revealed 377 articles. Titles and abstracts were reviewed for relevance. Those studies investigating sleep and CRS were deemed appropriate for this narrative review. An additional Ovid MEDLINE search was performed adding the keywords “nasal obstruction” OR “nasal polyp” OR “fatigue” to our original query which revealed 2 additional articles.

Literature findings were organized and discussed as associations between CRS, sleep, fatigue, and nasal obstruction. The biochemical/humoral regulation of sleep and CRS was reviewed separately followed by discussion of those immune mediators known to have dual roles both in the pathophysiology of CRS and their associated somnogenic activity. Therefore, this review article is organized into the following sections:

1. Chronic Rhinosinusitis and Sleep
2. Chronic Rhinosinusitis and Fatigue
3. Chronic Rhinosinusitis, Nasal Obstruction, and Sleep
4. Pathophysiology of Sleep in Chronic Rhinosinusitis
    a. Cytokines and Sleep Mechanisms

**b.** Cytokines Related to Chronic Rhinosinusitis and Sleep

**c.** Chronic Rhinosinusitis and the Neuroimmune Biology of Sleep

# RESULTS

## Chronic Rhinosinusitis and Sleep

Patients with CRS commonly describe sleep abnormalities, although this has not been thoroughly investigated. The vast majority of studies evaluating sleep and its role in CRS have been accomplished through the use of CRS disease-specific instruments, such as the Rhinosinusitis Disability Index (RSDI),[10,11] the Sinonasal Outcomes Test (SNOT-22),[12] and the Rhinosinusitis Outcome Measure-31 (RSOM-31).[13] Sleep was found to be one of the most severely affected domains in the RSOM-31 in patients with CRS.[13] Additional insight into sleep dysfunction has come from use of the RSDI and SNOT-22 surveys, which include sleep-specific survey items. For instance, early work by Benninger et al. using the RSDI demonstrated sleep improvement in patients with CRS following sinus surgery.[10] These CRS disease-specific studies demonstrate that sleep impairment is a substantial concern in patients with CRS.

There are limited studies prospectively evaluating sleep as it relates to CRS using sleep validated instruments such as the Epworth Sleepiness Scale (ESS)[14], Calgary Sleep Apnea Quality of Life Index[15] or the Pittsburgh Sleep Quality Index (PSQI).[16] A recent prospective multi-institutional investigation demonstrated that patients with CRS have impaired quality of sleep as measured by the PSQI survey. Patients reporting poor sleep were more likely to be female, have comorbid depression and abuse tobacco compared to patients reporting good sleep quality. Poor sleep quality did not correlate to disease severity as measured by endoscopy or CT staging, but was significantly correlated with disease-specific QOL, even after eliminating sleep-related questions from these instruments.[2] It is not yet known if improving CRS disease-specific QOL or disease severity can improve sleep in patients with CRS.

In summary, patients with symptomatic CRS have a high prevalence of sleep pathology. The relationship between sleep dysfunction and QOL in CRS is likely bi-directional, whereby disability predicts worse sleep and worse sleep may influence QOL. Further investigation into this relationship may provide insight into the function of sleep in both health and disease and ultimately result in treatment options for patients with CRS reporting sleep dysfunction.

## Chronic Rhinosinusitis and Fatigue

Often used in a similar sense by both patients and physicians alike, the terms “sleepiness” (sleep dysfunction) and “fatigue” can clearly be distinguished, as sleep dysfunction does not always correlate with a subjective feeling of fatigue.[17] Likewise, fatigue is a state of sustained exhaustion resulting in difficulty performing physical and mental tasks, which sleep alone cannot necessarily alleviate.

Fatigue and sleep dysfunction are two components of sickness behavior that can present simultaneously in the same patient, resulting in significant detriment to QOL.[18] Therefore, the inter-relationship between sleep and fatigue may be significant in patients with CRS. Sleep complaints and fatigue are two of the most debilitating symptoms reported by patients with CRS.[19] Both sleep quality and fatigue are associated with disease-specific QOL in patients with CRS.[2] A systematic review and meta-analysis demonstrated significant improvement in fatigue in patients with CRS following endoscopic sinus surgery.[20,21] It is not known whether the improvement in fatigue following endoscopic sinus surgery

improves patients' sleep dysfunction. However, it is likely that improvement in fatigue would result in improvement of sleep dysfunction, as higher levels of fatigue are associated with poor sleep quality,[22] disturbed circadian rhythms, and immune activation.[23,24] Further studies need to characterize both sleep and fatigue in patients with CRS, as fatigue is likely a confounding factor in regards to sleep disturbance and needs to be evaluated by systematically investigating both conditions.[25]

## Chronic Rhinosinusitis, Nasal Obstruction, and Sleep

The nose accounts for greater than 50% of the total resistance of the upper airway. Early studies evaluated the effects of nasal obstruction on sleep by artificially inducing occlusion and found significantly increased number of apneas and cortical arousals.[26,27] These early studies cemented the theory that nasal obstruction may predict sleep disordered breathing (SDB) and microarousals. SDB subsequently was thought to reduce sleep quality, thereby affecting daytime sleepiness and performance. However, the relationship between nasal obstruction, sleep quality and SDB in the literature is sometimes conflicted and continues to lack clarity.[28–30]

Nasal obstruction may play a role in sleep dysfunction in patients with CRS. For instance, patients with nasal obstruction related to nasal polyposis have a 2-fold higher risk of sleep dysfunction.[4] As such, patients with CRS and nasal obstruction due to nasal polyposis had significant improvement in nasal resistance and a mean reduction in excessive daytime sleepiness following endoscopic sinus surgery. However, improving nasal resistance did not significantly improve the apnea hypopnea index (AHI) in patients with CRS with nasal polyps.[31] This data suggests that *subjective* measures of sleep dysfunction do not correlate with *objective* measures of sleep dysfunction. In addition, these studies imply that nasal obstruction is only partially contributing to sleep dysfunction in patients with CRS.

Nasal congestion and obstruction are commonly reported symptoms in patients with CRS and allergic rhinitis (AR).[32,33] There is a paucity of literature evaluating nasal obstruction and sleep as it specifically pertains to CRS. In contrast, a larger body of evidence exists linking nasal obstruction with sleep dysfunction in AR, such that patients with AR and nasal obstruction have increased periodic breathing during sleep, snoring, microarousals and chronic non-restorative sleep.[34,35] Although higher levels of nasal resistance in AR appear to increase the risk for moderate to severe SDB by 1.8 times, it did not significantly correlate with increasing levels of AHI.[29] Nasal obstruction and/or nasal congestion in AR appear to be playing a role in sleep disruption that has not been systematically evaluated in patients with CRS. In summary, AR may partially contribute to and exacerbate both nasal obstruction and sleep dysfunction in patients with CRS.

Therapies aimed at relieving nasal obstruction have been shown to improve nasal resistance and sleep quality. However, reported outcomes and definitions of surgical success are inconsistent in the literature making it difficult to draw definitive conclusions. Evidence does suggest that nasal surgery can improve postoperative sleep quality in some patients.[36] For example, septoplasty and inferior turbinate reduction has been shown to improve snoring in up to 86% of patients[37] with associated improvement in nasal breathing by increasing nasal air temperature and humidity 4–6 months after surgery.[38] However, a recent meta-analysis assessed the effects of nasal surgery on SDB and found that nasal surgery does not improve objective sleep indices.[39]

In contrast to objective measures, treatment to address structural nasal defects has been shown to improve subjective measures of sleep quality. For example, correction of an obstructed nasal airway significantly improves disease-specific and general QOL in adult patients with obstructive sleep apnea 3 months after surgery.[40] Medical management with

nasal corticosteroids has been shown to improve subjective sleep[41,42] by reducing daytime sleepiness and fatigue,[43,44] significantly lowering AHI,[45] improving sleep quality,[46] but insufficiently improving objective sleep quality[41,45] or daytime sleepiness in chronic fatigue syndrome.[47] In contrast to these studies, one prospective multicenter study demonstrated that the use of intranasal steroids was not associated with improved sleep quality.[48]

In summary, the cumulative evidence suggests that nasal surgery is unreliable in improving objective measures of sleep quality but may improve subjective, patient-reported measures of sleep quality. Even less clear is whether nasal obstruction, addressed by surgery or medical management can improve sleep function and disease-specific QOL in patients with CRS.

The association between nasal obstruction and sleep dysfunction in patients with CRS remains unclear. Nasal obstruction has been shown to play a role in sleep disruption in AR and conclusions have been inferred to patients with CRS. We acknowledge that AR is a separate disease process with differing etiology, cytokine profile and possibly very different sleep mechanisms. Future studies are needed to further evaluate the role of nasal obstruction and sleep dysfunction in patients with CRS.

## Pathophysiology of Chronic Rhinosinusitis and Sleep

**Cytokines and Sleep Mechanisms—**The concept of sleep regulator substances (SRSs) influencing sleep at the molecular level was developed over 100 years ago when Ishimori transferred cerebral spinal fluid (CSF) from sleep - deprived dogs to normal dogs, thereby inducing sleep.[49] The isolation and characterization came many years later when the first substance was isolated in the 1970's and identified in the 1980's as a muramyl peptide. Muramyl peptides are components of microbial cell walls and contribute to our current knowledge of the biochemical regulation of sleep through what are termed SRSs.

Substances considered SRSs must meet criteria that have been previously published.[7,50] Briefly: 1) the substance and or its receptor oscillates with sleep propensity; 2) sleep is increased or decreased with administration of the substance; 3) blocking the action or inhibiting the production of the substance changes sleep; 4) disease states, such as infection associated with altered sleep, also change levels of the putative SRS; and finally, 5) the substance acts on known sleep regulatory circuits. Many substances that have been linked to CRS meet some of these criteria including pro-inflammatory cytokines, hormones, and bacterial cell wall products, but only a few meet all the required characteristics to be considered a SRS. Some of the key substances involved in both the biochemical regulation of sleep and CRS are summarized in Table 1. The best characterized substances involved in regulating non-rapid eye movement sleep (NREMS) include IL-Iβ, TNF-α, and growth hormone releasing hormone (GHRH). Nitric oxide (NO) and prolactin meet criteria for regulating rapid eye movement sleep (REMS). The ensuing discussion will primarily focus on IL- Iβ and TNF-α both linked to the physiological and pathological humoral regulation of sleep and the inflammatory cascade in CRS, followed by a limited discussion on other mediators linked to the biochemical regulation of sleep and CRS.

Peripherally produced cytokines or growth factors provide a signal to the brain that an infection is occurring, and thereby stimulate sleep through five main pathways including: 1) stimulation or alteration of afferent transmission (e.g., through the vagus) with consequential signaling to the brain; 2) transport across the blood brain barrier (BBB) through the circumventricular organs; 3) altering the level or activity of another substance that signals the brain; 4) altering the blood brain barrier; 5) direct passage across the BBB (Figure 1).[51,52] The fact that cytokines act in the brain to induce physiological adaptations may begin to help explain sickness behavior in patients with CRS.

**Cytokines related to Chronic Rhinosinusitis and Sleep—**We are gaining a better understanding of the molecular crosstalk that occurs between cytokines released by the immune system and the CNS. Cytokines up-regulated in response to infection and inflammation mediate CNS responses, including excess sleep via activation of the central nervous system possibly through the somatotropic and hypothalamic-pituitary-adrenal (HPA) axes.[9] Two of the most studied inflammatory cytokines involved in CRS include IL-Iβ and TNF-α, which are well known SRSs.

IL-1β and TNF-α are up-regulated in patients with CRS and regulate the inflammatory cascade in chronic inflammation.[6] TNF-α and IL-1β are produced by macrophages in response to stimuli such as bacterial lipopolysaccharide (LPS) [53–55] while TNF-α antagonist reduce inflammatory activity and nasal mucus hypersecretion.[56] Single nucleotide polymorphisms (SNPs) in IL-1β and TNF-α have been associated with CRS and nasal polyps.[57,58] In addition, the TNF-α induced protein 3 superfamily gene was found to be associated with severe CRS.[59] Karosi et al. investigated the inflammatory changes in patients with CRSwNP by measuring TNF-α receptors via immunofluorescent assays. These patients had increased expression of type I TNF-α receptor (TNFR-I) and type II TNF-α receptor (TNFR-II).[60] TNF mRNA and protein levels are elevated in nasal polyp patients, which subsequently up-regulates CC chemokine ligand 2 (CCL2). The up-regulation of CCL2, represents one pathway in which TNF-α stimulates monocytes, thereby, regulating the pathogenesis of CRSwNP.[61] In patients with CRS, mucosal levels of IL-1β, IL-6, IL-8, and TNF-α were all found to be elevated compared to controls.[62] Systemic steroid treatment significantly reduces levels of TNF-α, IL-1β and corresponding inflammation.[62]

**Chronic Rhinosinusitis and the Neuroimmune Biology of Sleep—**There is a considerable amount of literature implicating the pro-inflammatory cytokines TNF-α and IL1-β in sleep regulation.[63] TNF-α and IL1-β can signal via juxtacrine, autocrine, paracrine and even endocrine signaling pathways. Pro-inflammatory cytokines act within the CNS to induce sickness behavior (Figure 1). In humans, sleep loss and altered pro-inflammatory cytokine levels are associated with fatigue,[64,65] pain,[66] depression,[67] impaired cognition[68] and memory loss, [69] all of which are comorbidities of CRS.

Cytokines can exert their actions only if they are biologically active and if their receptors are present on target cells. For instance, current data shows: (1) IL-1 protein is present in normal brain and found primarily in neurons and glia; (2) IL-1 converting enzyme is found in normal brain, implicating biologically active IL-1; (3) IL-1 receptor proteins have a localized distribution in the brain primarily in the hypothalamus and hippocampus; (4) induction of NREMS by IL-1 and inhibition of NREMS by IL-1 antagonists; and (5) changes in IL-1 and its mRNA is associated with sleep.

TNF and IL-1 induce sleep when administered centrally or systemically.[7] IL-1β increases NREMS in non-primates.[5,70–72] At lower doses IL-1β increases sleep, whereas high-dose inhibits sleep.[5] The higher doses of IL-1β are thought to activate negative feedback mechanisms including corticotrophin releasing hormone (CRH). Antagonists (e.g., antibodies and soluble receptors) of IL-1β and TNF-α decrease sleep and rebound after sleep deprivation, whereas substances that activate or up-regulate IL-1 (e.g., murayml dipeptide) increase sleep.

IL-1β and TNF-α mRNA in the brain are elevated during sleep and lower during wakefulness, and correlate with sleep propensity. These brain levels also increase during sleep deprivation. TNF and IL-1 proteins also vary with the sleep-wake cycle and correlate to sleep propensity.[73,74] Additionally, plasma levels of TNF in humans correlate with EEG delta power (a measure of sleep intensity).[75] Mice lacking the IL-1 Type 1 receptor sleep

less during dark hours than do controls,[76] whereas mice lacking the TNF-55-kD receptor have attenuated NREMS during daylight hours.[77]

TNF and IL-1 exert their sleep-promoting actions on sleep-active neurons. IL-1 receptors are expressed in the pre-optic area/anterior hypothalamus.[76] Thus, IL-1β stimulates sleep-active neurons and inhibits wake-active neurons in the POA/anterior hypothalamus.[78,79] Furthermore, microinjection of TNF-α into the POA and IL-1 into the subarachnoid space underlying the ventral surface of the rostral basal forebrain enhances NREMS.[80,81]

Other cytokines and growth factors linked to CRS have also been connected to sleep regulation (Table 1). Histamine has well known central effects on sleep regulation, although it may also play a role locally. Histamine and the H-1 receptor have been localized to the CNS and regulate the sleep-wake-cycle and arousal.[82] One of the most common side effects of the first generation antihistamines includes drowsiness due to binding H-1 receptors centrally. Locally, histamine causes vasodilatation, vascular permeability and mucus production, which may impair sleep through nasal obstruction.

Cysteinyl leukotrienes (CystLTs) are well known for their effects locally on vascular permeability, mucus secretion and rhinorrhea, thereby causing nasal obstruction. Interestingly, nasal challenge studies with leukotrienes show at least a 10-fold greater potency of inducing nasal obstruction than histamine.[83,84] Leukotrienes directly injected into the CNS have been shown to increase slow wave sleep[85] and their expression has a diurnal variation.[86]

Cytokines, such as IL-1, IL-4, IL-6, IL-10 and IL-13 are released locally in CRS and have been linked to sleep regulation through their central effects. Of these IL-1 is the only interleukin that has met the published criteria of a somnogenic substance. We found that elevated expression of IL-4 and IL-13 was associated with worse sleep quality in patients with CRS.[87] Likewise, increased expression IL-4 and IL-10 are correlated with sleep dysfunction in CRS.[88] Intracerebral injections of IL- 4, IL-10 and IL-13 all decrease NREM sleep.[89–91] Interestingly, IL-4 has been shown to play a critical role in higher brain functions including sleep, memory and learning. Caregivers with high peripheral circulating levels of IL-6 perceived their sleep poorer than caregivers with low levels as measured by the PSQI.[92] Low-grade chronic systemic inflammation as measured by elevated IL-6 levels is associated with lower nighttime sleep[93] and its expression has diurnal variation.[94]

## CONCLUSION

Patients with CRS routinely demonstrate poor disease-specific and general QOL which may, in part, be secondary to sleep dysfunction. Nasal obstruction may be playing a role in sleep disordered breathing and/or overall sleep quality. Fatigue is a possible cofounder to sleep dysfunction in patients with CRS and needs to be independently evaluated and addressed. Immune mediators or “cytokines” convey to the brain that inflammation or infection has occurred in the periphery, although the mechanism of this communication is still unknown. Clinical evidence is accumulating to further illuminate the possibility that the subjective complaints of patients with CRS are either due to disease itself or the release of inflammatory mediators that are acting in the brain. Further investigation into this complex interaction will make it possible to design treatment strategies by blocking immune mediators, their downstream signaling molecules, or directly targeting these mediators.

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## SUMMARY

- Patients with CRS commonly report poor sleep quality that significantly correlates with poor QOL. Until recently, few studies have prospectively evaluated sleep in patients with CRS. Future work needs to specifically evaluate sleep in patients with CRS both utilizing patient-based and objective measures in a prospective manner.
- Patients with CRS report increased levels of fatigue that have profound effects on QOL. Fatigue can be considered a confounder when evaluating sleep function in CRS and needs to be considered and controlled.
- Patients with CRS commonly report nasal obstruction which may be playing a role in sleep dysfunction. It is not yet known whether improving nasal obstruction improves dysfunctional sleep in CRS, however data are accumulating that suggest improving nasal obstruction improves patient-perceived quality of sleep.
- IL-1 and TNF expression and actions in the CNS have been implicated in the regulation of sleep and have been strongly associated with the pathophysiology of CRS. Injection of IL-1 increases sleep, antagonists decrease sleep, substances that activate or upregulate IL-1 increase sleep, substances that inhibit IL-1 in turn decrease NREM sleep, levels of protein and mRNA are diurnal and correlate to sleep propensity, mice with mutated IL1-R sleep less and sleep deprivation increases IL-1.
- There are many other cytokines which have the capacity to enhance NREMS; the list includes IL1-α, IL2, IL15, IL18, acidic fibroblast growth factor (aFGF), nerve growth factor (NGF), TNF-β, IFN-gamma, EGF, and BDNF.
- The mechanisms by which cytokines signal the CNS to cause sickness behavior in patients with CRS are unknown. Prospective studies examining systemic and local cytokine profiles and their association to sickness behavior in patients with CRS will be instrumental in further delineating the complex neuro-immune interactions.

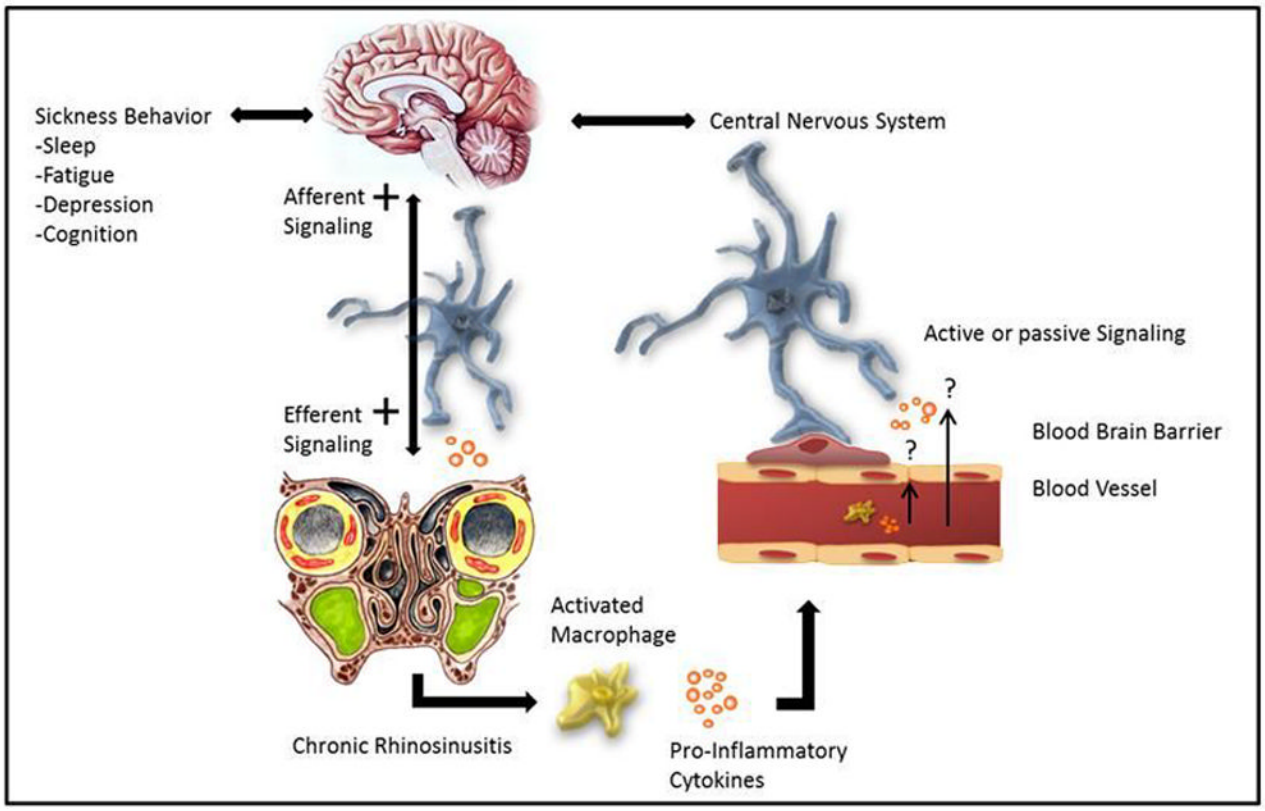


**Figure 1.**

Increased somnolence is an important component of sickness behavior and evidence demonstrates that inflammatory mediators are instrumental in eliciting these symptoms via central neuronal signaling. The pro-inflammatory cytokines interleukin (IL)-1β and tumor necrosis factor (TNF)- α released in chronic rhinosinusitis (CRS) are involved in the normal physiological regulation of sleep. The mechanisms by which local inflammatory cytokines might signal the central nervous system in patients with CRS to induce sickness behavior is unknown. However, preliminary evidence suggests they may: 1) Access or signal the brain via transport across the blood brain barrier (BBB), through the circumventricular organs (subfornical organ, vascular organ of the laminar terminalis, median eminence, intermediate and posterior lobes of the pituitary, pineal gland, subcommissural organ and the area postrema), 2) Act locally, as opposed to systemically, through the stimulation or alteration of afferent neuronal transmission, 3) Alter the level or activity of another substance that signals the brain, and/or 4) Act through direct passage across the BBB through molecular transporters.

IL-1β, Interleukin-1 *beta*; TNF-α, tumor necrosis factor-alpha.

## Table 1

Mediators implicated in non-rapid eye movement sleep, rapid eye movement sleep, and chronic rhinosinusitis.

| Somnogenic Substances/Immune Mediators | Effects NREMS | Effects REMS | CRS | References |
|---|---|---|---|---|
| Interleukin-1 | ↑↔↓ | | + | Krueger[7], Lennard,[62] Mullol[95] |
| Interleukin-1 Receptor Antagonist | ↓ | | | Opp [96] |
| Interleukin-2 | ↑ | | + | Kubota[97], Selezn'ov [98] |
| Interleukin-4 | ↓ | | + | Krueger[7], Kushikata[90], |
| Interleukin-8 | ↑ | | + | Selezn'ov,[98] Garcia-Garcia[99], Mullol[95], |
| Interleukin-6 | ↑↔↓ | | + | Bauer[100], Vgontzas[94], Hogan[101], Ghaffar[102] |
| Interleukin-10 | ↓ | | + | Krueger[7], Kushikata[89], Opp[103], Toth[104], Jyonouchi [105] |
| Interleukin-13 | ↓ | | + | Kubota[91], al Ghamdi,[106] Reh[107] |
| NF-kβ | ↑ | | + | Kubota,[108] (inhibitor attenuates IL1 sleep), Xu[109] |
| Interleukin-15 | ↑ | | | Kubota[97] |
| Interleukin-18 | ↑ | | + | Kubota,[110] Okano[111] |
| Inferferon alpha | ↑↔↓ | ↓ | | Bohnet[112] |
| Interferon gamma | ↑ | | + | Kubota,[113] Shin[114] |
| Tumor Necrosis Factor | ↑ | | + | Krueger,[7] Kubota,[63,80] Lennard[62] |
| Soluble tumor necrosis factor receptor | ↓ | | | Kubota[113] |
| Tissue Growth Factor Beta | ↓ | | + | Kubota,[91] Kuo[115] |
| Histamine | ↓ | | + | Tashiro,[82] |
| CystLT | ↑ | | + | Okuda,[83] Sri-Kantha,[85] Perez-Novo [116] |
| TLR | ↑ | ↓ | + | Wisor,[117] Sartorius,[118] Lane[119] |
| Prostaglandin | ↑↔↓ | ↑ | | Sri Kantha,[85] Hayaishi[120], Urade[121], Krueger[122] |
| Prolactin | | ↑ | + | Zhang,[123] Obal,[124] Platt[125] (prolactin-induced protein) |
| Nitric Oxide | ↑ | ↑ | + | Chen,[126] Cespuglio,[127] Zhang[128] |

NREMS, non-rapid eye movement sleep; REMS, rapid eye movement sleep; CRS, chronic rhinosinusitis; NF-kB, nuclear factor kappa beta; CystLT, cysteinyl-leukotriene; TLR, toll-like receptor; relative mean changes in sleep increase (↑), decrease (↓) or varied effect (↔)