Nature and Science of Sleep

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REVIEW

Mutual Influence Between Allergic Rhinitis and Sleep: Factors, Mechanisms, and interventions—A Narrative Review

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Abstract: Patients with allergic rhinitis (AR) have a high incidence of sleep disorders, such as insomnia, which can easily exacerbate nasal symptoms. The aggravation of nasal symptoms further promotes the deterioration of sleep disorders, forming a vicious cycle. Severe cases may even trigger psychological and neurological issues, such as anxiety, depression, and cognitive impairment, causing significant distress to patients, making clinical diagnosis and treatment difficult, and increasing costs. Furthermore, satisfactory therapeutics remain lacking. As the pathogenesis of AR-associated sleep disorders is not clear and research is still insufficient, paying attention to and understanding AR-related sleep disorders is crucial in clinical practice. Multiple studies have shown that the most crucial issues in current research on AR and sleep are analyzing the relationship between AR and sleep disorders, searching for the influencing factors, and investigating potential targets for diagnosis and treatment. This review aimed to identify and summarize the results of relevant studies using "AR" and "sleep disorders" as search terms. In addition, we evaluated the correlation between AR and sleep disorders and examined their interaction and potential mechanisms, offering a foundation for additional screening of potential diagnostic biomarkers and therapeutic targets.

Keywords: allergic rhinitis, biological rhythm, immune inflammatory, neurological regulation, sleep disorders

Introduction

Allergic rhinitis (AR) is a type I hypersensitivity reaction mediated by immunoglobulin E (IgE). The primary symptoms include nasal congestion, nasal itching, and sneezing. AR has emerged as an important global health concern and may significantly negatively impact the quality of life of patients. Currently, the global incidence rate of AR is 10–40%, and it affects more than 400 million people, with an annual increase in incidence as high as 50% in some countries.[1,2]

In addition, patients with AR may also experience varying degrees of sleep disorders, including insomnia,[3] sleep-disordered breathing (SDB),[4] and obstructive sleep apnea (OSA).[5] Once sleep disorders occur in patients with AR, the original nasal symptoms, such as nasal congestion, are easily exacerbated,[6] and this aggravation of nasal symptoms can in turn further amplify sleep disorders,[7] forming a vicious cycle. In severe cases, patients may be more susceptible to anxiety, depression, and other mental and psychological issues,[8] which may even result in malignant events such as suicide.[9] In some international diagnostic and treatment guidelines, the severity of sleep disorders has been included as one of the vital reference indicators for assessing AR.[10]

Received: 11 June 2024
Accepted: 11 September 2024
Published: 19 September 2024

However, currently, neither physicians nor patients pay sufficient attention to AR-related sleep disorders, leading to this vicious cycle being relatively common in clinical practice. Meanwhile, clear clinical diagnostic standards or effective prevention or therapeutic measures for AR-related sleep disorders remain lacking. Therefore, emphasizing and understanding AR-related sleep disorders is a significant challenge in clinical practice. The most crucial research topics that should be concentrated on are the analysis of the relationship between AR and sleep disorders, identification of the influencing factors, and exploration of potential diagnostic and therapeutic targets.

This study aimed to comprehensively summarizes the relevant studies on AR and sleep in recent years and thoroughly review the review interactions, influencing factors and mechanisms, and status of diagnosis and treatment. This review may serve as a basis for future screening of potential diagnostic markers and therapeutic targets and as a resource for subsequent research on AR-related sleep disorders.

Search Methodology

We searched the PubMed electronic database to obtain relevant articles. We performed a series of literature searches using the following keywords: "allergic rhinitis", "hay fever", "sleep disorders", "insomnia", "obstructive sleep apnea", "OSA", "sleep-disordered breathing", "SDB", "circadian rhythm", "sleep/awakening cycle" and "sleep deprivation". All keywords were used in all possible permutations and abstracts from the search results were assessed.

No date limits were imposed, older articles were identified manually by searching the reference lists of articles that met the inclusion criteria. Secondary documents from the reference lists of the primary designated papers were searched, assessed for suitability, and included, if appropriate.

Mutual Influence Between AR and Sleep

AR is a relatively common disease. Although it is rarely life-threatening, its major symptoms can severely interfere with the sleep and daily lives of individuals.[9] In a questionnaire evaluation, Leger et al found that up to 73.5% of patients with AR have concurrent sleep disorders,[11] and patients with moderate to severe AR are more likely to experience sleep disorders.[12] A summary of the studies included in our review (Table 1) indicated that individuals with AR suffer from a variety of sleep disorders, such as insomnia, sleep/awakening cycle disorders, SDB, OSA, and daytime sleepiness, and that pediatric patients may also experience parasomnias.[3–5,11–33] Of these, insomnia is the most common type of sleep disorder and has a strong positive correlation with the severity of AR,[18] which is also an important contributing factor to patients' daytime sleepiness, difficulty waking up in the morning, and lack of concentration. Furthermore, the incidence of SDB is higher in patients with AR than in healthy participants,[23] and those with more severe AR symptoms show a 1.8-fold increase in the likelihood SDB.[14] In pediatric patients, AR is also a key potential risk factor for OSA.[4,14,16,30]

Synergistically, compared with the normal population, individuals with sleep disorders are more susceptible to allergic diseases, such as AR, asthma, and atopic dermatitis.[31–33] This may be closely related to the fact that sleep disruption results in low-grade inflammatory reactions and a disruption of the immune balance in the body.[34,35] We collated clinical studies on the impacts of different types of sleep disorders on allergic airway diseases (Table 2). The results showed that SDB has the greatest influence on the body and that throughout the induction process, OSA, as the most frequent type of SDB, is closely linked to the incidence of allergic reaction.[31,36–44] Moreover, through a survey of health risk behaviors in a population of 274,480 individuals, Kwon et al found that sleep disorders are a potential risk factor for AR and that the correlation between the two becomes increasingly stronger with age.[40]

Unfortunately, objective criteria or methods for evaluating the mutual influence between AR and sleep disorders, which is the primary reason for the continued debate on the relationship between the two, remain lacking. Even though AR and sleep disorders can result in mutually increased incidence rates, more research is required to determine whether they are strong independent risk factors. Regarding the current research status, the techniques and inclusion criteria used by scholars significantly restrict the dependability of research results. Polysomnography (PSG), as a relatively objective method of assessing sleep quality, has been utilized to identify altered sleep phases[15] and heightened OSA severity[25] in individuals with AR. To further clarify the correlation between sleep and AR, Cheng et al conducted a study in 2022 in which they optically induced disruption of the sleep/awakening cycle in Balb/c mice and compared them with simple AR mice, finding that mice with sleep/awakening cycle disorders exhibited significant aggravation of AR symptoms and tissue inflammation.[43]

Table 1 Impact of AR on Sleep in Clinical Practice

Study and Date of Publication	Sample Age (Years)	Numbers (AR)	Evaluation Basis	Results					Research Methods
				Insomnia	SWD	SDB	OSA	Others	
Young et al 1997[14]	30–60	4927	Questionnaire investigation	/	/	√	/	/	Cohort study
Krouse et al 2002[15]	20–41	8(4)	PSG	√	/	/	/	Changes in sleep phase, increased latency to rapid eye movement sleep, decreased time in rapid eye movement sleep	Case-control study
Ersu et al 2004[16]	5–13	2147	Questionnaire investigation	/	/	/	√	Habitual snoring	Cross-sectional study
Ng et al 2005[17]	6–12	3047(1242)	Questionnaire investigation	/	/	/	√	Habitual snoring	Cross-sectional study
Léger et al 2006[18]	18–50	1093(591)	Questionnaire investigation	√	/	√	/	Daytime somnolence and fatigue, impaired memory, emotions, and sexual behavior	Cross-sectional study
Craig et al 2008[19]	Unknown	2355(2355)	Questionnaire investigation	√	/	/	/	Difficulty falling asleep, night awakening	Cross-sectional study
Meltzer et al 2009[13]	4–17	1004(500)	Questionnaire investigation	√	/	/	/	Difficulty falling asleep, night awakening	Case-control study
Colás et al 2012[12]	≥18	2275(2275)	Questionnaire investigation	/	/	/	/	Poor sleep quality, daytime somnolence	Cross-sectional study
Poachanukoon et al 2015[20]	6–15	169(65)	Questionnaire investigation	/	/	/	√	Daytime somnolence, not refreshed, daytime dysfunction, fretful and restless, night sweating, snoring, mouth breathing, dry throat, morning headache	Case-control study
Drumond et al 2017[21]	8–11	448(31)	Questionnaire investigation	/	/	/	/	Sleep bruxism	Cross-sectional study
Leger et al 2017[11]	5–17,≥18	1750(1750) (907adults, 843children)	Questionnaire investigation	√	/	√	/	Poor sleep quality, night awakening, daytime somnolence	Cross-sectional study
Tsai et al 2017[22]	5–18	8616(4191)	Database selection	/	/	/	/	Nocturnal enuresis	Case-control study

(*Continued*)

https://doi.org/10.2147/NSS.S482258 DovePress

Table 1 (Continued).

Study and Date of Publication	Sample Age (Years)	Numbers (AR)	Evaluation Basis	Results					Research Methods
				Insomnia	SWD	SDB	OSA	Others	
Roxbury et al 2018[3]	≥18	5556(1797)	Questionnaire investigation	√	√	√	/	Higher odds of sleep latency prolonged, sleep apnea, trouble falling asleep, increased arousal times, increased use of sleep medication, daytime somnolence, daytime dysfunction, feeling unrested	Cross-sectional study
Loekmanwidjaja et al 2018[23]	4–10	167(112)	Questionnaire investigation	√	/	√	/	Daytime somnolence, nocturnal awakenings, nocturnal enuresis, sleep bruxism, anxiety, nightmares, sleepwalking, excessive sweating	Case-control study
Lai et al 2018[24]	≤18	655,529 (327,928)	Follow-up study	/	/	/	/	Nocturnal enuresis	Cohort study
Giraldo-Cadavid et al 2020[25]	4–15	99(99)	Questionnaire investigation, PSG	/	/	/	√	/	Cross-sectional study
Romano et al 2020[26]	≥18	511(511)	Questionnaire investigation	√	√	√	/	Difficulty falling asleep, night awakening, daytime somnolence, attention impairment, daytime dysfunction	Cross-sectional study
Berson et al 2020[27]	Unknown	100(47)	PSG	/	/	√	/	Apnea-hypopnea, sleep-disordered breathing	Case-control study
Wang et al 2022[28]	3–14	1473(427)	Questionnaire investigation	/	/	/	/	Snoring, mouth breathing, restless sleep, sleep talking, hyperhidrosis	Case-control study
Wongvilairat et al 2022[29]	18–65	120(120)	Questionnaire investigation	/	/	/	√	/	Cross-sectional study
Li et al 2023[4]	6–11	3433(1309)	Questionnaire investigation	/	/	√	/	/	Cross-sectional study
Wang et al 2024[5]	5–8	372(93)	Questionnaire investigation	/	/	/	√	/	Cohort study
Yang et al 2024[30]	2–14	263(94)	PSG, AHI, LSaO2	/	/	/	√	/	Case-control study

Notes: √ indicates the presence of the disease; / means not mentioned.

Abbreviations: AR, allergic rhinitis; SDB, sleep-disordered breathing; OSA, obstructive sleep apnea; EEG, electroencephalogram; EOG, electrooculogram; EMG, electromyogram; PSG, polysomnography; AHI, apnea hypopnea index; HSAT, home sleep apnea testing analysis.; SWD, Sleep/Awakening Cycle Disorders; LSaO2, lowest oxygen saturation.

Table 2 Impact of Sleep on Allergic Airway Diseases in Clinical Practice

Study and Date of Publication	Types of Sleep Disorders	Sample	Age (Years)	Number of Patients	Research Methods	Affects Diseases	Results
Canova et al 2004[31]	OSA	Adults	50–80	72	Case-control study	AR	Subjects with OSA may have an increased risk of being allergic to perennial allergens and suffer from perennial rhinitis, nasal obstruction and/or runny nose and/or sneezing
Brinke et al 2005[36]	OSA	Adults	18–75	136	Cross-sectional study	Asthma	OSA is a significant risk factor of frequent asthma exacerbations
Sulit et al 2005[37]	SDB	Children	8–11	788	Prospective cohort study	Asthma	SDB is associated with asthma and wheeze.
Teodorescu et al 2010[38]	OSA	Adults	18–75	472	Prospective cohort study	Asthma	High OSA risk is significantly associated with not-well-controlled asthma
Ross et al 2012[39]	SDB	Children	4–18	108	Prospective cohort study	Asthma	Children with SDB had 3.62-fold increased odds of having severe asthma
Kwon et al 2013[40]	Sleep structure disturbance	Children	12–18	274,480	Cross-sectional study	AR	Duration and time of sleep increase the risk of AR
Teodorescu et al 2013[41]	OSA	Adults	18–75	813	Cross-sectional study	Asthma	OSA increases the risk for worse asthma control in older patients. Unrecognized OSA may be a reason for poor asthma control, particularly among older patients.
Wang et al 2016[42]	OSA	Adults	18–65	303	Prospective cohort study	Asthma	OSA is an important factor associated with severe asthma exacerbations
Cheng et al 2022[43]	Circadian rhythm disruption	Mice	Balb/c 6 weeks (body weight~18 g)	48	Experimental study	AR	Circadian rhythm disruption exacerbates local and systemic allergic reactions and immune response in AR mice
Wang et al 2023[44]	Short sleep duration	Adults	>18	522	Prospective cohort study	Asthma	Short sleep duration was associated with poor asthma control and was an independent risk factor for future moderate to severe asthma exacerbations.

Abbreviations: AR, allergic rhinitis; SDB, sleep-disordered breathing; OSA, obstructive sleep apnea; SD, Standard Deviation.

https://doi.org/10.2147/NSS.S482258

In summary, not only does AR lead to varying degrees and types of sleep disorders in patients, but the presence of sleep disorders is also associated with an increased incidence and symptom severity of many allergic diseases, including AR. Consequently, researching the mechanisms of mutual influence and identifying shared diagnostic and therapeutic targets between AR and sleep disorders is imperative for developing prevention and treatment strategies that effectively address both goals.

Factors Influencing the Interaction Between AR and Sleep

Organisms comprise a complex and precise mutual-aid network, in which the normal operation of various physiological systems requires a high degree of coordination between different organs and immune mechanisms. Changes in a certain structures or functions can often have mutual effects at different disease stages owing to their interactions. Similarly, in cases of AR and sleep disorders, a series of effects may occur through different mechanisms of action, as shown in Figure 1.

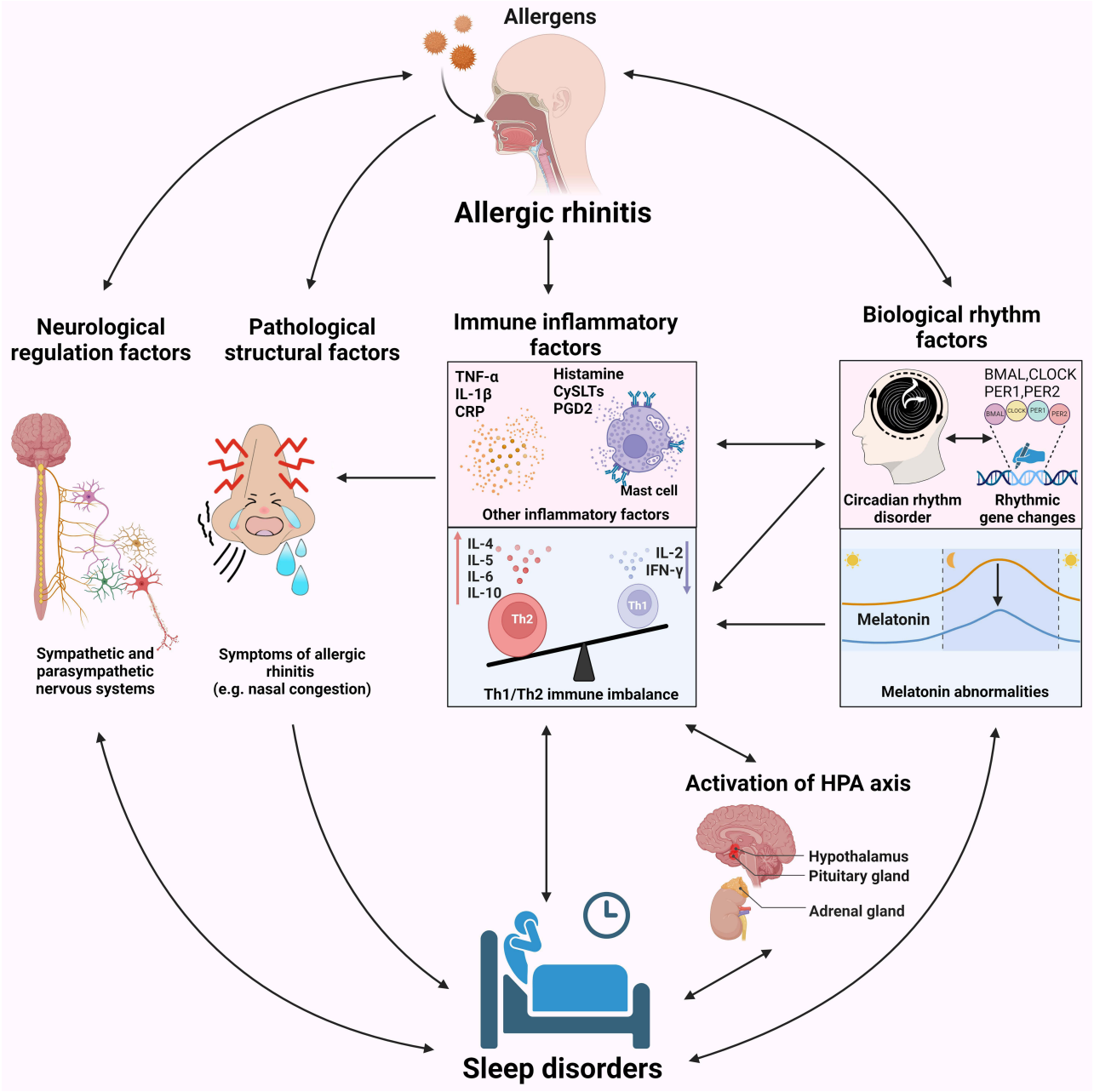

Figure 1 Factors influencing the interaction between AR and sleep. Created with BioRender.
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Pathological Structural Factors

The nose is the main pathway for breathing, and smooth ventilation of the nasal cavity and nasopharynx is of great significance for the diagnosis, therapy, and quality of daily life of patients with AR. Nasal congestion, one of the primary symptoms of AR, causes significant distress to patients, and is the most direct cause of sleep disorders.[13,45] Nasal congestion in patients with AR increases nasal resistance, which typically impairs breathing through the nasal pathway during sleep, playing a role in the pathogenesis of SDB, and potentially affecting its severity.[46] As early as 1997, Young et al conducted a survey on an adult population through questionnaires and objective tests and found that patients with nasal congestion are more likely to experience symptoms of SDB, such as habitual snoring, apnea, and hypopnea.[14] Subsequently, extensive studies have also found that nasal congestion is an important risk factor for SDB.[47,48]

After stimulation by allergens in patients with AR, stress-induced edema accompanied by congestion and swelling of the turbinate may occur in the nasal mucosa, leading to a narrowing of the nasal cavity. With changes in the physiological and anatomical structure of the nasal cavity, pathological changes in the internal airflow velocity and negative pressure during inhalation secondary to nasal congestion can further lead to nasal collapse, airway obstruction, and an increased number of sleep microarousals.[49] This is one of the key factors underlying SDB and daytime fatigue in patients with AR. To clarify the impact of nasal congestion on sleep, Millman et al induced an experimental nasal occlusion in a normal population, finding that participants who were given nasal packing experienced changes in sleep continuity, sleep structure, and respiratory function.[50] Moreover, patients with AR with apparent nasal congestion symptoms have an increased frequency and duration of sleep disorders.[51] In addition, clinical research by Craig et al[49] and Hughes et al[52] found that treatment with topical nasal corticosteroids in patients with AR can alleviate nasal congestion symptoms, effectively improve sleep, and enhance quality of life.

In pediatric patients, adenoid hypertrophy is prone to upper airway blockage and affects sleep.[53] AR is a predisposing factor for adenoid hypertrophy in children, and hyperplasia of the adenoids under allergen stimulation can cause posterior naris blockage and nasopharyngeal stenosis, leading to symptoms such as snoring and nocturnal arousal.[54] Adenoid hypertrophy has also repeatedly been proven to be the most common risk factor for OSA in children.[55,56] However, considering adenoid hypertrophy as a point of penetration to explore the relationship between AR and sleep is often limited to pediatric patients, resulting in age bias. Moreover, sleep structure and disease susceptibility have corresponding characteristics in different age groups. Therefore, future research on AR-related sleep disorders should critically analyze the role of age, anatomical structure, and other relevant factors.

Biological Rhythm Factors

All organisms, including humans, have a normal biological rhythm known as the circadian clock (CC). The CC regulates normal human physiological functions, including sleep/awakening, metabolic balance, and hormone secretion.[57] Disturbances in the biological clock typically manifest as sleep disorders and may disrupt the circadian rhythm of allergy-related cells, leading to abnormal responses to allergic reactions in the body.[58] To explore a potential new inducer of allergic diseases in current society, Cheng et al built an aberrant light/dark cycle-induced circadian rhythm-disruption mouse model and found that circadian rhythm disruption aggravates the T helper (Th)2-like immune response and damages the airway mucosal barrier, thus exacerbating the occurrence and development of AR inflammation.[43]

Furthermore, after sleep disorders, the body usually exhibits differential expression of clock genes such as BMAL1, CLOCK, and PER1/2.[59,60] In addition, research involving intervention in these CC sites revealed that the allergic symptoms, immune response, and effector cells or targets in hypersensitivity reactions (such as mast cells and IgE) cause varying degrees of change.[61,62] Moreover, in a study by Nakamura et al, PER2, an active inhibitory factor of BMAL1/CLOCK, was found to exert anti-inflammatory effects on allergic reactions by controlling the rhythmic secretion of adrenal glucocorticoids from the adrenal glands.[63] In recent years, research has also discovered that the PER2 gene can regulate the circadian rhythm of GATA-binding protein 3 and retinoic acid receptor-related orphan receptor-gamma-t levels in immune cells, subsequently modulating the severity of AR.[64] Similarly, under the stimulation of allergens, the occurrence of AR upregulates the expression of BMAL1 and CLOCK, further influencing biological clock activity.[65] Reverse transcription polymerase chain reaction (RT-PCR) is the primary method used to quantify and

analyze the expression of circadian genes in patient blood or tissue samples. However, to our knowledge, any pertinent clinical cohort study investigating the potential of circadian genes as a shared diagnostic standard and intervention target for sleep disorders and AR remains unavailable.

Melatonin, an important neuronal hormone, regulates circadian rhythms in vertebrates and mammals and is known as the "hormone of darkness". Sleep disorders, except for those induced by changes in rhythm genes, may also be accompanied by the abnormal secretion of melatonin, which subsequently induces immune dysfunction and inflammatory reactions.[66] Similarly, an advanced clinical controlled trial reported disturbed melatonin secretion in patients with AR.[67] In patients with allergies, melatonin expression variations are positively correlated with sleep disorders.[68] Exogenous administration of melatonin treatment is effective in treating sleep disorders,[69,70] and melatonin not only exerts an immune regulatory function but also has the ability to inhibit allergic inflammatory responses.[71] In animal studies conducted by Cetin et al, the application of melatonin effectively treated ovalbumin-induced AR, remarkably alleviated AR symptoms, and considerably reduced IgE and histological inflammation levels.[72] However, further exploration is needed regarding melatonin as a treatment option for AR-related sleep disorders.

Melatonin levels can be measured in blood, urine, or saliva samples conveniently to help diagnose sleep-related conditions.[73–75] Although no cutoff value for abnormal melatonin secretion has been determined, it seems to be more accessible and generalized in a clinic setting than rhythmic gene testing. However, clinical researches and optimized detection methods are still required to facilitate the accurate application of the aforementioned indicators in AR-related sleep disorders.

Immune Inflammatory Factors

Cytokines Released by Th Cells

Th1 and Th2 cells play crucial roles in balancing immune responses. During normal sleep, usually a Th1-dominated immune balance exists in an organism, but when sleep is disrupted, Th2 replaces Th1 as the dominant cell subpopulation in immune inflammation, thus disrupting homeostasis.[76] Extensive early-stage research has also verified that in individuals with sleep disorders, such as insomnia, sleep deprivation, OSA, and narcolepsy, along with a T cell-homeostasis shift towards Th2-predominance, corresponding cytokines, such as interleukin (IL)-4, IL-5, IL-6 and IL-10, are remarkably elevated, whereas the opposite is true for Th1 cytokines, such as IL-2 and interferon (IFN)-γ.[77–79]

An excessive shift of the Th1/Th2 balance towards Th2-predominance may cause an immune response in the nasal mucosa, thus potentially inducing AR.[80] Furthermore, diseases related to sleep deprivation and excessive daytime sleepiness, such as sleep apnea, narcolepsy, and idiopathic hypersomnia, can lead to the hypersecretion of IL-6.[81] Vgontzas et al found that in individuals suffering from sleep deprivation the secretion rhythm of IL-6 is disrupted, which can further affect the progression of inflammatory diseases and the quality of sleep in later stages.[82] Moreover, in previous case-control studies, patients with AR exhibited higher levels of the Th2-associated inflammatory cytokines, IL-4 and IL-10, along with disrupted phases of sleep, such as decreased time in rapid eye movement sleep.[15] Furthermore, in some basic studies of rats and rabbits, administering exogenous IL-4, IL-6, and IL-10 interfered with sleep, whereas administering IL-2 and IFN-γ promoted sleep, and these corresponding effect were significantly weakened by heat-inactivation of these cytokines.[83–87]

Th2-type inflammatory factors play a key role in the development of AR. A Phase III trial showed that the IL-4Rα monoclonal antibody, stapokibart (CM310), effectively treated seasonal AR. Therefore, it would be worthwhile to further investigate whether this can improve sleep disorders while treating AR.

Tumor Necrosis Factor (TNF)-α and IL-1β

TNF-α and IL-1β, which are key inflammatory cytokines, mutually promote each other's generation and activity during immune dysfunction in the body, and are thus commonly used as reference indices for various types of immune inflammation. Notably, TNF-α and IL-1β are both significantly higher in the blood, nasal secretions and mucosa of patients with AR, and the increase in these indicators is closely related to disease severity.[88,89] However, owing to the limitations of current sampling and detection methods, whether these indicators can be used as diagnostic markers for AR needs further exploration, along with the determination of the precise threshold sizes. Meanwhile, varying degrees of

elevated TNF-α and IL-1β are associated with different types of sleep disorders.[77,90] Some studies have reported elevated TNF-α and IL-1β levels, as well as fatigue and drowsiness, in patients with AR.[91,92]

Kapsimalis et al proposed that TNF-α and IL-1β could increase sleep duration and induce excessive sleepiness.[93] The multifunctional cytokine TNF-α plays a central role in the pathogenesis of many inflammatory diseases, including AR, and its elevation is a potential risk factor for the development of AR.[94] Moreover, mice deficient in the gene encoding TNF-α exhibited a marked reduction in the symptoms and cytokines related to AR.[95] Similarly, IL-1β is intimately related to allergic diseases and is an important accelerating factor in the occurrence and development of AR.[89,96] One possible strategy for preventing and treating AR is to induce the combined suppression of TNF-α and IL-1β.[97] Notably, the expression of TNF-α and IL-1β rises after sleep deprivation, whereas improving sleep disorders can lower their levels.[98,99] Exogenous administration of excessive TNF-α or IL-1β to simulate the accumulation of sleep disorders can induce similar symptoms.[100]

Although directly related basic research verifying the mechanism of action of the above factors in AR-related sleep disorders remains lacking, according to the above reports, it can be inferred that TNF-α and IL-1β are perhaps important potential mediators causing sleep disorders in patients with AR. Corresponding antagonists, such as the IL-1 receptor antagonist anakinra that controls refractory pityriasis rubra pilaris[101] and TNF-α inhibitor adalimumab that improves ankylosing spondylitis,[102] have been preliminarily validated. However, animal validation and further research are required to promote their application to AR-related sleep disorders in order to obtain dual efficacy in clinical practice.

Histamine

During AR occurrence and development, a large amount of histamine is released to induce pathological changes in local tissues, which has been proposed as an important target for AR prevention and therapy.[103] Histamine has a direct effect on the central nervous system and is a critical factor in maintaining wakefulness.[104] Notably, patients also experience corresponding disruptions in their sleep/awakening cycles with an increase in histamine levels.[105] In addition, high histamine levels deteriorate sleep quality in patients with AR with OSA.[92] In specific histamine transferase-knockout mice constructed by Naganuma et al enhanced histamine concentration led to disrupted sleep rhythms, whereas histamine receptor antagonists suppressed this type of sleep disorder.[106] Moreover, histidine decarboxylase knockout in mice resulting in the inhibition of histamine synthesis, permanently changed the sleep/wake cycle.[107]

In the context of the application of antihistamines as first-line therapy for AR, azelastine protects the epithelial integrity in patients with AR,[108] while simultaneously playing a role in improving sleep quality.[105] Similarly, pitolisant (previously known as BF2.649), a selective histamine H3 receptor inverse agonist, can effectively treat narcolepsy, a disorder characterized by excessive daytime sleepiness.[109] Although some antihistamines can relieve AR symptoms, they can also disrupt sleep architecture and exacerbate daytime drowsiness.[110] Therefore, future research should focus on clarifying the specific types and indications of antihistamines and the populations to which they are applicable, along with proposing comprehensive regulatory guidelines. Furthermore, histamine, as a key target of AR in relation to sleep, may also be a promising option for the diagnosis and treatment of patients with AR-related sleep disorders.

Others

In addition to the aforementioned factors, patients with AR and/or sleep disorders may present with elevated levels of C-reactive protein (CRP), prostaglandins, and cysteine leukotriene (CySLT).[103,111] Changes in these indicators can also affect the circadian rhythms and immune balance of an organism to a certain extent.[92,112,113] Furthermore, a previous clinical controlled study found that controlling immune inflammatory factors in AR through medication can improve sleep quality.[114]

In summary, the occurrence and development of AR and sleep disorders involve disturbances in immune regulation with seemingly independent but mutually interfering pathways through different cytokines. The factors that play a dominant role or exert specific regulatory functions should be a heading direction that cannot be ignored in future research. We anticipate conducting further research on potential mechanisms and viable targets for preventive and treatment.

Neurological Regulation Factors

The nervous system primarily transmits information and regulates functions in the internal and external environments of an organism. Its dysfunction is inextricably associated with the occurrence and development of diseases. The autonomic nervous system is an indivisible part of the entire neural network, and dysfunction of its internal sympathetic and parasympathetic nerves is strongly associated with AR and/or sleep disorders.[115,116] Sleep disorders are generally characterized by disorders of the autonomic nervous system.[117] A case-control study by Tascillar et al revealed that an autonomic nervous system imbalance may participate in the pathogenesis of hypersensitivity reactions, inducing the occurrence of AR.[118] Sympathetic excitability is abnormally increased in patients with sleep disorders, such as insomnia and OSA, and further activates β-adrenergic signaling, which in turn triggers the subsequent inflammatory cascade.[119,120]

The nasal hyperreactivity of AR is also closely related to disturbances between the adrenergic and cholinergic nerve responses.[121] Cholinergic inhibitor, such as atropine, not only exert sedative and hypnotic effects,[122] but also alleviate symptoms, such as sneezing and runny nose, in patients with AR.[123] Additionally, the levels of brain-derived neurotrophic factor (BDNF), which is frequently detected in the nervous system, alter during the occurrence and development of both AR and sleep disorders.[124,125] Whether regulating BDNF can simultaneously alleviate AR nasal symptoms and sleep disorders is worthy of exploration and may have research value and therapeutic potential. In addition, along with the occurrence of inflammation in patients with AR on stimulation by allergens, stress to the trigeminal nerve may also occur, involving the trigeminocardiac reflex (TCR) and nasopulmonary reflex.[126,127] Notably, TCR and the nasopulmonary reflex play critical regulatory roles in various sleep disorders, including sleep bruxism, SDB, and OSA.[127,128]

Endoscopic closure of the pterygoid and/or ethmoidal nerves can control symptoms in patients with AR who did not responded to conservative treatment; however, whether this procedure can also enhance sleep quality is uncertain. Furthermore, some non-invasive neurophysiological therapies, such as the Flexyx Neurotherapy System (FNS) and repetitive transcranial magnetic stimulation (rTMS) can also improve sleep to a certain extent, indicating their potential as neural therapy to treat AR-related sleep disorders.[129,130] Exploring peripheral nerve block surgery or nerve factor intervention that balances AR and sleep disorders may be a viable option for patients who do not respond to drug therapy and may be a promising research direction at present.

However, the main disadvantage of therapies targeting neural regulation using existing technologies is the possibility of greater loss for less gain. The key to solving this problem is to search for specific tiny nerve branches modulating AR-related sleep disorders. If a more precise local blockade can be achieved, it may provide more effective adjunctive therapeutic methods for the diagnosis and treatment of AR and sleep disorders. More detailed mechanisms can be explored in animal models of AR with or without sleep disorders using neural circuit tracing, optogenetics, electrophysiology, and other methods.

Multi-Factor Interaction Mechanisms

The occurrence and development of diseases are usually not solely influenced by a single factor, but are rather derived from the interaction and balance of various mechanisms in the body. Crosstalk between rhythm and immunity, as well as neural immune regulation, has been proposed to play a pivotal role in the occurrence and development of AR and sleep disorders. Based on the previous studies, inflammatory mediators in patients with AR can lead to sleep disorders by affecting the circadian rhythm, whereas circadian rhythm disturbances can also induce and enhance allergic diseases by regulating immune function. Moreover, as a classic feedback pathway governed by the nervous system to regulate the body's immunity, the hypothalamic-pituitary-adrenal axis (HPA) not only participates in the occurrence of sleep disorders such as insomnia and awakening, but also affects the balance of Th1/Th2 immune responses in the organism and intervenes in the symptoms and prognosis of AR.[81,131]

The interaction between these mechanisms potentially forms a vicious cycle between AR and sleep disorders. Therefore, searching for key targets for the interactions between various body systems, updating research plans with emerging technologies, exploring new diagnostic and therapeutic indicators, and developing precise targeted drugs are crucial to achieving dual-effect treatment and disease defense.

Interventions for AR Sleep Problems

Drug Therapy

The symptoms of AR and/or sleep disorders commonly have a significant impact on a patient's learning ability, work efficiency, and quality of life, while also inducing a heavy economic burden on the patient's family and society. Existing research has identified that treating one disease can also influence the symptoms or prognosis of another.

The conventional medications for AR include intranasal corticosteroids (ICS), leukotriene receptor antagonists, and antihistamines. In some early clinical trials, topical nasal corticosteroids were found to alleviate nasal congestion symptoms in patients with AR while improving their sleep quality.[52] Moreover, leukotriene antagonists (montelukast) can improve sleep disorders and reduce daytime somnolence in patients with AR,[7] while exerting a positive impact on patients with OSA by reducing nasal congestion.[132] In addition, antihistamines (triprolidine) have been proposed as treatments for temporary sleep disturbances.[133] Similarly, rhythm-regulating drugs also have the potential to treat allergic diseases. Chang et al found that melatonin, a medication that alleviates insomnia and jet lag, can simultaneously alleviate sleep disorders and inflammatory reactions in patients with allergic diseases.[68]

Unfortunately, to our knowledge, relevant research on sleep-medication interventions for symptoms in patients with AR remains unavailable. In one study, Nakamura et al attempted to regulate the circadian rhythm in mice via intraperitoneal injection of rhythm gene inhibitors (PF-670432), resulting in effective amelioration of AR-related allergic symptoms.[61] This suggests the necessity and potential of studying sleep medications to improve AR symptoms, which undoubtedly offers an alternative strategy for refractory patients with AR who are resistant to conventional treatments or cannot use corticosteroids.

Certain AR medications have the potential to affect sleep. Some first-generation antihistamines (such as diphenhydramine) have sedative effects that can disrupt sleep architecture and exacerbate daytime somnolence.[110] Therefore, second-generation antihistamines (such as loratadine and cetirizine) that significantly reduced these side effects have increasingly been used as first-line clinical medications for patients with AR. Moreover, in animal experiments, Honma et al found that intranasal corticosteroid therapy can affect the circadian rhythm of mice, whereas the administration of medication at specific times (such as in the early evening in diurnal humans) can prevent sleep disorders to some extent.[134] These findings highlight the fact that following medical advice and medication guidelines for patients with AR is a key step in treatment.

Non-Drug Therapy

In addition to medical treatment, some surgical procedures, such as inferior turbinectomy/inferior turbinate ablation and/or nasal septal reconstruction, can also effectively relieve nasal congestion and other symptoms in patients with AR to promote nighttime breathing and improve sleep quality.[135,136] Adenoidectomy in children can improve respiratory symptoms, reduce nocturnal arousal, and lower the occurrence of allergic symptoms, such as nasal congestion, runny nose, and itching.[137] These surgical methods exhibit a more pronounced therapeutic effect in children with OSA and AR.[138] In addition, as a safe and effective Traditional Chinese Medicine (TCM) therapy, acupuncture treatment exhibits significant durable, and stable therapeutic effects in alleviating AR symptoms and improving sleep quality in patients with insomnia.[139,140] Cognitive-behavioral psychotherapy and some forms of health education have also been shown to have different therapeutic effects on the relief of AR symptoms, including improvement of sleep quality and daytime dysfunction.[141,142] However, whether the above therapies can achieve a dual therapeutic effect of "one method and one treatment" requires further exploration. Consequently, surgery, acupuncture, and psychotherapy are emerging as alternatives for patients who did not respond to drug therapy.

Limitations

An increasing number of researchers are focusing on the association between AR and sleep. The mutual interference between the two not only reciprocally exacerbates their respective symptoms, but also increases the difficulty and cost of diagnosing and treating AR. A systematic review by Lin et al concluded that despite the fact that AR and SDB are correlated, the evidence supporting a relationship between the two is not very strong owing to the subjective nature of

diagnostic symptoms.[143] Consequently, one of the primary barriers for clinical physicians to diagnose AR-related sleep disorders is the absence of objective evaluation indices or measures, which is also a fundamental reason for the ongoing controversy regarding the relationship between the two. The most objective form of sleep quality evaluation is PSG, which is the gold standard for sleep monitoring. However, the complexity of the detection and data analysis processes of PSG severely restricts its clinical application. Notably, current objective, convenient, consistent, and specific detection methods and indicators remain insufficient to distinguish and diagnose AR-related sleep disorders.

The majority of pertinent studies included in this review were cross-sectional and case-control studies, which are very susceptible to selection and recall bias and are not able to determine causal relationships. The absence of large-scale, prospective, clinical cohort studies is a notable limitation in the current research; however, this also presents an opportunity for advancement. Therefore, we anticipate the publication of more high-quality randomized controlled trials to promote exploration related to this field. In addition, confounding factors, including age, research design, diagnostic standards, ethnicity, and geography, existed in the included studies, potentially influencing the researchers' interpretations of their findings. This emphasizes the necessity of conducting long-term studies with large sample sizes and multi-center cohorts that utilize objective data and are supported by professional institutions and teams to clarify the interaction between AR and sleep disorders. In addition, a shift from retrospective to prospective studies, with a gradual transition from exploring mechanisms in basic experiments, such as cells and animals, is imperative to applying interventional procedures in clinical diseases. Furthermore, investigation into additional indicators and intervention targets is required to achieve standardized diagnostic processes and efficient treatment guidelines for AR and sleep disorders.

Summary and Prospects

With ever-growing social pressure, the incidence rates of both AR and sleep disorders are increasing annually, with an increasing number of patients affected by both conditions. The present study comprehensively summarized and categorized recent research on AR and sleep, providing a detailed review of the current research status of the diagnosis, treatment, and mechanisms and offering novel research perspectives on this field, along with directions and recommendations for future clinical work.

AR and sleep disorders both involve overlapping interdisciplinary fields, including otolaryngology, neuroscience, and immunology. The mechanisms involved are intricate and complex, ranging from changes in patient symptoms to disruptions in the biological clock, to crosstalk between the nervous and immune systems, driving the vicious cycle between the two. Currently, clinical physicians use a combination of questionnaire investigations, patient symptoms, and PSG as part of their diagnostic strategy to assess AR-related sleep disorders. It is also crucial to explore whether certain factors, such as melatonin, IL-4, TNF-α, IL-1β, and histamine, may be useful as potential targets for future diagnosis and treatment. Furthermore, whether the application of targeted medications or neurotrophic factors or the development of corresponding nerve block surgery can achieve a therapeutic effect requires further research and innovation.

In summary, a great scope exists to investigate the correlation between AR and sleep disorders, and more researchers should pay widespread attention to this topic and conduct in-depth investigations, which may further clarify whether AR and sleep disorders constitute significant risk factors for each other. This may encourage the development and application of more convenient, efficient, objective, and accurate diagnostic and treatment strategies, as well as the formulation and implementation of relevant guidelines in the future.

Abbreviations

AR, allergic rhinitis; IgE, immunoglobulin E; SDB, sleep-disordered breathing; OSA, obstructive sleep apnea; PSG, Polysomnography; CC, circadian clock; Th, T helper; RT-PCR, Reverse transcription polymerase chain reaction; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; CRP, C-reactive protein (CRP); CySLT, cysteine leukotriene; BDNF, brain-derived neurotrophic factor; TCR, trigeminocardiac reflex; FNS, Flexyx Neurotherapy System; rTMS, repetitive transcranial magnetic stimulation; HPA, hypothalamic-pituitary-adrenal axis; ICS, intranasal corticosteroids; TCM, Traditional Chinese Medicine.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Natural Science Foundation of China (82371119, 82271146, 82071021); the Key Research and Development Program of Shandong Province (Major Science and Technology Innovation Project; 2020CXGC011302, 2022CXGC020506); the Taishan Scholar Project (No. tsqn202312392); Shandong Provincial Postdoctoral Foundation Project (Innovation Project; SDCX-ZG-202203077); Science and Technology Innovation development plan of Yantai (2023ZDCX033); the Outstanding Young Talents Project in Health of Qilu and the youth talent training program from Qingdao medical college of Qingdao University (No. RZ2300002690).

Disclosure

The authors report no conflicts of interest in this work.

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