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Rhinitis and sleep disorders: The trigeminocardiac reflex link?

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ABSTRACT

Rhinitis, allergic or non-allergic, is an inflammatory condition of the nose. It is associated with a wide range of sleep disorders that are generally attributed to nasal congestion and presence of inflammatory mediators like cytokines and interleukins. However, the pathophysiological mechanisms behind these sleep disorders remain unclear. On the other hand, the trigeminocardiac reflex (TCR) has recently been linked to various sleep disorders like obstructive sleep apnea, sleep bruxism and rapid eye movement (REM) sleep apnea. TCR can be incited by stimulation of the trigeminal nerve or the area innervated by its branches including the nasal mucosa. Trigeminal nasal afferents can be activated on exposure to noxious stimuli (mechanical or chemical) like ammonia vapors, carbon-dioxide, nicotine, hypertonic saline, air-puffs and smoke. In rhinitis, there is associated neuronal hyper-responsiveness of sensory nasal afferents due to inflammation (which can be suppressed by steroids). This may further lead to increased occurrence of TCR in rhinitis. Moreover, there is involvement of autonomic nervous system both in rhinitis and TCR. In TCR, parasympathetic over activity and sympathetic inhibition leads to sudden onset bradycardia, hypotension, apnea and gastric motility. Also, the autonomic imbalance reportedly plays a significant role in the pathophysiology of rhinitis. Thus, considering these facts we hypothesize that the TCR could be the link between rhinitis and sleep disorders and we believe that further research in this direction may yield significant development in our understanding of sleep disorders in rhinitis.

Introduction

Rhinitis, allergic as well as non-allergic, is a common respiratory condition that may often be chronic. Allergic rhinitis (AR) is a multifactorial condition with both inflammation and neurological involvement (neurogenic inflammation) playing significant roles [1]. Nasal congestion, seen in rhinitis, is a known risk factor for sleep-disordered breathing (including snoring, hypopnea, apnea), [2] while inflammation has been associated with suppression of both REM and NREM sleep [3]. The relationship between rhinitis, nasal obstruction and sleep disordered breathing is well established [4]. The resulting sleep impairment can have significant impact on quality of life. However, the mechanisms underlying sleep disorders in rhinitis are still not well established.

In recent years, trigeminocardiac reflex (TCR), one of the most powerful autonomic reflexes of the body, has been found to have a role in sleep disorders like sleep bruxism (SB), sleep apnea (SA) and obstructive sleep apnea (OSA) [5]. Another variant of the TCR, the diving reflex (DR), has recently been linked to sudden infant death syndrome (SIDS) [6] where there is unexplained death of a seemingly healthy infant, usually during asleep. The TCR can be activated by stimulation of the trigeminal nerve anywhere along its course and manifests as mild to severe negative cardiorespiratory changes such as bradycardia, asystole, hypotension or apnea, due to sympathetic withdrawal and parasympathetic overactivity via the vagus nerve. Various subtypes of the TCR are reported and include the peripheral TCR (occulocardiac reflex, nasocardiac reflex, maxillomandibular reflex), gasserian ganglion type and the central TCR [7]. The TCR assumes significance in clinical practice as its role in various neurosurgical and maxillofacial procedures is well established [8]. This reflex can be elicited by either mechanical, chemical or electrical stimuli [9] in the areas innervated by trigeminal nerve such as surgery, cold exposure, smoke, secretions or inflammation. Here, we intend to hypothesize the role of the TCR in nasal inflammation/ infection (rhinitis) associated sleep disorders.

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The hypothesis/theory

Allergic rhinitis and non-allergic rhinitis (NAR) are associated with a high incidence of different sleep disorders. In addition, there exists an autonomic imbalance in rhinitis, with parasympathetic overactivity. Also, the DR has been reported to be exaggerated in non-eosinophilic non-allergic rhinitis (NENAR) [10]. On the other hand, TCR has been implicated in sleep disorders like REM sleep apnea, SB and OSA [5]. It is also speculated that the nasotrigeminal reflex, a form of TCR, may have a role in REM sleep apnea [11]. Based on these facts, we speculate if there is a possibility of the TCR being the link between sleep disorders and rhinitis? If so, what could be the potential stimuli that activate the TCR in rhinitis? Does the TCR have any role in inflammatory conditions?

The TCR can be activated by stimulation of the fifth nerve anywhere along its course. The stimuli could be electrical, chemical or mechanical [9]. Trigeminal nasal afferents are generally activated on exposure to noxious stimuli like ammonia vapors, carbon dioxide or nicotine and mechanical stimuli like air-puffs [12,13]. Nasal reflexes can be initiated by a variety of stimuli including mechanical probing, hypertonic saline, cold/dry air, histamine, allergen, nicotine, bradykinin, capsaicin [14]. Nasal congestion and nasal discharge are prominent and common symptoms of rhinitis. The mechanisms behind sleep disturbances in rhinitis are poorly understood and multifactorial; however, this is commonly attributed to nasal congestion/obstruction. Cytokines and autonomic imbalance are also thought to have a potential role [3]. We hypothesize that nasal congestion and discharge seen in rhinitis can potentially stimulate the nasal trigeminal afferents and activate the nasotrigeminal reflex, causing sleep disorders in rhinitis, more so because there is a coexisting autonomic imbalance in patients with rhinitis.

Evaluation of the hypothesis/idea

Rhinitis and sleep disorders

AR affects up to 40% of population worldwide [15]. It occurs due to air borne particles (allergens) in people who are allergic to them [16] and is an important cause of nasal congestion. Sneezing, nasal obstruction, rhinorrhea and nasal itching are the most common signs of AR [17]. NAR most commonly presents with nasal obstruction and rhinorrhea, while sneezing and itching are less common [18].

Typical sleep disorders seen in AR include sleep disordered breathing (SDB), sleep apnea and snoring. OSA also has a higher prevalence in patients with AR and is attributed to nasal obstruction and anatomical factors. The mechanisms behind these sleep disturbances are largely attributed to nasal congestion and inflammatory mediators [19]. There is ample evidence underlining the fact that nasal obstruction has a prominent role in sleep disturbances in AR [20,21]. Furthermore, sleep disturbances in AR have been found to be associated with increased microarousals (MA) [22]. Increased upper airway resistance and nasal discharge in AR cause sleep disordered breathing and MA up to 10 times more than in normal controls [22].

Apart from this, autonomic imbalance in the form of sympathetic withdrawal and parasympathetic predominance is involved in the pathophysiology of rhinitis [23,24] and manifests as decreased heart rate variability. Autonomic nervous system (ANS) and eicosanoids are known to have complex interactions [18] and steroids used in treatment of rhinitis reduce inflammation largely by blocking eicosanoid biosynthesis. Autonomic dysfunction with cholinergic hyperactivity and diminished adrenergic activity is also speculated to have a role in sleep disturbances due to nasal congestion [20]. Autonomic disturbances are associated with mild OSA as well [25].

TCR and sleep disorders

The TCR has been implicated in various sleep disorders including OSA, SB, REM sleep apneas etc. Proposed mechanisms are stimulation of sensory trigeminal afferents (role in REM sleep apnea and SIDS), rhythmic masticatory movements via mandibular division of 5th nerve (role in SB), suppression of trigeminal motoneurons during sleep causing atonia of REM sleep (role in OSA), altered excitability of internuncial neurons causing increased firing of trigeminal motoneurons during MA causing excessive contractions of jaw muscles (role in SB) [5]. It is speculated that activation of sensory trigeminal afferents during REM sleep can trigger centrally mediated apneas and cause pathological conditions like REM sleep apnea or SIDS by activation of nasotrigeminal reflex, a form of peripheral TCR [11]. SB is a sleep related movement disorder characterized by rhythmic masticatory muscle activity (RMMA) and is associated with intense sleep arousal activity. MA have been implicated in the pathogenesis of SB. Microarousals refer to arousals of the brain that occur due to airway obstruction during sleep causing labored breathing and fall in blood oxygen content, which causes the body to put extra effort to obtain oxygen. MA manifest with tachycardia, increased muscle tone and increased brain activity, while the person is asleep [26]. MA occurring in sleep due to various reasons result in tachycardia, which stimulates RMMA manifesting as SB, and stimulates a vagal response via TCR causing bradycardia [27].

Thus, facts that are so far well established, as shown in Fig. 1, in the context of AR, sleep disorders and TCR are:

1. AR is associated with various sleep disorders.
2. Nasal discharge and inflammation are important components of rhinitis.
3. MA occur 10 times more commonly in AR.
4. Autonomic imbalance in the form of sympathetic withdrawal and parasympathetic predominance is involved in the pathophysiology of rhinitis.
5. Complex interactions exist between ANS and eicosanoids.
6. Steroids reduce inflammation in rhinitis by blocking eicosanoid synthesis.
7. TCR has a role in sleep disorders like OSA, REM sleep apnea, SB.
8. Nasal afferents can be activated by a variety of stimuli including mechanical probing, hypertonic saline, cold/dry air, histamine, allergen, nicotine, bradykinin, capsaicin.
9. MA stimulate the TCR in sleep and cause SB.

TCR and rhinitis

Allergic rhinitis is known to cause neuronal hyperresponsiveness of upper airways to stimuli that activate nasal afferents [14]. On a similar note, it has previously been described that intracranial infections can cause sensitization of trigeminal afferents in duramater such that they are easily activated by mechanical stimuli and cause TCR [1]. Presence of similar sensitization of nasal trigeminal afferents to mechanical stimuli in case of rhinitis (inflammation) may be possible. Dysregulation of nerves in the nose plays an integral role in the pathogenesis of rhinitis and causes nasal, respiratory and cardiac changes [23].

Nasal inhalation of particulate material or rubbing of inferior turbinate have been shown to cause bronchoconstriction and cardio-depression, through stimulation of trigeminal afferents and activation of TCR [28]. In this context, nasal discharge or nasal congestion can be potential stimuli for nasal trigeminal afferents in rhinitis. Owing to neuronal hyperresponsiveness of nasal afferents,