university of groningen

Circadian influences in allergic rhinitis

Life Science & Technology
Behavioural and neurosciences

Jamey Scheepe (s1853465)
Supervisor: Prof. Dr. D.G.M. Beersma

Abstract

Allergic rhinitis is the medical term for hay fever affecting 10% to 20% of all people worldwide. In this bachelor thesis the circadian influences on allergic rhinitis will be discussed.

There is some predictability of the concentration of pollen over the day. There is a peak in the pollen concentration between 12:00 h and 16:00 h. Weather conditions and speed and direction of the wind seem to be a great factor. Therefore, there is some day by day variation between sites.

Much is known about the mechanism and pathophysiology of allergic rhinitis. Also research has been done on the occurrence of symptoms over the day. Further research is needed to indicate a circadian component in the immune response to allergic rhinitis. The pattern of occurrence of symptoms over the day can be taken into account in the treatment of allergic rhinitis.

Appropriate treatment of allergic rhinitis is important to prevent the accumulation into a severe chronic upper-airway disease as well to maintain the quality of life. The therapeutic approach contains: avoiding allergens, pharmacotherapy and immunotherapy. Knowing at which time of the day symptoms of allergic rhinitis occur, the time of treatment can be adjusted so that the treatment is most effective and major reactions of side effects can be avoided. Antihistamines are most effective when taken in the evening.

In pollen there seems to be a circadian component. There is also a circadian pattern in the occurrence of symptoms of allergic rhinitis; a circadian pattern in the mechanism of the immune system has yet to be determined. The circadian component in the occurrence of symptoms of allergic rhinitis can be taken into account in the treatment of allergic rhinitis.

Contents

Introduction

Allergic rhinitis is the medical term for hay fever, an allergic reaction that mimics a chronic cold. It is the most common type of chronic rhinitis (Small et al., 2011). Allergic rhinitis is an inflammatory disorder of nasal mucosa, characterized by pruritus, sneezing, rhinorrhea and nasal congestion (Maurer et al., 2007). Other symptoms are a clear runny nose, eye itching and tearing of the eyes. Postnasal dripping of clear mucus frequently causes a cough, loss of smell and occasionally loss of taste. Even nosebleeds may occur. Allergic rhinitis affects 10% to 20% of all people worldwide, with high prevalence recorded in industrialized nations (Brozek et al., 2010). Boys are more likely to have allergic rhinitis than girls. This tendency reverses in puberty so that, by adulthood, men and women are affected equally. Allergic rhinitis is closely related to other inflammatory diseases affecting respiratory mucous membranes, such as asthma, rhinosinusitis and allergic conjunctivitis. Allergic rhinitis is a risk factor for asthma (Leynaert et al., 2004). Studies have shown that rhinitis is present in up to 95% of patients with asthma (Greiner et al., 2011). Comorbid allergic rhinitis and asthma can impact patients' well being and worsening allergic rhinitis symptoms in patients with asthma can be associated with worsening asthma symptoms (Magnan et al., 2008).

The allergic reaction is mediated by the immune system. The immune system protects the body against diseases through different types of cells and proteins, distinguishing between normal and abnormal cellular components and between self and non-self. The response to allergens in allergic rhinitis is off-balance (Akdis et al., 2004), leading to an overreaction of the immune system to allergens. Pollen are the key allergens in allergic rhinitis. Other allergens are dust and air pollution (Annesi-Maesano et al., 2012).

Circadian rhythms are ubiquitous in mammals governing many aspects of cellular and behavioral physiology. Circadian rhythms are endogenous oscillators with periods of approximately 24 h, which are generated by networks of central and peripheral clocks. Many immune parameters show systematic fluctuations over the 24 h day in human blood (Lange et al., 2010). The circadian information is transmitted to immune tissues by neural and endocrine signals and most, if not all, immune cells contain molecular clock components which have been shown to mediate immune responses, including natural-killer cell (NK) cytotoxicity, phagocytosis and inflammation (Logan et al., 2012).

In this bachelor thesis the effect of the time of day on the symptoms related to allergic rhinitis will be discussed. To come to this, there will be discussed if there is an effect of the time of day in the availability of allergens of allergic rhinitis, how the immune system responds to allergens in allergic rhinitis, and how the immune response is influenced by circadian rhythmicity. Also therapies on allergic rhinitis and their effectiveness related to the time of day will be discussed.

Rhythmicity in pollen emission

Airborne pollen are the key allergens to patients of allergic rhinitis. For an effective avoidance of the airborne pollen and treatment of allergic rhinitis, it is necessary to know at which time of the day there is the greatest risk to inhale the pollen. There can be a diurnal or a circadian rhythm in the emission of pollen. Also weather can be of influence.

According to Spieksma et al. (1986) the highest concentrations of airborne grass-pollen grains are observed in the afternoon, between 12:00 h and 16:00 h. At this time advection occurs from distant dry inland source areas. The afternoon peak is likely caused by the release of pollen grains from the anthers in the course of the day. The release of pollen is mediated by solar radiation and moderate wind speeds. Also the decrease of turbulence and convection in the afternoon might add to the pollen concentration in the lower atmosphere (Steel, 1983). The second high concentration period, in the study of Spieksma et al. (1986) is observed during the night. The occurrence depends on several processes: advection during dry weather conditions, stable temperature, the onset of fall-out of pollen grains, which are released during the daytime and absence of dew or shallow fogbanks in the open field, which often develop in the late night period (Steel, 1983).

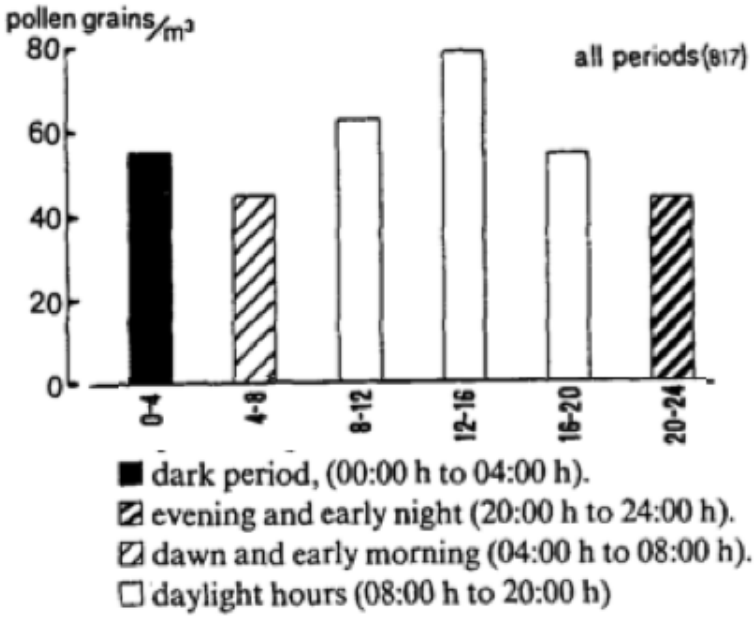

Figure 1 – From: Spieksma et al. (1986). Average concentrations of grass pollen (grains/m3) in the 6 four-hour periods of the day, June and first half of July, 1979, 1980, 1981; Leiden, The Netherlands.

Concentrations of Airborne grass-pollen are low when the source area, from where the air is advected, is wet by past or present rain, dew or fog. According to Spieksma et al. (1986), nightly peak concentrations may occur after a pollen productive day, with a not too large mixing height in the afternoon, and the development of pollen concentrating meteorological processes during the night, such as temperature inversion of the air, fall out of pollen grains, and the absence of permanent deposition of pollen grains and of dew or fog (Spieksma et al., 1986).

Norris-Hill and Emberlin (1991) have determined the diurnal variation in three types of pollen in the urban area. Small differences in pollen concentration are shown in their study as a result of changes in wind direction and temperature.

Kasprzyk et al. (2001) analyzed the incidence of airborne pollen at 5 sites in Poland. They found that there was no regional or annual difference in composition. Between years, there was only a difference in spring. According to Kasrzyk et al. (2001) there can be made a distinction between a regular pollen grain occurrence group and an irregular pollen grain occurrence group. In this study, three herb plants were looked at, Secale, Artemisia and Urtica. All of the herb plants were in the regular pollen grain occurrence group. The diurnal variations of concentration of pollen grains of these plants were constant and similar between sites and years. In all sites, a clear maximum was found in the middle of the day. In the evening and at night the concentrations of pollen were at a minimum. Also noticed by Kasrzyk et al. (2001) is that in Spain the maximum of pollen concentration was observed at midday, when the temperature is highest (Trigo et al., 1996), while in England it was observed in the early afternoon (Corden and Millington, 1991). This difference in results can be explained by the difference in climate. The diurnal pattern of Artemisia was more constant than the pattern of Urtica, although the genus Artemisia has many species, while there is only one common species of Urtica. This may be due to the fact that Urtica pollen grains are small and light and remain longer in the air. The second group is the irregular pollen grain occurrence group, which in the study of Kasrzyk et al. (2001) contains Alnus, Betula and Poaceae. The pollen in this group show irregular diurnal presence, with one or more maxima, and show no similarity between sites and years.

Studies on the circadian periodicity of Poaceae airborne pollen are ambiguous. In London two maxima are found, in the evening and at night (Norris-Hill and Emberlin, 1991). In Spain the maximum concentration was observed before noon (Galan et al., 1991). Possible cause of the difference in concentration of airborne pollen in the different sites is that the family of Poaceae has a large number of species opening their anthers at different times. Poaceae species also have a characteristic phenology of blooming. Norris-Hill and Emberlin (1991) report that meteorological factors, especially temperature, can also influence the diurnal periodicity of pollen grains. Examination by Kasrzyk et al. of results obtained in Finland, Spain, England and Poland confirms, that circadian periodicity of Poaceae pollen concentration is very irregular, differs between sites and between years and depends on several factors (Kasrzyk et al., 2001).

Meeuse and Morris (1984) reported that *Alnus* and *Betula* start to pollinate at about 2 p.m., when the temperature is the highest during the day. Their diurnal maxima were observed in the afternoon and in the evening as well as at night and in the early morning. In Poaceae, the time of pollen emission may be very long during the day) and is

related to the particular species that occur in the vicinity of sampling sites. Therefore, in the case of *Alnus, Betula* and Poaceae there is no clear relation between the time of anthesis, when the anther is fully open, and the time of diurnal maxima of pollen concentration (Mas´lankiewicz, 1957; Kasrzyk et al., 2001). According to Mas´lankiewicz (1957), *Secale cereale* opens its anthers between 6:00 h and 7:00 h. The maximum diurnal concentration of airborne pollen was observed from two to eight hours later. The lag is possibly induced by such weather conditions as speed and direction of wind, or air turbulence and the distance from pollen sources (Subba Reddi and Reddi, 1985).

The results of the study done by Kasrzyk et al. (2001) of diurnal periodicity of allergenic pollen also have a practical aspect as they can be used in the pollen forecasts. For example in Poland, persons allergic to *Urtica* pollen grains should avoid contact with pollen just before noon and in the afternoon, while those allergic to *Artemisia* pollen should stay indoors in the morning. Patients suffering from pollinosis because of Poaceae, *Alnus* and *Betula* allergens can be subjected to them almost all day, even at night. In general the concentration of those allergens is only low in the early morning (Kasrzyk et al., 2001).

The above studies showed that there is some predictability of the concentration of pollen over the day. Weather conditions and speed and direction of the wind seem to be a great factor. Therefore, there is some day by day variation between sites. The question that arises now is whether the immune system is adapted to the predictability of the concentration of pollen.

Circadian influences on the immune response

The immune system reacts to the allergens in the nasal mucosa. For understanding the basic mechanisms of allergic rhinitis, it is necessary to know if there is a circadian rhythm in the immune system, related to allergic rhinitis. A rhythm in the immune system can be beneficial. By dividing power of the reaction over the day, the reaction can become more effective. When the availability of allergens is low, the immune system does not have to react as alert as when the availability of allergens is high. In this part, an overview of the occurrence of symptoms over the day, as well as the mechanism of the response will be given.

Nicholson and Bogie in 1973 had 246 unmedicated British hay fever sufferers identify the time of day when their most troublesome symptoms, i.e., sneezing, wheezing, red itchy eyes, and stuffy nose, commenced. Each of the symptoms was found to occur most frequently before breakfast and in the morning and least frequently in the middle of the day. Overall, approximately 75% of the subjects indicated that their allergic rhinitis symptoms occurred overnight or in the morning (Nicholson and Bogie, 1973).

Binder et al. (1982) also explored the day–night distribution of allergic rhinitis symptoms in two groups of presumably untreated subjects. Recall methods were used to obtain information about the time of day of dominating symptoms. One group consisted of 512 persons who had a medical history of perennial allergic rhinitis, and the other consisted of 462 persons with a medical history of seasonal allergic rhinitis. Sneezing was the most common symptom of both seasonal (55% of participants) and perennial (42% of participants) allergic rhinitis, consistent with the study of Nicholson and Bogie. Nasal congestion (16%) and rhinorrhea (26%) were the next most common symptoms, which were experienced by the participants. About 10% experienced dyspnea, which is as a main symptom indicative for asthma. 56% of the seasonal and 66% of the perennial allergic rhinitis participants reported their most severe symptom occurred in the morning. Only a small proportion stated their most severe symptom occurred in the evening or at night (Binder et al., 1982).

Reinberg et al. in 1988 utilized a different and more thorough method to investigate and quantify the diurnal variation in allergic rhinitis symptom intensity. This chrono-epidemiologic study involved a total of 765 medication-free allergic patients who were recruited from 17 different clinical centers throughout France. The diagnosis of allergic rhinitis was based on conventional clinical criteria: positive skin reaction to allergens, total and differential white cell count, immunoglobulin E concentration, and medical history. Each participant self-assessed the severity of the allergic rhinitis symptoms using 100 mm visual analog scales (VAS) at least four times daily. The clock times of the self-assessments done by the 765 participants were almost uniformly distributed between 6:00 h and 12:00 h. The symptoms of sneezing, nasal congestion, and nasal rhinorrhea were most severe in the morning. There was a second peak in the early evening. The temporal pattern in symptom intensity was similar in men and women, in smokers and nonsmokers, and participants having only a recent or long medical history of allergic rhinitis. The magnitude of the variation over time of the response of each

individual symptom amounted to roughly 20–25% of its overall mean score, which was derived from all the self-assessment scores of each individual symptom (Reinberg et al., 1988). This clearly demonstrates that the immune system is differentially sensitive to stimuli at different times of the day.

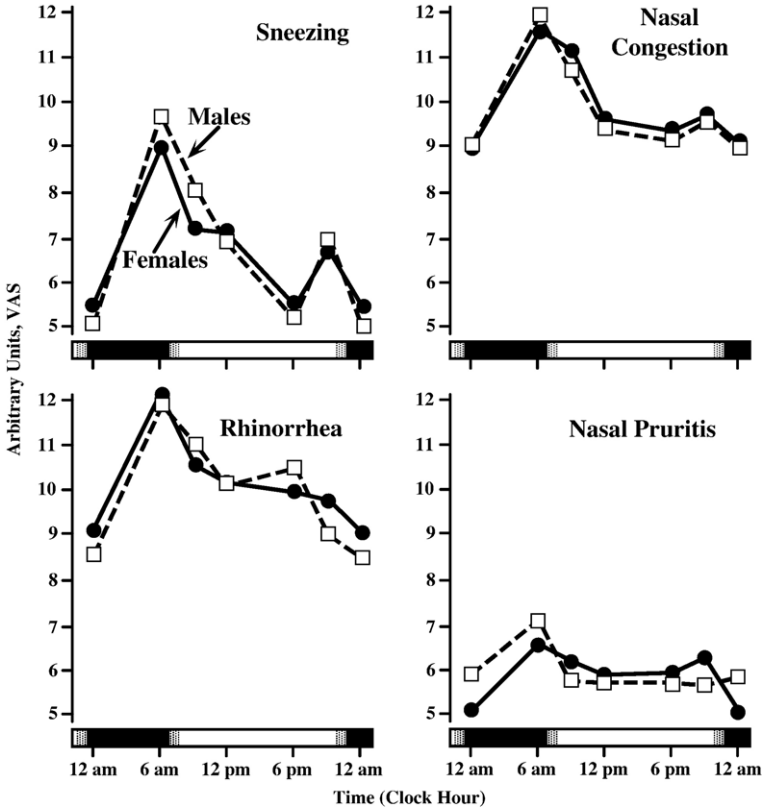

Figure 2 – From: Smolensky et al., 2007 based on data from Reinberg et al., 1988. Diurnal variation in allergic rhinitis symptoms — sneezing, nasal congestion, rhinorrhea and pruritis. Self-assessments were performed using visual analogue scales four equally spaced times during the waking span for 1 week. On average, the severity of all the symptoms was greatest in the morning, both in men and women. Open and shaded portions of the time axis indicate the clock time of activity and sleep of subjects.

The day–night difference in allergic rhinitis symptoms intensity may also represent, at least to some extent, circadian rhythm differences in nasal tissue vulnerability to allergen exposure (Aoyagi et al., 1999). Aoyagi et al. exposed groups of allergic rhinitis and non-allergic rhinitis medication-free children, with an average age of 11.3 years, to a 12 mg aerosol methacholine nasal challenge at two different times of the day, 6:00 h and 15:00 h. Nasal secretions were collected for 10 min after each clock-time challenge. The volume of nasal secretions collected following the 6:00 h challenge was significantly greater than that collected after the 15:00 h challenge. A greater concentration of inflammatory and related mediator chemical substances, eosinophil cationic protein, histamine, and tryptase, was detected in the nasal secretions of allergic rhinitis subjects following the morning than afternoon challenge. The findings of this two-time of day study on young children document a morning–afternoon difference in the concentration of inflammatory activation products in nasal secretions induced by the methacholine

chemical challenge. Such a day–night variation in nasal reactivity suggests a circadian rhythm-dependent difference in the ability of specific allergens as well as non-specific chemical substances to induce pro-inflammatory activities in the upper respiratory tract tissue (Aoyagi et al., 1999; Smolensky et al. 2007).

The above reviewed studies relied either on recall of the clock time or span of day when allergic rhinitis symptoms commenced or were most intense, or they relied on self-ratings done at specific times only during the daytime. None of these studies were specifically designed to gather data on symptom intensity during the night. More recent investigations document the inflammation, manifested as nasal congestion and nasal obstruction, of allergic rhinitis (Smolensky et al., 2007). They worsen significantly nocturnally, presumably due to so-called late-phase response pathophysiologic phenomena, staging of certain endogenous circadian rhythms, and supine posture for sleep, as discussed below (Smolensky et al., 2007). The findings of many studies show that the nasal congestion and obstruction of allergic rhinitis can become so great during the night that the sleep of moderately and severely affected persons can be disturbed, compromising quality of life with difficulty in awakening in the morning, daytime fatigue, poor daytime concentration, poor work and school performance, and altered or depressed mood and irritability. Taken together, many studies indicate the manifestation and severity of allergic rhinitis display marked and predictable 24-h variation (Smolensky et al., 2007). Symptoms are likely to be much more intense nocturnally, during intended sleep, and/or in the early morning on awakening (Stuck et al., 2004). During sleep, air exchange between the lungs and environment occurs primarily through the nose. The exacerbation of nasal rhinorrhea, congestion, and obstruction, due to the late-phase response, neuroendocrine circadian rhythms, and change in posture (from upright to supine) can easily impair the quality and continuity of nighttime sleep. The upper airway obstruction that results from nasal congestion is a known risk factor for sleep-disordered breathing events, i.e., apneas (momentary absence of breathing), hypopneas (shallow/slow breathing), and snoring (Smolensky et al., 2007). Compared to non-congested subjects, nasally congested allergic rhinitis sufferers are at nearly double the risk of moderate to severe sleep-disordered breathing (Young et al., 1997). Furthermore, allergic rhinitis sufferers are prone to fragmented sleep, as demonstrated by a tenfold greater number of microarousals (brief awakenings), compared to non-allergic rhinitis control subjects, that occur in association with episodes of periodic breathing, hypopnea, and hyperpnoea (abnormal deep/rapid breathing) during sleep (Lavie et al., 1981). The known consequences of allergic rhinitis are several and include daytime fatigue and somnolence, poor daytime performance, irritability and depression, and altered quality of life. Another yet to be explored and feasible clinical consequence of allergic rhinitis and associated sleep apnea disorder could include nocturnal (sleep-time) hypertension, which can increase one's risk of renal, heart, and blood vessel pathology (Smolensky et al., 2007).

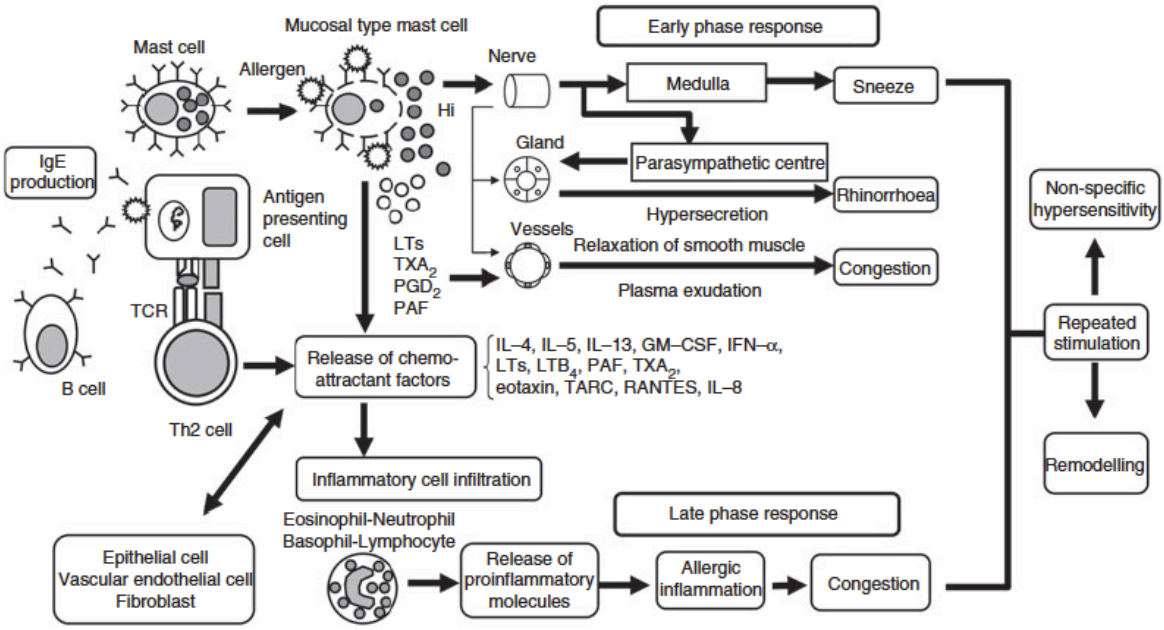

Figure 3 – From: Okano et al., 2009. Pathophysiology of allergic rhinitis. After allergens are inhaled into the nasal mucosa of sensitized subjects, they bind to immunoglobulin (Ig)E on the surface of mast cells, inducing the release of chemical mediators. The early-phase response, which is characterized by sneezing, rhinorrhoea and nasal congestion, is the response of the sensory nerve terminals and blood vessels on the nasal mucosa to these chemical mediators. After the nasal exposure to allergen, infiltration of inflammatory cells. This inflammation, referred to as the late-phase response, develops 6–10 h after allergen challenge and causes prolonged nasal congestion.

Besides the symptoms of allergic rhinitis, it is necessary to understand the mechanisms underlying the pathophysiology. The mechanisms of the 24-h pattern in allergic rhinitis symptom occurrence and severity have yet to be completely elucidated. Here I present an overview of what is known about the mechanisms.

When allergic rhinitis subjects inhale allergens, the allergens pass through the epithelial tight junctions in the nasal mucosa to bind immunoglobulin E on the surface of mast cells in the epithelial layer of the nasal mucosa. In the epithelial layer of the nasal mucosa the release of chemical mediators including histamine, prostaglandins and cysLTs by aggregation of FceRI is induced (Okano, 2009). Histamine regulates tight junctions via the coupling of histamine receptors and increases paracellular permeability (Flynn et al., 2009). This increased permeability allows dendritic cells to penetrate epithelial tight junctions easily and enhance allergen presentation to T cells (Takano et al., 2005).

Experimental studies reveal challenge of the nasal tissue of allergic rhinitis subjects with specific allergens, e.g., grass pollens results in both early (developing within minutes) and late (developing several hours later) phase responses (Smolensky, 2007).

The late-phase response, which may not be fully developed and manifested until 12–16 hours after the initial allergen exposure earlier in the day, primarily involves cellular events, i.e., the elaboration, adhesion, and infiltration of circulating leukocytes, T cells,

and eosinophils, in particular. Eosinophils when chemically activated release histamine, prostaglandins, and leukotrienes, resulting in local vasomotor changes and local tissue edema, inflammation, and injury, plus mucus secretion (Smolensky et al., 2007). The early-phase response in allergic rhinitis typically evokes the symptoms of sneezing, nasal itch, and rhinorrhea, while the late-phase response typically evokes the symptoms of nasal congestion and obstruction due to the exacerbation of inflammation of the nasal, sinus, and other tissue of the upper airway (Storms, 2004; Smolensky et al., 2007). The worsening of nasal rhinorrhea and congestion nocturnally arises mainly from the exacerbation of inflammation of the nasal mucosa as a manifestation of the late-phase response to provoking environmental allergens encountered earlier in the day. The greater severity of late-phase allergic rhinitis symptoms, i.e., nasal congestion, obstruction, and rhinorrhea, than the early-phase response ones, could also involve key neuroendocrine circadian rhythms. For example, cortisol, which modulates tissue inflammation, attains near peak or peak blood concentration in the morning around the time of commencing daily activity and remains elevated throughout the waking span; cortisol declines in the late evening and reaches its lowest concentration of the 24 h around the middle of the nighttime sleep period. The circadian rhythms in adrenaline and noradrenaline may also be involved since they can play a role in controlling the trafficking of eosinophils and the stability of their membranes. The circadian rhythm in adrenaline could result in differential release of pro-inflammatory mediator substances during the 24 h (Smolensky et al., 2007). In this regard, plasma histamine and other eosinophil-derived mediators are circadian rhythmic in bronchial asthmatic subjects; plasma histamine concentrations are greatest during the night when plasma adrenaline and noradrenaline concentrations are lowest (Barnes et al., 1980).

In healthy individuals there is a good balance between the T-helper type 1 cells and the T-helper type 2 cells. In allergic rhinitis patients there is an inbalance between the T-helper type 1 cells and the T-helper type 2 cells with a surplus of the T-helper type 2 cells. The T-helper type 2 cells are the key effector cells in the mediation of allergic diseases (Akdis et al., 2004). Early IL-4 and thymic stromal lymphopoietin (TSLP) produced by basophils in response to allergens with protease activity may contribute to the differentiation of T-helper type 2 cells. These T-helper type 2 cells induce the production of immunoglobulin E by producing interleukins IL-4, IL-5 and IL-13 and expressing CD40L (Romagnani et al., 1994). CD40L promotes the class switching of B cells to immunoglobulin E (Okano, 2000). Interleukins such as IL-4, IL-5, IL-13 and granulocyte–macrophage colony stimulating factor (GM-CSF) are produced mainly in T-helper type 2 cells and mast cells. However, eosinophils also have the potential to produce these cytokines (Hogan et al., 2008). Chemical mediators such as platelet-activating factor (PAF), leukotriene B4 (LTB4), cysteinyl leukotrienes (cysLTs) and thromboxane A2 (TXA2) are also released mainly from mast cells and eosinophils (Durham et al., 1992). Chemokines such as eotaxin, chemokine ligand 5 (CCL5) and thymus and activation regulated chemokine (TARC) are produced mainly in fibroblasts, epithelial cells and vascular endothelial cells (Okano, 2009; Takahashi et al., 2006). Pro-inflammatory cytokines such as tumor necrosis factor, TNF-α, are also produced and participate in allergic inflammation (Marcucci et al., 2001; Iwasaki et al., 2003). The sensitivity of the nasal mucosa to different stimulants increases along with the progress of allergic inflammation in the nasal mucosa. The increased sensitivity is referred to as the priming effect (Bousquet et al., 1996). The secondary reaction with inflammatory cells and their mediators, especially the cysLTs produced by eosinophils, causes oedema

of the nasal mucosa (Fujita et al., 1999; Okano 2009).

Much is known about the mechanism and pathophysiology of allergic rhinitis. Also research has been done on the occurrence of symptoms over the day. Further research is needed to indicate a circadian component in the immune response to allergic rhinitis. The pattern in the occurrence of symptoms over the day gives an implication of a circadian component. Although, when the occurrence of allergens is rhythmic over the day there can be rhythmicity in the occurrence of symptoms over the day even when the immune system acts independently on the time of the day. The pattern of occurrence of symptoms over the day can be taken into account in the treatment of allergic rhinitis.

Therapies

When not treated properly, allergic rhinitis can cause a severe chronic upper-airway disease (Bousquet et al., 2009). Also allergic rhinitis can cause a decrease in the quality of life. Patients can have difficulties as fatigue, irritability and reduced alertness. These difficulties can lead to lower work performance in adults and a learning impairment in children (Arrighi et al., 1996). Allergic rhinitis impairs the health related quality of life as much as asthma (Leynaert et al., 2000). Appropriate treatment of allergic rhinitis is important to prevent the accumulation into a severe chronic upper-airway disease as well to maintain the quality of life. The therapeutic approach contains: avoiding allergens, pharmacotherapy and immunotherapy.

Allergen avoidance
The immune response is activated by allergens. When allergens are completely avoided the immune response won't be activated. Complete avoidance and reduction of allergens is very hard to achieve. Pollen cannot access the nasal mucosa when a nasal filter is used, leading to reduction of the symptoms of allergic rhinitis (O'Meara et al., 2005). Pollen are the key allergens of allergic rhinitis, the non-specific stimuli, e.g. changes in temperature and pollution should be avoided as well. Reduction of pollen can be established through limiting the amount of time spent out-doors, especially during peak pollen seasons. In-doors the use of an air conditioner and keeping the windows closed are of help.

Pharmacotherapy
Pharmacotherapy is the treatment of disease through the administration of drugs. There is a variety of types of pharmacotherapy to allergic rhinitis e.g. histamine-receptor antagonists also antihistamines, decongestants, and anti-inflammatory drugs (luekotriene-receptor antagonists and modifiers and aerosol glucocorticoid). Antihistamines and corticosteroids are the major used types of pharmacotherapy in treatment of allergic rhinitis.

Antihistamines
Antihistamines are the first-line of pharmacological treatments recommended for all patients with allergic rhinitis. These agents have been found to effectively reduce sneezing, itching and rhinorrhea when taken regularly at the time of maximal symptoms or before exposure to an allergen. Older types of antihistamines have a negative impact on cognition and functioning and, therefore, they are not routinely recommended for the treatment of allergic rhinitis (Small et al., 2007).

Corticosteroids
Intranasal corticosteroids are also first-line therapeutic options for patients with allergic rhinitis. When used regularly and correctly, intranasal corticosteroids effectively reduce inflammation of the nasal mucosa and improve mucosal pathology. Studies and meta-analyses have shown that intranasal corticosteroids are superior to antihistamines and leukotriene receptor antagonists in controlling the symptoms of allergic rhinitis,

including nasal congestion, and rhinorrhea (Yanez et al., 2002). They have also been shown to improve ocular symptoms and reduce lower airway symptoms in patients with concurrent asthma and allergic rhinitis (Watson et al., 1993). Ideally, intranasal corticosteroids are best started just prior to exposure to relevant allergens and, because their peak effect may take several days to develop, they should be used regularly (Lee et al., 2009).
It is important to note that most patients with allergic rhinitis presenting to their primary-care physician have moderate-to-severe symptoms and will require an intra-nasal corticosteroid. Bousquet et al. (2003) noted improved outcomes in patients with moderate-to-severe symptoms treated with a combination of these agents.
Oral corticosteroids have also been shown to be effective in patients with severe allergic rhinitis that is refractory to treatment with oral antihistamines and intranasal corticosteroids (Lee et al., 2009). Intramuscular corticosteroid injections are associated with potentially severe adverse events such as systemic side effects and subcutaneous and muscular necrosis and are therefore not recommended (Nasser et al., 2001).

Immunotherapy
By contrast with symptom suppression by pharmacotherapy, immunotherapy aims to alter the immune system by sensibilize it through allergens and could represent a cure for allergic rhinitis. Subcutaneous immunotherapy is effective in people with allergic rhinitis, with long-lasting reduction of symptoms and drug requirements, and it seems to prevent new sensitisations and asthma (Calderon et al., 2008; Greiner et al., 2011). Allergen immunotherapy involves the subcutaneous administration of gradually increasing quantities of the patient's relevant allergens until a dose is reached that is effective in inducing immunologic tolerance to the allergen. Allergen immunotherapy can be used when symptoms of allergic rhinitis are not controlled sufficiently with pharmacotherapy or who get side effects from drugs that restrict treatment choices. Although subcutaneous allergen immunotherapy is effective, a small but definite risk of inducing a systemic allergic reaction is possible, which arises in less than 0·1% of those treated. Patients should only be given subcutaneous allergen immunotherapy in clinics supervised by doctors who are trained and skilled in adjustment of doses of immunotherapy. Because of the risk of severe systemic side effects, patients need to be observed for 30-60 min after injection. The injections should only be undertaken in medical settings where resuscitation equipment and expertise are available.
Sublingual immunotherapy is also effective in adults and children (Canonica et al., 2009). It seems to be safer than subcutaneous immunotherapy because side-effects are usually restricted to the upper airways and gastrointestinal tract; rare anaphylactic episodes, but no deaths, have been reported (James et al., 2008). Although patients will be able to self-administer the sublingual formulation, close monitoring by a physician will still be required. Evidence suggests that clinical and immunological benefits of sublingual immunotherapy persist after 3 years of continuous use similar to benefits noted with subcutaneous immunotherapy. Furthermore, local oral changes unique to sublingual immunotherapy are seen (Durham et al., 2010; Greiner et al., 2011). Although further studies on longevity and concordance, especially in children, are needed, there is some cautiously optimism about sublingual immunotherapy as an effective treatment and possible preventer of asthma (Kuo et al., 2009). Note that mild, intermittent allergic rhinitis can generally be managed effectively with avoidance measures and oral antihistamines.

Knowing at which time of the day symptoms of allergic rhinitis occur, the time of treatment can be adjusted so that the treatment is most effective. Treatments can have side effects. Especially in the case of immunotherapy the side effects can be very dangerous. The occurrence of the symptoms over the day can be taken into account to avoid major reactions of side effects.

Chronopharmacology

Chronopharmacology is the study of biological rhythm influences, in relation to drug administration-time, on the pharmacokinetics and dynamics of medications and other chemical substances. Chronotherapy is either the delivery of medications in synchrony with endogenous biological rhythms to optimize treatment outcomes or the timed delivery of medications according to biological rhythm determinants to minimize or avoid troublesome and/or dose-limiting adverse events. In certain instances chronotherapy also entails the high frequency-modulated delivery of therapeutic agents (Smolensky et al., 2007).

Even though a large segment of the population suffers from allergic rhinitis, so far only the chronopharmacology of histamine-receptor antagonist medications have been explored (Smolensky et al., 2007).

Effect of antihistamine

The area of the cutaneous reactions to histamine, as well as several different antigens like house dust, grass pollens, and feathers, in persons is threefold greater on average in tests conducted in the evening, between 19:00 h and 23:00 h, than in the morning, between 7:00 h and 11:00 h (Smolensky et al., 2007). The high-amplitude circadian rhythm in the cutaneous reaction to histamine and antigens invalidates the findings of before–after test paradigms used to assess the potency, effect duration, and other pharmacodynamic parameters of antihistamine medications. The magnitude of the cutaneous reaction to intradermally injected histamine solution increases in a near linear manner from the morning to late evening and declines in a near linear manner from the late evening to morning. (Smolensky et al., 2007; Lee et al., 1977).

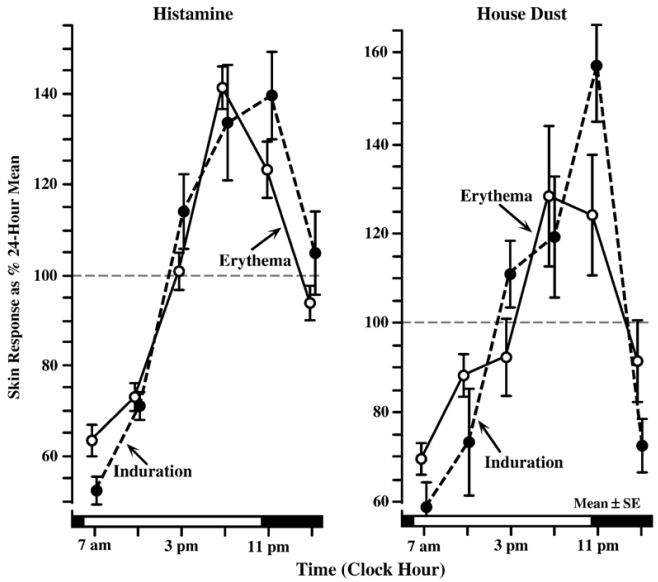

Figure 4 - Circadian rhythm in skin reactivity to intradermal injections of histamine, a mediator of allergic reactions (11 subjects) and house dust antigen (7 subjects). Tests were

conducted at 4-h intervals using sites of comparable cutaneous reactivity on the forearms. For histamine, reactivity is highest between 7 and 11 p.m., exceeding by 40% the 24-h mean area of the respective erythema and induration values, and it was lowest at 7 a.m., by 40% of the respective 24-h mean areas. (Figure drawn by Smolensky et al., 2007 using data of Lee et al., 1977).

The chronotherapy of allergic rhinitis takes into consideration the 24-h pattern in the manifestation and intensity of symptoms and known circadian differences in the pharmacodynamics of individual therapies (Smolensky et al., 2007). The subsequent discussion of the chronotherapy of allergic rhinitis focuses exclusively on histamine-receptor antagonist medications, since only these have been tested by acceptable investigative methods. The chronotherapy of other commonly prescribed medications, such as gluco-corticoids, luekotriene antagonists, vagolytics, and mast cell stabilizers, has yet to be explored in allergic rhinitis (Smolensky et al., 2007).

Surprisingly few studies have explored the role of the administration time of the histamine-receptor antagonists as a means of better controlling symptoms or drug-associated adverse effects.
Smolensky et al. (2007) reviewed the study of Reinberg et al. (1985). The administration-time differences in the effects of histamine-receptor antagonist mequitazine through a large multicenter study involving 1053 French allergic rhinitis patients. Different dose and morning and evening treatment-time schedules of mequitazine were trialed in comparable groups of adult allergic rhinitis subjects. Participants did self-assessments of allergic rhinitis symptom intensity as well as adverse drug effects at four equally spaced times during the daytime for a control day and thereafter for at least six consecutive days during treatment with one of seven different mequitazine regimens. Mequitazine was effective in moderating the morning peak and overall 24-h mean level of allergic rhinitis symptom intensity no matter the schedule trialed. However, its therapeutic effect was optimized when two-thirds or the entire daily dose was ingested around dinnertime. The medication was least effective when most or all the daily dose was ingested in the morning. Evening administration of the 10 mg dose was especially effective for persons who exhibited very prominent morning allergic rhinitis symptoms. No sedative effect of this histamine-receptor antagonist was observed, no matter the dosing time or schedule. The chronotherapy of the histamine-receptor antagonist medication mequitazine thus entails a treatment regimen in which most or the entire daily dose is ingested in the evening (Reinberg et al., 1985; Smolensky et al., 2007).

Research has been done on the effect of the time of administration of antihistamine on occurrence of symptoms in the morning. The antihistamines were most effective when taken in the evening. There is a circadian component in the occurrence of the symptoms of allergic rhinitis. By adjusting the time of treatment on the circadian component, the peak of effectiveness of the medication can be matched to the peak of the symptoms. Immunotherapy aims to alter the immune system by sensibilization. By taking the circadian component of the occurrence of the symptoms and the availability of pollen into account, the time of the treatment can be adjusted so that side effects can be limited.

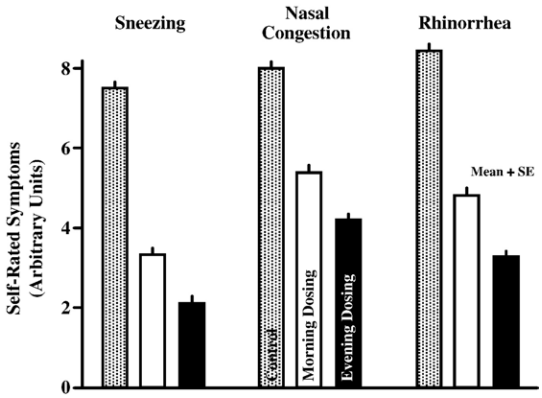

Figure 5 – From Smolensky et al., 2007 based on data from Reinberg et al., 1985 Chronoeffectiveness of the antihistamine (10 mg) mequitazine evaluated by control of the morning allergic rhinitis symptoms — sneezing, nasal congestion, and nasal rhinorrhea — of 98 allergic rhinitis subjects experiencing very intense morning symptoms of allergic rhinitis. Mequitazine, in comparison to the control baseline condition, reduced the severity of all the allergic rhinitis symptoms whether ingested in the morning or evening; however, evening dosing exerted best effect (p .005).

Discussion

In this bachelor thesis the effect of the time of day on the symptoms related to allergic rhinitis is discussed. There has been given insight on effect of the time of day in the availability of the key allergens of allergic rhinitis, how the immune system responds to allergens in allergic rhinitis, how the immune response is influenced by circadian rhythmicity. Also therapies on allergic rhinitis and their effectiveness related to the time of day are discussed.

In pollen, the key allergens in allergic rhinitis, there is no consistent circadian pattern. The emission of pollen depends mostly on weather conditions, but also on the taxa of the plant or tree. As a consequence there is large day to day variation. Yet, on average, a peak of airborne pollen can be found between 12:00 h and 16:00 h and a second peak during the night. These peaks occur when advection is from dry inland source areas. The concentration of airborne grass pollen is always low when the advected source area is wet by rain, dew or fog.
People living or working in large urban areas are more likely to suffer from allergic rhinitis than those from rural areas (Emanuel 1988). The peak concentrations occur mostly in the late afternoon and early evening, a time when many people are outdoors, returning from work, and so will be exposed to high concentrations of pollen.

Each of the allergic rhinitis symptoms was found to occur most frequently before breakfast and in the morning and least frequently in the middle of the day. Major symptoms are: sneezing, nasal congestion, rhinorrhea and nasal pruritus. After waking up, most people do not go outside before breakfast, so they won't have contact with pollen. Therefore the occurring symptoms in the morning have to be a delayed reaction to allergens. The early phase response of the immune system occurs within minutes after contact with allergens. The early-phase response represents the cascade of multiple mediators leading to sneezing, rhinorrhea and nasal congestion. The late phase, occurring several hours after contact with allergens, is mediated by molecular/cellular factors leading to inflammation of the nasal mucosa.

There are different types of treatment including pharmacotherapy and immunotherapy. Also avoidance is seen as a treatment to allergic rhinitis, effective but hard to accomplish. Immunotherapy is the second line of defense for a structural approach to desensitize the immune response. Antihistamines and corticosteroids are the major used types of pharmacotherapy in treatment of allergic rhinitis. Research has been done on the effect of the time of administration of antihistamine on occurrence of symptoms in the morning. The antihistamines were most effective when taken in the evening.

As indicated above, the availability of pollen is high in the afternoon and early evening. Therefore it is expected that the symptoms of the early phase will occur mostly in the afternoon and early evening. This seems not to be the case, the symptoms of the early phase are indicated to occur mostly in the morning. Antihistamine prevents the release of histamine, which is released just after contact with allergens. This lowers the early phase response as well as the late phase response. When antihistamine is taken just

after contact with allergens, the antihistamines are expected to be more effective. This is supported by the study of Reinberg et al., 1985 which indicates a more effective evening dose than the morning dose of antihistamines.

In pollen there seems to be a circadian component, although there is a great influence of weather conditions and wind direction and speed. There is a circadian pattern in the occurrence of symptoms of allergic rhinitis; a circadian pattern in the mechanism of the immune system has yet to be determined. The circadian component in the occurrence of symptoms of allergic rhinitis can be taken into account in the treatment of allergic rhinitis. There are circadian influences on allergic rhinitis, although further research, especially on the mechanism of the immune system has to be done.

References

Akdis M, Verhagen J, Taylor A, Karambloo F, Karaginnidis C, Crameri R, Thunberg S, Deniz G, Valenta R, Fiebig H, Kegel C, Disch R, Schmidt-Weber C, Blaser K, Akdis C. (2004). Immune responses in healthy and allergic individuals are characterized by a fine balance between allergen-specific T regulatory 1 and T helper 2 cells, *The Journal of Experimental Medicine,* 199(11), 1567–1575.

Annesi-Maesano I, Rouve S, Desqueyroux H, Jankovski R, Klossek J, Thibaudon M, Demoly P, Didier A. (2012). Grass Pollen Counts, Air Pollution Levels and Allergic Rhinitis Severity. *Int Arch Allergy Immunol*, 158(4), 397–404.

Aoyagi M, Watanabe H, Sekine K, Nishimuta T, Konno A, Shimojo N, Kohno Y. (1999). Circadian variations in nasal reactivity in children with allergic rhinitis: correlation with the activity of eosinophils and basophilic cells. *Int. Arch. Allergy Immunol*, 120 (Suppl 1), 95–99.

Arrighi HM, Cook CK, Redding GJ. (1996). The prevalence and impact of allergic rhinitis among teenagers. *J Allergy Clin Immunol*, 94, 430.

Barnes PJ, Fitzgerald G, Brown M, Dollery C. (1980). Nocturnal asthma and changes in circulating epinephrine, histamine, and cortisol. *N. Engl. J. Med.,* 303, 263–267.

Binder E, Holopainen E, Malmberg H, Salo O. (1982). Anamnestic data in allergic rhinitis, *Allergy,* 37, 389–396.

Bousquet J, Vignola AM, Campbell AM, Michel FB. (1996). Pathophysiology of allergic rhinitis. *Int Arch Allergy Immunol,* 110, 207–18.

Bousquet J, Lund VJ, Van Cauwenberge P, Bremard-Oury C, Mounedji N, Stevens MT, El-Akkad T. (2003). Implementation of guidelines for seasonal allergic rhinitis: a randomized controlled trial. *Allergy*, 58, 733–41.

Bousquet J, Bachert C, Canonica GW, Casale TB, Cruz AA, Lockey RJ, Zuberbier T. (2009). On behalf of the extended Global Allergy and Asthma European Network, World Allergy Organization and Allergic Rhinitis and its Impact on Asthma Study Group. Unmet needs in severe chronic upper airway disease (SCUAD). *J Allergy Clin Immunol*, 124, 428–33.

Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica G, Casale T, van Wijk R, Ohta K, Zuberbier T, Schunemann J. (2010). Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J. Allergy Clin. Immunol.*, 126(3), 466–476.

Calderon MA. (2008). Meta-analyses of specific immunotherapy trials. *Drugs Today (Barc),* 44 (suppl B), 31–34.

Canonica GW, Bousquet J, Casale T, Lockey R, Baena-Cagnani C, Pawankar R, Potter P,

Bousquet PJ, Cox LS, Durham SR, Nelson HS, Passalacqua G, Ryan DP Brozek JL, Compalati E, Dahl R, Delgado L, van Wijk RG, Gower RG, Ledford DK, Filho NR, Valovirta EJ, Yusuf OM, Zuberbier T. (2009). Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy*, 64 (suppl 91), 1–59.

Corden JM, Millington WM. (1991) A study of Gramineae and Urticaceae pollen in the Derby area. *Aerobiologia,* 7, 100–106.

Durham SR, Ying S, Varney VA, Jacobson MR, Sudderick RM, Macaky IS, Kay AB, Hamid QA. (1992). Cytokine messenger RNA expression for IL-3, IL-4, IL-5, and granulocyte/ macrophage colony-stimulating factor in the nasal mucosa after local allergen provocation: relationship to tissue eosinophilia. *J Immunol*, 148, 2390-2394.

Durham SR, Emminger W, Kapp A, Colombo G, Monchy JG, Rak S, Scadding GK, Andersen JS, Rijs B, Dahl R. (2010). Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol*, 125, 131–8.

Durham SR, Birk AO, Andersen JS. (2011). Days with severe symptoms: an additional efficacy endpoint in immunotherapy trials. *Allergy*, 66(1), 120–123.

Emanuci MB. (1988). Hay fever, a post industrial revolution epidemic: a history of its growth during the 19th century. *Clin. Allergy,* 18, 295-301.

Flynn AN, Itani OA, Moninger TO, Welsh MJ. (2009). Acute regulation of tight junction ion selectivity in human airway epithelia. *Proc. Natl. Acad. Sci. U.S.A.*, 106(9), 3591–3596.

Fujita M, Yonetomi Y, Shimouchi K, Takeda H, Aze Y, Kawabata K, Ohno H. (1999). Involvement of cysteinyl leukotriens in biphasic increase of nasal airway resistance of antigen-induced rhinitis in guinea pigs. *Eur J Pharmacol*, 369, 349–56.

Galan C, Tormo R, Cuevas J, Infante F, Domingez E. (1991). Theoretical daily variation patterns of airborne pollen in the South-West of Spain. *Grana*, 30, 201–209.

Greiner AN, Hellings PW, Rotiroti G, Scadding GK. (2011). Allergic rhinitis. *Lancet*, 378, 2112–2122.

Hogan SP, Rosenberg HF, Moqbel R, Phipps S, Foster PS, Lacy P. (2008). Eosinophil: biological properties and role in health and disease. *Clin Exp Allergy*, 38, 709–50.

Iwasaki M, Saito K, Tekemura M, Sekikawa K, Fuji H, Yamada Y, Wada H, Mizuta K, Seishima M, Ito Y. (2003). TNF-alpha contributes to the development of allergic rhinitis in mice. *J Allergy Clin Immunol*, 112, 134–40.

James LK, Durham SR. (2008). Update on mechanisms of allergen injection immunotherapy. *Clin. Exp. Allergy*, 38(7), 1074–1088.

Kasprzyk I, Harmata K, Myszkowska D, Stach A, Stepalska D. (2001). Diurnal variation of chosen airborne pollen at five sites in Poland. *Aerobiologia*, 17, 327–345.

Ko CH, Takahashi JS. (2006). Molecular components of the mammalian circadian clock. *Hum. Mol. Genet.* 15 (Spec No 2), R271-7.

Kuo CH, Wang WL, Chu YT, Lee MS, Hung CH. (2009). Sublingual immunotherapy in children: an updated review. *Pediatr Neonatol*, 50, 44–49.

Lange T, Dimitrov S, Born J. (2010). Effects of sleep and circadian rhythm on the human immune system. *Ann. N. Y. Acad. Sci,* 1193, 48–59.

Lavie P, Gertner R, Zomer J, Podoshin L. (1981). Breathing disorders in sleep associated with "microarousals" in patients with allergic rhinitis. *Acta Otolaryngol*, 92, 529–533.

Leynaert B, Neukirch C, Kony S, Guenegou A, Bousquet J, Aubier M, Neukirch F. (2004). Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol*, 113, 86–93

Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F. (2000). Quality of life in allergic rhinitis and asthma: a population-based study of young adults. *Am J Respir Crit Care Med*, 162, 1391–96.

Lee P, Mace S. (2009). An approach to allergic rhinitis. *Allergy Rounds*, 1.

Lee RE, Smolensky MH, Leach C, McGovern JP. (1977). Circadian rhythms in cutaneous sensitivity to histamine and selected antigens including phase relationship to urinary cortisol excretion. *Ann. Allergy,* 38, 231–236.

Logan RW, Sarkar DK. (2012). Circadian nature of immune function. *Molecular and Cellular Endocrinology*, 349(1), 82–90.

Magnan A, Meunier JP, Saugnac C, Gasteau J, Neukirch F. (2008). Frequency and impact of allergic rhinitis in asthma patients in everyday general medical practice: a French observational cross-sectional study. *Allergy*, 63(3), 292–298.

Marcucci F, Sensi LG, Migali E, Coniglio G. (2001). Eosinophilic cationic protein and specific IgE in serumand nasalmucosa of patients with grass-pollen-allergic rhinitis and asthma. *Allergy*, 56, 231–6.

Mas´lankiewicz K. (1957). *Mała Encyklopedia Przyrodnicza,* Warszawa, PWN.

Maurer M, Zuberbier T. (2007). Undertreatment of rhinitis symptoms in Europe: findings from a cross-sectional questionnaire survey. *Allergy*, 62(9), 1057–1063.

Meeuse B, Morris S. (1984). *Sex life of flowers,* London-Boston, Faber and Faber.

Nasser SMS, Ewan PW. (2001). Depot corticosteroid treatment for hay fever causing avascular necrosis of both hips. *BMJ*, 322, 1589–91.

Nicholson PA, Bogie W. (1973). Diurnal variation in the symptoms of hay fever: implications for pharmaceutical development. *Curr. Med. Res. Opin*., 1, 395–401.

Norris-Hill J, Emberlin J. (1991). Diurnal variation of pollen concentration in the air of north-central london, *Grana*, 30(1), 229-234.

Norris-Hill J. (1999). The diurnal variation of Poaceae pollen concentrations in a rural area. *Grana*, 38(5), 301–305.

Okano M, Satoskar AR, Abe M, Harn DA, Okano M, Nishizaki K, Takeda Y, Yoshino T, Brombacher F, Satokar AA. (2000). Interleukin-4-independent production of Th2 cytokines by nasal lymphocytes and nasal eosinophilia in murine allergic rhinitis. *Allergy*, 55(8), 723–731.

Okano M. (2009). Mechanisms and clinical implications of glucocorticosteroids in the treatment of allergic rhinitis. *Clinical & Experimental Immunology*, 158(2), 164–173.

O'Meara TJ, Sercombe JK, Morgan G, Reddel HK, Xuan W, Tovey ER. (2005). The reduction of rhinitis symptoms by nasal filters during natural exposure to ragweed and grass pollen. *Allergy*, 60, 529–32.

Reinberg A, Gervais P, Ugolini C, Del Cerrro L, Bicakova-Rocher A. (1985). A multicentric chronotherapeutic study of mequitazine in allergic rhinitis. *Annu. Rev. Chronopharmacol*, 3, 441–444.

Reinberg A, Gervais P, Lévi F, Smolensky MH, Del Cerro L, Ugolini C. (1988). Circadian and circannual rhythms of allergic rhinitis: an epidemiologic study involving chronobiologic methods. *J. Allergy Clin. Immunol*, 81, 51–62.

Romagnani S. (1994). Lymphokine production by human T cells in disease states. *Annu. Rev. Immunol.*, 12, 227–257.

Small P, Frenkiel S, Becker A, Boisvert P, Bouchard J, Carr S, Cockcroft D, Denburg J, Desrosiers M, Gall R, Hamid Q, Hébert J, Javer A, Keith P, Kim H, Lavigne F, Lemièr C, Massoud E, Payton K, Schellenberg B, Sussman G, Tannenbaum D, Watson W, Witterick I, Wright E. (2007). The Canadian Rhinitis Working Group: Rhinitis: A practical and comprehensive approach to assessment and therapy. *J Otolaryngol.,* 36(Suppl 1), S5-S27.

Small P, Kim H. (2011). Allergic rhinitis. *Allergy Asthma Clin Immunol*. 7 Suppl 1, S3.

Smolensky MH, Lemmer B, Reinberg AE. (2007). Chronobiology and chronotherapy of allergic rhinitis and bronchial asthma. *Adv. Drug Deliv. Rev.*, 59(9-10), 852–882.

Spieksma F, Tonkelaar JF. (1986). Four hourly fluctuations in grass pollen concentrations in relation to wet versus dry weather and to short versus long overland convection. *Int. J. Biometeorol.,* 30, 351- 358.

Steel HL. 1983. Grass pollen in the atmosphere and its effect on hayfever. *Weather,* 38(13), 139.

Storms WW. (2004). Pharmacologic approaches to daytime and nighttime symptoms of allergic rhinitis. *J. Allergy Clin. Immunol.*, 114(5 Suppl), S146–53.

Stuck BA, Czajkowshi J, Hagner AE, Klimek L, Verse T, Hörmann K, Maurer TJ. (2004). Changes in daytime sleepiness, quality of life, and objective sleep patterns in seasonal allergic rhinitis: a controlled clinical trial. *J. Allergy Clin. Immunol.*, 113, 663–668.

Subba Reddi C, Reddi NS. (1985). Relation of pollen release to pollen concentrations in air. *Grana,* 24, 109–113.

Takano KI, Kojima T, Go M, Murata M, Ichimiya S, Himi T, Saw ada N. (2005). HLA-DR- and CD11c-positive dendritic cells penetrate beyond well-developed epithelial tight junctions in human nasal mucosa of allergic rhinitis. *J. Histochem. Cytochem.,* 53(5), 611–619.

Trigo M, Cabezduzo B, Recio M, Toro FJ. (1996). Annual, daily and diurnal variations of Urticaceae airborne pollen in Málaga (Spain). *Aerobiologia,* 12, 85–90.

Yanez A, Rodrigo GJ. (2002). Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol*, 89, 479-484.

Young T, Finn L, Kim H. (1997). Nasal obstruction as a risk factor for sleep- disordered breathing, *J. Allergy Clin. Immunol*. 99, S757–S762 (Suppl).

Watson WT, Becker AB, Simons FER. (1993). Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway hyperresponsiveness. *J Allergy Clin Immunol,* 91(1 Pt 1), 97-101.