Magnesium depletion with hypo- or hyper-function of the biological clock may be involved in chronopathological forms of asthma

J. Durlach1, N. Pagès2, P. Bac3, M. Bara4, A. Guiet-Bara4
1 SDRM, Université Pierre et Marie Curie, 75252 Paris Cedex 05, France; 2 Laboratoire de Toxicologie, Faculté de Pharmacie, Strasbourg, 67400 Illkirch-Graffenstaden, France; 3 Laboratoire de Pharmacologie, Faculté de Pharmacie, Paris XI, 92290 Chatenay-Malabry, France; 4 Laboratoire de Physiologie et de Pathologie, UPMC, 75252 Paris Cedex 05, France

Correspondence: Dr. Jean Durlach, Président de la SDRM, Rédacteur en Chef de Magnesium Research, 64 Rue de Longchamp, 92200 Neuilly-sur-Seine, France or Dr. N. Pagès, 12 Rue R. Thomas, 91400 Saclay, France <jean.durlach@wanadoo.fr>, <nicole.pages4@wanadoo.fr>

Abstract. Asthma is a chronic, inflammatory disorder of the airways leading to airflow limitation. Its worldwide rise, mainly in developed countries, is a matter of concern. Nocturnal asthma (NA) frequently occurs and concerns two thirds of asthmatics. But, it remains controversial whether NA is a distinct entity or is a manifestation of more severe asthma. Generally, it is considered as an exacerbation of the underlying pathology. The pathological mechanisms most likely involve endogenous circadian rhythms with pathological consequences on both respiratory inflammation and hyperresponsiveness. A decrease in blood and tissue magnesium levels is frequently reported in asthma and often testifies to a true magnesium depletion. The link with magnesium status and chronobiology are well established. The quality of magnesium status directly influences the Biological Clock (BC) function, represented by the suprachiasmatic nuclei and the pineal gland. Conversely, BC dysrhythmias influence the magnesium status. Two types of magnesium deficits must be clearly distinguished: deficiency corresponding to an insufficient intake which can be corrected through mere nutritional Mg supplementation and depletion due to a dysregulation of the magnesium status which cannot be corrected through nutritional supplementation only, but requires the more or less specific correction of the dysregulation mechanisms. Both in clinical and in animal experiments, the dysregulation mechanisms of magnesium depletion associate a reduced magnesium intake with various types of stress including biological clock dysrhythmias. The differentiation between Mg depletion forms with hyperfunction of BC (HBC) and forms with hypofunction of BC (hBC) is seminal and the main biological marker is melatonin (MT) production alteration. We hypothesize that magnesium depletion with HBC or hBC may be involved in chronopathological forms of asthma. Nocturnal asthma would be linked to HBC, represented by an increase in MT levels. The corresponding clinical forms associate diverse expressions of nervous hypexcitability such as depression, cluster headaches, dyssomnia, mainly advanced sleep phase syndrome, some clinical forms of chronic fatigue syndrome and of fibromyalgia. The main comorbidities are depression and/or asthenia. They take place during the night or the “bad” seasons (autumn and winter) when sunshine is at a minimum. The corresponding chronopathological therapy relies on bright light phototherapy sometimes with additional psychoanaleptics. Conversely, asthma forms linked to
hBC are less frequently studied as a whole and present a decrease in MT levels. They associate various signs of nervous hyperexcitability such as anxiety, diurnal cephalalgia (mainly migraine), dyssomnia, mainly delayed sleep phase syndrome, and some clinical forms of chronic fatigue syndrome and of fibromyalgia. The treatment relies on diverse forms of "darkness therapy", possibly with the help of some psycholeptics. Finally, the treatment of asthma involves the maintenance of a standard dosing schedule of anti-asthma drugs, a balanced magnesium intake and the appropriate treatment of the chronopathological disorders.

Key words: asthma, magnesium-deficiency, hyperfunction of the biological clock (HBC), hypofunction of the biological clock (hBC), melatonin, phototherapy, darkness therapy

Introduction

Asthma is increasing in prevalence and severity worldwide despite effective treatment and innovative research developments [1]. It affects approximately 5% of the population and is a frequent cause of emergency hospital admission [2]. It is the most common inflammatory chronic disease in childhood [3-6]. Asthma is a chronic inflammatory disease of the airways, characterized by hyperresponsiveness to a variety of stimuli [7], and expiratory airflow limitation with recurring episodes of wheezing, dyspnea, tightness in the chest, and a cough that reverses after bronchodilator treatment [8]. The prognosis for asthma depends on the levels of obstruction and bronchial hyperresponsiveness [9].

Accumulating evidence points towards environmental factors in the cause of asthma, although which environmental factors are responsible is still not clear [10], but an important role for diet, obesity, and gastroesophageal reflux [6, 11, 12], genetic factors [13] and psychological factors [14, 15] have been implicated in determining individual susceptibility to asthma.

It has long been recognized that asthma presents a diurnal rhythm in its occurrence and severity of symptoms, with nocturnal worsening between 4 am and 8 am [16, 17]. It has been reported that up to 74% of asthmatics awaken at night at least once a week due to wheezing, chest tightness or coughing [18]. Nocturnal asthma (NA) indicates severe asthma and deaths generally occur between midnight and 8 am [19]. It is generally admitted that it results both from several circadian rhythms and the fading effect of medication administered at bedtime [20]. However, it remains controversial whether NA is a distinct entity or is a manifestation of more severe asthma [12].

We showed recently that different manifestations of the chronopathological forms of magnesium (Mg) depletion were regularly observed in various rather common pathologies including migraine, sudden infant death and multiple sclerosis [21-25] that greatly improved from treatments based upon these chronobiological data [26]. Magnesium deficiency corresponds to an insufficient intake which can be corrected through mere nutritional Mg supplementation, whereas Mg depletion, due to a dysregulation of the magnesium status, cannot be corrected through nutritional supplementation only, and requests the more or less specific correction of the dysregulation mechanisms. Depletion is frequently due to the association of a reduced magnesium intake with various types of stress including biological clock dysrhythmias. The differentiation between Mg depletion forms with hyperfunction and forms with hypofunction of the Biological Clock (BC) is seminal and the main biological marker is melatonin (MT) production alteration [24].

We hypothesize hereafter that some NA forms may correspond to chronopathological forms of asthma due to magnesium depletion with Hyperfunction of the Biological Clock (HBC). Correlatively, we show that some other forms of asthma among non-NA patients could be, on the contrary, linked to a magnesium depletion with hypofunction of the Biological Clock (hBC). It may be assumed that all these asthma patients must be treated with the same usual asthma treatment, the same balanced magnesium intake but will benefit from either light or darkness treatment according to their asthma chronobiological phenotype.

The aim of the present study is to consider: (i) the frequency of magnesium depletion in asthma (ii) the two opposite forms of associated chronopathological disorders i.e hyperfunction (HBC) or hypofunction (hBC) of the biological clock (BC) (iii) the interaction between magnesium and the various treatments with light (phototherapies) or dark (darkness therapies) on the chronopathological forms of magnesium depletion.
Magnesium deficit in asthma

Magnesium has been implicated in respiratory diseases although too often it was considered after extrapolation from pharmacological properties of parenteral magnesium [27, 28]. For example, MgSO4 bronchodilates asthmatic airways in vivo through direct relaxing effects [27-30] including calcium channel blocking properties, inhibition of cholinergic neuromuscular transmission with decreased sensibility to depolarizing action of acetylcholine, stabilization of mast cells and T-lymphocytes and stimulation of nitric oxide (NO) and prostacyclin [31-33].

Magnesium favors many pulmonary immunological defense mechanisms [33] and intervenes in melatonin regulation [23].

Hypomagnesemia in asthma

Relevant epidemiologic studies showed that plasma Mg concentrations in asthmatics from various countries are generally lower compared to healthy controls [34]. A serum total Mg level under 0.74 mmol/L is almost always associated with more severe asthma and more hospitalizations, while patients with mild or moderate asthma may have normal Mg levels (0.82±0.08 mmol/L) [35, 36]. Multiple regression analysis showed that severe asthma is the only factor associated significantly with hypomagnesemia. No effect is observed for inhaled beta-agonist, inhaled steroid or theophylline therapy on the serum Mg level [35]. No alteration in the serum Mg level was observed during asthmatic attacks [37] or histamine and metacholine challenge [32, 36].

Other magnesium disturbances in asthma

- Placebo-treated persistent moderately asthmatic children had a significant urinary Mg loss as compared to Mg-treated asthma patients (6.81±3.9 vs 2.79±1.39 mmol/day respectively, p=0.01) [38].
- Reduced erythrocyte levels were observed during asthmatic attacks or histamine and metacholine challenge [32, 36, 39] whereas they normalized in the symptom-free period [40].
- A low skeletal Mg content, which reveals Mg deficit, was also reported in stable asthmatics [41].
- Finally, the deficit in Mg body stores was revealed by parenteral loading tests in some patients with stable bronchial asthma: the ratio of Mg retention to urinary excretion and bronchial reactivity to inhaled metacholine was significantly inversely correlated with the erythrocyte Mg level [42].

The two forms of magnesium deficits in asthma

The Mg deficit can result from both an insufficient Mg intake and also from alterations in Mg retention mechanisms. In addition, beta-2 agonists which are the first line of asthma therapy, can stimulate Mg efflux in peripheral tissues [43-47], leading to an aggravated Mg deficit of the cells [38].

The biological markers of Mg deficit previously described may not be due to Mg deficiency, but testify to a clinical form of Mg depletion. We will highlight the possible importance of several types of Mg depletion in the aetiopathogenesis of asthma, particularly of Mg depletion caused by the association between an insufficient intake of magnesium and a chronopathological stress [21-25].

Magnesium deficiency in asthma

Poor magnesium intake is associated with impairment of pulmonary function, determined by a decrease in forced expiratory volume in one second (FEV₁) and a higher risk of both wheezing and airway hyperreactivity, especially in childhood [6, 48]. Consequently, individuals with a low Mg intake may be at increased risk of developing asthma or a chronic airflow obstruction [49].

Atoxic nutritional magnesium therapy may palliate the magnesium deficiency. A beneficial effect of magnesium on lung function, airway reactivity or wheeze was observed in two observational studies [49-51] but not confirmed in others [52, 53]. These conflicting results could be attributable to the fact that supplementation is only effective in Mg deficiency whereas it is without effect in Mg depletion [23]. Pharmacological magnesium treatment for chronic obstructive pulmonary diseases or asthma is not very efficient and may be potentially hazardous [23].

To sum up, Mg deficiency may be considered as an adjuvant nutritional disorder in asthma but asthma per se does not depend only on Mg deficiency.

Magnesium depletion in asthma

Mg depletion is generally due to the sum of an insufficient Mg intake (Mg deficiency) plus a stress [23, 25]. Among the dysregulating factors of Mg status, dysrhythmias through dysregulation of the BC must be considered.
Chronopathological forms of asthma

Hyperfunction of the Biological Clock in asthma

HBC may be due to either primary disorders of BC (SCN and pineal gland) or secondary disorders with an increased homeostatic response linked to BC hypoxosensitivity to inducing light. Consequently, BC behaves in homeostatic hyperfunction (determined through melatonin increase) resulting in Nervous hypoExcitability (NhE). The corresponding clinical forms associate diverse expressions of NhE depression, nocturnal cephalalgia without photophobia (i.e. cluster headaches), dyssomnia, mainly advanced sleep phase syndrome (ASPS), some clinical forms of chronic fatigue syndrome and fibromyalgia. The main comorbidities are depression and/or asthenia. They take place during the night or the “bad” seasons (autumn and winter) when sunshine is at a minimum. Therapy relies on classic asthma treatment, a balanced magnesium intake and sometimes additional psychoanaleptics and adequate chronopathological therapy [23, 24].

Clinical form of asthma with HBC: Nocturnal Asthma

A circadian variation in lung function exists both in healthy subjects and asthmatics with peak lung function occurring near 4:00 PM (16:00 hours) and minimal lung function occurring near 4:00 AM (04:00 hours). An episode of nocturnal asthma (NA) is characterized by an exaggeration in this normal variation in lung function (decreases in peak expiratory flow rate (PEF) and forced expiratory volume in one second (FEV1)) from daytime to nighttime, with diurnal changes in PEF generally of more than 15% [12, 54-56]. There is also a circadian variation in bronchial hyperresponsiveness with an eightfold increase in bronchial reactivity overnight as opposed to a twofold increase in non nocturnal asthma (NNA) [7, 59]. Approximately, 75% of asthmatics suffering from nighttime symptoms awakened one night per week, 64% three nights per week and 39% every night [18]. The occurrence of NA is associated with increased morbidity and inadequate asthma control, and has an important negative impact on quality of life [12, 57]. The mechanisms of the worsening of asthma are probably multifactorial and interactive [60]. According to the National Heart, Lung and Blood Institute, NA is a variable nighttime exacerbation of the underlying asthma condition associated with an increase in symptoms, need for medication, airway responsiveness, and/or worsening of lung function [7, 17]. The difference is due to a change in airway size at night [61]. The distal lung units, specifically the collateral channels, are selectively altered at night in NA, possibly because of smooth muscle contraction, inflammation and/or edema [62]. In addition, several factors may contribute to NA (allergen exposure in bed, supine position, interruption of the bronchodilator therapy, gastro-oesophageal reflux, tenseseness of the airways and secretory accumulation) but they do not constitute a general concept for the explanation of nightly exacerbation [63].

According to Sutherland et al. [8, 64], in this asthma phenotype, the circadian worsening in NA is associated with increased airway inflammation, increased airway responsiveness [10], and worsened airflow limitation [64]. Aggravation of dyspnoea at night, reduction of PEF when waking [65], stage 2 asthmatic attacks [66], bronchostriction, mainly during rapid eye movement, [67] have been often reported. Many hormonal, neural, cellular and humoral factors show diurnal fluctuations which favour a constrictive bronchial response in the night [63]. For instance, elevated histamine and other mediator levels that occur between midnight and 4 am and nadirs in epinephrine and cortisol levels that occur around 10 pm to 4 am play a major role in NA [68]. But other circadian variations were reported in NA, including peripheral blood inflammatory cell numbers and functions [69-72], alveolar tissue inflammation [73, 74], intrinsic adrenergic hormonal milieu changes [75], vagal tone [7], hypothalamic-pituitary-adrenal axis dysfunction [76], alterations of both the affinity and activity of glucocorticoid receptors [77] and β-adrenergic receptors [78]. Upper airway diseases such as chronic sinusitis and obstructive sleep apnea can modulate several of these factors [7]. The cells contributing to the nocturnal inflammatory process include (i) mast cells which release various mediators after antigen activation, contributing to cellular influx into the lung [79]. Melatonin also plays a major role in the control of cell recruitment from the bone marrow and the migration of inflammatory cells to the lungs, since in an experimental model of allergic airway inflammation in rats, pinealectomy reduced the total cell number count in the lung and at the same time reduced bone marrow proliferation, which were both reversed by melatonin administration [79] (ii) cell influx includes eosinophils, neutrophils and lymphocytes secreting various inflammatory mediators that lead to subsequent tissue damage, bronchoconstriction and airway hyperreactivity. Airway neutrophilia has been reported in severe persistent asthma which is often associated with increased nocturnal symptoms [80, 81]. All these chronobiological events promote noc-
MAGNESIUM DEPLETION AND DYSFUNCTION OF THE BIOLOGICAL CLOCK IN ASThma

Characteristics of HBC in asthma
An increase in the melatonin levels in various fluids, corresponding to the elective marker of the BC, is the main biological characteristic of HBC [23, 64]. A 1 hour delay of peak serum melatonin levels was reported in NA [64]. In this NA phenotype alone, melatonin levels are negatively correlated with overnight change in FEV1, suggesting a chronopathological mechanism of asthma. However, recent data must be taken into account (i) melatonin is also synthetized by several other tissues of the body including the immune system [82] (ii) melatonin exhibits immunoenhancing properties by regulating cytokine production of immunocompetent cells [83] (iii) melatonin may have a role in modulating airway function, since melatonin receptors are present in experimental animal lungs [84]. It might affect asthma severity because it enhances airway smooth muscle tone in animal models [85, 86] and allergic airway inflammation both in vitro, in animal models [79] and in vivo [8]. In addition, in NA patient airways, melatonin was shown to be responsible for a chronic overstimulation of inflammatory mediators [8].

In agreement with our hypothesis of various forms of asthma with HBC, we found in the literature that asthma may abate in situations where a physiological decrease in melatonin probably occurs. This is the case in puberty where melatonin decreases correspond to a real improvement of both NA prevalence and severity [87, 88]. Various stresses in pregnant women may convert a simple Mg deficiency into Mg depletion, including environmental factors such as smoking, viruses, and pollens but the role of chronopathological stress appears to be too often neglected [89]. The measurement of melatonin levels in pregnant asthmatic women has never been reported to our knowledge but aggravations were reported in 16-22% of mild asthmatics and in 83% of severe asthmatics, the majority of them improving after delivery [90, 91]. An immediate and long term efficacy of a chronic overstimulation of inflammatory mediators (i) melatonin is also synthetized by several other tissues of the body including the immune system [82] (ii) melatonin exhibits immunoenhancing properties by regulating cytokine production of immunocompetent cells [83] (iii) melatonin may have a role in modulating airway function, since melatonin receptors are present in experimental animal lungs [84]. It might affect asthma severity because it enhances airway smooth muscle tone in animal models [85, 86] and allergic airway inflammation both in vitro, in animal models [79] and in vivo [8]. In addition, in NA patient airways, melatonin was shown to be responsible for a chronic overstimulation of inflammatory mediators [8].

The clinical forms of nervous hypoexcitability (NhE) resulting from HBC are both central and peripheric. All these clinical forms may coexist with the same chronobiological characteristics: nocturnal and hibernal pathologies, increase in melatonin levels, and clear improvement by light. The major comorbidity is represented by depressive states and asthenia. We called that type “photophile” patients, in that they are clearly improved during daylight and the “nice seasons” [23].

– The central forms associate psychic, hypnic and algic manifestations:
  a) Depression, the main type of which corresponds to seasonal affective disorder (SAD) or winter depression. An important comorbidity of depression with asthma (31-34% of asthma patients) was shown in random and representative population samples [95-97]. Three specific symptoms – dyspnoea, waking at night with asthma symptoms, and morning symptoms – are particularly strongly associated with depression. A link between asthma and respiratory disease and suicidal ideation and suicide attempts has been reported [98].

b) Sleep disturbances. The changes which characterize NA have been reported not only to circadian events but also to sleep [7, 17]. The most common sleep disturbances among asthmatic patients were (i) obstructive sleep apnea representing a source of severe sleep fragmentation [99, 100] and (ii) advanced sleep phase syndrome with early morning awakening (51%), difficulty in maintaining sleep (44%) and excessive daytime sleepiness (44%) [60, 101-104]. In asthmatic shift workers, exacerbations took place during the daytime, when they slept. Circadian variation was intimately related to sleep (when melatonin increases) and virtually independent of solar time [105] but these results were replicated later by the same group [106]. In a rat model of asthma, sleep (particularly rapid eye movement, REM) deprivation, reliably suppressed eosinophils in either the bronchoalveolar lavage fluid or the bronchial lamina propria, underlying the role of REM sleep in NA [107].

c) Cephalalgia without photophobia (and even with “photophobia”) represents a nocturnal and hibernal disorder. It is the case of cephalalgia with obstructive sleep apnea periods and of cluster headaches [108]. The patient is much healthier during the “nice” seasons [23, 25].

– The peripheral manifestations are neuro-muscular, mainly represented by myalgia and muscular asthenia. Some clinical forms of the fibromyalgic syndrome with HBC associating to muscular troubles, depression, chronic fatigue syndrome, cepha-
nalgia and dyssomnia may be a type of nervous hyporeactiblity linked to hBC [109-113]. In women with endometriosis, hypothroidism, fibromyalgia, chronic fatigue syndrome, autoimmune diseases, allergies and asthma are significantly more common than in women in the general population [114].

**Hypofunction of the biological clock in asthma**

Whereas nocturnal asthma gave rise to a great number of clinical and epidemiological studies, non nocturnal asthma (NNA) is rarely studied as a whole. We show that some forms of NNA may be related to hBC when they associate decreased melatonin levels and clinical symptoms of nervous hyperexcitability (NHE) *i.e.* anxiety ranging from generalized anxiety to panic attacks, diurnal cephalalgia (mainly migraine), dyssomnia, such as delayed sleep phase syndrome (DSPS), some clinical forms of chronic fatigue syndrome and of fibromyalgia [23, 25]. They may be due to either primary disorders of the BC or to a secondary homeostatic response to light hypersensitivity. The organism responds to the pathogenic effect of this light hypersensitivity by a protective reactive *photophobia*, the mechanism of which is still unclear [115]. Treatment relies on diverse forms of darkness therapy, possibly with the help of some psycholeptics [23, 25].

**Biological characteristics**

The main biological marker of hBC is a *decrease in melatonin (or its metabolite) levels* in various fluids [23, 25]. An important decrease in the 24 h mean level and amplitude of both plasma melatonin [116] and salivary melatonin [117] was observed in mild intermittent or persistent and moderate to severe asthma patients.

The decrease in amplitude (difference between the low daytime melatonin and the higher level at night) observed in asthma patients might be related to the pathological state of asthma [117]. The underlying mechanism of the decrease in melatonin parameters is unknown. However, in stressed rats, Barriga *et al.* [118] proposed that increased corticosterone may have a direct effect on pinealocytes or that melatonin is more rapidly metabolized during stress [17].

**Clinical characteristics**

The clinical characteristics of the secondary forms of chronobiological NHE are of circadian as well as of seasonal type: the symptomatology is mainly *diurnal* and observed in *spring and summer*, when *light hyperstimulation is obviously maximum* during daylight or during the fair seasons. The clinical forms of NHE are both central and peripheral [22-25].

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### The central forms

associate psychic, alagic and hypnic manifestations:

**a) Nervous hyperexcitability and sensitization.** Migraine and chronic respiratory inflammation like rhinitis, sinusitis and asthma have been reported to be the most commonly seen disorders in patients reporting sensitivity to multiple chemicals at levels usually tolerated by the healthy population [119]. A concomitant chemical odor intolerance in those patients suggests a phenomenon of dishabituation leading to hypersensitivity to at least light and odors (generalization) [120]. Dishabituation is the contrary of habituation, a physiological phenomenon characterized by a more or less gradual decrease of the responses to repetitive stimuli of constant parameters [121]. Dishabituation, corresponds first to a decrease in habituation leading to a rapid recovery of the initial sensory reactivity and secondly may even lead to potentiation (or sensibilization) and sometimes to generalization involving other stimuli [121]. Dishabituation is often reported nowadays in pathological studies, such as photic cephalalgia (headaches with *photophobia* *i.e.* migraine). A common background of these "dishabituated" patients is the presence of a magnesium depletion with hypofunction of the biological clock (hBC) [25]. Chemical odor intolerance and anxiety sensitivity in asthma patients seem to be significant predictors of physical symptoms [120].

**b) Cephalalgia, mainly migraine.** A frequent association between migraines and various allergic disorders has been reported [122-124]. Bronchial asthma is, like migraine, a paroxysmal disorder with attacks and symptom-free intervals which alter the quality of life. In addition, both migraine and asthma are psychosomatic disorders [15, 125, 126]. Finally, recent studies using anti-inflammatory drugs (montelukast, a leukotriene receptor antagonist or coxibs, inhibitors of cyclooxygenase) demonstrated consistent beneficial results in both asthma and migraine prevention [127-129]. Among children whose mothers had neither migraine nor asthma/allergies, 3.2% had asthma, while this incidence was found to be more than 6% for children whose mothers had migraine, but not asthma/allergies [130, 131]. The risk of asthma among children born of women who had both migraine and asthma/allergies was greater than the risk associated with either maternal disease [125]. Headaches in adults were found to be more prevalent among those whose family members were reported to have allergy, asthma and migraine [132]. Genetic-epidemiological studies showed that migraine and asthma co-segregate in the family, indicating a possible common genetic background,
involve some specific HLAs [125, 130, 133]. The comorbidity asthma-migraine may rely on increased plasma levels of endothelin-1, a potent vasoconstrictor and a mediator in the inflammatory process (through matrix-metalloproteinase 9 (MMP-9) particularly [134, 135]. These disorders are in keeping with the well-known similar disturbances due to magnesium deficit [24, 136].

c) Dyssomnia, mainly represented by the delayed sleep phase syndrome. In chronic obstructive pulmonary disorders (COPD), night sleep is delayed or shortened and deep sleep is often reduced or even absent [96]. A large study showed that asthma individuals are in addition at increased risk for complaints of difficulty with inducing sleep [17].

d) Anxiety. An important comorbidity of anxiety with asthma (40-53% of asthma patients) was shown in random and representative population samples and in clinical samples [97, 95, 137, 138]. These relationships appear strongest among those with more severe disorders in terms of both asthma and anxiety disorders. The strongest links appear between lifetime severe asthma and generalized anxiety disorder (GAD), as well as panic attacks and panic disorder [95, 97, 138, 139]. An association between respiratory diseases and panic attacks was documented among adults [138, 139] and youths [96, 138]. Several studies have also noted elevated rates of asthma among psychiatric inpatients and outpatients with anxiety disorders [140, 141].

– Peripheral manifestations. The central and peripheral manifestations are neuromuscular, mainly represented by photosensitive epilepsy, which may be either generalized or focal, authenticated through EEG with intermittent light stimulation (ILS) with its corresponding form observed among TV viewers and video game players [24, 142-144]. Some migraine equivalents may be associated in this context. In addition, the nervous form of chronopathological magnesium depletion with hBC may appear clinically as chronic fatigue syndrome (CFS) [145, 146] or as fibromyalgia [24, 147].

Indirect evidences underly the possible role of hBC in asthma

– For instance, in some mild or moderate asthma patients (about 12%) asthma improved during pregnancy. This result mirrors the warnings previously described in a majority of severe asthma patients with hBC and would indicate an increase in melatonin [91].

– Aspirin sensitive asthma patients usually suffer from an active disease, despite the avoidance of aspirin and cross-reactive drugs, attributed to a decreased melatonin synthesis and an increased sensitivity of platelet to melatonin (and its metabolite) as compared to aspirin-tolerant asthma patients [148].

– Diurnal, seasonal and climatic photostimulation must be risk factors in those patients. In a retrospective study, Jorgensen et al. [149] showed on a cohort of 108 cases of asthma death in 1-19-year-olds in Denmark that death occurred predominantly in summer in the 15-19-year age group. The authors attributed the death to an insufficient medical survey. But we suggest that the decrease in melatonin levels at puberty aggravated by light exposure in summer could be also involved. Increased visits to the hospital were also reported during the wet season in Trinidad, i.e. during summer, when sunlight is obviously important [150].

Treatment of asthma with dysfunctions of BC

According to the current US guidelines, nocturnal symptoms of asthma occurring more often than once weekly may indicate inadequate control of asthma [151].

Anti-asthma drugs

Treatment of asthma is not in the scope of the present paper and will not be developed hereafter. Briefly, the therapeutic agents used for the management of chronic asthma are mainly inhaled beta-2 agonists and steroids. Acute exacerbations can occur and are challenging to manage. Beta-2 agonists, corticosteroids and supplemental oxygen [152] are the mainstay therapies used to relieve bronchospasm and airway obstruction. Because not all patients respond to maximal therapy, other strategies, either older (theophylline, magnesium) or more recent (heliox, leukotriene modifiers) are being evaluated [153].

Understanding the kinetics of the different drug preparations allowed the most effective timing of doses [57]. Chronopharmacology should optimize the desired effects of medications and minimize undesired ones in asthmatic patients [117].

Indirect asthma therapy

– Environmental control measures are essential and should focus on limiting the patient’s exposure to allergens.

– All the pathological entities accompanying asthma should be diagnosed and treated appropriately [7].

a) Allergic rhinitis should be treated with anti-inflammatory medications;
b) Obstructive sleep apnea syndrome and snoring may be improved by continuous positive airway pressure;

c) Classical pharmacotherapy using psychoanaesthetics (HBC) or psycholeptics (HBC) may be successful.

– Asthma education programs that teach about the nature of the disease, medications, and trigger avoidance tend to reduce asthma morbidity. Other promising psychological interventions as adjutants to medical treatment, including training in symptom perception, stress management, hypnosis, yoga and several biofeedback procedures, may be beneficial [125].

Balanced magnesium intake

The RDA for Mg intake is 350 mg/day for an adult male, 280 mg/day for a female and 10-13 mg/kg/day for growing children [154]. The Mg requirement of almost all healthy adults is 6 mg/kg/day [46]. More than 50% of reaginic allergic asthma is accompanied by symptoms of latent tetany due to primary Mg deficiency. Conversely, the frequency of allergic antecedents is high in cases of neural forms of primary magnesium deficit (39%) [26]. A large epidemiological study carried out in 2633 subjects showed that a high dietary magnesium intake is associated with better lung function and reduced risk of airway hyperreactivity and wheezing [50]. Nutritional Mg supplementation brings on specific reversibility of the symptoms of asthma and COPD. Such supplementation in 20 asthmatics was associated with significant improvement of asthma symptom scores whereas FEV1, PEF variables or decrease in use of a bronchodilator was not improved. However, the duration of Mg supplementation may have been too short to detect any improvement in their pulmonary function [51]. A decrease in airway responsiveness was observed in hyperresponsive asthmatics after 6 weeks of nutritional Mg supplementation [155]. Long lasting Mg supplementation (200 mg/day for 7-year olds and 290 mg/day for older children) is clearly of benefit in moderate asthma children and is recommended as a concomitant drug in stable asthma [38].

In general, nutritional magnesium therapy for pulmonary obstructive diseases physiologically palliates the coexistent primary Mg deficiency. The atoxic adjuvant therapy is always beneficial without side effects [21-26, 46, 47].

But, when different stresses transform the Mg deficiency into Mg depletion related to a dysregulation of the control mechanisms of magnesium status, nutritional physiological magnesium supplementation alone is ineffective. Mg depletion needs not only a balanced Mg intake but also and mainly the correction of its causal dysregulation. In the case of chronic biological forms of asthma treatment must include either “phototherapies” or “darkness therapies”.

Chronobiological treatments

Asthma with HBC

The different forms of HBC may be treated by various phototherapies. It is obvious that in chronobiological asthma with HBC, supplemental over-the-counter melatonin must be carefully avoided since it is still present in a large excess.

– **Bright light therapy** (BLT). As for the other diseases based upon Mg depletion with HBC, BLT may be beneficial in this clinical form of NA. Even though not yet evaluated in proper clinical trials, three studies reported on a small number of patients the beneficial effects of BLT in asthma [156-158]. The aim of BLT is to lengthen the photoperiod, the marker of its efficiency being the decrease in plasma MT. Its protective effect may result not only from melatonin suppression and accessory mechanisms but also from multiple other mechanisms i.e. depression of the immune response with suppression of inflammatory leukotrienes and cytokines [23, 159]. It is operative through various neural and perhaps humoral mechanisms. Today, the mean central neural mechanisms of classical phototherapy seem to be increased serotonineray, hypoactivity of inhibitory modulators such as GABA, taurine and kappa opioid receptors, and finally stimulation of inflammatory and oxidative processes [23]. An evolutive perspective suggests that heme moieties and bile pigments in animals mediate some non visual influence of light upon neuroactive gases (including CO and NO) and upon biorhythms [160] through humoral phototransduction. Bright light can break the carboxyhemoglobin (HbCO) bond releasing CO and stimulate nitric oxide synthase to produce NO. If one considers hemoglobin not only as a scavenger but also as a transporter, it may convey photic information to all tissues through the neuroactive gases: CO and NO in blood [160-163]. Bright light is also able to reduce circulating levels of bilirubin and biliverdin, thus removing their vasoconstrictive and sedative effects [160].

– **Chromatotherapy**. Chromatotherapy is an original aspect of phototherapy that may lead to clinical improvement in asthma with HBC [164, 165]. It uses a short exposure to a specific wavelength once a week and like other energetic therapies carefully takes into account the nocturnal or diurnal prevalence of clinical symptoms. In asthma with nocturnal preva-
lence, purple irradiation of the chest for 4 minutes followed by 20 min of darkness would be beneficial. More specific treatment of asthma using chromotherapy on acupuncture points would give better results but may only be used by specialists. Even though successfully used in clinical practice, this method has not yet been validated [23-25].

**Asthma with HBC**

Both *stimulating* and *palliative* darkness therapy are available.

- **Stimulating “darkness therapies”**

  Four different types may be used: physiologic, psychotherapeutic, physiotherapeutic and pharmacological.

  a) **Physiological darkness therapy**

  - *Darkness therapy per se.* Light deprivation may be obtained by placing the patient in a closed room, in a totally dark environment, with an eye mask on. This genuine darkness therapy may be used in acute indications, but should be of short duration. It is not compatible with any activity and is frequently associated with induction of bed rest, inactivity and sleep [23, 165, 166]. Relative darkness therapy may be obtained by wearing dark goggles or dark sun glasses but the number of lux passing through is not negligible. This relative darkness therapy may be used as an accessory treatment in the restoration of a light dark schedule: a transition before a totally dark environment [23, 160].

  b) **Chromatotherapy.** Diurnal forms of asthma may be benefit from a 4-min exposure of the chest to yellow wavelength, the complementary color of purple indicated in the treatment of asthma with HBC. It must be followed by 20 minutes of darkness. Chromatotherapy on acupuncture points may be even more efficient. This method, although successfully used in practice, has not been validated yet [23-25, 89, 164, 165].

  c) **Psychotherapeutic darkness therapies.** Asthma education programs are important (see upper). Cognitive behavioral strategies have been efficient for the treatment of photosensitivity. The treatment was to gradually increase exposure to computer monitor and television screen photostimulation. This desensitization procedure resulted in a complete removal of the patient’s phobic anxiety from photostimulation and of avoidant behavior. This behavioral therapy has been used in photosensitive epilepsy [167]. Finally, psychological therapies of migraine in childhood, such as relaxation training and biofeedback, were potentially superior to pharmacological treatment [123, 168].

  d) **Pharmacological darkness therapies**. Three agents may stimulate the BC i.e. magnesium, L-tryptophan and taurine but their efficiency seems limited.

  - *Magnesium.* To stimulate the biological clock, it seems well advised to facilitate the neural function of SCN and the hormonal pineal production of MT. The deleterious effects of light and those of magnesium deficiency are often found together and might be partly palliated by a nutritional magnesium supply, when Mg deficiency exists, providing the best possible link between photoperiod and magnesium status [21-25, 89]. It is efficient and atoxic but when there is a balanced Mg status, it is illogical and inefficient. Pharmacological use of magnesium is uncertain and may induce toxicity. Choice and doses of the Mg salts, of oral or parenteral route (high oral doses or parenteral administration), association with « Mg-fixing agents » remain imprecise [21-25, 89, 170].

  - *L-tryptophan* (or 5-OH tryptophan) may stimulate the tryptophan pathway but they are unspecific as they concern not only melatonin production but also serotonin synthesis. They may induce toxicity, even leading to eosinophilia-myalgia syndrome [21-25, 80, 171-173].

  - *Taurine* is a sulfonated aminoacid which is present in the whole body in high concentrations, mainly in the brain. It has a multiple function in cell homeostasis such as membrane stabilization, buffering, osmoregulation and antioxidant activities together with effects on neurotransmitter release and receptor modulation. Taurine may act as a protective inhibitory neuromodulator which participates in a balanced function of the nervous tissues and in melatonin production and action. Taurine plays a role in the maintenance of homeostasis in the central nervous system, particularly during central nervous hyperexcitability. This volume-regulating aminoacid is released upon excitotoxicity induced cell swelling. It has an established function as an osmolyte in the central nervous system. In the course of Mg deficit, the organism appears to stimulate taurine mobilization to play the role of a "magnesium vicariant to stimulate the biological clock in asthma."
agent”. But this compensatory action is rather limited [21-26, 89, 145, 174-179].

“Substitutive darkness therapies” (or darkness mimicking agents).

Because of the limited efficiency of previous chemical agents, palliative treatments of hBC may be necessary.

a) Mechanisms of the action of darkness.
The mechanisms of action of darkness appear to be the reverse of those observed with bright light, where direct cellular and neural effects intervene. Increased melatonin production is the best marker of darkness but it is only an accessory mechanism in the darkness effect. The main central nervous mechanisms of darkness therapy associate decreased serotonin together with stimulation of the inhibitory neuromodulators (GABA, taurine) and stimulation of anti-inflammatory and anti-oxidative processes, which may lead to neural hypoexcitability (sedative and anticonvulsant). Humoral transduction may reinforce these last effects by decreasing neuroactive gases (CO and NO) through binding of CO with haemoglobin and by increasing melatonin, bilirubin and biliverdin, three antioxidants which have the capacity to quench NO. Apart from the decreased serotonin, these effects of darkness are similar to those of magnesium. Substitutive darkness therapy should palliate all the mechanisms of the action of darkness. The only available darkness mimicking agents are melatonin (its analogous and its precursors, L-tryptophan, 5-hydroxytryptophan) [23, 25].

b) Melatonin, an accessory darkness mimicking agent. Melatonin is the prototype of darkness mimicking agents. But, although the production of melatonin is the best marker of photoperiod, it appears to be only an accessory factor among the mechanisms of photoperiod actions. Most of the other mechanisms of the effects of darkness have been overlooked, which may account for the controversy around the therapeutic efficiency of MT. Its dosage varies from physiological doses (around 0.3 mg) to pharmacological doses (usually 3 mg/per dose and per day and even up to 300 mg as a contracep-
tive). In case of chronopathology, with decreased MT production, MT constitutes a substitutive treatment of its deficiency [23-25, 89, 180-185].

c) Melatonin analogs or precursors might be tested as darkness mimicking agents.

Conclusion

Asthma prevalence is increasing all over the world despite effective treatments and may lead in some cases to death. Many factors may interact in the physiopathology of the disease and contribute to the severity of asthma. Nocturnal asthma seems to be very frequent and represents a severe form of asthma, leading to the idea that asthma is chronopathological.

We recently suggested that various pathologies, including asthma, are linked to a chronopathological magnesium depletion corresponding to the association of both magnesium deficiency and any types of stress, including chronobiological dysfunction of the biological clock, either HBC or hBC. These forms are determined mainly by variations of their marker, melatonin and by well identified clinical symptoms of either hypo- or hyper-nervous excitability, respectively. This leads us to suggest the measurement of melatonin, extra- and intracellular magnesium levels in asthma patients. This would allow an additional beneficial treatment including a balanced magnesium intake and either phototherapy or darkness therapy for asthmatics with either HBC or hBC.

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