Mg Acetyltaurinate as a photic inhibitor in photosensitive magnesium depletion: a physiological pathway in headache with photophobia treatment.

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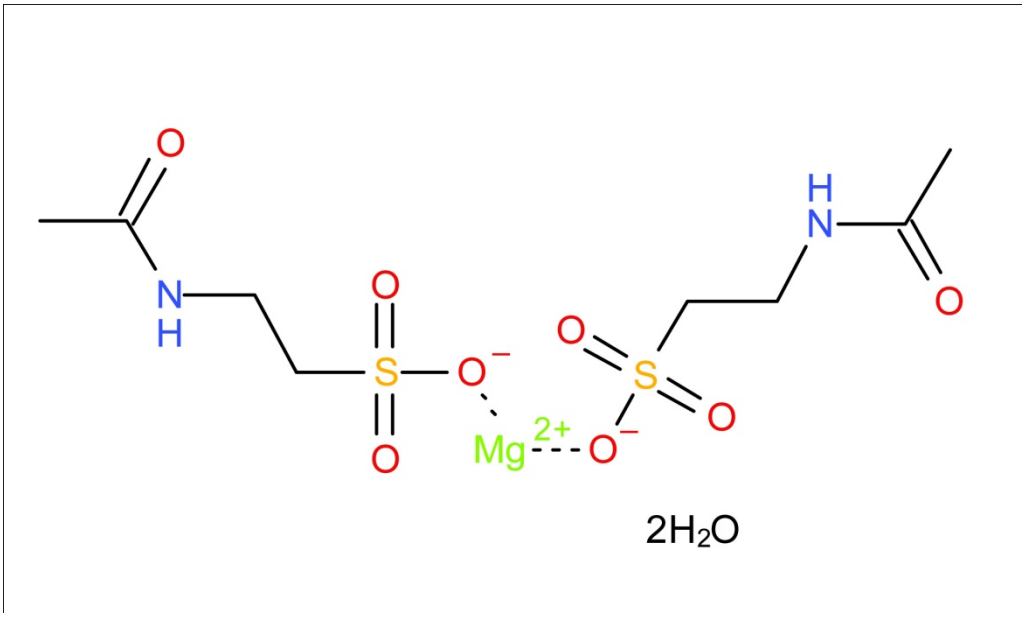

ETHANE SULFONIC ACID (ACETYLAMINO)MAGNESIUM 2-1.
ATA Mg®; Acetyltaurinate magnesium dihydrate; Magnesium acetyltaurate.
CAS Number : 75350-40-2 (Monograph on request by Synapharm)

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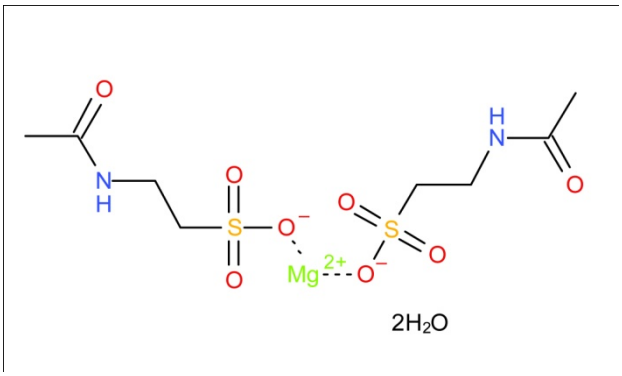
INTRODUCTION

We previously described an actimetry-based test of photosensitization in mice, which can be used for a rapid and efficient screening of drugs of interest for photic cephalalgia and other photosensitive diseases (1, 2). In summary, in absence of photostimulation, control mice had a basic motor activity (around 180 crossings per 5 minutes of an actimeter photocell) whereas magnesium-deficient mice suffered nervous hyperactivity (NHE) with increased motor activity. While in each group, control and magnesium-deficient mice, were submitted to photostimulation using a stroboscope, control mice developed the phenomenon of habituation (*i.e.* a gradual decrease in the responses to repetitive stimuli) whereas magnesium-deficient mice presented both sensitization with higher NHE and generalization, involving hypersensitivity to other type of stimuli. In the present study, we studied the efficiency of a new magnesium salt, which was not yet commercially available, magnesium N-acetyltaurinate (ATA Mg) on senzitisation suppression suggesting a possible therapeutic use in photosensitive diseases.



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MATERIALS AND METHODS

- Female Swiss OF1 mice, 6 weeks old (Janvier, France) were fed either:
    - a standard magnesium-diet (950 ± 50 ppm mg/kg)
    - or a magnesium-deficient diet prepared as previously described (50 ± 5 mg/kg).
- Magnesium deficient mice were or not intraperitoneally injected 30 minutes before photostimulation with ATA Mg (100 mg/kg). They were compared to groups exposed to either $MgCl_2$ (59 mg/kg), taurine (100 mg/kg) or ATA Na (100 mg/kg).
- Photostimulation test was done as previously described. Briefly, after acclimatization to darkness, individually caged mice were exposed to repeated light stimulation *via* a stroboscope for 15 min (1000 lumens, 50 Hz frequency).
- Then, locomotor activity was measured for 5 min by the crossing of a photocell actimeter (Appelex type 01-1668B).

- Five groups of mice were compared:

    - Group A : non magnesium-deficient, nonphotostimulated;
    - Group B: non magnesium-deficient, subjected to photostimulation;
    - Group C: magnesium-deficient, nonphotostimulated;
    - Group D: magnesium-deficient, subjected to photostimulation;
    - Groups E: magnesium-deficient, subjected to photostimulation and treated with 100 mg/kg ATAMg.

RESULTS

Plasmatic magnesium concentrations of magnesium deficient groups were about 5.7 +/- 0.51 mg/L, *i.e.*, reduction of 73.5% compared to the control groups (21.53 +/- 1.26 mg/L).

The effect of ATA-Mg in the actimetry-based test is reported in table 1.

Table 1: Effect of 100 mg/kg ATA-Mg in magnesium-deficient, photostimulated mice

Magnesium status	Photostimulation	ATA-Mg treatment	Results
Normal	No	No	181.8 ± 17.1
	Yes	No	66.9 ± 19.4***
Depletion	No	No	267.6 ± 30.1***
	Yes	No	458.0 ± 86.5**
	Yes	100 mg/kg	210.2 ± 17.4

***Statistically different from controls ($p < 0.001$);

DISCUSSION

The phenomenon of habituation was checked; group B mice (non magnesium-deficient, non-treated, but photostimulated) had a lower motor activity (66.9 ± 19.4) than the control group (non magnesium-deficient, non-treated, non-photostimulated) (181.8 ± 17.2). Magnesium-deficient mice presented the classical NHE in absence of photostimulation (267.6 ± 36.1) and severe NHE after photostimulation (458 ± 86.5), which corresponds to the phenomenon of potentiation (hypersensitivity).

In the E group (magnesium-deficient, ATA-Mg-treated at dose of 100 mg/kg and photostimulated) the phenomenon of sensitization disappeared. In the same conditions, neither magnesium ion under the form of $MgCl_2$, nor taurine or acetyltaurine were efficient (data not shown).

Within our experimental conditions, ATA Mg among other commercial magnesium salts (data not shown) was the most efficient in restoring the habituation capacity.

CONCLUSION

ATA Mg is a magnesic analogue of taurine whose N-acetylation eliminates the zwitterionic character of taurine and improves its entry into the central nervous system.

The inhibiting properties of ATA Mg on the kainic acid receptor have been demonstrated in a model of magnesium depletion (3). Kainic acid is a neurotransmitter involved in NHE which is present in photosensitive diseases (migraine, convulsion, epilepsy) (4) (5). Other signs of NHE such as audiogenic seizures inferred by magnesium depletion and sound stimulation were significantly inhibited by ATA Mg (6).

Consequently, ATA Mg should be a therapeutic approach of interest to the treatment of headaches, migraine with reactional photophobia particularly . Clinical studies should confirm the results observed *in vivo*.

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Headache due to photosensitive magnesium depletion

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Abstract. Clinical and paraclinical data (visual stress tests, electroencephalographic and cerebrovascular photic driving, visual evoked potentials) demonstrate that the concept of photosensitive headache is fully justified. The interictal hallmark of photosensitive cephalalgic patients is potentiation (or sensitization) instead of habituation. The aetiopathogenic mechanisms of photosensitive headache associate hypofunction of the biological clock and magnesium depletion. The new concept of headache due to photosensitive magnesium depletion seems justified. It appears logical to add the treatments of magnesium depletion and of photosensitivity to classical treatment of headache. Prophylactic magnesium treatment relies on atoxic nutritional magnesium supplementation in case of primary magnesium deficiency. Pharmacological doses of parenteral magnesium may be used but may induce toxicity. Therefore it is necessary to know the therapeutic index of magnesium compound used: the larger its value, the greater the safety margin. Treatment of photosensitivity uses various types of « darkness therapies »: darkness therapy through physiologic, psychotherapic, physiotherapic, pharmacologic stimulating techniques and substitutive darkness therapy through palliative treatment. Melatonin is only a partial substitutive treatment of photosensitivity. A new model of photosensitive magnesium depletion with potentiation should be a useful tool for discriminating the most efficient « darkness-mimicking » agent.

Key words: headache, magnesium, migraine, photosensitivity, visual stimuli

Patients complain of headache very often, since approximatively 70-75% of men and more than 80% of women are concerned. The great majority of headaches are idiopathic in origin. Although they are currently classified as Tension Type Headache (TTH) or Migraine (M), this classification does not result in the delineation of separate headache types. A clinical approach shows a *continuum* ranging from mild to moderate then severe headaches, with clinical symptoms, pathophysiological mechanisms and therapies similar in both M and TTH. Clinicians and researchers alike may find it more logical to use a *continuum* approach to primary headaches [1-3].

Headache patients often exhibit a hypersensitivity to light, usually with **photophobia** – its clinical marker –, during and between the algic attacks [4-17].

Headache frequently appears as related to magnesium deficit. Cephalalgia represents a symptom of the nervous form of magnesium deficient balance and magnesium depletion in particular may play a role in the pathophysiology of migraine [3, 18, 19].

The aim of this study was to stress the importance of photosensitivity in headache; to analyze the place of magnesium deficit in photosensitive cephalalgic patients; to hypothesize a causality link between these factors with the clinical and pathophysiologi-

cal notion of « **headache due to photosensitive magnesium depletion** »; to conclude with the therapeutic consequences of this new concept, which encompasses a large part of the so-called primary headaches.

Importance of the light sensitivity in headache patients

Clinical symptoms

Reported symptoms

In photosensitive headaches - of the migraine type - during algic attacks (ictal period) but alsobetween episodes (interictal period), light stimuli can trigger **photophobia**, the clinical marker of light sensitivity and a common symptom in primary headache. The term photophobia is derived from the Greek photo (light) and phobia (fear or dread of) -hence « fear of light ». This abnormal sensitivity to light may appear as pain on exposure to light or an uncomfortable sense of glare. This symptom is generally self-reported or diagnosed when questioning patients. As early as the second century, A.D. Aretaei Cappadocis had written (in *liber IV*) « *fugiunt enim quodam modo lucem, tenebrae aegritudinem solentur* » (they avoid light by all possible means and the dark subsides their feeling of sickness). Today light intolerance is a well recognized symptom of primary headache, and the patient may be improved by retreating into a dark room [3-16].

Abbreviations
BC = biological clock
M = migraine
CT = cranial tomography
MRI = Magnetic Resonance Imaging
MMPI = Minnesota multiphasic personality inventory
ED50 = median effective dose; MRI, magnetic resonance imaging
EEG = electro encephalogram; MT, melatonin
GABA = gamma-aminobutyric acid
RDA = recommended dietary allowances
Hb = hemoglobin
SCN = supra chiasmatic nuclei
hBC = hypofunction of the biological clock
TA = taurine
HBC = hyperfunction of the biological clock
TCD = transcranial Doppler
kO = kappa opioid
TTH = tension type headache
LD50 = median lethal dose
VEPs = visual evoked potentials

Physical symptoms

The so-called « tinted glass sign » may be considered as an indirect symptom of light hypersentivity. Photophobic patients wear sunglasses in normal daylight. Frequent wearing of tinted spectacles indoors is pathological. Though it may be a physical sign of photosensibility, it may also be recorded as « a marker of neurotic and hypochondrial personality » or « a valid indicator of psychological distress ». All of these various interpretations may be valid: photosensitivity may induce anxiety, anxiety may be a precipitating factor of photosensitive headache, the symptomatology may be increased by a neurotic personality and by distress [20-23].

Paraclinical examinations

Objective paraclinical examinations involve: **visual stress tests which evaluate visual stress thresholds**, in order to obtain quantitative assessment of light induced-discomfort; **electrical photic response**, studied through EEG tracings; **circulating photic response**, studied through either Transcranial Doppler, or Magnetic Resonance Imaging; **visual Evoked Potentials.**

Visual stress tests

Several types of exposure to light during interictal periods may induce visual discomfort in cephalalgic patients such as certain **geometric patterns** such as parallel lines of alternate light and dark stripes, **flicker**, **colors** and **fluorescent light**.

To sum up: photosensitive headache patients exhibit a hyper-sensitivity to light during and between the attacks. Pain thresholds are lower than in controls. Migraineurs are more sensitive interictally to light stimuli than TTH patients during attack and than controls [8, 12, 14, 15, 20-24].

ElectroEncephaloGram (EEG) photic response

In 1953, Mundy-Castle reported « considerably greater mean response amplitude to photic stimulation » in headache patients, during routine EEG.

Later Golla and Winter (1959) described persistance of photic driving to 20 Hz flashes or above (**the H response**) in headache patients.

Although many studies considered the H response as an EEG marker of migraine, it is no longer considered as valid in routine evaluation since « the sensitivity and specificity of the H response are too low to change the probability of the presence of migraine in a clinically significant way... », so « we do not recommend the use of EEG instead of head cranial tomography or magnetic resonance imaging in evaluating headache patients with suspected intracranial

pathology ». But a prominent photic driving may identify clinical subsets of photosensitive headache patients [29]. In addition a dynamic notion must be stressed since photic driving power decreases (towards normal values) during the headache phase [30, 31]. In any case there is a complete overlap of the H response between the two main primary headache subgroups TTH and M which agrees with the so-called *continuum* severity theory: the lower limit of the *continuum* is TTH which progressively evolves into migraine and finally into migraine with aura [30].

These various clinical forms of primary headache with abnormal visual reactivity are compatible with the concept of « photosensitive headache » [7, 10, 24-32].

Cerebrovascular photic responses

Circulatory responses have been studied through either TransCranial Doppler (TCD), or Magnetic Resonance Imaging (MRI).

Changes in the cerebral perfusion were studied during repetitive visual stimulation by functional TCD in the right posterior cerebral artery and the left middle cerebral artery in interictal migraineurs. They exhibited a steady increase in cerebral blood flow velocity while normal subjects showed habituation. **The lack of habituation** of the cerebrovascular response in migraineurs was significantly more pronounced among patients with a high attack frequency (at least 4 per month) compared with migraineurs with a low attack frequency (less than 4 per month) [33]. These cerebrovascular data, in accordance with neurophysiological findings in migraineurs highlight the importance of **the lack of habituation** in the pathophysiology of migraine.

Another study, using functional MRI, examined changes in resting perfusion and in activation within the occipital cortex due to photic stimulation in both controls and true menstrual migraine patients. No difference in resting baseline perfusion was observed between the two groups during either phase of the menstrual cycle. But the results differed after photic stimulation. During the late luteal phase, changes in perfusion within the occipital lobe were similar for both groups. whereas it **decreased** in controls, but significantly **increased** in menstrual migraine patients during the mid-follicular phase.

A significant difference ($p < 0.05$) was observed in the mean values for photic activation among **the true menstrual migraine** patients compared to normals, after allowing for effects of differences in cycle (late luteal phase *versus* mid-follicular phase) [34].

Visual evoked potentials

Classical Visual Evoked Potentials (VEPs) concern the reactivity of electrocortical activity to visual stimuli generated by either transient flash (luminance stimulus) or checkerboard pattern (contrast stimulus).

Stimulation produced surprising contradictory results since an increased amplitude was often found in migraine, the typical form of photoreactive headache.

Habituation has been studied after **repetitive** visual stimuli. Visual stimuli were presented for example, as a checkerboard pattern of 8 min of arc, black and white squares (contrast 80%), at a reversal frequency of 3.1 Hz. Five consecutive blocks of 50 responses averaging a total number of 250 responses were analyzed separately for latencies, peak to peak amplitudes and areas under the components. Habituation was assessed as the amplitude changes in blocks 2-5 compared to block 1. Habituation was observed in healthy subjects. Migraine patients were characterized by an amplitude increment (potentiation) of VEPs components which reached their maximum value in the second to the fourth blocks. Potentiation instead of habituation characterizes VEPs in migraine patients between attacks [39]. Electrophysiologic studies demonstrate that, **the hallmark of migraine** between attack, is **a deficient habituation**.

Lack of habituation has been observed not only in migraineurs' visual evoked potentials (and in related parents'), but also in many other neurophysiologic data: other sensory and somato sensory evoked potentials, event-evoked potentials (contingent negative variation), cerebrovascular responses to visual stimuli [3-7, 35-60].

Habituation is a physiological phenomenon characterized by a decrease in the responses to repetitive stimuli. It is considered to be a protective mechanism against overstimulation.

Dishabituation, by contrast, is a process that liberates the nervous system from the habituation process. Dishabituation stimuli act as **sensitization or potentiation** processes which rely on a dysfunctioning of cortical information processing. The dysfunction might result from the high level of cortical arousal with increased energy demands and from hypofunction of the subcortico-cortical pathways. Visual potentiation depends on the type of visual subsystem which is preferentially activated, either the magnocellular (luminance and motion sensitive) or the parvocellular (contrast and colour sensitive) systems. The cortical arousal level depends on the effects of various neurotransmitters from the brain-

stem projecting to the cortex. Serotonin acts as a gain control between a noradrenergic, unspecific, facilitating system and a cholinergic, specific, inhibitory system.

Dishabituation may finally induce **generalization** when the nervous alteration involves other stimuli or invades other substrates. Generalization may concern various selective or global targets such as hearing in particular (with phonophobia), smell (with cacosmia), touch (with allodynia), diet (with alimentary intolerance).

To sum up: there is an adaptative dysfunction to environmental conditions in migraine [3, 9, 16, 24, 30, 41, 46-88].

Finally, the clinical and paraclinical data on the importance of light sensitivity in primary headache demonstrate that: i) **the concept of photoreactive headache** is fully justified. It may correspond to a large number of **the so-called primary headaches, M and TTH** particularly. Photosensitivity, as well as its clinical marker photophobia, may be inherited or acquired; ii) the interictal hallmark of such cephalalgic patients is **dishabituation** with pathophysiologic **potentiation (or sensitization)** instead of physiologic habituation; this dishabituation is observed in all the studied types of repetitive stimuli: sensory (i.e. auditory), cognitive (i.e. contingent negative variation), painful (i.e. laser), sensory motor (i.e. blink reflex), cerebrovascular (through TCD or MRI).

Photosensitive headache and magnesium status

Migraine may be considered as the paradigm for PhotoSensitive Headache. An oral magnesium load test was performed to determine whether migraineurs had a disorder of magnesium status. Two groups of either migraineurs (n = 20) and to healthy volunteers (n = 20) were given 3000 mg of magnesium lactate during a 24h period (interictal for migraineurs. The 24h urinary magnesium excretions were significantly lower ($p = 0.0007$) in migraineurs than in controls after loading, suggesting a systemic magnesium deficit [89].

A body of evidence has already stressed the difference between two types of magnesium **deficits**:

– **deficiency** linked to an insufficient intake which may be corrected, through physiological nutritional oral magnesium supplementation, over a long period of time;

– **depletion** due to a dysregulation of the magnesium status which cannot be corrected through nutritional supplementation only, but requests the most specific control of the dysregulation mechanism. There exist as many clinical forms of magnesium depletion as numerous possibilities of dysregulation of the magnesium status. But in both clinical and experimental studies, the dysregulating mechanisms of magnesium depletion associate a reduced magnesium intake with various types of stress. Among them chronobiological dysrhythmias, such as hypofunction of the biological clock (hBC) are often overlooked. Photosensitive Headache is the main clinical form of photosensitive disorders due to a secondary reactive response of the biological clock (BC) to light neurostimulating effects through hBC [3, 81-83] *(figure 1)*.

In migraine, the typical form of photosensitive headache, the nature of the magnesium deficit must be determined.

– When chronic primary magnesium **deficiency** coexists with migraine, it only constitutes a decompensatory factor whose control with simple oral nutritional magnesium supplementation should help in migraine therapy as **an adjuvant treatment** since magnesium deficiency **does not constitute the cause for migraine** *per se* [3, 18, 19];

– Clinical studies on magnesium status in migraineurs have shown heterogeneous and inconstant decreases in extra- or intra-cellular, total or ionized magnesium concentrations in serum, saliva, erythrocytes, mononuclear cells, thrombocyte and even in brain. Positive therapeutic responses to oral physiological load are unreliable. These data agree with magnesium **depletion** corresponding to a magnesium deficit with dysregulation of the magnesium status in migraine [3, 89-106].

The importance of magnesium deficit in the pathophysiology of migraine should be stressed. Optokinetic stimulation may aggravate clinical and paraclinical symptomatology of both primary magnesium deficit [107] and migraine [108]; their MMPI patterns (with elevation of neuroticism scales) are similar [19, 109, 110] and nitric oxide is instrumental in the pathophysiology of these two disorders [19, 31, 109-111].

To sum up: the aetiopathogenic mechanisms of photosensitive headache associate hBC and magnesium depletion [3, 81-83, 89-107].

Headache due to photosensitive magnesium depletion

The coexistence of chronobiological stress and of magnesium deficit does not necessarily involve a

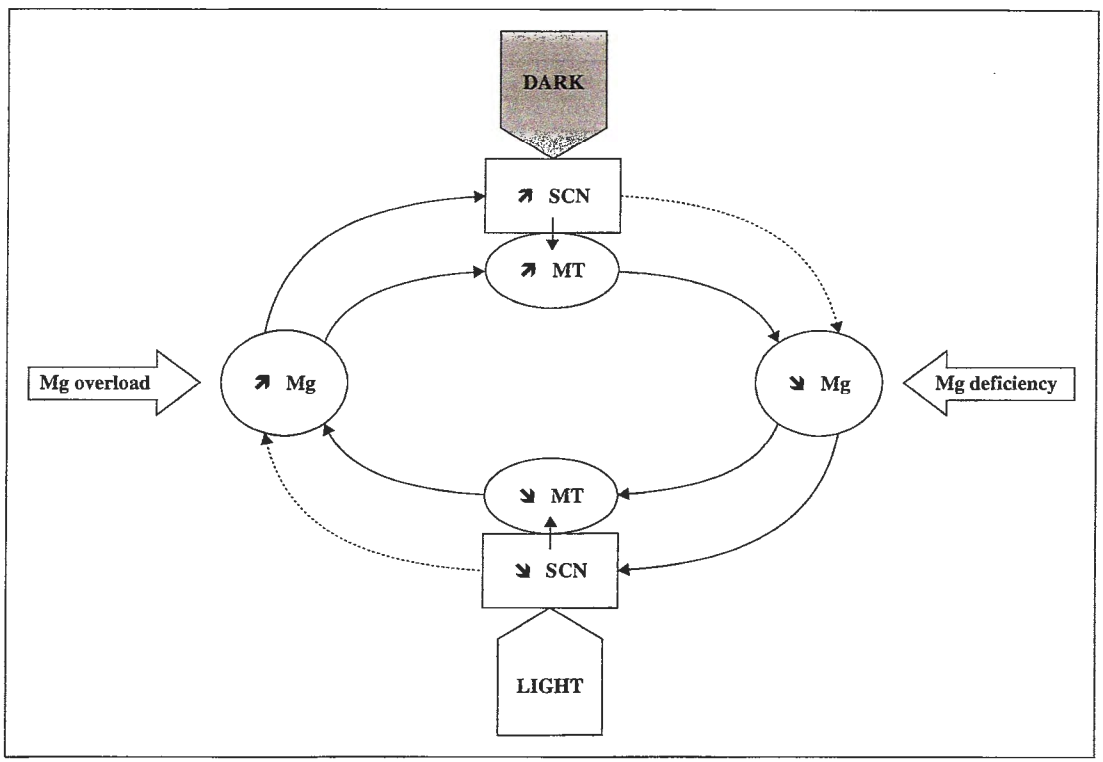

Figure 1. Possible central regulation of magnesium status and chronobiology. **1)** Mg from physiological to pharmacological concentration is able to directly enhance melatonin secretion by stimulating serotonin N-acetyltransferase, the magnesium key enzyme for synthesis of melatonin (MT), and to enhance indirectly the production of MT through an increased activity of the SNC. **2)** MT can decrease magnesemia through its effects on Mg distribution and the SNC may directly increase MT production. **3)** The same mechanisms induce two symmetrical effects. Darkness stimulates and light decreases MT production. Mg overload stimulates and Mg deficiency decreases MT synthesis and SNC activities. Balanced Mg status might enhance the effect of darkness treatments and reversely darkness treatments may potentiate the effects of Mg therapy. Link demonstrated (—); Link probable (.....).

causality link between these two factors but it does not, however, rule it out.

The inductive aetiopathogenic mechanism of magnesium depletion with hBC may be due to the sum of nutritional magnesium deficiency and of a stress: possibly a chronobiological stress such as hBC through photosensitivity.

Chronic primary magnesium deficiency is frequent: about 20 per cent of the population consumes less than two-thirds of the RDA for magnesium [112]. In nutritionally magnesium deficient patients a photosensitive chronobiological stress can induce **a photosensitive magnesium depletion** whose main clinical form is **headache with photophobia** (M and TTH particularly). **Comorbidity with other clinical forms of this photosensitive pathology** may concern the psychic, hypnic and neuromuscular fields. Comorbidity with **anxiety** (panic attack or generalized anxiety disorder) is frequent, but photosensitive headache may also be associated with **dyssomnias** (i.e. delayed sleep phase syndrome) or local or generalized **epilepsy**.

To summarize: the new concept of **headache due to photosensitive magnesium depletion** appears well founded and may induce various therapeutic consequences [3, 19, 81, 112].

Treatment of headaches due to photosensitive magnesium depletion

Classical medications used for the treatment of headaches: antalgic drugs, anticonvulsivants, β-blockers, ergot derivatives, triptans... although useful, will not to be considered in this study.

The following therapeutic approach concerns only the treatment of magnesium depletion due to light hypersensitivity: i) magnesium depletion treatment, ii) photosensitivity treatment.

Treatment of magnesium depletion

Preventive treatment

Preventive treatment is more efficient than curative treatment. Since magnesium depletion is usually due to both a primary chronic magnesium deficiency and of a stress, the prophylactic treatment must rely on **a balanced magnesium status** and the most specific possible antistress treatment.

To insure a balanced magnesium status, in case of chronic primary magnesium deficiency, **atoxic nutritional magnesium supplementation will be carried out** *via* the diet or with supplemental magnesium salts [112]. The dietetic supplement should have a high magnesium density with the greatest availability. Magnesium in drinking water is of particular interest as it associates a high bioavailability with the lowest nutritional density. The magnesium salt used would be hydrosoluble and the properties of the anion should be considered [112-115]

No specific anti-photosensitive drug currently exists which could be used as a preventive treatment of photosensitive magnesium depletion.

Curative treatment

The aspecific treatments of **magnesium depletion** which are available, such as **pharmacological doses of parenteral magnesium,** may be used. Several studies have shown that 1 gram of intravenous magnesium sulfate may be considered as efficient, safe and well tolerated in migraine headache [116-120], but its efficiency as an antalgic drug and as an anti-migraine treatment remains controversial [121-124].

Pharmacological doses of magnesium salts may induce a toxicity which varies according to the nature of anions. For example, the effects of $MgCl_2$ and $MgSO_4$ on the ionic transfer components through isolated amniotic membrane were studied and revealed major differences. $MgCl_2$ interacts with all the exchangers, whereas the effects of $MgSO_4$ are limited to paracellular components. $MgCl_2$ mainly increases the ionic flux ratio of this asymmetric human membrane while $MgSO_4$ decreases it, with many deleterious fetal consequences.

It seems therefore necessary to determine **the therapeutic index** (LD 50 / ED 50) of the various available magnesium salts before pharmacological use. The selection of one magnesium salt among others should take into account reliable pharmacological and toxicological data and **the comparative therapeutic index of the various salts**: the larger its value, the greater the safety margin [125]. This logical prerequisite is lacking in most protocols: $MgSO_4$ is just routinely used without justification.

Magnesium acetyltaurinate appeared as an efficient treatment in another type of magnesium depletion: **kainate magnesium depletion** experimentally induced by systemic kainic acid injection in magnesium deficient rats [126]. But it is not possible to extrapolate from the previous model concerning the efficiency of this magnesium salt in photosensitive magnesium depletion [3, 81, 82, 112-126].

Treatment of photosensitivity (« darkness therapy »)

The reactive response to photosensitivity induces a hBC. But, in case of photosensitive headache, hBC is aggravated because the repetitive stimulating effects of light induce potentiation (sensitization) – sometimes with generalization – instead of habituation [3].

Treatment of photosensitivity – the so-called « darkness therapy » – mirrors « phototherapy » the treatment of hyperfunction of the biological clock.

Darkness therapy aims either at **stimulating** the BC, or at **palliating** its hypofunction.

Stimulation of the biological clock may be obtained through physiologic, psychotherapic, physiotherapic or pharmacologic agents.

Palliative treatments of hBC are dependent on melatonin, its analogs or its precursors.

Stimulating darkness therapies

a) Physiologic darkness therapies (Darkness therapy *per se*)

The best physiologic stimulation of the BC is induced by light deprivation.

It 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 [3, 10, 81, 82, 127, 130].

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. A successful double-blind study demonstrated a significant difference between placebo and salicoside (*salicin*) in association with a photoprotective mask in treating the two main clinical forms of photosensitive headaches: M and TTH [128]. The good results of this controlled clinical trial have not been confirmed [3, 81, 84, 128, 129].

Chromatotherapy uses a short exposure (4 min) to a precise yellow wavelength, once a week for the treatment of hBC. This method, even though successfully used in practice, has not been validated yet [3, 81, 82].

Some studies have reported benefit from using colored filters in headache patients: in childhood migraine particularly. A double masked randomized controlled study with crossover design compared the effectiveness of precision ophthalmic tints (optimal tint) or glasses that provided a slightly different colour (control tint). Using individually prescribed coloured filters selected by each migraineur seems more helpful than the conventional practice of using a neutral grey or sometimes brown tint, but the effect is statistically marginal; it is suggestive rather than conclusive [23, 24, 130].

b) Psychotherapic darkness therapies

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 **desensitisation procedure** resulted in a complete removal of the patient's phobic anxiety of photo-stimulation and of avoidant behavior. This **behavioral** therapy has been used in photo-sensitive epilepsy [131]. It is akin to **deconditioning techniques** used as a non-pharmacological approach to prevent photosensitive headache. For example: Variable Frequency Photostimulation (VFP) goggles i.e. a portable stroboscope using red Light Emitting Diodes (LED) to illuminate the right and the left eye alternately were used with limited efficacy. Various biofeedback treatments for migraine were disappointing since a reduction in the number of migraine headaches was observed, but with no change in the intensity, duration or disability of the headaches [132-135].

The concept of headache due to photosensitive magnesium depletion places this clinical form of headache among the indications of psychological darkness therapies.

c) Physiotherapic darkness therapies

Magnetic fields may be used to stimulate the biological clock in a variety of treatment methods using very weak (picotesla), extremely low frequency (2 to 7 Hz) electromagnetic fields. Transcranial treatment with alternative current pulsed electromagnetic fields of picotesla flux density may stimulate various brain areas (the hypothalamus particularly) and the pineal gland (which functions as a magneto receptor). Several studies concern its use for treatment of headaches. A double blind placebo controlled trial has shown that this physiotherapy can alleviate symptoms of M but not of TTH. Electromagnetic fields for at least three weeks may be considered as an effective, short term intervention for migraine, although the clinical effects were small [136-139].

d) Pharmacologic darkness therapies

Three agents may stimulate the biological clock: magnesium, L-tryptophan and taurine.

– **Magnesium** To stimulate the BC, it seems well advised to facilitate the neural function of suprachiasmatic nuclei (↗ SCN) and the hormonal pineal production (↗ MT). The deleterious effects of light and those of magnesium deficiency are often found together and may be partly palliated by a nutritional magnesium supply (↗ Mg), providing the best possible link between photoperiod and magnesium status. Palliative nutritional magnesium supplementation is efficient and atoxic when magnesium deficiency is present, but when there is a balanced magnesium status, it is illogical and inefficient. Pharmacological use of magnesium (high oral doses, or parenteral administration) is uncertain and susceptible of inducing toxicity. Many data remain imprecise, such as nature and doses of the magnesium salts, oral or parenteral routes, association with magnesium fixing agents [3, 81, 82, 113].

– **L-tryptophan** (or 5OH-tryptophan) may stimulate the tryptophan pathway [140]. But they are unspecific as they not only concern melatonin production, but also serotonin synthesis.. LTP supplementation **may induce toxicity**, eosinophiliamyalgia syndrome particularly [141-145].

– **Taurine** is a sulphonated aminoacid which is present in the whole body in high concentrations, particularly in the brain. It has multiple functions 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 the functional quality of the neural apparatus and in melatonin production and action. It plays a role in the maintenance of homeostasis in the central nervous system, particularly during central nervous hyperexcitability. Taurine, a volume-regulating aminoacid, is released upon excitotoxicity-induced cell swelling. It has an established function as an osmolyte in the central nervous system [3, 18, 81, 82, 109, 122, 146-154].

In the course of magnesium deficit, the organism appears to stimulate taurine mobilisation to play the role of «a magnesium vicarious agent ». Usually, this compensatory action is rather limited. However, it allows us to observe the latent form of the least severe form of **magnesium deficiency** [18, 109, 122, 148, 149]. During M, the typical form of headache due to photosensitive **magnesium depletion**, taurine mobilisation may be considered as a defensive reaction but it is less effective than in case of magnesium deficiency [155-160] *(figure 2)*.

To sum up, magnesium, tryptophan and taurine may be used to stimulate the biological clock, but their efficiency seems limited.

Palliative treatments of hypofunction of the biological clock may be necessary.

« Substitutive darkness therapy »
(darkness mimicking agents)

a) Mechanisms of the action of darkness

The mechanisms of action of darkness appear to be the reverse of those described with bright light,

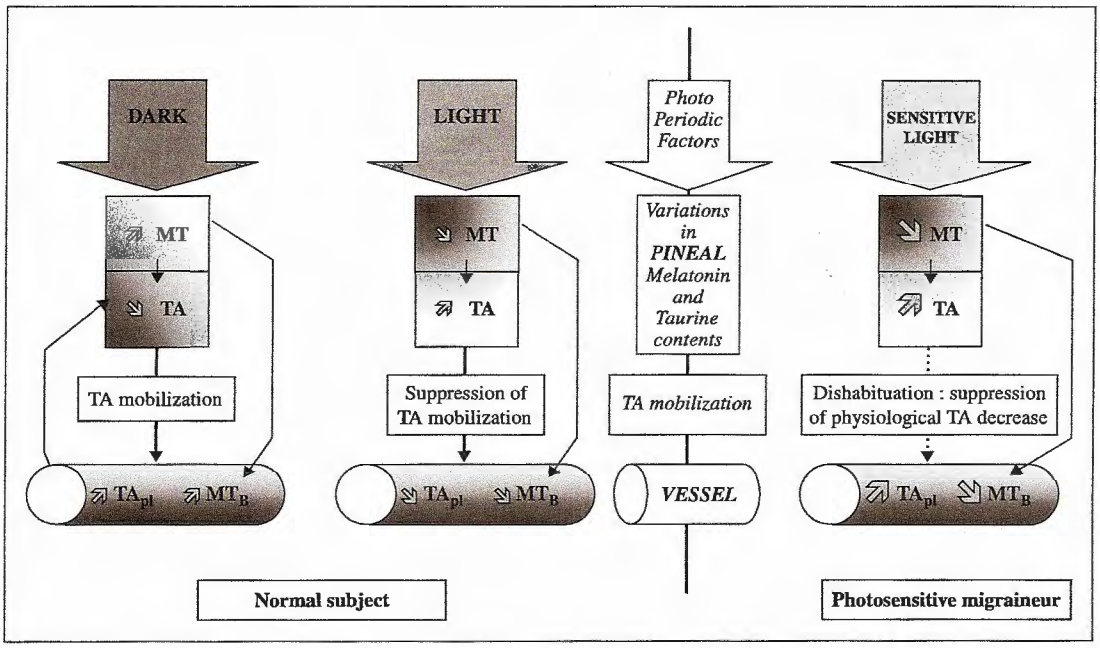

Figure 2. Photoperiod, pineal, melatonin and taurine. In normal subject, darkness (a) increases the pineal melatonin synthesis (↑**MT**). Since this MT synthesis is taurine-dependant, pineal taurine levels decrease (↓**TA**) during darkness. This induces a down reglated compensatory increase in taurine mobolization wich marker is an increase in platelet taurine content (↑$\mathbf{TA_{Pl}}$). Reversely, light (b) decreases pineal melatonin synthesis (↓**MT**). Consequently, by increasing the pineal taurine content, the down regulated compensatory increase in taurine mobilization is suppressed leading to a major decrase in pineal MT (↓↓**MT**) and correlatively to a major increase in pineal taurine (↑↑**TA**). The pathological disabituation induced by iterative photosensitivity pathologically reverses the taurine mobilization. Platelet taurine levels increase instead of decraseing (↑↑$\mathbf{TA_{Pl}}$). This important increase in TAPl does not compensate the pathological decrease in pineal melatonin, but may appear as defense mechanism having osmolyte beneficial effects on extra-pineal tissues such as central nervous or cardio-vascular systems. MT: pineal melatonin; TA: pineal taurine; MTb: circulating blood melatonin; TAPl: platelet taurine.

where direct cellular effects (membraneous and redox) and neural mediated effects intervene.

Increased production of melatonin (↗ MT) constitutes the best marker of darkness, but it is only an accessory mechanism in its action.

The main central neural mechanisms of darkness therapy associate decreased serotoninergy (↘ 5HT) -which could account for the antimigraine effect- and stimulation of inhibitory neuromodulators gamma-aminobutyric acid, taurine, kappa opiods (↗ GABA, ↗ TA, ↗ kO) and stimulation of anti-inflammatory and antioxidative processes. These effects may induce neural-hypoexcitability i.e. sedative and anti-convulsant effects.

Humoral transduction may reinforce these last effects by decreasing neuroactive gases (↘ CO, ↘ NO) through binding of CO with hemoglobin (Hb) and by increasing melatonin, bilirubin and biliverdin, three antioxidants which are able to quench NO.

Apart from the exception of decreased serotonergy, these effects of darkness are similar to those of magnesium [3, 81, 82].

Substitutive darkness therapy should palliate all the mechanisms of action of darkness. The only available darkness mimicking agents are at present melatonin (its analogs and its precursors, L-tryptophan, 5 hydroxytryptophan).

b) Melatonin: an accessory darkness mimicking agent

Melatonin is the prototype of darkness mimicking agents. But, although its production is the best marker of photoperiod, melatonin 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 posology varies from physiological doses (around 3 mg) to pharmacological doses, usually 3 mg/*per* dose *per* day and even up to 300 mg as a contraceptive, which testifies to the weak toxicity of the hormone. In case of chronopathology with decreased MT production, MT constitutes a **partial** substitutive treatment of its deficiency [3, 81, 82, 161-164].

To summarize: at the present time, substitutive darkness therapy using melatonin as a **partial** substitutive treatment of hBC is possible, though melatonin is only an accessory mechanism of the action of darkness.

Conclusion

The treatment of headache due to photosensitive magnesium depletion must, at present,associate:

– **the classical treatments of headache** (antalgic drugs, anticonvulsants, ergot derivatives, β-blockers, triptans...)

– **a balanced magnesium status** (through nutritional or careful pharmacological magnesium supplementation)

– **the control of hBC through physiologic, psychotherapic, physiotherapic** or **pharmacologic stimulation of the BC** or **through MT: partial darkness mimicking agents.**

Further research must study other agents with more efficient darkness mimicking properties. A new model of photosensitive magnesium depletion with potentiation is currently described [165]. This test should be a useful tool for discriminating the most efficient darkness mimicking agent in photosensitive magnesium depleted mice.

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